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Original Article

Paediatrics Section

Validity and Usefulness of Revised WHO Guidelines in Children with Dengue Fever

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ABSTRACT

Introduction: Dengue fever is the most rapidly spreading mosquito borne viral infection with a 30-fold increase in the disease burden over last five decades with a variable clinical course and outcome. The World Health Organization (WHO) published treatment guidelines in 1997 and further revised in 2009 to facilitate early diagnosis and intervention in severe cases.

Aim: To evaluate the validity and usefulness of Revised 2009 WHO guidelines in comparison to 1997 guidelines in children with dengue fever.

Materials and Methods: All children (0-12 yrs of age) diagnosed and confirmed as dengue fever admitted at a tertiary care hospital in Puducherry from 1st August 2012 to 31st December 2015 were reviewed retrospectively from hospital case records. All children were classified as per the 1997 and 2009 Revised WHO guidelines for dengue fever.

Results: Out of 434 children admitted with dengue fever the diagnosis was confirmed in 294 cases (67.7%). The mean age of presentation was 7.0(3.3) years. M:F ratio was 1.1:1. As per 1997 WHO guidelines the cases were classified as dengue fever 246(83.7%), dengue haemorrhagic fever 22(7.5%) and dengue shock syndrome 26(8.6%). As per WHO 2009 guidelines they were classified as dengue without warning signs 42(14.3%), dengue with warning signs 215(73.1%), and severe dengue 37(12.6%). Dengue fever requiring early intervention as per 1997 and 2009 WHO guidelines were seen in 96(27.2%) and 153 cases(52%) respectively. The most common manifestation of severe dengue infection was shock (40.1%), bleeding (20.4%) and multiorgan failure (2.0%).

Conclusion: The revised WHO 2009 dengue fever guidelines classified more cases requiring early and timely intervention but remained to be too broad and non-specific in terms of pathophysiology, fluid management and use of blood products. Our experience recommends a need for further modifications in the guidelines especially with changing epidemic pattern of presentation.

Keywords: Dengue haemorrhagic fever, Severe dengue, Shock, World Health Organization

INTRODUCTION

Dengue fever is the most rapidly spreading mosquito borne viral infection with a 30-fold increase in the disease burden over last five decades with a variable clinical course and outcome [1]. The World Health Organization (WHO) published treatment guidelines in 1997 to facilitate early diagnosis and intervention in severe cases [1]. Dengue fever cases were either classified as Dengue Fever (DF), Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [Table/Fig-1]. The classification proved useful but problems were identified in large number of cases in its application where they did not fulfill the WHO criteria of DHF in a clinical situation [2-6]. On the other hand, there was difficulty in classifying children with comorbidities, haemorrhagic manifestations without thrombocytopenia or plasma leakage and shock but with normal platelet counts. It also failed to identify a significant proportion of severe dengue cases with unusual manifestations such as encephalopathy, myocarditis or hepatic failure [7-9]. Thus, this classification underwent a revision by the WHO in 2009 to overcome the shortcomings and limitations of the older classification based on the findings of a multicenter retrospective study done under the auspices of the WHO Special programme for Research and Training in Tropical diseases (TDR) [10,11].

The revised 2009 WHO guidelines, according to the levels of severity has focused on recognized warning signs for early detection and timely intervention and reclassified dengue fever as " Dengue" without warning signs (D), "Dengue with Warning signs" (DW), "Severe Dengue" (SD) and children with unusual manifestations were termed as expanded dengue syndrome [Table/Fig-1]. The recently published studies have highlighted the better accuracy of the revised guidelines over the older guidelines of dengue fever in adults [12]. There are other studies which have highlighted the problems in the revised guidelines and their practical applicability in adults, there by a conclusion could not be drawn about its applicability [13-16]. For, physicians, an appropriate dengue classification system should be one that appropriately identifies Dengue Requiring Intervention (DRI).

Since 2012, Pondicherry has seen unprecedented rise in dengue fever cases with changing epidemic pattern of presentation. The objective of the study was to compare the validity and usefulness of revised WHO guidelines 2009 in comparison to the 1997 WHO guidelines of dengue fever in children for early detection of cases requiring intervention.

MATERIALS AND METHODS

This hospital based simple observational study was conducted at a tertiary care teaching hospital at Puducherry from 1st August 2012 to 31st December 2015 was reviewed retrospectively from hospital case records after approval by the Institute Ethics committee. All children (0-12 yrs of age) admitted and confirmed with diagnosis of dengue fever were included in the study. Total numbers of cases included were 294 with convenient sample size of 210. Children who left against medical advice, unconfirmed cases, missing data, with underlying haematological diseases or simultaneous infections were excluded from the study. Informed consent was obtained at the

WHO 1997 Dengue Classification
Dengue Fever (DF) Acute Febrile illness with two or more of the following: • Headache • Retro-orbital pain • Myalgia • Leukopenia • Arthralgia • Rash • Laboratory confirmation with Leucopenia (WBC<5000/mm^3, Thrombocytopenia (Platelet count<1,50,000/mm^3, Rising HCT (5-10%), No evidence of plasma loss)
Dengue Haemorrhagic Fever (DHF) The presence of 4 criteria: Fever, haemorrhagic manifestations, Haematocrit >20%, Platelet count<1,00,000/mm^3 DHF-I: haemorrhagic manifestations DHF-II-spontaneous bleeding DHFIII- circulatory failure DHFIV- profound shock with undetectable BP and Pulse DSS included DHF III & IV
WHO 2009 guidelines for Dengue fever
Dengue fever without warning signs (D) Fever with any of the following: • Nausea, vomiting • Rash • Myalgia • Leukopenia • Positive tourniquet test
Dengue fever with warning signs (DW) • Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleeding • Lethargy, restlessness • Liver enlargement>2cm • Laboratory: increase in HCT with concurrent rapid decrease in platelet count
Severe Dengue (SD) Dengue with alteast one of the following criteria: • Severe plasma leakage leading to shock (DSS) or fluid accumulation with respiratory distress • Severe bleeding • Severe organ involvement

[Table/Fig-1]: World Health Organization guidelines of Dengue Fever (1997 and 2009).

time of admission. The case definition, diagnosis and management were based on WHO guidelines for dengue fever. Each case was classified using both the WHO 1997 and 2009 guidelines for dengue fever. Children were further categorized based on Dengue Infection Requiring Intervention (DRI). Category I were those children who presented as dengue fever and did not require any intervention. Category II were hospitalized patients who received intravenous fluids for rehydration and maintenance and did not suffer organ damage. Category III were patients hospitalized in the Intensive Care Unit (ICU), administered ionotropic drugs, blood products, severe organ failure and received mechanical ventilation. Data were entered in a structured proforma which included demographic data, signs and symptoms and relevant investigations done as per the clinical course of illness. The diagnosis was confirmed by NS1 antigen-based ELISA test (J. Mitra kit, India) or dengue serology for IgM and IgG antibodies (Kit from National vector born disease control programme, Pondicherry and National Institute of Virology Pune, India).

STATISTICAL ANALYSIS

The data were evaluated by using SPSS version 16.0 statistical software. After collecting all the data, all the variables were summarized by descriptive statistics. Continuous data, expressed as mean±SD, or median (range) wherever appropriate. Categorical variables were expressed as frequencies and percentages.

RESULTS

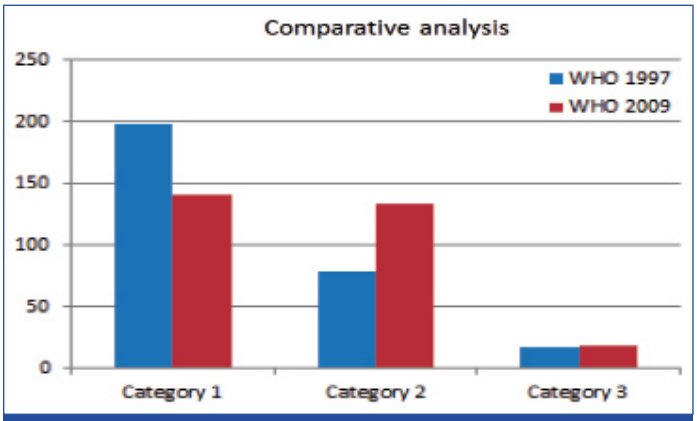
Out of 434 children admitted with dengue fever the diagnosis were confirmed in 294 cases (67.7%). The mean age of presentation was 7.0(3.3) years. M:F ratio was 1.1:1 and most cases were from Pondicherry and neighboring states [Table/Fig-2]. As per

Demographic Profile	Number (%)
Number of cases	294
Mean age in years	7.0(3.3)
Age>6 years	155(52.7)
Male to Female ratio	1.1:1
Pondicherry	211(72)
Tamilnadu	83(28)
Duration of fever at admission (days)	4.8(1.8)
Duration of hospital stay (days)	6.5(2.7)
Mortality	6.0(2.0)

[Table/Fig-2]: Demographic profile of dengue fever.
Data represented as Mean (SD) and Number (%)

WHO classification	Dengue Fever	DHF	DSS	Total
Dengue	42(17.1)	0	0	42(14.3)
Dengue with Warning signs	195(79.3)	02(9.1)	18(69.2)	215(73.1)
Severe Dengue	09(3.6)	20(90.9)	08(30.8)	37(12.6)
Total	246(83.7)	22(7.5)	26(8.8)	294

[Table/Fig-3]: WHO 1997 and 2009 classification for dengue fever.
Data as Number (%); DHF: Dengue haemorrhagic fever; DSS: Dengue shock syndrome.



[Table/Fig-4]: Comparative analysis of Dengue requiring intervention WHO 1997 and 2009 guidelines.
(Category 1-no intervention, Category 2-Intravenous fluids, Category 3-Inotropes & blood products)

1997 WHO guidelines the cases were classified as dengue fever 246(83.7%), dengue haemorrhagic fever 22(7.5%) and dengue shock syndrome 26(8.6%). As per WHO 2009 guidelines they were classified as dengue without warning signs 42(14.3%), dengue with warning signs 215(73.1%), and severe dengue 37(12.6%). 79.3% of cases were classified as dengue fever in 1997 guidelines were classified as dengue fever with warning signs in the revised guidelines. Severe dengue infection detection in WHO 1997 and 2009 revised guidelines were seen in 8.8% cases and 12.6% respectively [Table/Fig-3]. As per the 1997 guidelines, children in category I were 198 cases (67.3%), Category II were 79(26.9%) and Category III were 17 cases (5.8%). As per 2009 revised guidelines, children in category I were 141(47.9%), category II were 134(45.6%) and category III were 19(6.5%). Dengue fever requiring early intervention as per 1997 and 2009 WHO guidelines were seen in 96(27.2%) and 153 cases(52%) respectively. The revised guidelines captured more number of cases in category II and III in comparison to the 1997 guidelines due to the presence of early warning signs requiring intervention [Table/Fig-4].

The common clinical presentation of dengue fever included fever 278(94.5%), conjunctival congestion 244(82.9%), myalgia 229 (77.9%), coryza 223 (75.8%), headache 216(73.5%), palmar erythema 162(55.1%), retro-orbital pain 139(47.2%), facial flush 100(34.0%), joint pain 75(25.5%), and rash 43(14.6%) cases.

Clinical profile	Dengue Fever (WHO 1997)	DHF*** (WHO1997)	Dengue with warning signs (WHO 2009)
*Pain abdomen	91(65.5)	48(34.5)	139(47.2)
*Persistent vomiting	176(78.6)	48(21.4)	224(76.2)
*Mucosal bleeding	38(63.3)	22(36.7)	60(20.4)
*Fluid accumulation	04(16)	21(84)	25(8.5)
*Restlessness	52(58.4)	37(54.1)	89(30.2)
*Hepatomegaly>2cm	134(77)	40(33)	174(59.2)
*Shock	84(71.2)	34(28.8)	118(40.1)
**Severe organ involvement	0(0)	21(100)	21(7.1)
**Significant bleeding	12(54.5)	22(45.5)	34(11.6)
**Deranged LFT	22(75.8)	07(24.2)	29(4.1)
*HCT>20% with PLT <50,000/mm^3	12(33.3)	24(66.7)	36(12.2)
Total platelet count<1.0 lac/mm^3	75(66.4)	38(33.6)	113(38.4)
Leukopenia (Total Leukocyte count<5000/mm^3)	35(61.4)	23(38.6)	57(19.4)

[Table/Fig-5]: Comparison of Clinical and laboratory profile of WHO 1997 and 2009 guidelines.
Data as number (%);*Warning signs; **Severe dengue infection***Dengue haemorrhagic fever

The most common early warning signs at the time of admission as per the revised WHO guidelines 2009 were persistent vomiting 224(76.1%), hepatomegaly 174(59.2%), cold and calmy extremities 124(42.1%), pain abdomen 139(47.2%), hypotension 85(28.9%), restlessness 89(30.3%), giddiness 64(21.7%), mucosal bleed 60(20.4%), clinical fluid accumulation 25(8.5%) oliguria 58(19.7%), Haematocrit >20% with concomitant platelet count <50,000/mm^3 were seen in 36(12.2%) cases and severe thrombocytopenia (platelet count<20,000/mm^3) in 12(4.1%) cases. A total of 51(17.2%) children who had warning signs developed severe dengue infection.

The most common manifestation of severe dengue infection was shock 118(40.1%), bleeding 60 (20.4%) and multiorgan failure 6(2.0%) [Table/Fig-5]. Out of 118 children (40.1%) with shock only 34 cases (28.8%) had bleeding. A total of 97 children (82.2%) had compensated shock and 21 children (17.8%) had decompensated shock out of which only 7 fulfiled all the 4 criteria of DHF. Among the children having shock only 37(31.3%) children could be classified as severe dengue infection as per revised guidelines due to its nonspecific criteria.

Atypical manifestations with life threatening complications were seen in 16 cases (5.4%). Acute kidney injury, encephalopathy and fluid refractory shock were present in six cases (2.0%). Myocarditis, Acute Respiratory Distress Syndrome (ARDS), pulmonary haemorrhage and disseminated intravascular coagulopathy were observed in four cases (1.4%). Myositis and pericardial effusion were seen in two cases (0.7%).

Bleeding manifestations were present in 60 children (20.4%), which included gum bleeding 21(35.0%), melena 21(35.0%), petechiae 20(33.3%), epistaxis 14(23.3%), haematemesis 5(8.3%), pulmonary bleed 4(6.6%) and intracranial bleed 2(3.3%). Tourniquet test was positive in 33 cases (11.2%) and among them only 13 children (39.3%) had bleeding.

The Dengue NS1Ag was positive in 247 cases (84.0%) and 47 children (16.0%) were NS1Ag negative and positive for IgM MAC ELISA. Dengue IgG was positive in 19 cases (6.5%). Anemia (Hb<10gm/dl) was seen in 79 cases (26.9%). The mean haematocrit at presentation was 38.8(4.4). Haematocrit value>40 was seen in 126(42.8%) cases. Leucopenia (TLC<5000/mm^3) was seen in 57 (19.4%) cases only though it is an important criteria for diagnosing dengue fever as per WHO 1997 guidelines [Table/Fig-5]. Thrombocytopenia was present in 233(79.2%) cases. Twelve children (4.1%) had platelet counts less than 20,000/mm^3, 35 children (11.9%) were between 20,000-50,000/mm^3, 66(22.4%) were between 50,000-1,00,000/mm^3, 120(40.8%) children had platelet count between 1-1.5 lac/mm^3 and 61 children (20.7%) had platelet count >1.5 lac/mm^3. Bleeding manifestations were present in 24 (40.0%), 13 (12.6%), 12 (20.0%) and 11 (18.3%) cases with platelet count between <50,000/mm^3, 50,000-100,000/mm^3, 1-1.5 lac/mm^3 and >1.5 lac/mm^3 respectively. USG abdomen showed features of gall bladder wall oedema in 27 cases (9.2%) and out them 25 cases (92.6%) had severe dengue infection. Deranged liver function test (SGOT & SGPT>150 IU/L) was abnormal in 29 cases (9.8%) and among them 24 cases (82.7%) had severe dengue infection [Table/Fig-5]. Disordered Coagulation profile (prolongation of the prothrombin and/or partial thromboplastin time) was seen in 10 children (3.9%).

As per 1997 WHO classification, among the children presented with clinical features of DHF, only 22 cases (7.5%) of DHF and 26 children (8.6%) with DSS fulfilled all the four essential criteria of DHF which included fever, haemorrhagic manifestation, leukopenia and thrombocytopenia (Platelet count<1,00,000/mm^3) were seen [Table/Fig-3]. Out of 118 children with shock, bleeding was seen in 34 cases (28.8%), Haematocrit> 20% with platelet count <50,000/mm^3 in 36 cases (30.5%), signs of severe plasma leakage in 18 cases (15.2%) and thrombocytopenia in 18 (15.2%) children. On comparison of clinical and laboratory parameters, the revised guidelines picked up more cases with dengue fever with warning signs requiring early intervention in comparison to 1997 guidelines. These children could not be categorized as DHF but required intervention in the form intravenous fluids and vigilant monitoring. Atypical manifestations, severe organomegaly which could not be classified as DHF were classified as dengue with warning signs and severe dengue respectively [Table/Fig-5].

Platelet transfusion was given in 20 children (6.8%) with severe dengue infection and out of them 12 children (60%) had a platelet count <20,000/mm^3; whereas 8 children (40%) had platelet count in the range of 20,000-50,000/mm^3. Apart from platelet transfusion blood transfusion was given in 11 (3.7%) cases, fresh frozen plasma in 6 (2.0%) cases, colloids in 3 (1.0) intravenous fluids in 129 (43.9%) cases, and inotropes in 6 (2.0%) cases.

DISCUSSION

The main objectives of the revised WHO guidelines for dengue fever were to overcome the deficiencies of the 1997 guidelines [1]. Several studies reported that the revised WHO classification was more sensitive as well as specific in identifying severe cases [16-21]. In contrast, some studies indicated that WHO 1997 guidelines were far more specific in capturing severe cases [15,16,22].

In our study the application of revised and traditional WHO classification yielded different results in diagnosis and assessment of the severity of the disease [1]. When classified as per WHO 1997 guidelines, highest percentage cases were of dengue fever followed by DHF which is agreement with earlier studies [3-9]. However, when revised guidelines were used highest percentages were with dengue fever with warning signs followed by dengue without warning signs and severe dengue infection and were similar to the study by Barniol J et al., [10]. Severe dengue infection requiring intervention in the form of intravenous fluids and monitoring were seen in 27.2% and 52% in the 1997 and 2009 WHO guidelines respectively. The revised guidelines picked up more number of cases that required intervention and also helped us in the assessment of the severity of the disease contrary to the few previous studies [17-19].

In our study we experienced change in epidemic pattern of presentation with more number of atypical manifestations of dengue fever and with clinical resemblance to other febrile illnesses like typhoid fever, malaria and scrub typhus there by making clinical decision more difficult. The coexistence of malaria and dengue has been similarly reported in the previous studies [23-26]. Children with

severe organ involvement like hepatitis and encephalopathy, and atypical manifestations and which could not be classified in the 1997 guidelines were all classified as severe dengue infection in 2009 guidelines in our study and has been also previously reported [27-33].

There was lower percentage of DHF in comparison to dengue fever in our study. DHF required the presence of four criteria of fever, haemorrhagic manifestations, haematocrit >20%, and platelet count <1, 00,000/mm^3 as per the WHO 1997 guidelines and only 16.3% of cases fulfilled all the four criteria in our study and similar to the few previous studies [34-36]. Dengue fever with shock and without bleeding was most common mode of presentation of severe dengue infection which could not be categorized as DHF but required intervention in the form intravenous fluids and vigilant monitoring [1,8,14]. As it was difficult to classify them as DHF alternative definitions such as dengue fever associated with shock without bleeding (DSAS) and Dengue fever with bleeding without shock (DFB) were used and from our experience there is a need for revision of the existing case definitions as reported in previous studies [7-9]. Bleeding manifestations, thrombocytopenia, signs of plasma leakage and tourniquet test did not always correlate in our study unlike the previous studies [36-38]. Shock without bleeding, bleeding without thrombocytopenia, and shock without thrombocytopenia were seen in 84(71.2%), 11(18.3%) and 18(15.2%) of cases respectively contrary to the 1997 guidelines where bleeding and thrombocytopenia have been considered reliable indicators of /or prerequisites for the subsequent development of DSS [1]. Leukopenia an essential component of the diagnosis of dengue fever as the WHO 1997 guidelines was only present in 19.7% of cases similar to previous studies [19,20].

The revised WHO 2009 guidelines were more pragmatic in terms of early recognition of the different phases of the disease, and allowed us to capture more patients potentially at risk of developing severe manifestations as it is based on identifying clinical warning signs [1,2]. The higher percentage of hospitalized patients classified as dengue fever with warning signs in our study was in line with the revised guidelines for admission in dengue fever [1]. From the treating physician viewpoint, it allowed the patient to be classified and treated in real time that is during their hospital stay, allowed proper triage of severe cases unlike the 1997 WHO guidelines where the majority of cases tended to be retrospectively classified so as to detect the presence of the four criteria that define severity (DHF/DSS). This is reflected in the observed difficulty in correctly classifying the patient according to the traditional classification in our study.

The demerit of the revised classification was that it lacked specificity in comparison to the traditional classification and similar to few previous studies. [14,16,23]. We found that “Severe dengue” and “Dengue with warning signs” are very broad definitions that make it difficult to determine the pathophysiology of the disease. The assessment was subjective and generalized especially in relation to management of DRI thereby creating confusion of when to use fluids, inotropes and blood products. Since the traditional and revised guidelines are not equivalent it had created confusion in classification of dengue among the clinicians. In our study only that 17.2% of children with warning signs developed severe dengue infection. It is therefore important to analyse the frequency of the warning signs and its relationship to severe manifestations in order to obtain a clearer picture of the disease profile rather than just the presence of enlisted warning signs. The specific syndrome of plasma leakage (DHF/DSS), so characteristic of the critical phase of dengue, is lost in the new classification.

LIMITATION

There are several limitations to this study. The study is a simple observational study of dengue fever cases from a single centre and included only those cases that were admitted to the hospital. The diagnosis was confirmed by either dengue NS1 antigen test or dengue serology. Viral isolation and serotype identification were not done in the present study. There were practical limitations in documenting base line haematocrit and round the clock haematocrit monitoring in our study. The lack of availability of bedside ultrasound to document early signs of plasma leakage in the form of ascites, pleural effusion and gall bladder wall oedema was another limitation in our study. A large multicentric prospective study including a larger sample size focusing on pathophysiology of disease in children with severe dengue infection would be ideal. Furthermore, research on the revised 2009 classification system is necessary in order to optimize case definitions of warning signs and severe dengue infection to enable optimal triaging for more accurate identification of patients who require hospitalization as opposed to those who can be treated as outpatients.

CONCLUSION

The revised WHO 2009 dengue fever guidelines classified more cases requiring early and timely intervention but remained to be too broad and non-specific in terms of pathophysiology, fluid management and use of blood products. Ideally, a classification needs to be both sensitive and specific for detection of severe cases, in order to avoid oversaturation of health units, especially at the secondary level, but neither of the two classification schemes completely possesses these characteristics. Our experience recommends a need for further modifications in the guidelines especially with changing epidemic pattern of presentation.

CONTRIBUTIONS

SP designed the study, collected the data, did data analysis, wrote first draft, approved the final manuscript and shall act as guarantor of the study; VS conceived the idea, designed the study, helped in data analysis, reviewed and edited the manuscript BK collected the data. MT did the statistics, and data analysis.

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