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Disease Severity and Mortality Caused by Dengue in a Dominican Pediatric Population

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Abstract. Millions are infected with dengue yearly. We evaluated the epidemiological and clinical characteristics of pediatric patients infected with dengue in the Dominican Republic. The applicability of World Health Organization (WHO) warning signs for predicting severe dengue and mortality was also studied. This study was a cross-sectional retrospective review of patients with a clinical diagnosis of dengue. Univariate and multivariate analyses were performed to evaluate characteristics associated with severity and mortality. The study included 796 subjects: 288 subjects were classified as dengue, 290 subjects had alarm signs, and 207 subjects were classified as severe dengue. Common findings included thrombocytopenia (96%), abdominal pain (71%), and vomiting (59%). The most important factors associated with severe dengue were rash ($P < 0.01$), severe thrombocytopenia ($P < 0.01$), and anemia ($P < 0.01$). These signs and symptoms were also associated with mortality. This study validates the current WHO warning signs of severity. Rash and severe thrombocytopenia may be early warning signs and need additional study.

INTRODUCTION

Dengue is a febrile illness caused by the dengue virus (DENV), an RNA virus of the genus flavivirus with four serotypes (DENV1 to -4). The virus is transmitted to humans by a mosquito vector, and it occurs in tropical and subtropical regions of the world. Rapid population growth and urban development fueled a dramatic spread of the virus during the second half of the 20th century. Dengue is endemic in over 100 countries, with estimates of 50 million cases of the disease occurring each year.[1] The countries with the highest numbers of cases in the Latin Caribbean this past decade were Cuba, Puerto Rico, and the Dominican Republic (DR).[1,2] The DR reported a dengue case fatality rate of 20.89% during the period from 2003 to 2009.[3]

The definition and classification of dengue have evolved over the past three decades. The disease was formerly classified as dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS).[4,5] The applicability and clinical use of this classification have been questioned, because it is believed to underestimate cases of shock and severe dengue.[6] A large multicenter study led to a change in the case classification by the World Health Organization (WHO).[6,7] The most recent classification system seems more accurate in predicting severe disease.[8,9] Nonetheless, other local factors may contribute to disease presentation and severity, making it difficult to standardize case definitions and clinical predictors across different countries. Some have argued that variability in case definitions should exist at the local level.[10] The applicability of the newer case definition to predict disease severity, the clinical profile of pediatric patients infected with dengue in the DR, and the factors associated with poor prognosis in this population have not been well-studied. The objective of this study was to evaluate the epidemiological characteristics, clinical profile, and factors associated with severe dengue and mortality in pediatric patients infected with dengue in the DR. We used the current WHO classification system to assess if it accurately predicted patients at risk for progression to severe disease or death.[11]

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METHODS

Ethics statement. This study was a retrospective chart review. Patients' identifiable information was not collected or used during data analysis. The Institutional Review Board of the University of Illinois and the Institutional Independent Review Board of the Dominican Infectious Diseases Foundation approved the study.

Data collection. This cross-sectional retrospective study was conducted from 2011 to 2012 at the Robert Reid Cabral Children's Hospital (RRCH) in Santo Domingo, DR. This hospital is a 350-bed referral general pediatric hospital with 13,000 hospitalizations per year.[12] All records of patients admitted with a clinical diagnosis of dengue made by an expert clinician during 2008 and 2009 were reviewed. A review of all deaths that listed dengue as the cause during the study period was also conducted. Demographic, clinical, and laboratory data were extracted using an instrument designed for this purpose.

Dengue case definition. The clinical diagnosis of dengue was made based on the clinical presentation and laboratory parameters using the 2009 WHO case definition based on severity.[11] A probable diagnosis was established in patients presenting with fever plus two other relevant clinical signs as recommended in the guidelines. Similarly, cases of severe dengue and dengue with alarm signs were classified using the same document. Cases diagnosed as severe dengue were subclassified into severe plasma leakage, severe bleeding, and severe organ involvement.

Case identification. Experts regularly transfer all cases of dengue admitted to the RRCH to a dengue unit, where they receive specialized care by physicians with ample experience in the management of this disease. Comprehensive clinical forms, which include demographic, clinical, and laboratory information, are completed for each patient that is admitted to this unit. Cases analyzed for this study were all diagnosed with dengue in the outpatient department or emergency room, and they were transferred to the dengue unit for ongoing care. Deaths were identified by reviewing individual records in the dengue unit and a thorough review of all deaths reported to the epidemiology department of the hospital during the period of study.

Data analysis. Most variables were dichotomized based on the presence or absence of the characteristic being examined.

Platelet count and anemia were dichotomized at 30,000/mm^3 and 9 g, respectively, because these levels are the levels at which complications occur more frequently. Measures of central tendency, such as mean and median, were calculated for numeric variables, and frequencies of symptoms and signs were obtained. The main outcomes of interest were severe dengue and all-cause mortality. Univariate analyses were performed to investigate the association of the relevant independent variables with the outcomes; χ^2 tests, Fisher exact tests, and odds ratios were calculated where appropriate. Multivariate logistic regression analyses were performed to identify factors associated with severity of disease and mortality. Included in the model were variables showing a statistically significant association ($P < 0.05$) with the outcomes of interest in the univariate analyses. The databases were created in Excel (Microsoft Corp., Redmond, WA) and analyzed using SAS 9.1.3 (SAS Institute Inc., Cary, NC).

RESULTS

In total, 796 patients were admitted to the hospital with a clinical diagnosis of dengue and included in the study ($N = 255$ in 2008 and $N = 541$ in 2009). Table 1 describes the demographics and important clinical characteristics of the subjects. About one-half of the patients were female, and the median age was 6 years (range = 1–16). More than one-half of the patients resided in an urban area. About one-quarter had severe dengue based on the WHO classification (Table 2). Table 3 describes the characteristics of patients with dengue, severe dengue, and death. Ninety-six percent ($N = 761$) of patients were thrombocytopenic (platelet count < 150,000/mm^3) at the time of admission, and most of the subjects had gastrointestinal symptoms, such as abdominal pain and vomiting. Rash was observed in 15% of patients. Infants were more likely to develop severe dengue than pre-teens and adolescents (Table 4). The overall case fatality rate in the study population was 5.1% (3% for 2008 and 6.2% for 2009).

Age, sex, and place of residence were not associated with disease severity or mortality (Tables 5 and 6). The presence of a rash was strongly predictive of severity and mortality. Gastrointestinal symptoms and signs, such as abdominal pain, were associated with severity but not mortality. Thrombocytopenia and anemia were also associated with severe disease and mortality. Although a cutoff of 30,000/mm^3 platelets was used for the bivariate analysis, the association between thrombocytopenia and disease severity was observed with platelet counts as high as 58,000/mm^3 (odds ratio = 2.9, 95% confidence interval = 2.1–4.1).

Table 1
Demographics and other variables

Variable	N ($N = 796$)
Sex	
Female	388 (48.7%)
Male	408 (51.3%)
Place of residence	
Urban	465 (59%)
Rural	326 (41%)
Median age (years)	6 (0–16)
Mean hemoglobin (g)	10.5 ± 1.9
Mean hospital stay (days)	3 ± 1.7
Days of fever (mean)	5 ± 2.6
Median platelet count (mm^3)	54,000 (4,000–857,000)
Mean arterial pressure (mmHg)	66.9 ± 8.7
Deaths	41

Table 2
Number of patients by WHO clinical definition

Disease Classification	N (%)
Dengue	288 (37%)
Dengue with alarm signs	290 (37%)
Severe dengue	207 (26%)
With plasma leakage	183
With severe bleeding	21
With severe organ impairment	3
Total	785 (98%)
Deaths	41 (2%)
Severe dengue	31 (76%)
With plasma leakage	19
With severe bleeding	12
Unclassified	10
Total number of cases	796 (100%)

Although all common signs of capillary leakage were associated with worse outcomes, they were excluded from the final analyses, because they are part of the definition of severe disease; therefore, they are expected to be associated with the outcomes of interest.

DISCUSSION

Our study validated most of the clinical variables present in the current WHO guidelines and showed the applicability of using these guidelines in the DR. The presence of abdominal pain, gallbladder edema, and hepatomegaly have been validated in prior studies.[7,13,14] The original studies in Southeast Asia mentioned some of these variables as potential markers of more severe disease, and they are represented in the current guidelines as warning signs. Our study found additional variables that may predict the risk of progression to severe dengue and death (notably, the degree of thrombocytopenia and the presence of a rash). Thrombocytopenia carried an increased risk of progression to severe dengue and mortality. Patients with platelet counts of < 30,000/mm^3 had double the odds of poor outcomes. This increment was observed at all analyzed cutoffs below 58,000/mm^3. A study conducted in Nicaragua reported that platelet counts of < 50,000/mm^3 markedly increased the odds of progression to severe disease.[15]

Current WHO guidelines do not list degree of thrombocytopenia as a warning sign. The recent criteria mention

Table 3
Frequencies of symptoms and clinical findings by severe dengue and mortality

Variable	All ($N = 796$) N (%)	Severe dengue ($N = 207$) n (%)	Death ($N = 41$) n (%)
Age (≤ 1 year)	122 (15)	38 (18)	10 (24)
Sex (female)	388 (48.7)	107 (52)	23 (56)
Residence (rural)	326 (41)	92 (45)	21 (51)
Febrile days (≤ 5)	554 (70)	145 (70)	26 (63)
Rash	118 (15)	48 (23)	13 (32)
Vomiting	468 (59)	138 (67)	38 (93)
Hepatomegaly	305 (38)	123 (59)	19 (46)
Abdominal pain	567 (71)	182 (88)	36 (88)
Platelet count (< 30,000/mm^3)	145 (18)	65 (31)	18 (44)
Anemia (hemoglobin < 9 g)	149 (19)	67 (32)	21 (51)
Mean arterial pressure (< 66 mmHg)	228 (29)	85 (41)	28 (68)

TABLE 4
Severe dengue by age group

Age group	Odds ratio	95% CI
Infants (< 1 year)	2.2	1.2–3.9
Toddlers (2–5 years)	1.7	1.0–2.8
Young children (6–10 years)	1.7	1.1–2.9
Pre-teens/teens (11–16 years)	Reference	–

CI = confidence interval.

hematological abnormalities in the context of hemoconcentration and rapidity of decline in platelet numbers. We believe that the degree of thrombocytopenia should be further studied and perhaps, added to current warning signs. In resource-limited settings, where specific diagnostic tests are seldom available, this finding may be of importance to help identify patients at higher risk of severe disease.

Rash was also associated with worse outcomes. The odds of severe dengue were more than double when a rash was present. The mechanism for this observation is unclear. The clinical description of skin lesions can be subjective, and without biopsies for histologic analysis, it is difficult to establish a specific etiology. It is plausible that the rash observed on the sickest patients was secondary to vasculitis or an immunopathologic process. An older study examining skin biopsies by immunofluorescence in patients with DHF showed that a significant proportion of these rashes contain immune deposits and dengue antigen.[16] Others have observed a correlation between rash and DHF, which could be secondary to an increased production of cytokines at this stage of the illness.[17] We believe rash could have an independent correlation with morbidity, but this correlation needs to be validated in a prospective fashion.

Anemia was associated with severe disease. This finding is contrary to the classic understanding of DHF and DSS as conditions that enhance vascular permeability and lead to hemoconcentration. It is important to note that hemoglobin values used in the analysis were obtained at the time of admission. Therefore, these values are more representative of the health status of the patient at presentation rather than a marker of disease progression. A significant proportion of these children come from remote areas of the country, where chronic malnutrition and intercurrent illnesses are frequent.

Severe dengue was more common in infants younger than 12 months of age. The association between younger age groups and disease severity has been described in other studies and population groups.[18,19] In a large study of pediatric patients with dengue in Vietnam, the risk of mortality and DSS was highest among younger children. This study also found an association between female sex and poor outcomes, a finding that we did not observe in our study.[19]

TABLE 5
Odds ratios for severe dengue by demographics and clinical findings

Variable	Unadjusted	Adjusted
Age (< 1 year)	1.4 (0.9–2.1)	
Sex (female vs. male)	1.2 (0.9–1.6)	
Residence (rural vs. urban)	1.2 (0.8–1.7)	
Febrile days (< 5)	1.0 (0.7–1.5)	
Rash (yes vs. no)	2.2 (1.5–3.4)	2.1 (1.4–3.4)
Vomiting (yes vs. no)	1.6 (1.1–2.2)	1.2 (0.8–1.8)
Hepatomegaly (yes vs. no)	3.3 (2.4–4.5)	2.6 (1.8–3.7)
Abdominal pain (yes vs. no)	3.9 (2.5–6.1)	3.0 (1.9–4.9)
Platelet count (< 30,000/mm^3)	2.9 (2.0–4.2)	2.4 (1.6–3.6)
Anemia (hemoglobin < 9 g)	2.9 (2.0–4.3)	1.9 (1.3–3.0)

TABLE 6
Odds ratios for mortality by demographics and clinical findings

Variable	Unadjusted	Adjusted
Age (< 1 year)	1.9 (0.9–3.9)	
Sex (female vs. male)	1.4 (0.7–2.6)	
Residence (rural vs. urban)	1.5 (0.8–2.9)	
Hepatomegaly (yes vs. no)	1.4 (0.8–2.7)	
Rash (yes vs. no)	2.9 (1.4–5.7)	2.6 (1.2–5.7)
Vomiting (yes vs. no)	9.5 (2.9–31.3)	9.8 (2.9–33.3)
Abdominal pain (yes vs. no)	3.0 (1.2–7.8)	2.2 (0.8–6.0)
Platelet count (< 30,000/mm^3)	3.9 (2.0–7.4)	2.9 (1.4–5.9)
Anemia (hemoglobin < 9 g)	5.1 (2.7–9.8)	3.0 (1.5–6.1)
Mean arterial pressure (< 66 mmHg)	5.9 (3.0–11.7)	6.2 (2.9–12.8)

The limitations of this study are its retrospective design, the fact that data was collected from a single center, and the lack of laboratory confirmation of dengue. The latter has been a limitation of most dengue studies because of the lack of availability and expense of laboratory testing in resource-constrained settings. However, we believe that the sensitivity of the triad of self-limited fever, thrombocytopenia, and generalized pain as markers of dengue infection in the DR is high, especially when cases are diagnosed by expert infectious diseases pediatricians devoting most of their time to caring for these patients in a true dengue ward. The frequency of missing values is a common problem with this type of study. We estimate that the proportion of missing data for specific variables was minimal in this study and did not lead to differential bias, because most of the clinical parameters analyzed were well-documented in the dengue unit's medical records. The high mortality in our cohort is likely because of referral bias to a large center that cares for the sickest patients. Thus, the results may not be applicable to community healthcare settings.

The main strength of this study is its large sample size of a geographically diverse Dominican pediatric population. The clinical profile of patients with dengue in the DR and the demographic characteristics and laboratory parameters associated with poor prognosis have not been well-studied previously. In addition, this study explored the applicability of current WHO guidelines to Dominican pediatric patients, and it identified potential new warning signs of severe dengue. We found that, when pronounced thrombocytopenia or rash is present, there is an increased risk of morbidity. This information can help clinicians initiate early triage and institute goal-directed management in cases at high risk of progression. A larger multicenter prospective observational study is needed to validate these findings.

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