Dengue Classification: Current WHO vs. the Newly Suggested Classification for Better Clinical Application?

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Introduction: *There has been confusion regarding the clinical classification of dengue. The current WHO classification used since the 70s classifies dengue into dengue fever (DF), dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS). In 2009, a new classification of dengue proposed by WHO Tropical Disease Research (TDR) was published in the WHO TDR 2009 dengue guidelines. This new classification classifies dengue into dengue (D), dengue with warning signs (DW) and severe dengue (SD).*

Objective: *To compare the effectiveness in clinical management between the current WHO classification and the newly suggested classification (TDR) and to assess the 4 criteria of the DHF case definition of the current WHO classification for possible modification.*

Material and Method: *A prospective study of suspected dengue patients admitted to the Dengue Unit, Queen Sirikit National Institute of Child Health between June-August 2009 was done. All cases were managed according to the Thai National Dengue Guidelines 2008. The final diagnoses were based on the current WHO Classification together with dengue laboratory confirmation. TDR classification was applied later by the author, using the data from the present study case report forms of each patient. Statistical analysis comparing clinical and laboratory data between each group of patients was done by using SPSS version 14.*

Results: *Total 274 confirmed dengue patients and 24 non-dengue febrile illnesses (ND) were used for analysis. There were 180 DF (65.7%), 53 DHF grade I (19.3%), 19 DHF grade II (6.9%), 19 DHF grade III (6.9%) and 3 DHF grade IV (1.1%) as classified by the current WHO classification while the suggested TDR classified 85(31%), 160(58.4%) and 29(1.1%) as D, DW and SD respectively. At least one of the warning signs were found in 50, 53.3, 83, 88.2, 100 and 100% of ND, DF, DHF grade I, DHF grade II, DHF grade III and DHF grade IV patients. Vomiting and abdominal pain were the 2 most common warning signs found in both ND and dengue patients. Intensive monitoring and careful medical and IV fluid management were needed for 94 DHF patients compared to 189 DW and SD patients by the new TDR classification. There were 8 DSS patients who had AST > 1,000U and one patient presented with encephalopathy. These 8 patients cannot be classified properly in the current WHO classification. One non-dengue patient who presented with gastrointestinal bleeding was classified as SD. Bleeding and/or positive tourniquet test was found in and 69.7% of DHF patients. Plasma leakage detected using hemoconcentration, chest x-ray (CXR) and ultrasonography. Hemoconcentration could detect plasma leakage in 44.7% and CXR added up evidence of plasma leakage to 86.3%. Ultrasonography was the most sensitive technique to add evidence of plasma leakage up to 100%. Platelet $\leq$ 100,000 cells/mm3 was found in 93.5% of DHF patients.*

Conclusion: *Current WHO classification is recommended for continuing use because the newly suggested TDR classification creates about 2 times the workload to health care personnel. In addition, the TDR classification needs dengue confirmatory tests. More than 90% of DHF defined by WHO case definition are dengue confirmed. However, current WHO classification needs to be modified for more simple and friendly use. The suggested modification is to address plasma leakage as the major criteria. Tourniquet test positive or bleeding symptoms can be considered as minor criteria. Unusual dengue is proposed to be added to the current WHO classification to cover those patients who do not fit with the current WHO classification*

Keywords: *Dengue WHO classification, Dengue fever, DF, Dengue hemorrhagic fever, DHF, Dengue shock syndrome, DSS, Warning signs*

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Dengue has been increasing worldwide with 50-100 million new cases a year[1,2]. Most of the newly dengue outbreak countries and previous endemic countries, especially those with high case fatality rate (CFR) had reported more severe and unusual presentations that they have never seen before[3]. The healthcare personnel in those countries with dengue problems have limited experience in diagnosis and management. The WHO classification[4]: dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) has been criticized by many doctors that most of the cases could not fulfill the requirement for diagnosis of DHF[5]. Most of the patients they found could not fulfill the DHF case definition: plasma leakage (rising Hematocrit (Hct) $\geq 20\%$) and thrombocytopenia $\leq 100,000$ cells/mm^3. In addition, more patients with multiple organ(s) involvement, *e.g.* encephalopathy, liver failure, renal failure and heart involvement were seen and cannot be classified according to the current WHO classification[6].

A group of scientists and doctors had set up a multi-country collaborative dengue study, called DENCO to evaluate the WHO classification including the clinical presentations of dengue in order to find the best solution for the management of suspected dengue patients and minimize the CFR. This DENCO project was supported by the European Union and WHO Special Program for Research and Training in Tropical Diseases (TDR) and this clinical part was done during 2005-2006. The group has proposed the new classification based on the results of the DENCO study. WHO Tropical Diseases research (TDR) had published this new suggested classification in the 2009 new guidelines for diagnosis, treatment, prevention and control[7] for possible replacement of the current WHO classification that has been used effectively in reducing CFR, especially in the Southeast Asia and Western Pacific Regions for more than 3 decades[8].

The objectives of the present study were to compare the effectiveness in clinical management between the current WHO classification to the newly suggested TDR classification, and to assess the 4 criteria of the DHF case definition of the current WHO classification: fever, tourniquet test and/or bleeding manifestations, plasma leakage and thrombocytopenia.

Material and Method

A prospective study of the suspected dengue patients who were admitted to the Dengue Unit, Queen Sirikit National Institute of Child Health (QSNICH)

between June-August 2009 was done. The suspected dengue admitted patients were those who presented with shock or had a history of high fever with bleeding symptoms (including positive tourniquet test), leukopenia (WBC $\leq 5,000$ cells/mm^3) and/or platelet count around 100,000 cells/mm^3. All cases were managed according to the Thai National Dengue Guidelines 2008[9]. The admitted cases represented the more severe cases or cases with more families' concern. Patients were classified using the 1997 WHO Classification and the new TDR classification was applied later using the data from the case report form. Dengue virus infections were determined by polymerase chain reaction (PCR) and/or by serology. WHO Classification 1997: DF, DHF grade I, II, III and IV. DSS = DHF grade III or DHF grade IV.

Probable DF: Fever with 2 of the following: headache, retro-orbital pain, myalgia, arthralgia/bone pain, bleeding manifestations, rash and leukopenia.

DHF case definition using 4 criteria: Fever, bleeding manifestation including positive tourniquet test (≥ 10 petechiae/sq. inch), plasma leakage (hemoconcentration $\geq 20\%$, pleural effusion, ascites detected by physical examination, chest film-right lateral decubitus technique or ultrasound) and thrombocytopenia (platelet count $\leq 100,000$ cells/mm^3.

Plasma leakage is determined in most cases by hemoconcentration (rising Hct $\geq 20\%$). Some of the cases, pleural effusion and ascites were detected by physical examination, chest x-ray (right lateral decubitus technique), ultrasonography, hypoalbuminemia (serum albumin ≤ 3.5 gm% or change of albumin ≥ 0.5 gm%) or hypocholesterolemia (serum cholesterol ≤ 100 mg% or change of cholesterol ≥ 20 mg%). Ultrasonography was performed in suspected DHF cases without evidence of hemoconcentration or pleural effusion by CXR.

TDR Classification: Dengue (D), Dengue with warning signs (DW) and severe dengue (SD).

D: Fever with 2 of the followings: Nausea/vomiting, rash, aches and pain, tourniquet test positive, leukopenia, any warning sign.

Warning signs: abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy/restlessness, liver enlargement > 2 cms. and laboratory: increase in Hct concurrent with rapid decrease in platelet count.

SD-severe plasma leakage (shock, fluid accumulation with respiratory distress), severe bleeding evaluated by clinicians and severe organ involvement (AST or ALT $\geq 1,000$ U, CNS-impair consciousness and heart and other organs involvement).

SPSS version 14 was used for statistical analysis in the present study.

Results
Diagnoses
There were 356 suspected dengue patients admitted to the Dengue Unit, QSNICH between June-August 2009 and 298 cases with the complete dengue serologic and virological diagnoses were eligible for analysis. There were 274 confirmed dengue patients and 24 non-dengue febrile illnesses. There were 180 DF (65.7%%), 53 DHF grade I (19.3%), 19 DHF grade II (6.9%), 19 DHF grade III (6.9%) and 3 DHF grade IV (1.1%) as classified by the 1997 WHO classification while the suggested TDR classified 85 D (31%), 160 DW (58.4%) and 29 SD (10.6%) (Fig. 1). Among 24 non-dengue cases (ND), the clinical diagnoses were 19 DF and 4 DHF grade I and 1 DHF grade II by the current WHO classification while using TDR classified as 10 D, 13 DW and 1 SD (Fig. 2). Comparison between t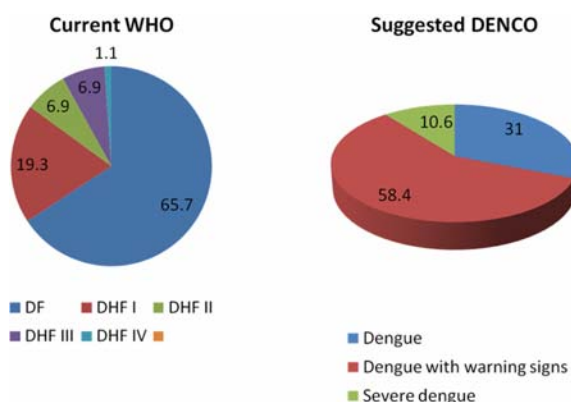he diagnoses by current WHO and T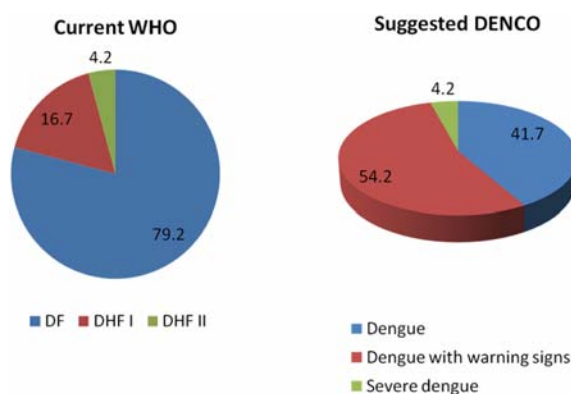DR classification is shown in Table 1. Among 180 DF confirmed cases which were considered to be mild, TDR classified as 105 DW and 1 SD and among non-dengue suspected 19 DF cases TDR classified as 9D and 10DW cases (Table 2). There was no death in the present study.

Demographic data
The mean age of ND, DF, DHF were 6.7 ± 4.1, 8.3 ± 3.9 and 9.3 ± 4.4 years respectively (p = 0.049). The male to female ratios were 1.5: 1, 1.3: 1 and 1: 1.05 respectively (p = 0.383).

Serology
Serologic findings in dengue patients were 16.1% primary, 77.7% secondary, 1.8% of acute dengue infections, 3% of no serologic diagnosis and 1.7% with negative dengue serology. Seventy-five, 80.6 and 90.9% of DF, DHF and DSS patients had secondary dengue infection respectively (p = 0.783) (Fig. 3).

Serotypes
There were 77.4% dengue serotypes identified from 212 dengue patients as 110 dengue 1 (52.1%), 36 dengue 2 (17.1%), 55 dengue 3 (26.1%) and 10 dengue 4 (4.7%) (Fig. 3). Dengue 1, 2 and 3 were identified in one DF patient. Dengue 4 was found in only 10 patients and 9 of them (90%) was DF while 65.6, 55.6 and 67.3% of dengue 1, 2 and 3 were found in DF patients (p = 0.729). DSS patients were found to be caused by 7.3% of dengue 1, 11.1% of dengue 2, 9.1% of dengue 3 and none of dengue 4 infections.

Criteria for WHO case definition of DHF
Tourniquet test positive, hemoconcentration (rising Hct $\geq$ 20%), thrombocytopenia (platelet counts $\leq$ 100,000 cells/mm^3) were found in 69.7, 44.7 and 93.5% of DHF patients, respectively (Table 3).

Warning signs
At least one of the warning signs was found in 50, 53.3, 83, 88.2, 100 and 100% of ND, DF, DHF grade I, II, III and IV patients, respectively (p < 0.001) (Fig. 4, 5).

Abdominal pain or tenderness was found in 15, 29.5, 45.8, 72.2 and 73.7% of ND, DF, DHF grade I, II, III and IV, respectively (p < 0.001).

Persistent vomiting was found in 40.9, 33.3, 63.3, 50, 57.9 and 54.4% of ND, DF, DHF grade I, II, III and IV, respectively (p = 0.008).

Clinical fluid accumulation was found in 0, 0, 8, 20, 61.5 and 29.4% of ND, DF, DHF grade I, II, III and

Fig. 1 Dengue Classification n = 274 (Confirmed dengue)

Fig. 2 Dengue Classification n = 24 (Non-dengue)

Table 1. Comparison of Dengue Diagnoses between Current WHO Classification with suggested DENCO classification in confirmed dengue cases

	DF (%)	DHF I (%)	DHF II (%)	DHF III (%)	DHF IV (%)	Total DHF (%)	Total (%)
Dengue	74	10	1	0	0	11	85
Dengue with warning signs	105	41	14	0	0	55	160
Severe Dengue	1	2	4	19	3	28	29
Total	180	53	19	19	3	94	274

Table 2. Comparison of Dengue Diagnoses between Current WHO Classification with suggested DENCO classification in non dengue cases

	DF (%)	DHF I (%)	DHF II (%)	DHF III (%)	DHF IV (%)	Total DHF (%)	Total (%)
Dengue	9	1	0	0	0	1	10
Dengue with warning signs	10	3	0	0	0	3	13
Severe Dengue	0	0	1	0	0	1	1
Total	19	4	1	0	0	5	24

Table 3. The percentage of each criteria in WHO case definition

	Non dengue (%)	Dengue	p-value	Note
Tourniquet test	58.3	69.7	0.581	
Plasma leakage	16.7	100	0.000	
Hemoconcentration	4.2	44.7	0.000	
Platelet $\leq$ 100,000 cell/mm^3	41.7	93.5	0.000	

IV, respectively ($p < 0.001$).

Mucosal bleed was found in 4.5, 16.6, 17, 37.5, 41.2 and 100% of ND, DF, DHF grade I, II, III and IV, respectively ($p = 0.052$).

Lethargy was found in 9.1, 2.5, 4.4, 67, 33.3 and 100% of ND, DF, DHF grade I, II, III and IV, respectively ($p < 0.001$).

Liver enlargement > 2 cms was found in 4.8, 1.9, 8.9, 26.7, 18.8 and 66.7% of ND, DF, DHF grade I, II, III and IV, respectively ($p < 0.001$).

Plasma leakage
Hemoconcentration
Rising HCT of $\geq$ 20% was found in 4.2, 4.5, 37.7, 36.8, 63.2, 100 and 44.7% in ND, DF, DHF grade I, II, III, IV and total DHF patients ($p < 0.001$) while hemoconcentration $\geq$ 15-19.9% was found in 12.5, 19.4, 22.6, 36.8, 21.1% in ND, DF, DHF grade I, DHF grade II and DHF grade III ($p < 0.001$) (Fig. 6).

Chest film
A chest x-ray was done in 92 patients (30.9% of total study patients) and pleural effusion was documented in 41.6% of DHF patients who did not have hemoconcentration $\geq$ 20%.

Ultrasonography
Ultrasonography was done in cases of DHF who had no hemoconcentration, no pleural effusion by chest x-ray and pleural effusion and/or ascites were detected.

Hypoalbuminemia/Hypocholesterolemia
Mean minimum serum albumin in ND, DF and DHF grade I, II, III and IV were 4.53, 3.93, 3.50, 3.04, 2.52 and 2.66 gm% respectively ($p < 0.001$) Fig. 7.
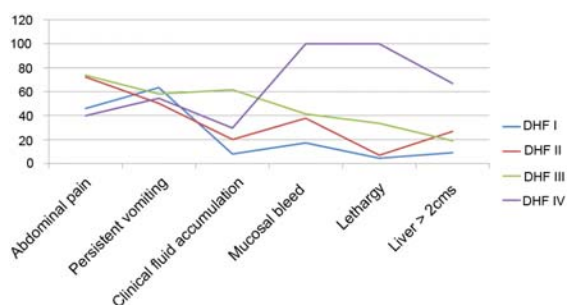
Mean minimum serum cholesterol in ND, DF and DHF grade I, II, III and IV were 170.0, 168.3, 108.9, 81.5, 82.3 and 33 mg% ($p < 0.001$) Fig. 7.
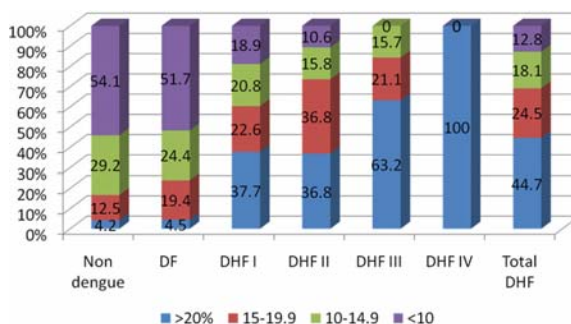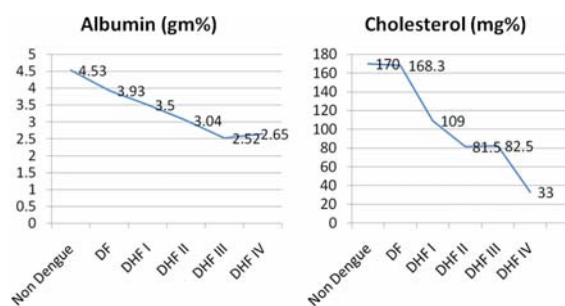
Serology
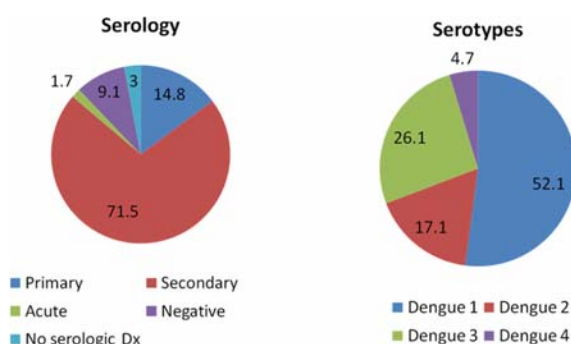
Serotypes

Fig. 3 Dengue Serology & Serotypes

Albumin (gm%)

Cholesterol (mg%)

Fig. 7 Mean Minimum Albumin & Cholesterol
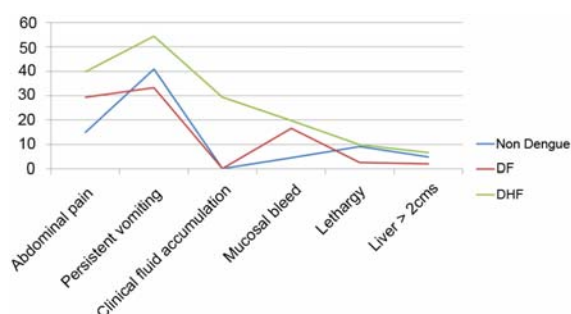
Fig. 4 Warning signs

Fig. 5 Warning signs in DHF

Fig. 6 Hemoconcentration

Thrombocytopenia

The mean nadir platelet count in ND, DF and DHF grade I, II, III and IV were 108,174; 96,578; 63,098; 50,474; 46,700 and 51,333 cells/mm^3 respectively (p < 0.001). Platelet count $\leq$ 100,000 cells/mm^3 was found in 41.7, 60.6 and 91.5% of ND, DF and DHF patients. Platelet count $\leq$ 50,000 cells/mm^3 was found in 12.5, 15 and 54.4% of ND, DF and DHF patients Fig. 8.

Leukopenia

The mean nadir WBC in ND, DF and DHF grade I, II, III and IV were 3,098; 3,032; 3,253; 3,544; 3,523 and 3,890 cells/mm^3 respectively (p = 0.551). Leukopenia was found in 95.7, 92, 88.7, 77.8, 84.2 and 100% of ND, DF, DHF grade I, II, III and IV respectively (p = 0.632).

Tourniquet test

Positive tourniquet test was found in 58.3, 68, 75.5, 66.7, 68.4 and 100% of ND, DF, DHF grade I, II, III and IV respectively (p = 0.581).

AST/ALT

The mean AST values were 65, 101, 153, 146, 1,178 and 2,832 in ND, DF, DHF grade I, II, III and IV (p < 0.001) while the mean ALT values were 24, 51, 82, 57, 427 and 1,131 in ND, DF, DHF grade I, II, III and IV respectively (p < 0.001) Fig. 9.

Normal AST values were found in 90.5, 56.9, 50, 58.8, 33.3 and 0 in ND, DF, DHF grade I, II, III and IV respectively. Elevation of AST in almost all dengue patients were usually < 200 U. Six DHF grade III and 2 DHF grade IV had AST > 1,000 U. Fig. 10.

Normal ALT values were found in 100, 98.9, 84.6, 94.1, 50 and 33.3% in ND, DF, DHF grade I, II, III and IV respectively. Elevation of ALT in almost all dengue patients were usually < 200 U. Six DHF grade III and 2 DHF grade IV had ALT > 1,000 U. Fig. 10.

Management Fig. 11

IV fluid was given in 68.1% of dengue patients: 28% for DF, 58.5% for DHF grade I, 64.7% for DHF grade II, 100% for DSS patients while ND patients received IV fluid in 33.3%.

Dextran-40 was given in 17% of DHF patients; 9.4, 17.7, 36.8 and 33.3% of DHF grade I, II, III and IV, respectively.

Blood was transfused in 8.5% of DHF patients: 16.2 and 26.3% of DHF grade II and III. One ND patient received blood transfusion for the upper GI bleeding.

Platelet concentrate was given in 2 DHF patients: DHF grade II and III who also had blood transfusion.

Discussion

The percentage of dengue patients in the present study was very high, 92% because the 2 criteria of positive tourniquet test or bleeding and leukopenia with the better positive predictive value for dengue infection[10] ± thrombocytopenia was used for the dengue admission instead of using any 2 combinations of the signs and symptoms of the WHO criteria for probable dengue; headache, retro-orbital pain, myalgia, arthralgia, rash, leukopenia and bleeding manifestations. The increased awareness of dengue illness among the general population has made the percentage of DF which is considered to be mild illness admission is very high (65.7%) compared to previously observed at QSNICH, 10.7% in 1982-1986 (80s) and 19% between 1995-1999 (90s). The better dengue case management with the updated national dengue guidelines for all healthcare levels (1999) has made the percentage of shock patients decrease to 8% in the present study compared to the percentage of 66.6 and 24.7% shock in the 80s and 90s[11]. The case fatality rate (CFR) at QSNICH in the 80s and 90s were 1.36 and 0.2% respectively while in 2009 the CFR was 0.63%. The reason for high CFR is because all the death cases were severe/complicated referred cases. The CFR of the walk in dengue patients at QSNICH was 0. The country CFR were 1.0%, 0.66% and 0.13% in 1980, 1990 1nd 2009 respectively[12].

Primary and secondary dengue infections were found in 17.2% of DF and 85.7% of DHF patients which is comparable to the 80s and 90s. Alternate dengue serotypes circulate in Thailand with different predominant dengue serotypes every years as in the present study Dengue 1 (51.9%) was predominated (2009) while dengue 2 (42.1%) and dengue 3 (50.6%) were predominated in the 80s and 90s[12].
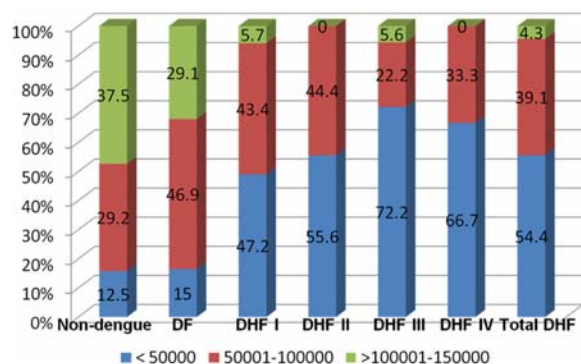
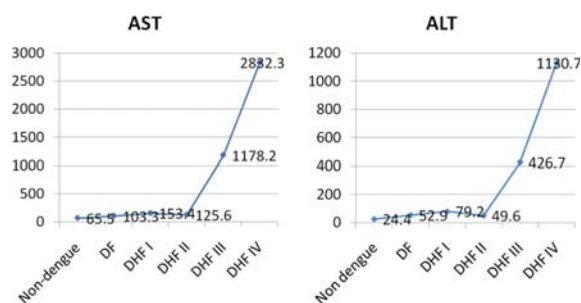Twenty-four of the suspected dengue cases

Fig. 8 Platelet counts

Fig. 10 AST and ALT range

Fig. 9 Mean Maximum AST/ALT
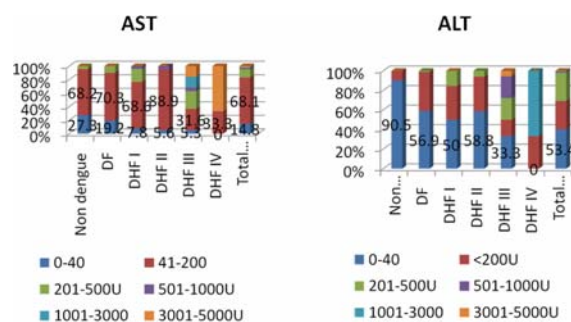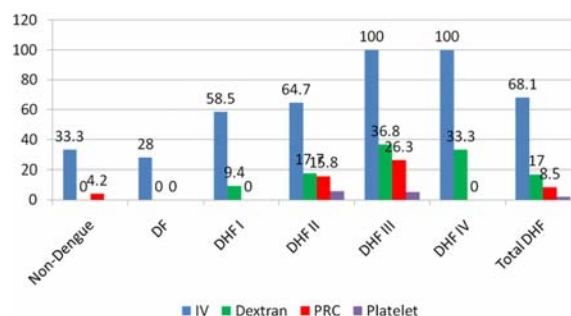

Fig. 11 IV fluid, Dextran, Blood and Platelet transfusion

were confirmed not to be dengue. The clinical diagnoses of these 24 confirmed non-dengue cases by the current WHO classification were 19 DF, 4 DHF grade I and 1 DHF grade II; four DHF grade I, 1 DHF grade II were misdiagnosed because of the thrombocytopenia in all 5 cases; rising HCT $\geq$ 20% in 4 cases; massive upper GI bleeding in 1 case. The 19 misdiagnosed as DF cases because of the following criteria were met with the probable dengue cases: 23 cases had leukopenia, 14 positive tourniquet test, 12 cases with rash, 5 cases with headache, 3 cases with thrombocytopenia, 3 cases with myalgia and 1 case with arthralgia. The current WHO classification did not miss any severe DHF cases and over-diagnosed 19 DF and 5 DHF (8.1%).

The TDR classified the 24 non-dengue cases as 1 SD, 13 DW, 9 Dengue and 1 ND. SD was diagnosed because of massive upper GI bleed that needed blood transfusion. TDR classification for severe dengue needed serologic and virological laboratory confirmation or else more patients who required blood transfusion in dengue endemic countries will be diagnosed as SD. For the 13 DW, the above criteria for probable dengue and additional warning signs were found: 9 cases with persistent vomiting, 4 cases with rising Hct and decrease platelet, 3 cases with abdominal pain, 2 cases with lethargy and 1 case each had mucosal bleeding and enlarged liver > 2 cms. TDR classification made a false alarm for possible more severe disease that need intensive monitoring in 13 cases (4.4%), misdiagnosed 1 severe case and 9 mild cases.

In the present study, 103 cases satisfied the DHF/DSS clinical criteria (98 dengue and 5 non-dengue cases), *i.e.* 34.6% of total suspected dengue cases were at risk for severe disease and needed close monitoring. In contrast, the TDR classification identified 217 cases of DW and SD (203 dengue and 14 non-dengue cases, 72.8% of suspected dengue patients) which needed close monitoring according to the new guideline.

Warning signs that was emphasized in the TDR classification for strict observation and medical intervention were found in half of the non-dengue cases in the present study: 15% abdominal pain, 40.9% persistent vomiting, 9.1% lethargy and 4.8% of liver enlargement. In the scenario of OPD where many non-dengue acute febrile illnesses patients are seen and non-specific warning signs as above would be observed in half of these patients and they will be diagnosed as dengue and admitted for strict observation and medical intervention, most likely IV fluid administration. Then an enormous number of patients diagnosed as dengue will receive unnecessary

IV fluid by this TDR classification as recommended in the new edition 2009 of WHO/ TDR Dengue, guidelines for diagnosis, treatment, prevention and control. The unnecessary observation/ admission will increase the workload in the hospitals in most resource-poor dengue endemic countries. As a result of the workload, the quality of services, monitoring may be lower and severe cases may be missed if there are not enough personnel to take care of the increase in the number of suspected dengue patients. Besides the inflation of dengue cases, more complications of fluid overload will also be increased in true DHF cases and may lead to death in some cases as fluid overload is one of the major causes of death in DHF patients in Thailand.

If the author defined severity by the need of IV fluid as one criteria for severity in the DENCO study, 33.3% of ND, 28% of DF and 68.1% of all DHF patients (all DSS patients received IV fluid resuscitation) had received IV fluid in the present study. The previous observation is more or less the same as the present study; 15% of ND, 12% of DF and 58% of DHF patients received IV fluid[13]. This means that DF is not always mild and DHF is not all severe. The severity of dengue depends on many factors including management prior to and after hospitalization. The decision to give IV fluid to the patients varies from place to place so it may not reflex true severity of dengue illness.

The suggested TDR classification is claimed to be simple, user friendly, help in clinical triage and accepted by the surveillance personal including the epidemiologists. But this suggestion is a paradigm shift from the previous WHO dengue classification and guidelines that most of the endemic countries have developed their own guidelines and all the relevant health care personnel are tuned to that. In lieu of updating the shift put them and the program into jeopardy to attain the program target of control and prevention of dengue. In addition it may not be consistently affordable. Even though it is simple and user friendly, most clinicians found that this won't help in the clinical triage of the patients. More suspected dengue patients with warning signs, at least 2 times as in the present study will be found and observed/ admitted to the hospital for close monitoring and probably IV fluid administration. Double the workload of the already hard-working healthcare personnel at the Dengue Unit of QSNICH is expected with the using of the new TDR classification.

Rising HCT $\geq$ 20% as the evidence of plasmaleakage was observed in only 44.7% of DHF patients. Chest x-ray, right lateral decubitus technique

(which is not routinely done or not available) had added the evidence of plasma leakage in DHF patients by hemoconcentration alone up to 86.3%. Low albumin ≤ 3.5 gm% and low cholesterol ≤ 100 mg% may be used as evidence of plasma leakage in the majority of DHF patients in the present study. Ultrasonography is the most sensitive investigation to detect plasma leakage (either by detecting pleural effusion or ascites) in cases where the above techniques had failed. The previous study confirmed that ultrasound could helped to document plasma leakage in 70.6% of DHF patients who had no rising Hct $\geq 20\%$ [14].

Patients who have platelet count $\leq 50,000$ cells/mm^3 are likely to be cases of DSS as 68.2% of DSS patients in the present study had. The present study had made the diagnosis of DHF by including those cases with definite evidence of plasma leakage but their platelet count was low and close to 100,000 cells/mm^3, as 91.5% of DHF patients had a platelet count $\leq 100,000$ cells/mm^3. The authors suggest that the current WHO case definition should be modified to include these cases as had been done. Platelet count might not be done repeatedly in some cases so that real thrombocytopenia is missed.

Though leukopenia and a positive tourniquet test are 2 of the good criteria for suspected dengue infection[11] but both of them can also be found in some other diseases. Other diseases that have leukopenia include serious bacterial infections, chikungunya, avian influenza and Influenza A 2009. In the present study used these 2 criteria for admission, *i.e.* why the ND and dengue group had no significant difference in the present finding. In general, a combination of leukopenia and positive tourniquet test had shown to have high positive predictive values (PPV)[11,15].

Liver involvement has been reported[16,17] and the present study had confirmed the findings that only 14.8 and 53.4% of total dengue patients had normal level of AST and ALT respectively. Degree of liver injury was related to the severity. DSS had higher AST/ALT than DHF and DHF had higher level AST/ ALT than DF patients. Elevation of AST may help to rule in dengue infections as 85.2% of dengue patient had AST elevation while only 9.5% of non-dengue acute febrile illness had. This elevation of AST adds more PPV to the above 2 criteria (leukopenia and positive tourniquet test) for the diagnosis of dengue[11].

There were 8 patients; 6 DHF grade III and 2 DHF grade IV with AST elevation > 1,000 U. Among these cases with marked elevation of AST, one DHF grade IV (AST > 5,000 U) presented with encephalopathy and recovered completely with supportive and symptomatic treatment.

Conclusion

Current WHO classification is recommended for continuing use because the newly suggested TDR classification which emphasizes on warnings signs creates more than 2 times the workload to health care personnel, *i.e.* increase the number of suspected dengue patients who need close monitoring from 99 DHF to 217 DW and SD. In addition this suggested classification included a non-specific warning signs as the criteria so confirm dengue laboratory is needed compared to the current WHO case definition with 4 criteria that was confirmed in > 90%.

Plasma leakage is the distinct finding in DHF but it is sometimes difficult to document. Extensive investigation for other evidence of plasma leakage is highly recommended in suspected DHF patients. Patients who have definite evidence of plasma leakage are likely to be cases of DHF and few of them may or may not necessarily have bleeding manifestations and/or platelet count $\leq 100,000$ cells/mm^3 as found in the present study. Current WHO classification, which emphasizes plasma leakage helps in clinical triaging of the patients, needs to be modified for more simple and friendly use. The suggested modification is to address plasma leakage as the major criteria. Tourniquet test positive or bleeding symptoms and thrombocytopenia can be considered as minor criteria. Unusual dengue is proposed to be added to cover those patients who do not fit the current WHO classification.

Potential conflicts of interest

None.

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การแบ่งชนิดของการติดเชื้อไวรัสเดงกี: เปรียบเทียบเกณฑ์เดิมขององค์การอนามัยโลกกับเกณฑ์ที่เสนอใหม่เพื่อการประยุกต์ใช้ทางคลินิก

ศิริเพ็ญ กัลยาณรุจ

ภูมิหลัง: *โรคไข้เลือดออกเป็นปัญหาทางสาธารณสุขที่สำคัญในมากกว่า 100 ประเทศทั่วโลก เกณฑ์การวินิจฉัยการติดเชื้อเดงกีแบ่งเป็น dengue fever (DF) dengue hemorrhagic fever (DHF) และ dengue shock syndrome (DSS) ซึ่งเกณฑ์นี้ใช้มาตั้งแต่ปี พ.ศ. 2517 แต่ในปี พ.ศ. 2553 องค์การอนามัยโลกโดย Tropical Disease Research (TDR) ได้ตีพิมพ์หนังสือแนวทางการวินิจฉัยและรักษาผู้ป่วยไข้เลือดออก และได้เสนอหลักเกณฑ์การวินิจฉัยการติดเชื้อเดงกีใหม่โดยอ้างอิงถึงโครงการศึกษา DENCO และ TDR โดยแบ่งการวินิจฉัยเป็น dengue (D), dengue with warning signs (DW) และ severe dengue (SD) ทำให้มีความสับสนในการเลือกใช้เกณฑ์ในการวินิจฉัยโรคในหลายประเทศทั่วโลก*

วัตถุประสงค์: *เพื่อเปรียบเทียบประสิทธิผลในการดูแลรักษาผู้ป่วย จากการใช้หลักเกณฑ์การวินิจฉัยดั้งเดิมขององค์การอนามัยโลกกับหลักเกณฑ์ที่เสนอใหม่ของ WHO TDR และประเมินหลักเกณฑ์ในการวินิจฉัยโรคไข้เลือดออกขององค์การอนามัยโล 4 ข้อ ที่ใช้อยู่ในปัจจุบันว่าจำเป็นต้องดัดแปลงหรือไม่*

วัสดุและวิธีการ: *ได้ทำการศึกษาแบบไปข้างหน้าในผู้ป่วยที่สงสัยว่าจะติดเชื้อไวรัสเดงกีเข้ารับการรักษาที่หอผู้ป่วยไข้เลือดออก สถาบันสุขภาพเด็กแห่งชาติมหาราชินีระหว่างเดือนมิถุนายน ถึง สิงหาคม พ.ศ. 2552 ผู้ป่วยทุกรายจะได้รับการดูแลรักษาตามแนวทางการวินิจฉัยและดูแลรักษาโรคไข้เลือดออกของกระทรวงสาธารณสุข พ.ศ. 2551 ตามปกติการวินิจฉัยของผู้ป่วยทุกรายตามเกณฑ์การวินิจฉัยขององค์การอนามัยโลกที่ใช้เป็นประจำ โดยผู้ป่วยที่ศึกษาทุกรายจะได้รับการตรวจเลือดเพื่อยืนยันการติดเชื้อไวรัสเดงกี การวินิจฉัยตามเกณฑ์ TDR ที่เสนอใหม่จะทำโดยใช้ข้อมูลจากแฟ้มประวัติผู้ป่วยการวิเคราะห์ข้อมูลทางคลินิก และทางห้องปฏิบัติการเพื่อการเปรียบเทียบระหว่างกลุ่มผู้ป่วยจะใช้โปรแกรมสำเร็จรูป SPSS version 14*

ผลการศึกษา: *มีผู้ป่วยเดงกีทั้งหมด 274 ราย (ร้อยละ 92) และ ไม่ใช่เดงกี (ND) 24 ราย (ร้อยละ 8.1) ในการศึกษานี้ โดยพบว่าผู้ป่วยเดงกีติดเชื้อครั้งแรก ร้อยละ 14.8 ติดเชื้อซ้ำร้อยละ 71.5 สามารถบอกชนิดของเดงกีได้ในผู้ป่วยร้อยละ 77.4 โดยเป็น เดงกี 1, 2, 3 และ 4 ร้อยละ 52.1, 17.1, 26.1 และ 4.7 ตามลำดับ การวินิจฉัยตามเกณฑ์เดิมขององค์การอนามัยโลกเป็นผู้ป่วยไข้เดงกี 180 ราย (ร้อยละ 65.7) ไข้เลือดออกเกรด 1 - 53 ราย (ร้อยละ19.3) ไข้เลือดออกเกรด 2 - 19 ราย (ร้อยละ 6.9) ไข้เลือดออกเกรด 3 -19 ราย (ร้อยละ 6.9) ไข้เลือดออกเกรด 4 - 3 ราย (ร้อยละ 1.1) การวินิจฉัยตามหลักเกณฑ์ TDR จะเป็นผู้ป่วยเดงกี (Dengue-D) 85 ราย (ร้อยละ 31) ผู้ป่วยเดงกีที่มีอาการเสี่ยง (Dengue with warning signs-DW) 160 ราย (ร้อยละ 58.4) และผู้ป่วยไข้เลือดออกชนิดรุนแรง (Severe dengue-SD) 29 ราย (ร้อยละ 10.6) อาการเสี่ยงอย่างใดอย่างหนึ่งพบได้ร้อยละ 50, 53.3, 83, 88.2, 100 และ 100 ในผู้ป่วยไม่ใช่เดงกี, DF, DHF grade 1, 2, 3 และ 4 ตามลำดับ อาการเสี่ยงที่พบบ่อยมากทั้งในผู้ป่วยไม่ใช่เดงกีและเดงกีคือ อาเจียนและปวดท้องมีผู้ป่วย DSS 8 ราย ที่มีค่า AST > 1,000 U หนึ่งในจำนวนผู้ป่วยเหล่านี้มีอาการทางสมอง ไม่มีผู้ป่วยเสียชีวิต*

อาการเลือดออก และการตรวจทูนิเกตให้ผลบวกร้อยละ 69.7 การรั่วของพลาสมาในการศึกษานี้โดย hemoconcentration พบร้อยละ 44.7 และโดย chest x-ray จะพบหลักฐานการรั่วของพลาสมาเพิ่มขึ้นเป็น 86.3 การตรวจด้วย คลื่นเสียงจะไวต่อการตรวจพบน้ำในช่องปอดช่องท้องได้ดีที่สุด พบผู้ป่วยที่มีเกล็ดเลือด ≤ 100,000 เซลล์/

ลบ.มม. ร้อยละ 93.5

สรุป: *จากการศึกษานี้แนะนำให้ใช้หลักเกณฑ์การวินิจฉัยขององค์การอนามัยโลกที่เน้นการรั่วของพลาสมาต่อไป เพราะง่ายสะดวก และความถูกต้องสูงโดยไม่ต้องใช้การตรวจเลือดยืนยันการติดเชื้อไวรัสเดงกีสามารถใช้ เป็นแนวทางในการดูแลรักษาผู้ป่วยที่น่าจะมีอาการหนักได้ดี ในขณะที่หลักเกณฑ์ของ TDR ที่เน้นเรื่องอาการเสี่ยง จะทำให้มีผู้ป่วยที่ต้องดูแลอย่างใกล้ชิดเพิ่มขึ้นมากกว่า 2 เท่าเมื่อเทียบกับหลักเกณฑ์ขององค์การอนามัยโลก คือเพิ่มจำนวนผู้ป่วยที่ต้องการการดูแลอย่างใกล้ชิดจาก 99 ราย เป็น 217 นอกจากนี้การวินิจฉัยตาม TDR ต้องมี การตรวจยืนยันในผู้ป่วยทุกรายเนื่องจากไม่มีความจำเพาะ อย่างไรก็ตามควรมีการปรับเปลี่ยนเกณฑ์ การวินิจฉัยโรคไข้เลือดออกขององค์การอนามัยโลกเล็กน้อยเพื่อให้ง่าย และได้รับการยอมรับมากขึ้น โดยเสนอให้ ใช้หลักฐานการรั่วของพลาสมาเป็นเกณฑ์หลักในการวินิจฉัย ส่วนอาการเลือดออกและเกล็ดเลือดต่ำเป็นเกณฑ์ ย่อยซึ่งอาจตรวจไม่พบได้ในผู้ป่วยไข้เลือดออกส่วนน้อย นอกจากนี้ควรเพิ่มผู้ป่วยเดงกีที่มีอาการแสดงแปลกออกไป (Unusual dengue) เพื่อที่จะสามารถวินิจฉัยผู้ป่วยส่วนน้อยที่มีอาการแปลกออกไปจากปกติโดยมีอาการแสดงของ อวัยวะอื่น ๆ ร่วมด้วย*