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A comparison of WHO guidelines issued in 1997 and 2009 for dengue fever — single centre experience

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Abstract

Objective: To compare the original (1997) and revised (2009) versions of World Health Organization guidelines for dengue patients

Methods: Adult patients with a positive dengue Immunoglobulin M serology, and a diagnosis of dengue were included in the study at Aga Khan University Hospital during a three-year period from January 2005 to December 2007. Data related to these dengue patients was collected from their medical records. Guidelines were then applied by the research assistant and correlation among these guidelines was computed. SPSS 19 was used for statistical analysis.

Results: A total of 612 patients were found with a diagnosis of dengue, but only 439 (71.73%) had a positive IgM. The median age of these 439 patients was 28 (interquartile range: 18) years and majority of them were males, 295 (67%). According to the 1997 guidelines, 383 (87%) patients were classified as having dengue, while according to the 2009 guidelines, all the 439 (100%) patients were classified with a dengue infection. Under WHO 1997, 21 (5.5%) cases were classified as dengue shock syndrome, while 2009 guidelines labelled 88 (20%) cases as severe dengue. There was a consensus on only 11 severe cases by both the guidelines, showing different results between the two.

Conclusion: By using 2009 guidelines, a physician would classify more dengue patients as having severe disease.

Keywords: Pakistan, Dengue, WHO guidelines. (JPMA 63: 670; 2013)

Introduction

Dengue infection is caused by Flavivirus and spreads through *Aedes aegypti* mosquito. The virus infects over 50 million people worldwide, resulting in over 24,000 deaths annually.^{1,2} Billions of people remain exposed to the disease across Africa, Eastern Mediterranean, Southeast Asia and Western Pacific region.³

Clinical presentation of patients with dengue infection varies from a self-limiting, non-specific acute febrile illness to a syndrome characterised by bleeding, severe intravascular volume depletion and shock.⁴ Given its vague presentation, early identification of severe infections can be challenging, causing delays in the institution of life-saving interventions. To assist clinicians in making triage decisions, the World Health Organisation (WHO) published a dengue infection triage and treatment guideline in 1997.⁵ It was based on the data from paediatric population of Bangkok and divided the clinical syndrome into dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).⁶⁻⁸ A revised version of the guideline was published in 2009 to address the low sensitivity in high-risk patients and was

more inclusive of adult patients as well.^{2,9,10} The new classification, while retaining the three-level severity grading, divided the infection into dengue without warning signs, dengue with warning signs and severe dengue.^{2,6,10}

Pakistan has experienced a major epidemic of dengue infection since 2005.¹¹ Hospitals, especially the emergency departments (ED), have seen a major surge in the dengue patient volume. In the beginning of the epidemic, triage decisions were based on the clinician's judgment, while WHO guidelines were slowly being accepted as the decision-making tool. Recently published studies from other settings have shown better accuracy of the revised guidelines.^{2,12,13} This study was carried out to compare the performance of 1997 and 2009 WHO guidelines based on the dengue Immunoglobulin (IgM) results in our setting.^{2,5}

Patients and Methods

This was a case series of Dengue patients recruited by retrospective chart review conducted at the Aga Khan University Hospital (AKUH) Karachi, Pakistan. All adult patients with a diagnosis of dengue who had a positive dengue IgM serology between January 2005 and December 2007 were included in the study. Cases with incomplete information such as signs, symptoms and

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laboratory figures were excluded. By using a standard tool, trained research assistants extracted data regarding clinical features, laboratory investigations, on-admission diagnosis in ED and diagnosis of hospital with serological test (IgM anti-dengue). In our current clinical setting, we send dengue IgM test on all suspicious patients. Anti-IgM becomes positive on the fifth day of dengue illness and can remain positive for 90 days.

No patient had polymerase chain reaction (PCR) test or culture of the virus. Each patient was classified/graded both according to 1997 (Dengue Fever, Dengue Haemorrhagic Fever and Dengue Shock Syndrome) and 2009 guidelines (dengue without warning signs, dengue with warning signs and severe dengue) (Table-1, Figure-1) by the research assistant using the standard definitions. The three categories of dengue used in each of the

Table-1: WHO guidelines (1999) for the treatment of dengue fever/ dengue hemorrhagic fever.

| DF/DHF | Grade* | Symptoms | Laboratory picture |
|--------|--------|--|--|
| DF | | Fever with two or more of the following signs: headache, retro-orbital pain, myalgia, arthralgia | Leukopenia occasionally. Thrombocytopenia may be present. No evidence of plasma loss |
| DHF | I | Above signs plus positive tourniquet test | Thrombocytopenia positive tourniquet < 100,000, Hct rise \geq 20% |
| DHF | II | Above signs plus spontaneous bleeding | Thrombocytopenia < 100,000, Hct rise \geq 20% |
| DHF | III | Above signs plus circulatory failure (weak pulse, hypotension restlessness) | Thrombocytopenia < 100,000, Hct rise > 20% |
| DHF | IV | Profound shock with undetectable blood pressure and pulse | Thrombocytopenia < 100,000, Hct rise \geq 20% |

DHF Grade III and IV are also called as Dengue Shock Syndrome (DSS).

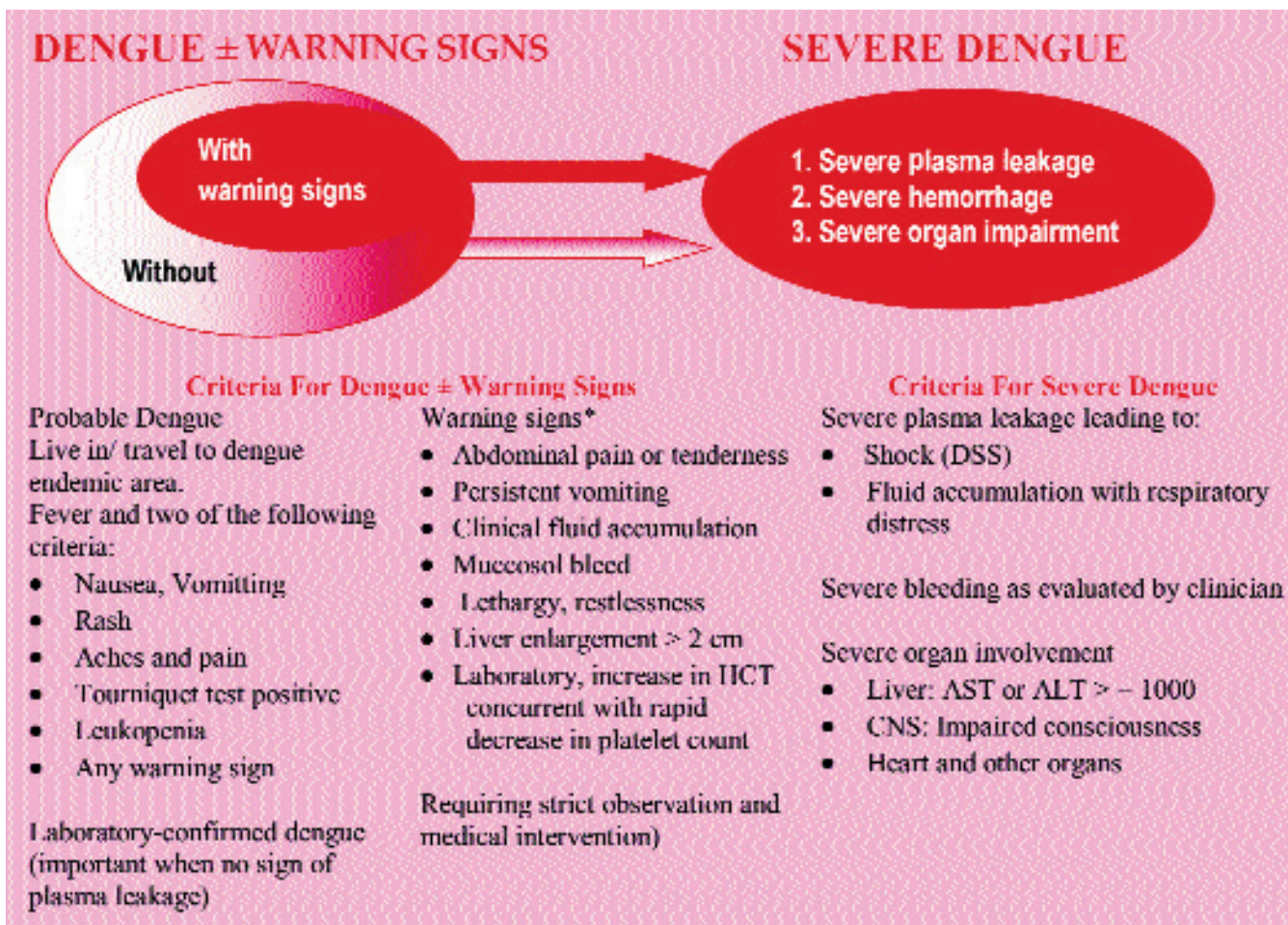


Figure-1: Dengue, guidelines for diagnosis, treatment, prevention and control new edition 2009.

guidelines were referred to as minor, moderate and severe. Minor dengue was used for DF (1997 guidelines) and dengue without warning signs (2009 guidelines); moderate dengue for DHF (1997) and dengue with warning signs (2009); and severe dengue for DSS (1997) and severe dengue (2009).

Descriptive analysis was done using SPSS, version 19.0 and frequencies and percentages were calculated. Median with interquartile range (IQR) was reported for skewed data such as age and platelet count, while mean \pm standard deviation (SD) was used for normal data. Ethical approval was obtained from the institutional ethics review committee.

Results

A total of 612 patients were located with a diagnosis of dengue out of which 439 (71.73%) had a positive IgM. According to 1997 guidelines, 383 (87%) patients were classified as having dengue. On the other hand, 2009 guidelines classified 439 (100%) patients as dengue infected (Figure-2). Of the 56 (13%) cases which could not be labelled as dengue using the 1997 guidelines, 30 (54%) were classified as probable dengue without warning signs, 19 (34%) were classified as dengue with warning signs, and 7 (12%) as severe dengue using the 2009 guidelines.

The median age of the participants was 28 (IQR 18) years; 295 (67%) were males. All patients were discharged from the hospital except one patient who died in the hospital. Only 167 (38%) patients had three or more symptoms on history. Most (n=248; 56%) had no signs on examination (Table-2). All the patients presented with fever (100%), vomiting 281 (64%) and body ache 173 (39%). Rash (27%), petechiae (10%) and purpura (1%) were present in less number of patients.

Table-3 shows the comparison of both guidelines. The two guidelines classified approximately 50% of cases similarly as minor, moderate and severe dengue (Table-2). WHO 1997 had classified 21 (5.5%) cases as DSS while 2009 guidelines labelled 81 (21%) cases as severe dengue, with consensus on only 11 (52.4%) severe cases by both

Table-2: Clinical features of study population (n = 439).

| Clinical Symptoms | n(%) |
|---|---------------------------------|
| Fever | 439 (100) |
| Vomiting | 281(64) |
| Body ache | 173(39) |
| Abdominal pain | 152(35) |
| Bleeding other than nose and gum | 75(17) |
| Headache | 35(8) |
| Gum Bleed | 32(7) |
| Nose Bleed | 26(5) |
| Haematemesis | 22(5) |
| Drowsiness | 21(5) |
| Shortness of Breath | 14(3) |
| Examination Findings | n(%) |
| Rash | 120(27) |
| Ascites | 44(10) |
| Petechie | 45(10) |
| Hepatomegaly | 19(4) |
| Pulmonary Effusion | 16(4) |
| Splenomegaly | 9(2) |
| Purpura | 6(1) |
| Vital Examination Readings | Mean \pm SD |
| Temperature(oC) | 38 \pm 3 |
| Systolic Blood Pressure(mm Hg) | 112 \pm 17 |
| Diastolic Blood Pressure(mm Hg) | 72 \pm 12 |
| Pulse Pressure(beats/min) | 40 \pm 14 |
| Laboratory Parameters | Mean \pm SD |
| White Blood Count(x109/L)(n=431) | 5 \pm 4 |
| Haematocrit(gm/dl)(n=426) | 41 \pm 7 |
| Prothrombin Time(secs)(n=362) | 13 \pm 8 |
| International Normalized Ratio(n=359) | 1 \pm 2 |
| Activated Partial Thromboplastin Time(secs)(n=367) | 37 \pm 20 |
| Sodium(mEq/L)(n=406) | 138 \pm 75 |
| Bicarbonate(mEq/L)(n=332) | 22 \pm 5 |
| | Median |
| (IQR) | |
| Platelet(x109/L)(n=427) | 45(67) |
| Blood Urea Nitrogen(mg/dL)(n=368) | 9(6) |
| Creatinine(mg/dL)(n=409) | 1(0.4) |
| Serum Glutamate-Oxaloacetate Transaminase(units/L)(n=388) | 174(274) |

the guidelines. The alarming result was that more than a quarter cases (29%) that were classified as moderate by the 1997 guideline were severe dengue according to the 2009 guidelines.

Table-3: Comparison of WHO guidelines for dengue cases (n=383).

| Disease Severity as per 1997 Classification | Dengue Fever n(%) | Disease Severity as per 2009 Classification | | Total n(%) |
|---|-------------------|---|----------------------------|------------|
| | | Dengue Haemorrhagic Fever n(%) | Dengue Shock Syndrome n(%) | |
| Probable Dengue without warning signs | 68 (45.3) | 48(22.6) | 4(19) | 120(31.3) |
| Probable Dengue with warning signs | 73(48.7) | 103(48.6) | 6(28.6) | 182(45.7) |
| Severe dengue | 9(6) | 61(28.8) | 11(52.4) | 81(21.1) |
| Total | 150(100) | 212(100) | 21(100) | 383(100) |

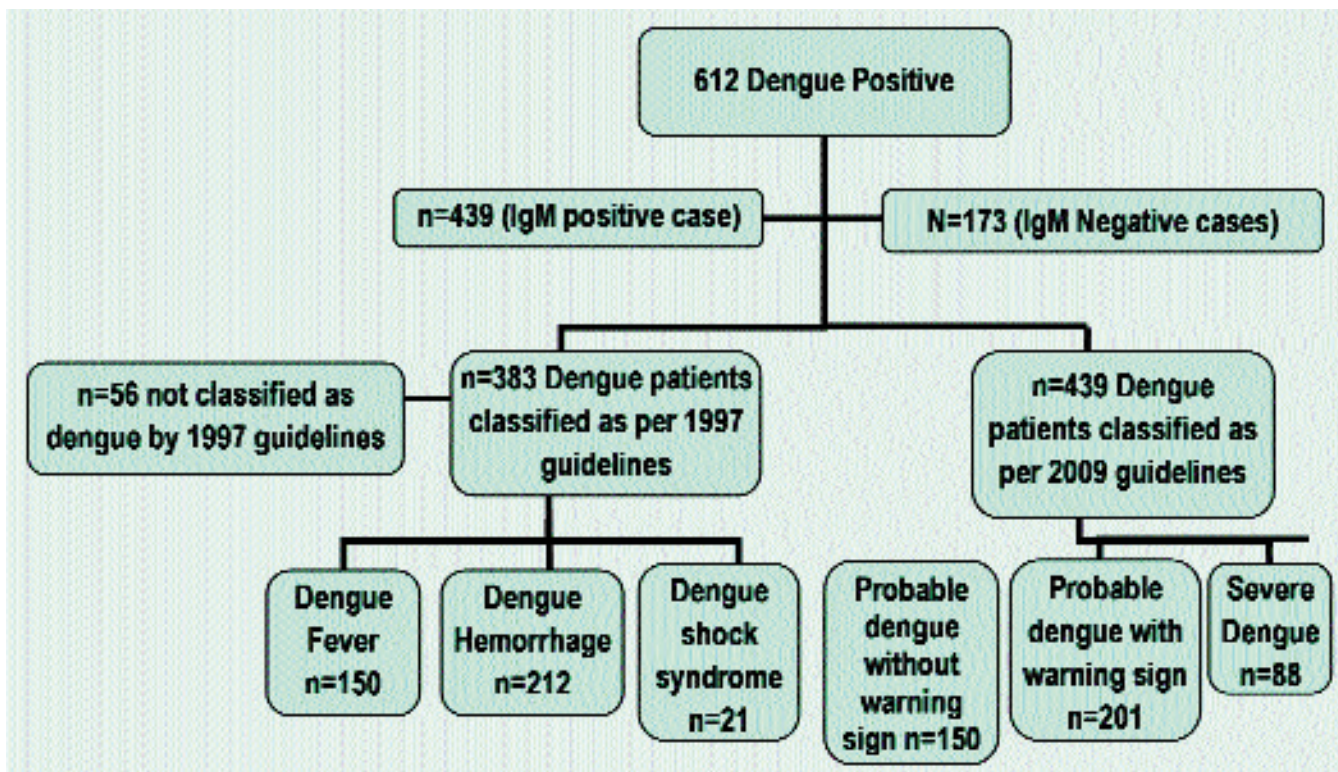


Figure-2: Flow chart of dengue patients recruitment (January 2005- December 2007).

Discussion

We not only found a difference between 1997 and 2009 guidelines in the accuracy of dengue diagnosis, but also in the assessment of the severity of the disease.^{2,5} There was a four-fold increase in the diagnosis of severe form of dengue using 2009 guidelines compared to the 1997 guidelines.

The diagnostic challenge is likely to be higher in our setting where other febrile illnesses are more common. Diseases such as typhoid fever or malaria contribute to a major bulk of acute clinical practice in Pakistan and, like dengue, they often present with non-specific fever, few signs or symptoms and a blood picture showing low white blood cell (WBC) and platelet counts.^{14,15} Atypical presentations such as abdominal pain, vomiting, diarrhoea, cough and headache resembling enteric fever have been reported in other studies from Pakistan, making clinical decision more difficult.¹⁶ In such endemic settings, concurrent infections such as dengue and malaria could mislead physician's initial impression. Coexistence of malaria and dengue have been reported to be in the range of 20% to as high as 80%.^{17,18} While malaria testing is more widely available, diagnostic tests for dengue (IgM) are either not available or not able to

detect dengue in the first few days of the disease onset, biasing the clinical diagnosis towards malaria.

Patients in our setting tend to start the use of antibiotic and other medicines either in consultation with a general physician or by themselves. In Pakistan, there are no strict prescription regulations and drugs are easily available over the counter. Patients visit the hospital only when their condition deteriorates, and this makes correct diagnosis challenging for the physicians.

Time also affects accuracy of diagnosis even when WHO guidelines are used. Leo et al reported an increase in the accuracy of diagnosis by the WHO guidelines from 14% to 32% and 61% to 79% from day 1 to day 7 of admission using the 1997 and 2009 guidelines respectively.¹³ A study from Karachi, showed that almost one-fourth of children with final diagnosis of DF were initially labelled as undifferentiated fever.¹⁹ Similarly, in Vietnam about a third of cases with DF were initially diagnosed as acute undifferentiated fever.²⁰

Revised guidelines were found to be better in diagnosing dengue cases overall, particularly those with severe form of illness. This is corroborated by work done in other settings, both among adults and children.^{12,21} DENCO, a

multi-country prospective study, found comparable results where 15% of patients with clinical shock were not correctly classified by 1997 classification as severe cases.²² One reason is, perhaps, paediatric focus of the 1997 guidelines which limited its application to adult population.^{7,9,23} The 2009 classification included more non-specific alarming signs such as mental status changes, abdominal pains and involvement of other organs such as liver.

The current study has several limitations. First, it is based on the retrospective data obtained from medical records. Not all features, for example, tourniquet test, were universally captured in the medical records. Second, we could not include dengue patients who were misdiagnosed and sent home and also those who were sent home because they had mild disease.²⁴ Third, we did not know if the individual physician applied the guidelines or was even aware of the guidelines.

Conclusion

By using the WHO guidelines 2009, a physician would end up classifying more dengue patients as having moderate or severe disease compared to the 1997 guideline. Widespread use of these guidelines needs to be encouraged among physicians.

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