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## Predictors of severe manifestations in a cohort of adult dengue patients

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### ABSTRACT

**Background:** Key symptoms observed during the febrile phase of dengue may identify patients who are likely to progress to severe disease.

**Objectives:** To test this hypothesis, we examined the relationships between symptoms reported by patients at presentation and the development of severe outcomes.

**Study design:** Retrospective analysis of data recorded prospectively in 560 adult dengue patients admitted to an emergency department. A logistic regression analysis was used to quantify the association between symptoms reported at presentation and outcome.

**Results:** Plasma leakage was observed in 95 patients (17%), severe thrombocytopenia (platelet counts  $<20 \times 10^9/L$ ) in 93 patients (16.6%) and acute hepatitis in 42 patients (7.5%). Severe thrombocytopenia developed in 57% of patients with plasma leakage and 40.5% of patients with hepatitis. Patients who developed a plasma leakage syndrome were older, mainly male, and reported more often an abdominal pain and a cough. Diarrhea and taking paracetamol  $>60$  mg/kg/day before admission were associated with the development of acute hepatitis. Seven patients died. The mortality rate was 6/95 (6.3%) in patients who developed plasma leakage, 3/42 (7.1%) in patients who developed hepatitis, 5/93 (5.4%) in patients with severe thrombocytopenia, and 3/12 (25%) in the patients who demonstrated together all these severe manifestations.

**Conclusion:** Plasma leakage, severe thrombocytopenia and acute hepatitis identified subgroups of adult dengue patients with increased mortality rates. Key symptoms reported by the patients at presentation such as abdominal pain, cough or diarrhea were significantly associated with the development of severe manifestations and should be considered as warning signs.

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## 1. Background

Since its first descriptions about 40 years ago, dengue fever with its clinical presentation has been extensively described in the medical literature.<sup>1</sup> Although most infections are asymptomatic or associated with minor illness, millions of people across the tropical and subtropical world develop overt clinical forms of dengue infections every year. When symptomatic, the clinical presentation

of dengue ranges from a non-specific, acute febrile illness which lasts for less than 1 week (classical dengue fever—DF) to severe forms of dengue hemorrhagic fever (DHF), as described in the World Health Organization (WHO) classification system. The central pathophysiological feature that distinguishes DF from DHF is a transient increase in vascular permeability which may lead to the life threatening dengue shock syndrome (DSS).<sup>1</sup> The progression of illness to DHF/DSS may develop within 3–5 days following an undifferentiated symptomatic febrile phase. Typically, development of signs and symptoms of plasma leakage coincide with defervescence, as demonstrated by the occurrence of serous effusions in the pleural and peritoneal spaces, elevation of hematocrit and hypoalbuminemia. Liver enlargement, bleeding, and thrombocytopenia are other typical features of the progression of illness to DHF. In the most severe cases, signs of circulatory failure develop indicating

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**Table 1**

Clinical characteristics and basic symptoms observed in adult dengue patients on admission time in the emergency room according to outcome features.

Patients demographics and basic symptoms	Uncomplicated dengue fever, n = 277	Platelet counts <20 × 10 <sup>9</sup> /L, n = 93	Plasma leakage, n = 95	Acute hepatitis, n = 42
Age (years) <sup>a</sup>	29 (14–78)	45.5 (16–83) (c) <sup>b</sup>	43.5 (16–83) (c)	39 (14–63) (a)
Male to female ratio	0.63	1.54 (c)	2.92 (c)	1.21
DENV-2 (%)	61.7	72.3	74.5	71.4
Secondary dengue (%)	39.6	66.7 (c)	68.2 (c)	79.5 (c)
Hospitalized (%)	8.5	75.5 (c)	80.9 (c)	57.1 (c)
Headache (%)	88.1	83	74.5 (b)	78.6
Myalgia (%)	80	79.6	75.5	76.2
Arthralgia (%)	58.7	63.7	58.2	58.5
Back pain (%)	76.1	70.2	72.3	64.3
Intense asthenia (%)	58.6	76.9 (b)	79.1 (c)	75.6 (a)
Abdominal pain (%)	42.7	60.9 (b)	62.6 (b)	68.3 (b)
Vomiting (%)	38.3	52.2 (a)	53.3 (a)	66.7 (c)
Anorexia (%)	31.4	50.5 (b)	51.1 (b)	55 (b)
Pharyngitis (%)	29.1	22.6	23.7	22
Cough (%)	20.6	31.2 (a)	37.6 (b)	29.3
Diarrhea (%)	19.3	44 (c)	44.4 (c)	65.9 (c)
Presyncope/syncope (%)	13.8	27.7 (b)	24.5 (a)	26.2
Rash (%)	9.5	13.2	14.3	9.8
Minor bleeding (%)	8.7	41.5 (c)	37.2 (c)	26.2 (b)

<sup>a</sup> Median values (range).<sup>b</sup> When compared with patients with uncomplicated dengue fever, (a)  $p < 0.05$ , (b)  $p < 0.01$ , (c)  $p < 0.001$ , by Mann–Whitney test (age) or chi-square analysis (other categorical data).

the progression of illness to DSS. However, significant differences in clinical presentation of dengue infections exist between children and adults and DHF/DSS is primarily a disease of childhood.<sup>1</sup>

In addition to these classical syndromes, other severe manifestations have been reported.<sup>2,3</sup> These involve mainly the central nervous system, cardiac alterations, and liver damage. Among these severe manifestations, acute hepatitis has been frequently demonstrated in clinical settings<sup>4–8</sup> and on autopsy.<sup>9</sup>

It is believed that early recognition of signs and symptoms of severity is crucial in guiding the management of dengue patients.<sup>10</sup> However, when faced with an apparently uncomplicated case of dengue fever seen during the acute febrile phase, there are still no reliable symptoms to predict the occurrence of a severe outcome.<sup>3</sup>

## 2. Objectives

The purpose of this study was to explore the possibility that some key symptoms observed during the early febrile phase of dengue fever may help health care providers in identifying patients who are likely to progress to severe disease. For this purpose, we reviewed the records of a cohort of adult dengue patients and examined the statistical relationships between symptoms reported by the patients on admission to an emergency department and the development of severe outcomes.

## 3. Study design

### 3.1. Study population

A prospective observational study of acute febrile illnesses was conducted in the emergency department for adults of the University Hospital of Fort-de-France, Martinique, between January 2005 and December 2008. Among the 1353 consecutive febrile patients admitted during the study period, 560 were diagnosed with confirmed dengue infections. The laboratory methods used for the diagnosis of dengue infections have been described elsewhere.<sup>11</sup> The diagnosis was based on positive RT-PCR determinations in 463 patients (82.7%). Serotype 2 was most frequently isolated (64.8% of patients), followed by serotype 4 (12.5%), serotype 3 (3.4%) and serotype 1 (2%). Other patients had only positive anti dengue IgM antibodies ( $n = 97$ , 17.3%). Primary dengue was demonstrated

in 128 patients (22.9%) and secondary dengue in 271 patients (48.4%).

### 3.2. Data collection

Each patient's informed consent was obtained. Data were recorded at the bedside into the computerized medical records system (DxCare, Medasys, Gif sur Yvette, France) by means of a questionnaire implemented for acute febrile illnesses. Clinical forms were identified retrospectively, based on the clinical and biological data recorded at presentation and during the follow-up.<sup>11</sup>

### 3.3. Covariates included in the analysis

Symptoms included as covariates in the analysis are listed in Table 1. Because the aim of this study was to identify reported symptoms that were associated with a severe course, direct indicators of clinical severity, such as hypotension, signs and symptoms of encephalopathy, severe bleeding, and respiratory failure, were not included in the analysis.

### 3.4. Definition of severe manifestations

Severe manifestations were defined by the development at any time during the course of illness of any of the following: (1) hypotension (systolic arterial pressure <90 mmHg), (2) signs and symptoms of encephalopathy (alteration of consciousness, convulsions), (3) signs and symptoms of plasma leakage (pleural effusion, ascites, hypoproteinemia and/or hemoconcentration), (4) platelet counts <20 × 10<sup>9</sup>/L, (5) acute hepatitis (aminotransaminases of more than 10-fold the normal upper limits), (6) severe bleeding (bleeding sufficient to warrant consideration for blood transfusion).

### 3.5. Statistical analysis

Data were analysed with a statistical program (StatView 4.5, Abacus Concepts Inc., Berkeley, CA). First, a bivariate analysis was performed to detect factors significantly associated with severe manifestations. Pearson chi-square tests were used to test for independence in contingency tables. The Mann–Whitney test was used to compare the distribution of continuous variables between two groups. To control for confounding, logistic regression analysis was

**Table 2**  
Multivariate analysis of clinical features associated with severe manifestations in 560 adult dengue patients.

Covariates <sup>a</sup>	Platelet counts <20 × 10 <sup>9</sup> /L, n = 93	Plasma leakage, n = 95	Acute hepatitis, n = 42
Odds ratio [95% confidence interval] (p) <sup>b</sup>			
Age > 37 years, n = 281	3.2 [1.9–5.4] (<0.001)	1.9 [1.2–3.2] (0.017)	NS <sup>c</sup>
Male, n = 263	1.8 [1.1–3] (0.020)	4.9 [2.8–8.5] (<0.001)	NS
Intense asthenia, n = 363	1.9 [1.1–3.4] (0.027)	2.2 [1.2–4.1] (0.008)	NS
Abdominal pain, n = 275	NS	1.9 [1.1–3.2] (0.015)	NS
Diarrhea, n = 155	2.4 [1.4–4] (<0.001)	NS	5.8 [2.9–11.6] (<0.001)
Cough, n = 141	NS	2 [1.2–3.3] (0.014)	NS
Minor bleeding, n = 103	3.8 [2.9–6.5] (<0.001)	3.3 [1.9–5.7] (<0.001)	NS

<sup>a</sup> The table shows only the covariates which demonstrated a significant independent association with at least one severe manifestation of dengue.

<sup>b</sup> Wald test.

<sup>c</sup> Non-significant.

used to quantify the association of symptoms with clinical outcome. Variables found to be statistically significant in bivariate analyses were entered into multivariate analysis to identify the independent factors for acquisition of severe manifestations. In addition, demographic variables ( $\leq 37$  or  $> 37$  years, sex), dengue serotype (DENV-1 to -4, or unknown), and immune status (primary or secondary infections, or unknown) were forced into the model.

## 4. Results

### 4.1. Clinical features

Male to female ratio was 0.9. Median age was 37 years (range 14–91 years). Median time from the onset of fever to examination was 4 days (range 1–9 days). Patients who developed signs of plasma leakage were included in a “DHF/DSS-like” group ( $n = 95$ , 17%). This group included patients who met all the WHO criteria for the diagnosis of DHF/DSS ( $n = 49$ , 8.8%) and other patients who missed at least one criterion (thrombocytopenia and/or bleeding) ( $n = 46$ , 8.2%). Other patients who demonstrated no sign of plasma leakage were classified as having a classical DF ( $n = 465$ , 83%), including 277 patients (49.5%) diagnosed as having uncomplicated dengue fever, 14 (2.5%) who developed clinically significant hemorrhages, 90 (16.1%) who had unusual manifestations, and 84 (15%) who had platelet counts nadir  $< 50 \times 10^9/L$  without any other sign of severity.

### 4.2. Severe manifestations

Hypotension was observed in 22 patients (3.9%), 23 other patients developed signs of encephalopathy (4.1%). Severe bleeding was observed in 10 patients (1.2%). Plasma leakage was observed in 95 patients (17%), acute hepatitis in 42 patients (7.5%) and severe thrombocytopenia in 93 patients (16.6%) (Table 1). Hepatitis developed in 18.1% of patients with plasma leakage and in 18.5% of patients with platelet counts of less than  $20 \times 10^9/L$ . Severe thrombocytopenia developed in 57% of patients with plasma leakage and 40.5% of patients with hepatitis. Plasma leakage, severe thrombocytopenia, and hepatitis developed all together in 12 patients (2.1%).

### 4.3. Outcome

Seven patients died (1.3%). Death resulted mostly from severe acute organ failure: fulminant hepatitis (2 patients), myocarditis (1 patient), encephalitis (1 patient), acute respiratory failure (1 patient), gangrenous cholecystitis (1 patient), and post-traumatic intracranial hemorrhage (1 patient). The mortality rate was 6/95 (6.3%) in the subgroup of patients who developed plasma leakage, 3/42 (7.1%) in the patients who developed hepatitis, 5/93

(5.4%) in patients with platelet counts  $< 20 \times 10^9/L$ , and 3/12 (25%) in the patients who demonstrated together all these severe manifestations. However, the clinical severity of the patients who died from dengue was obvious at the time of admission: coma (3 patients), massive hepatic cytolysis (2 patients), shock with multiple organ failure (1 patient), and severe left ventricular failure (1 patient). Apart from the patient with intracranial bleeding, no death was reported from severe hemorrhage or DSS as defined by the WHO classification. All other patients recovered.

### 4.4. Bivariate analysis

The distribution of clinical characteristics and key symptoms recorded in patients with uncomplicated dengue fever and in those who developed the most frequent severe manifestations is shown in Table 1. In addition, home medication before admission was recorded in 281 patients. Absorption of paracetamol of more than 60 mg/kg for at least 1 day was documented in 31 patients (median dose 80 mg/kg/day, range 61–120 mg/kg/day) and was more frequently reported in patients who developed hepatitis than in other patients (22.6% versus 7.8%;  $p = 0.006$ ).

### 4.5. Multivariate analysis of predictors of severe manifestations

Results of the multivariate analysis are detailed in Table 2. Older age, male gender, intense asthenia and minor bleeding were independently associated with the development of severe thrombocytopenia and plasma leakage. Moderate to intense abdominal pain and cough were independent predictors for occurrence of plasma leakage. Diarrhea was an independent predictor for development of hepatitis. The introduction of the doses of paracetamol into the regression analysis ( $\leq 60$  mg/kg/day,  $> 60$  mg/kg/day, unknown) demonstrated that taking paracetamol  $> 60$  mg/kg/day before admission was independently associated with the occurrence of hepatitis (odds ratio 3.4, 95% confidence interval 1.2–9.6,  $p = 0.018$ ). All these predictors were independent of immune status and dengue serotype.

### 4.6. Indexes of diagnostic accuracy

The sensitivity and specificity of symptoms identified as independent predictors for the development of severe manifestations were, respectively, 62.6% and 52.7% for abdominal pain, 37.6% and 77.3% for cough, and 65.9% and 74.4% for diarrhea. Among patients without cough, 85.1% did not develop subsequent plasma leakage (negative predictive value) and among those without abdominal pain that proportion was 87.7%. Among patients without diarrhea, 96.3% did not develop hepatitis.

## 5. Discussion

Dengue fever is mostly described as a benign disease. The majority of patients have a favourable outcome without therapeutic intervention. The WHO reports mention an overall yearly mortality rate of about 25,000 deaths per 50 million clinical dengue cases.<sup>1</sup> However, the mortality rate may vary considerably in selected groups of patients. During an epidemic in Cuba in 1981, the mortality rate in children was 15 times higher than in adults.<sup>12</sup> The fatality rates reported in hospitalized patients vary from about 2% in children diagnosed with DHF<sup>5</sup> to 50% in dengue patients developing fulminant hepatitis.<sup>13</sup>

Our study confirms that plasma leakage, acute hepatitis and severe thrombocytopenia defined subgroups of patients with increased hospitalization and mortality rates. Symptoms recorded on admission and the severe manifestations observed during follow-up showed considerable overlap between the different clinical forms of dengue infections. However, we identified several symptoms reported by the patients at presentation that were predictive of severe outcome whatever the serotype and the immune status were. Abdominal pain and cough were predictors of the development of plasma leakage. We hypothesize that abdominal pain might be considered as a clinical symptom of plasma leakage in the peritoneal space and that cough might be an early manifestation of plasma leakage at the bronchoalveolar and/or pleural level.

The correlation between diarrhea and hepatitis is a new finding of particular clinical interest. Great care should be taken when prescribing hepatotoxic medications to patients with dengue fever that report diarrhea. The potential hepatotoxicity of paracetamol in dengue patients has previously been suggested.<sup>7</sup> However, it has been poorly investigated and is mostly attributed to multiple supra-therapeutic doses.<sup>13,14</sup> Apart from self-treatment, the most common prescription which produced doses >60 mg/kg/day in the study population was 4 g of paracetamol per day. We suggest that 3 g per day should be the maximum dosage given to adult patients during dengue epidemics.

Our results are likely to have been biased by a number of factors. The study was conducted in patients admitted at a single emergency department of a tertiary hospital. Consequently, the patient population and the clinical characteristics might be biased by referral patterns and diagnostic procedures. Our results might also be confounded by variables we did not account for in our analysis, such as race, co-morbidities, or alcohol consumption. In addition, we lacked serotype information, as well as information on immune status and paracetamol dosage for a substantial number of patients. Because these findings were observed in adult patients, there are also limits in generalizing our results to pediatric population.

However, our findings are of potential interest to general practitioners and emergency physicians who need basic warning signs pointing to the identification of patients likely to develop severe clinical outcomes. The monitoring of warning signs is an important

component of the triage of patients seen during the acute febrile phase of dengue.<sup>15</sup> In our opinion, cough and diarrhea should be included on list of warning signs.

## Conflict of interest

None declared.

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