Clinical Presentation of Dengue Among Patients Admitted to the Adult Emergency Department of a Tertiary Care Hospital in Martinique: Implications for Triage, Management, and Reporting

Laurent Thomas, MD, Victor Moravie, MD, François Besnier, MD, Ruddy Valentino, MD, Stéphane Kaidomar, MD, Laurent Villain Coquet, MD, Fatiha Najioullah, PharmD, PhD, François Lengellé, MD, Raymond Césaire, MD, PhD, André Cabié, MD, Working Group on Dengue*

From the Emergency and Intensive Care Department, University Hospital, Fort-de-France, Martinique (Thomas, Moravie, Besnier, Valentino, Kaidomar, Coquet, Lengellé); the Laboratory of Virology and Immunology, University Hospital, Fort-de-France, Martinique (Najioullah, Lengellé, Césaire); and the Department of Infectious and Tropical Diseases and CIC-EC (Inserm CIE 802) (Cabié), University Hospital, Fort-de-France, Martinique.

Study objective: During dengue epidemics, emergency physicians face large numbers of patients with acute febrile illness. Triage algorithms and appropriate reporting systems are useful to manage patients and prioritize resources. We identify possible adaptations to these systems to improve the management of patients during epidemics.

Methods: In a prospective observational study in the adult emergency department (ED) of a tertiary care hospital, we enrolled all patients with febrile illness and a confirmed diagnosis of dengue (ribonucleic acid identification). We then retrospectively classified cases according to the initial clinical presentation at the ED.

Results: We enrolled 715 patients (332 male patients), aged 14 to 91 years (median 35 years). Severe illness was documented in 332 cases (46.4%) and was mostly caused by serotype 2, or a secondary infection of any serotype. Severe forms included dengue hemorrhagic fever or dengue shock syndrome (104/332; 31.3%), severe bleeding (9/332; 2.7%), and acute organ failure (56/332; 16.9%). The other patients with severe illness (171/332; 51.5%) presented with symptoms of presyncope, intense weakness, prolonged gastrointestinal symptoms, and hypotension. This presentation was common during epidemics and appeared to be associated with dehydration and electrolyte loss that improved markedly within 24 hours with saline solution infusion. This group did not have evidence of plasma leakage, although similar features were observed in patients with dengue hemorrhagic fever/dengue shock syndrome.

Conclusion: Dengue has a wide range of clinical presentations in the ED. Many patients who appear seriously ill on presentation will respond to intravenous fluids. [Ann Emerg Med. 2012;59:42-50.]

Please see page 43 for the Editor's Capsule Summary of this article.

Provide **feedback** on this article at the journal's Web site, www.annemergmed.com.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter
Copyright © 2011 by the American College of Emergency Physicians.
doi:10.1016/j.annemergmed.2011.08.010

INTRODUCTION

Background

Dengue is the most widespread mosquito-borne viral disease transmitted to humans by mosquitoes of genus *Aedes*, mostly *A aegypti*.[1] It is considered an emerging and neglected tropical disease.[2] It is estimated that more than 3 billion people living in tropical and subtropical areas are susceptible to infection by one of the 4 serotypes of dengue virus (DENV-1 to -4).[3] The first infection by one serotype (primary infection), often asymptomatic, is thought to produce lifelong, serotype-specific immunity but not lasting protection against infection by another serotype (secondary infection).[4] It has been recognized that secondary dengue infections may lead to the development of more severe disease.[4] When symptomatic, dengue infection may exhibit a wide range of clinical forms, from uncomplicated dengue fever from which patients recover within 1 week without therapeutic intervention, to severe forms associated with the unpredictable development of plasma leakage, bleeding, or acute organ failure.[5] Among those who develop severe disease, patients receiving a diagnosis of plasma leakage can be classified according to the historical description of dengue hemorrhagic fever and dengue shock syndrome.[6]

Importance

In Martinique, a French Caribbean island with a population of 400,000 inhabitants mostly of African ancestry, dengue is

*All members are listed in the Appendix.

Editor's Capsule Summary

What is already known on this topic

Dengue is a potentially severe mosquito-borne viral infection that is becoming more common in people living or traveling in tropical areas.

What question this study addressed

What is the clinical presentation of dengue?

What this study adds to our knowledge

Dengue had a range of clinical presentations in this analysis of 715 confirmed cases from an emergency department in Martinique. About half of patients had severe illness, including hemorrhagic fever and shock. Many who initially appeared seriously ill responded well to intravenous hydration.

How this is relevant to clinical practice

Patients with suspected dengue should be evaluated for signs of shock and plasma leakage and receive aggressive fluid and electrolyte replacement.

endemoepidemic.[7] During the last decade, the island has experienced epidemics of DENV-3 in 2001, DENV-2 and DENV-4 in 2005, DENV-2 in 2007, and DENV-1 and DENV-4 in 2010.[8] The attack rate of symptomatic dengue during these epidemics ranged from approximately 4% to 6% between 2001 and 2007 and was higher than 10% in 2010.[8] In 2007 and 2010, emergency physicians, general practitioners, and other health care workers were faced with large numbers of patients presenting with acute febrile illnesses, requiring triage algorithms and appropriate reporting systems to suitably manage patients and prioritize resources.

Goals of This Investigation

We sought to improve our triage and patient management practices for patients presenting with febrile illness during dengue epidemics and, after reviewing the available guidelines, recommend a model for reporting dengue cases that reflects the observed clinical features.

MATERIALS AND METHODS

The protocol for this retrospective study was approved by the Clinical Research Committee of the University Hospital of Fort de France, Martinique, and by the Regional Research Ethical Committee. Patients provided consent to the anonymous use of clinical data recorded in the hospital's electronic information system.

Selection of Participants

Patients were eligible for the study if they were admitted to the emergency department (ED) for adults at the University Hospital of Fort de France between January 1, 2005, and December 31, 2010, with a history of acute febrile illness lasting less than 1 week. Patients were examined by senior assistants and qualified emergency physicians. Signs and symptoms were recorded prospectively at the bedside in an electronic medical record system (DxCare; Medasys, Gif-sur-Yvette, France) using a case report form including mandatory answers to key questions about vital signs and clinical presentation of acute febrile illnesses. The date of the onset of fever was recorded and defined as the first day of illness. Routine blood tests, blood culture, and bacteriologic examination of urine were performed at admission. Biochemistry, CBC counts, and coagulation tests were immediately carried out on automatic analyzers. Serum aliquots were stored at −70°C (−94°F) for remote virologic and immunologic testing. Pending the results of the blood tests performed at admission, an intravenous drip of isotonic saline solution was initiated at 50 mL/kg per 24 hours. Other investigations, clinical management, and decision to hospitalize were at the discretion of the attending physician, according to the individual clinical presentation of each patient.

Ambulatory patients were followed by their general practitioner or at outpatient clinics. In addition, many patients who were discharged from the ED were followed by serial telephone calls until recovery, using a predefined protocol. When necessary (such as the occurrence of signs and symptoms of severity), the patients were referred for a second medical assessment. Final outcome data were collected from general practitioner records, hospital records, and in some cases during telephone interviews with patients. On the small island of Martinique, epidemics were followed by using a sentinel network coordinated by the regional health authority.[9] All severe cases were reported by the out-of-hospital emergency network (Service d'Aide Médicale Urgente, SAMU 972).

From the eligible population above, we included all patients aged 14 years or older and infected with dengue virus, as demonstrated by ribonucleic acid identification. Detailed laboratory diagnostic procedures have been published elsewhere.[10] Briefly, a heminested reverse transcription–polymerase chain reaction was performed with DENV generic and serotype-specific primers, as described by Lanciotti et al.[11] In addition, dengue-specific antibodies were detected by using immunoglobilin M (IgM) capture, immunoglobulin G (IgG) capture, and IgG indirect enzyme-linked immunosorbent assay kits (Panbio, Brisbane, Australia). A positive IgG capture test result for a serum sample obtained within 6 days of fever onset indicated a secondary dengue infection. Serum samples with negative results by IgG capture and IgG enzyme-linked immunosorbent assay indicated a primary infection.[12]

All medical charts were reviewed by 2 medical experts who had worked with dengue patients for more than 15 years and were familiar with the case classification systems (L.T., A.C.). Cases with missing data were excluded from the analysis. Using the signs and symptoms recorded at admission to the ED, the

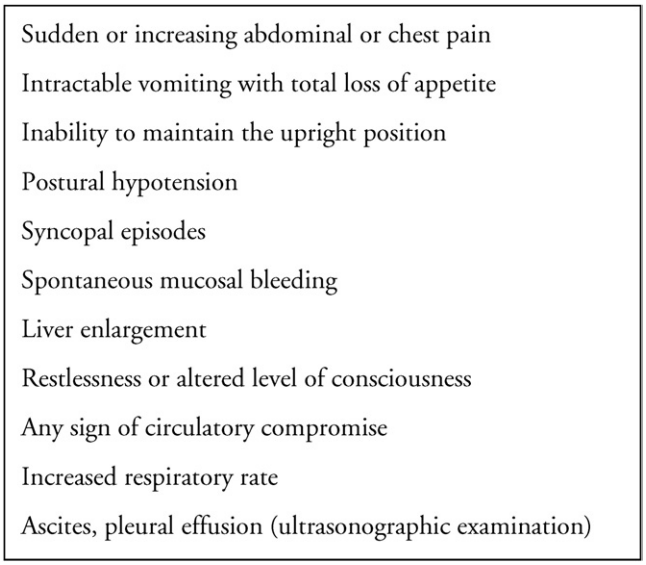

Figure 1. Warning signs suggesting the progression to a severe clinical form of dengue (adapted from 2009 WHO guidelines[5]).

reviewers classified each case into one of the 3 phases of dengue illness, as defined in the 2009 World Health Organization (WHO) recommendations: acute febrile phase, critical phase, and recovery phase.[5] Briefly, during the acute febrile phase patients report a sudden onset of fever, headache, myalgia, backache, and gastrointestinal symptoms. Facial flushing and diffuse skin erythema are frequently observed. Most patients progress to recovery within 7 days without developing any signs of severity, although prolonged fatigue lasting several days or weeks is occasionally observed. Some patients, however, develop warning signs, including altered vital signs indicating the progression to the critical phase of the disease (Figure 1).[5] This phase may develop around the time of defervescence, after 3 to 5 days of fever. It may be associated with a rapid decrease in platelet counts and the development of vascular permeability leading to plasma leakage, hemoconcentration, and hypovolemia, suggesting the progression to dengue hemorrhagic fever/dengue shock syndrome. During the recovery phase, starting days 6 to 8 after fever onset, plasma leakage and thrombocytopenia resolve rapidly and the patient reports feeling much better. The patient typically recovers appetite and normal body temperature after 2 days.

We then classified dengue cases into the following diagnostic categories, according to initial clinical presentation, vital signs, and routine blood test results: uncomplicated dengue fever included the patients presenting mostly with an undifferentiated acute febrile illness, with normal vital signs and none of the warning signs described above. Severe dengue included patients with plasma leakage and those who developed other severe manifestations. Plasma leakage was diagnosed if ultrasonography revealed ascites or pleural effusion or if hemoconcentration was demonstrated according to the measurement of hematocrit at admission. The hematocrit threshold for hemoconcentration was set at 45% in female patients and 47% in male patients, corresponding to a 20% increase of the normal levels recorded in Martinique. Hence, this group included patients who met all criteria defined by WHO[6] for dengue hemorrhagic fever or dengue shock syndrome (ie, plasma leakage, hemorrhagic manifestations, platelet count less than or equal to 100×10^9/L, with or without signs of shock), as well as those with plasma leakage but without hemorrhagic manifestations or thrombocytopenia.

Other severe manifestations included any sign of circulatory compromise, increased respiratory rate, severe bleeding (any hemorrhage associated with decreased arterial pressure or a rapid decrease in hemoglobin levels of more than 30 g/L), acute encephalopathy or coma (according to alteration of consciousness, magnetic resonance imaging examination, and, when indicated, cerebrospinal fluid analysis), acute hepatitis (aminotransaminase levels higher than 10 times the upper normal limit), cardiomyopathy (arrhythmia or abnormalities of ST-segment, increased troponin 1c levels, signs of left ventricular failure, or documented abnormalities on echocardiography), rhabdomyolysis (creatine kinase level higher than 20 times the upper normal limit), acute renal failure (creatinemia >200 μmol/L), and acute respiratory failure (respiratory distress, crepitations, cyanosis, and interstitial or alveolar infiltrates).

Primary Data Analysis

Data were extracted from electronic records with a data extraction tool (DxExtract; Medasys) and analyzed with StatView (version 4.5; Abacus Concepts, Berkeley, CA). Data, where indicated, were expressed as median and range or proportions.

RESULTS

Characteristics of Study Subjects

We enrolled 715 patients, 332 male and 383 female patients, aged 14 to 91 years (median 35 years), mostly during the 2005, 2007, and 2010 epidemics (Figure 2). The median time from the onset of fever to examination and sampling was 3 days (range 1 to 10 days). The number of days of illness at admission was 1, 2, 3, 4, 5, 6, and 7 or more for, respectively, 115 (16%), 134 (18.7%), 114 (15.9%), 134 (18.7%), 113 (15.8%), 78 (10.9%), and 27 (3.8%) of the 715 patients. Virus was confirmed as DENV-1 in 161 patients (22.5%), DENV-2 in 365 patients (51.1%), DENV-3 in 18 patients (2.5%) and DENV-4 in 171 patients (23.9). Immune status could be determined for 591 patients (82.7%) for whom enough serum was available. Secondary dengue infections were detected in 385 patients (65.1% of patients tested) and were more frequent among DENV-2 infections (224/287; 78%) than DENV-1 (74/144; 51.4%), DENV-3 (1/11; 9.1%) and DENV-4 (86/149; 57.7%) infections.

Associated pathologies were documented in 65 cases (9.1% of the cohort). These were mainly cardiovascular diseases (31

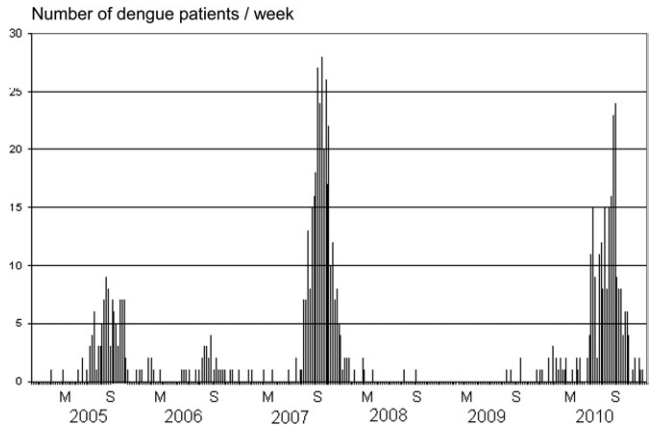

Figure 2. Weekly distribution of 715 adult dengue patients admitted to the ED between January 1, 2005, and December 31, 2010. *M*, March; *S*, September.

patients), type 2 diabetes (9 patients), chronic inflammatory diseases (6 patients), epilepsy (6 patients), cancer/chemotherapy (5 patients), sickle cell disease (1 patient), and hemophilia B (1 patient). Other patients had coinfections: HIV (3 patients), pyelonephritis (5 patients), acute prostatitis (1 patient), *Plasmodium vivax* malaria (1 patient), and *Proteus* septicemia (1 patient). Six patients were pregnant (3 in the first trimester, 2 in the second, and 1 in the third) and 2 women were admitted after childbirth.

After evaluation in the ED by emergency physicians, 192 (26.9%) patients, 101 women and 91 men, were admitted and hospitalized (ie, for more than 24 hours) for a median duration of 4 days (range 2 to 34 days). Among the 523 (73.1%) patients who were discharged within 24 hours and followed as ambulatory patients, 40 (7.7%) returned to the ED for a second visit. Most of these (28/523; 5.4%) had confirmed uncomplicated dengue fever. Others (12/523; 2.3%) presented with severe manifestations related to dengue illness or associated pathologies and were subsequently hospitalized.

Main Results

Signs and symptoms recorded at initial admission are listed in Table 1. Most patients (416/715; 58.2%) were admitted during the acute febrile phase, followed by the critical phase (206/715; 28.8%) and the recovery phase (69/715; 9.7%). In the remaining cases (24/715; 3.3%), classification was confounded by associated pathologies.

Uncomplicated dengue fever was recorded for 383 of 715 patients (54.6%) (Tables 2 and 3). No fatalities were reported by the sentinel and emergency networks for any of these patients. Plasma leakage (dengue hemorrhagic fever/dengue shock syndrome–like condition) was documented for 102 of 715 patients (14.3%). Criteria for the diagnosis of dengue hemorrhagic fever/dengue shock syndrome were fulfilled by 53 of the102 patients with plasma leakage (52%). Bleeding, hepatitis, acute renal failure, and rhabdomyolysis overlapped frequently and occurred in patients with or without plasma leakage (Table 2). In all, severe bleeding was recorded for 9 of 715 patients (1.3%) and acute organ failure for 54 of 715 patients (7.6%). Patients developing dengue fever with acute organ failure formed an eclectic group (Table 2). Most patients with acute encephalopathy presented at the beginning of the acute febrile phase. This feature was observed mostly in adolescents and demonstrated a rapid recovery within 24 hours, together with the control of hyperthermia. Acute hepatitis and renal failure developed mostly in patients admitted during the critical phase of illness. Rhabdomyolysis developed mostly in patients with a

Table 1. Prevalence of signs and symptoms reported on admission to the ED among 715 adult patients receiving a diagnosis of confirmed dengue infection.

Symptom	Prevalence, %
Body temperature >38°C (100.4°F)	60
Body temperature >39°C (102.2°F)	28
Body temperature >40°C (104°F)	4
Headache	84
Myalgia	75
Gastrointestinal signs	61 (diarrhea 24)
Malaise	57
Total loss of appetite	36
Cough	21
Presyncope or syncope	20
Mucosal bleeding	17
Intense pain	14
Decreased blood pressure	10

Table 2. Retrospective classification of clinical forms observed among 715 adult patients receiving a diagnosis of confirmed dengue infection.*

Clinical Forms of Dengue Illnesses	No. (%)
Uncomplicated dengue fever	383 (54.6)
Plasma leakage (dengue hemorrhagic fever/ dengue shock syndrome–like)	102 (14.3)
Severe bleeding	7
Acute hepatitis	10
Rhabdomyolysis	4
Acute renal failure	12
Myocarditis	3
Other severe manifestation (DF-like)	
DF with acute organ failure	33 (4.6)
Encephalopathy	12
Acute hepatitis	7
Rhabdomyolysis	7
Acute renal failure	6
Myocarditis	1
DF with severe bleeding	2 (0.3)
DF with dehydration	171 (23.9)
Outliers (because of comorbidity)	24 (3.4)

DF, Dengue fever.
*Dengue hemorrhagic fever/dengue shock syndrome–like included the patients with dengue hemorrhagic fever/dengue shock syndrome and all other patients demonstrating plasma leakage. Others groups had no signs of plasma leakage (DF-like).

Table 3. Clinical characteristics in adult dengue patients according to the clinical form of illness observed at admission to the ED.

Clinical Characteristics	Uncomplicated DF (n=383)	Plasma Leakage (n=102)	DF With AOF (n=33)	DF With Dehydration (n=171)
Age, y (range)	30 (14–89)	42.5 (16–82)	42 (15–76)	36 (15–83)
Male, %	43.9	75.5	60.6	33.3
DENV-2, %	45.4	71.6	51.5	53.8
Secondary dengue infection, %	48.2 (n=371)	69.6	54.5	60.7 (n=168)
Day of illness on admission (range)	2 (1–9)	5 (1–10)	2 (1–6)	5 (3–8)
Acute febrile phase, %	77.5	6.9	69.7	42.7
Body temperature, °C (range)	38.5 (35.9–40.9)	37.7 (36–40.2)	38.5 (36–40.3)	38 (36–40.3)
Body temperature, °F (range)	101.3 (96.6–105.6)	99.9 (96.8–104.4)	101.3 (96.8–104.5)	100.4 (96.8–104.5)
Pulse rate, beats/min (range)	90 (51–189)	82 (47–133)	89 (50–141)	81 (56–128)
Blood pressure, mm Hg (range)	48 (8–100)	45.5 (13–92)	46 (23–81)	43 (24–92)
Epigastric pain, %	33.4	57.6	19.4	58.7
Vomiting, %	34.2	52.5	57.6	58.3
Loss of appetite, %	21.4	51.5	25.8	62
Diarrhea, %	14.1	41.2	24.2	36.3
Cough, %	17.2	32.4	24.2	22.8
Intense weakness, %	40	68	62.5	84.5
Syncopal episodes, %	9.8	25.5	28.1	35.5
Mucosal bleeding, %	8.1	28.4	15.2	22.8
Hospital stay >1 day, %	8.9	60.8	51.5	36.8

AOF, Acute organ failure.

body temperature of greater than 40°C (104°C). In severe cases, rhabdomyolysis presented with intense muscle pains, decreased muscle strength and deep tendon reflexes, and acute renal failure with hyperkaliemia requiring emergency dialysis. Cardiomyopathy was infrequent and occurred later during the course of illness (data not presented). Severe clinical forms were mostly associated with DENV-2 and secondary dengue infection of any serotype (Table 3). Seven of the 137 (5.1%) patients with severe manifestations died.

Other patients presented with concerning symptoms such as intense weakness, complete loss of appetite, intractable vomiting, and dehydration by days 3 to 5 of illness. This was often reported together with persistent fever, intolerable pain, and signs of postural hypotension (syncopal or presyncopal episodes, fainting, refusing the upright position) or transient hypotension. These patients demonstrated a dramatic improvement after saline solution infusion without developing signs of plasma leakage. Most of these patients were discharged within 24 hours and subsequently followed as ambulatory patients. These features were characteristic of a group of 171 of 715 patients (23.9%) with disease of intermediate severity. Because this condition showed a rapid improvement after saline solution infusion, it was called "dengue fever with dehydration" (Table 2 and 3). No fatalities were reported for any of these patients.

The evolution of CBC counts and biochemical findings from the day of fever onset followed typical trends (Figure 3). All patients who presented on the first day of illness demonstrated low lymphocyte counts that persisted until days 4 to 5 of illness. From day 1 to days 5 to 6 of illness, a progressive elevation of hematocrit level was observed, together with a decrease of neutrophil and platelet counts. The progressive decrease in plasma chloride level, together with the increase in bicarbonate, and increase of aminotransaminase levels were observed in most patients. However, notable differences in the distribution of biological data were observed between the main clinical presentations (Figure 4). When compared with patients with uncomplicated dengue fever, the patients with dehydration and the patients with plasma leakage demonstrated lower plasma sodium and chloride, higher bicarbonate, and higher aminotransaminase levels and lower platelet and neutrophil counts (Figure 4).

LIMITATIONS

Our results may have been biased by a number of factors. We enrolled patients from a single ED. Consequently, the patient population and the clinical characteristics might be biased by referral patterns and the lack of a validation study about the diagnostic procedures. Given the variability in clinical symptoms caused by dengue infection during the first few days of illness, the reporting of clinical categories might be biased by the short observation time in the ED. In addition, the knowledge of the outcome could have influenced the reviewers' classification of cases. Consequently, this study could not specifically determine how predictive the early clinical or hematologic presentation was in determining the progression to a more severe illness that was observed in some patients. In this respect, dengue patients receiving intravenous fluids should be closely monitored for the potential development of pleural effusion and respiratory distress.[5,6]

Our results might also be confounded by variables not accounted for in our analysis, such as ethnogeographic origin and comorbidity. Because these findings were observed in adolescent and adult patients, there are also limits in generalizing our results to the pediatric population. Significant differences in clinical presentation exist between children and adults, and dengue hemorrhagic fever/dengue shock syndrome is primarily a disease of childhood.[13,14] During the last 6

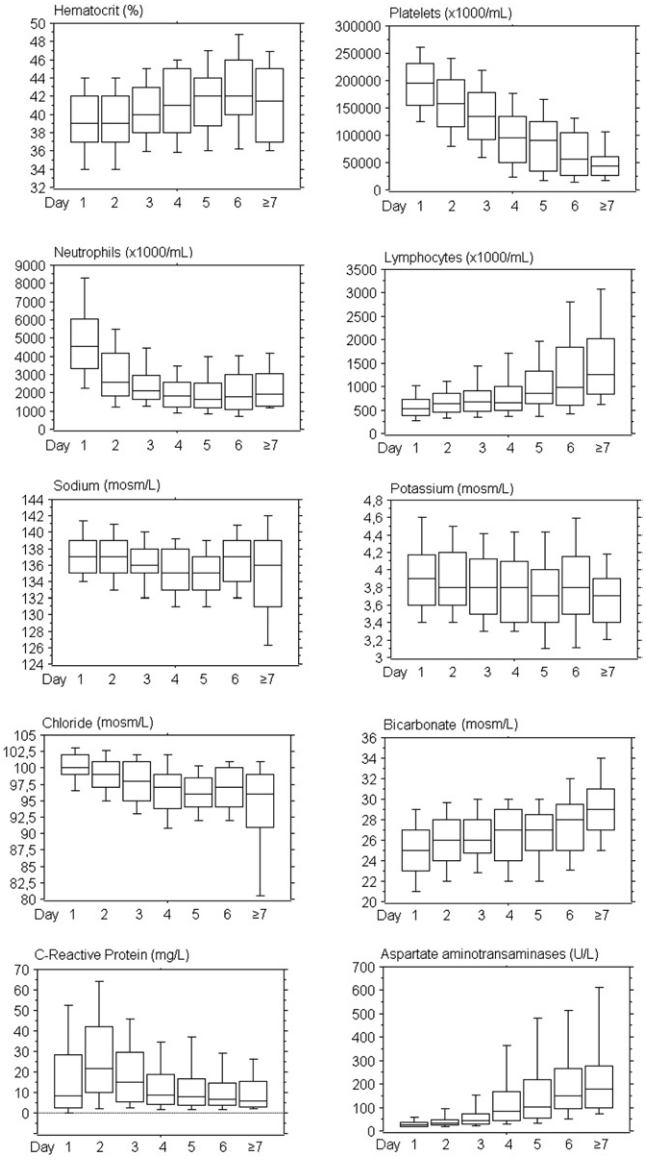

Figure 3. Distribution of biological data recorded for 715 adult dengue patients according to the time since onset of fever. Blood was sampled on admission to the ED. Day 1 was the day of fever onset. Box plots show median values (horizontal line in the box), 25% to 75% interquartile range (lower and upper limits of the box), and 90% range of data (additional bars).

Figure 4. Distribution of biological data recorded for adult dengue patients according to the clinical form of dengue observed at admission to the ED. Blood was sampled on admission to the ED. Box plots show median values (horizontal line in the box), 25% to 75% interquartile range (lower to upper limits of the box), and 90% range of data (additional bars).

years in Martinique, dengue epidemics were mainly due to DENV-1, -2, and -4. Indeed, DENV-3 has circulated only rarely in the last decade. Our findings might therefore not be predictive of the outcome of a DENV-3 epidemic.[15]

DISCUSSION

We examined the clinical features of dengue in patients presenting to the adult ED of a tertiary care hospital during a 6-year period. The most severe illnesses were recorded in patients with DENV-2 and secondary dengue infections, as observed by others.[16] In most cases, emergency physicians used the initial clinical presentation for hospital admission decisions. However, for some patients with uncertain clinical severity, no decision could be made until after the patient had been monitored and received saline solution infusion for a few hours at the ED to observe the evolution of symptoms. During an epidemic of dengue, it is highly probable that patients presenting with flulike illness and developing a typical rash or leucopenia have a dengue infection. However, when physicians are faced with a large number of febrile and thrombocytopenic patients, there is a risk that acute febrile illnesses caused by other pathogens may be misdiagnosed as dengue. Examples

include bacterial infections (mainly pyelonephritis, meningitis, pneumonia, and leptospirosis) or imported malaria (proximity to malaria endemic regions), all of which require specific emergency investigations and treatments.

Distinguishing dengue from other infections has been the subject of many articles.[17-22] In our bedside practice, the diagnosis was based on a careful examination of risk factors (such as medical history or recent stay in malaria endemic zone), the characteristics of fever (in dengue, typically a sudden attack of fever with 1 paroxysm and without shaking chills that decreases in 4 to 6 days), and other examinations carried out according to clinical presentation (such as medical imagery or lumbar puncture). In addition, the interpretation of routine blood tests according to the day of illness was of critical importance for diagnosis and management (Figure 3). Three days after the onset of fever, patients with C-reactive protein levels higher than 60 mg/L and neutrophil counts higher than 4 giga/L were unlikely to have dengue. After 6 to 7 days of illness, patients with very low platelet counts but without bleeding or other signs of clinical severity did not need any specific therapeutic intervention.[23]

The out-of-hospital triage of patients was conducted first by considering the risk factors and then the warning signs, and then by evaluating the clinical phase of illness. In Martinique, the main risk factors are pregnancy (third trimester and near delivery), sickle cell disease, and other comorbidities (eg, diabetes, chronic heart failure, chemotherapy, chronic inflammatory diseases) (unpublished data). The relatives of patients treated during the acute febrile phase of the disease and selected for ambulatory follow-up were informed of the potential risk of developing severe symptoms by days 3 to 6 of illness, with a particular attention to the day of defervescence.[5,6] Warning signs were clearly listed and explained in a tutorial administered to patients and relatives. Patients with risk factors, warning signs, or other signs of clinical severity were fully investigated in the hospital, and virologic confirmation of dengue infection was sought as soon as possible. In this respect, the highly specific NS1 antigen determination looks promising, but currently available tests, including rapid tests for bedside use, may lack sufficient sensitivity.[10]

Patients developing plasma leakage need special attention because when left unmanaged, it can lead to irreversible shock and death within a few hours.[5,6] Consequently, the diagnosis of plasma leakage and dengue hemorrhagic fever should be considered first for all patients. Dengue hemorrhagic fever/dengue shock syndrome–like patients (ie, those showing signs of plasma leakage) may develop acute organ failure (mainly acute hepatitis and acute renal failure) or severe bleeding but may also present with clinically uncomplicated dengue fever associated with abnormal laboratory findings such as elevation of hematocrit level and low platelet counts (dengue hemorrhagic fever grade 1 of the 1997 WHO classification). In such patients, outcome is unpredictable and excessive fluid infusion may lead to diffuse edema, ascites, pleural effusion, and respiratory distress.[5,6]

Acute organ failure should be considered next because of the potential lethality, the need for intensive care procedures (mechanical ventilation, dialysis, extracorporeal membrane oxygenation), or, more rarely, the need for emergency organ transplantation. In our cohort, 2 patients with fulminating hepatitis and 1 with acute myocarditis exhibiting terminal heart failure were entered into the emergency organ transplantation program. In patients developing acute hepatitis, paracetamol toxicity should be considered, and if confirmed, N-acetyl cysteine infusion should be commenced without delay.[24]

Severe bleeding requiring blood transfusions were infrequently observed in patients without plasma leakage. These cases were mostly gastrointestinal bleeding in patients with a history of peptic gastric ulcer or colonic diverticulosis or treatment with nonsteroidal antiinflammatory drugs, aspirin, or anticoagulants. Severe bleeding can also be observed in dengue patients requiring emergency surgery (such as cesarean section), invasive intensive care procedures (including puncture of large vessels, urinary catheterization, or pleural drainage), or after trauma.[23]

Among the dengue patients presenting to the ED with signs of severe illness, those not showing any sign of plasma leakage or acute organ failure included a large number of patients. This presentation was relatively common, particularly during the 2007 and 2010 epidemics, when large numbers of febrile patients were rushed to health care centers. Although many of these patients presented with syncopal episodes and signs of hypotension, the rapid improvement in response to saline solution infusion and the absence of overt plasma leakage permitted rapid discharge and follow-up as ambulatory patients. In response to large dengue epidemics, primary health care centers, EDs, and outpatient clinics should consider developing short-term hospitalization wards to manage these patients. However, the risk of trauma after syncope-associated falls is particularly worrying for thrombocytopenic patients and should be prevented. In our cohort, there were 2 cases with traumatic cerebral hemorrhage (one fatal) and 1 case with nasal fracture and severe epistaxis.

Our data suggest that this presentation was associated with dehydration and loss of electrolytes during the acute febrile phase of the disease. In addition to gastrointestinal loss and sweating, use of plain drinking water without concomitant salt intake may contribute to the electrolyte imbalance. This syndrome is most likely preventable, at least partially, through correct oral rehydration and electrolyte intake during this initial febrile phase.[25] Guidelines should emphasize the use of oral rehydration salts formulated by the WHO or soups supplemented with salt, or the prescription of sodium chloride pills in addition to oral rehydration for patients with total loss of appetite, and tutorials for patients should specify the dietary needs during the acute febrile phase. Such recommendations may be of critical importance during large epidemics because their implementation could be expected to reduce the number of patients requiring saline solution infusion.[25] During the 2009 dengue epidemic in Cape Verde, the widespread distribution of oral rehydration salts to the population is likely to have reduced the number of patients needing hospital care (personal communication, Dra Mecilde Fontes Costa, Hospital Agostinho Neto, Praia, Santiago, Cape Verde, April 2010).

The decrease of plasma chloride and concurrent increase of bicarbonate were more important in patients developing plasma leakage (Figure 4). According to the 1997 WHO guidelines, these patients were mostly identified from increased hematocrit levels 3 to 5

days after fever onset.[6] This suggests that, in addition to plasma leakage, dehydration and gastrointestinal leakage of electrolytes contribute to hemoconcentration. Because most patients exhibiting overt dengue symptoms develop water and electrolytes losses, those who subsequently develop plasma leakage and shock should first be challenged with saline solution rather than colloidal solutions. Nonresponders should preferably be treated with albumin 40% saline solution to maintain osmotic pressure and correct hyponatremia and, if necessary, receive transfusion to maintain the level of hemoglobin above 100 g/L. In Martinique, we do not recommend the use of colloids that are potentially deleterious in patients with thrombocytopenia, coagulation disorders, and renal failure.[26]

In Retrospect

The reporting of clinical cases of dengue suffers from a lack of international consensus on classification.[27,28] The historical WHO classification focuses on the description and the management of dengue hemorrhagic fever/dengue shock syndrome in children.[6] Its use has markedly reduced the case fatality rate of dengue in children throughout the world.[1] However, this reporting system omits many severe clinical forms of dengue, particularly acute organ failure such as encephalopathy, acute hepatitis, and cardiomyopathy.[27,28] From a clinical viewpoint, the term *dengue hemorrhagic fever* is inappropriate for patients developing vascular permeability rather than clinically significant bleeding. The term *dengue shock syndrome* is inappropriate to hypotensive dehydrated patients who recover with 1 L of saline solution infusion. In addition, the criteria for the diagnosis of plasma leakage in dengue patients (such as the use of ultrasonography or hematocrit-level testing) should be reevaluated at an international level.

The description of dengue illnesses proposed in 2009 by the DENCO group, which is essentially based on actual clinical presentation of patients and warning signs,[5] is therefore very helpful for clinicians for bedside monitoring, triage, and patient management. Unfortunately, it omitted the basic description of dengue hemorrhagic fever. Thus, the use of these 2 classification systems is potentially confusing for clinicians and introduces bias in the reporting of dengue cases in different countries.[16,22,29,30] In addition, our study suggests that more emphasis should be given to dehydration and electrolyte loss developing during the acute febrile phase of dengue illness and to the potential interest of the use of oral rehydration salts in preventing the development of warning signs. Many patients who appear seriously ill on presentation will respond to intravenous fluids.

In Martinique during the last 6 years, severe clinical forms of dengue, including dehydration and electrolyte imbalance, dengue hemorrhagic fever/dengue shock syndrome, bleeding, and acute organ failure, were mostly observed in patients infected by serotype 2 dengue virus and in patients with secondary dengue infections of any serotype. This observational study was the opportunity to revisit the dengue classification systems and propose models of triage, management, and reporting that reflect the clinical picture of dengue as it exists today. More effort will be needed to propose an alternative severity grading system useful for public health and vaccine development purposes.

The authors thank Grenville Marsh at Sanofi Pasteur for editorial guidance.

Supervising editor: Gregory J. Moran, MD

Author contributions: LT, RC, and AC conceived and designed the study. LT, VM, RV, SK, LVC, and AC supervised the data collection. LT and AC performed the retrospective classification of clinical forms and analyzed the data. FN and RC supervised the virologic and immunologic testing, including quality control. LT drafted the article, and all authors contributed substantially to its revision. All authors approved the final version. LT chaired the working group on dengue and takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). Dr. Thomas has received fees for consulting from Sanofi Pasteur France, manufacturer of an investigational dengue vaccine. The University Hospital of Fort-de-France, Martinique, supported this study.

Publication dates: Received for publication April 22, 2011. Revisions received July 17, 2011, and August 5, 2011. Accepted for publication August 11, 2011. Available online September 8, 2011.

Address for correspondence: Laurent Thomas, MD, E-mail laurent.thomas@chu-fortdefrance.fr.

REFERENCES

1. Halstead SB. Dengue. *Lancet*. 2007;370:1644-1652.
2. World Health Organization. Neglected tropical diseases. Available at: http://whqlibdoc.who.int/publications/2009/9789241598705_eng.pdf. Accessed October 12, 2010.
3. Beatty ME, Stone A, Fitzsimons DW, et al. Best practices in dengue surveillance: a report from the Asia-Pacific and Americas Dengue Prevention Boards. *PLoS Negl Trop Dis*. 2010;4:e890.
4. Murphy BR, Whitehead SS. Immune response to dengue virus and prospects for a vaccine. *Annu Rev Immunol*. 2011;29:587-619.
5. World Health Organization. 2009. Dengue guidelines for diagnosis, treatment, prevention and control. WHO/HTM/NTD/DEN/2009.1. Available at: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf. Accessed May 17, 2010.
6. World Health Organization. *Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention and Control*. 2nd ed. Geneva, Switzerland: World Health Organization; 1997. Available at: http://www.who.int/csr/resources/publications/dengue/Denguepublication/en. Accessed January 20, 2010.
7. Césaire R, Cabié A, Djossou F, et al. Aspects récents de la dengue dans les départements français d'Amérique. *Virologie*. 2008;12:1-7.
8. Institut National de Veille Sanitaire. CIRE-AG (2010). Surveillance de la dengue. Bulletin bimensuel: semaines 2010–44 à 2010-45. Available at: http://www.ars.martinique.sante.fr/fileadmin/MARTINIQUE/Votre_Sante/Veille_sanitaire/Les_champs_de_competences/Dengue/PEP/PEP_Martinique/pep_mq_2010/pe_den_mar_10_26.pdf. Accessed November 22, 2010.
9. Cardoso T, Quénel P. Les réseaux de médecins sentinelles dans les départements français d'Amérique. Institut National de Veille

Sanitaire. CIRE-AG (2008). Available at: http://www.invs.sante.fr/publications/basag/basag2008_10.pdf. Accessed October 1, 2008.
10. Najioullah F, Combet E, Paturel L, et al. Prospective evaluation of nonstructural 1 enzyme-linked immunosorbent assay and rapid immunochromatographic tests to detect dengue virus in patients with acute febrile illness. *Diagn Microbiol Infect Dis*. 2011;69:172-178.
11. Lanciotti RS, Calisher CH, Gubler DJ, et al. Rapid detection and typing of dengue viruses from clinical samples by using reverse transcriptase–polymerase chain reaction. *J Clin Microbiol*. 1992;30:545-551.
12. Vazquez S, Hafner G, Ruiz D, et al. Evaluation of immunoglobulin M and G capture enzyme-linked immunosorbent assay Panbio kits for diagnostic dengue infections. *J Clin Virol*. 2007;39:194-198.
13. Guzmán MG, Kouri G, Bravo J, et al. Effect of age on outcome of secondary dengue 2 infections. *Int J Infect Dis*. 2002;6:118-124.
14. Hammond SN, Balmaseda A, Pérez L, et al. Differences in dengue severity in infants, children, and adults in a 3-year hospital-based study in Nicaragua. *Am J Trop Med Hyg*. 2005;73:1063-1070.
15. Guilarde AO, Turchi MD, Siqueira JB Jr, et al. Dengue and dengue hemorrhagic fever among adults: clinical outcomes related to viremia, serotypes, and antibody response. *J Infect Dis*. 2008; 197:817-824.
16. Fox A, le Hoa NM, Simmons CP, et al. Immunological and viral determinants of dengue severity in hospitalized adults in Hanoi, Vietnam. *PLoS Negl Trop Dis*. 2011;5:e967.
17. Chadwick D, Arch B, Wilder-Smith A, et al. Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: application of logistic regression analysis. *J Clin Virol*. 2006;35:147-153.
18. Phuong HL, de Vries PJ, Nga TT, et al. Dengue as a cause of acute undifferentiated fever in Vietnam. *BMC Infect Dis*. 2006;6:123.
19. Libraty DH, Myint KS, Murray CK, et al. A comparative study of leptospirosis and dengue in Thai children. *PLoS Negl Trop Dis*. 2007;1:e111.
20. Potts JA, Rothman AL. Clinical and laboratory features that distinguish dengue from other febrile illnesses in endemic populations. *Trop Med Int Health*. 2008;13:1328-1340.
21. Gregory CJ, Santiago LM, Argüello DF, et al. Clinical and laboratory features that differentiate dengue from other febrile illnesses in an endemic area—Puerto Rico, 2007-2008. *Am J Trop Med Hyg*. 2010;82:922-929.
22. Low JG, Ong A, Tan LK, et al. The early clinical features of dengue in adults: challenges for early clinical diagnosis. *PLoS Negl Trop Dis*. 2011;5:e1191.
23. Thomas L, Kaidomar S, Kerob-Bauchet B, et al. Prospective observational study of low thresholds for platelet transfusion in adult dengue patients. *Transfusion*. 2009;49:1400-1411.
24. Thomas L, Brouste Y, Najioullah F, et al. Predictors of severe manifestations in a cohort of adult dengue patients. *J Clin Virol*. 2010;48:96-99.
25. Rocha C, Silva S, Gordon A, et al. Improvement in hospital indicators after changes in dengue case management in Nicaragua. *Am J Trop Med Hyg*. 2009;81:287-292.
26. Groeneveld AB, Navickis RJ, Wilkes MM. Update on the comparative safety of colloids: a systematic review of clinical studies. *Ann Surg*. 2011;253:470-483.
27. Deen JL, Harris E, Wills B, et al. The WHO dengue classification and case definitions: time for a reassessment. *Lancet*. 2006; 368:170-173.
28. Rigau-Pérez JG. Severe dengue: the need for new case definitions. *Lancet Infect Dis*. 2006;6:297-302.
29. Potts JA, Gibbons RV, Rothman AL, et al. Prediction of dengue disease severity among pediatric Thai patients using early clinical laboratory indicators. *PLoS Negl Trop Dis*. 2010;4:e769.
30. Barniol J, Gaczkowski R, Barbato EV, et al. Usefulness and applicability of the revised dengue case classification by disease: multi-centre study in 18 countries. *BMC Infect Dis*. 2011;11:106.

APPENDIX.

Working Group on Dengue. Members were clinicians or biologists involved in the collection of data, and a certified clinical research associate was involved in the control of data files.

Sylvie Abel, MD, Department of Infectious and Tropical Diseases and CIC-EC (Inserm CIE 802), University Hospital, Fort-de-France, Martinique; Guillaume Avenin, MD, CIC-EC (Inserm CIE 802), University Hospital, Fort-de-France, Martinique; Pierre Brihier, MD, Emergency and Intensive Care Department, University Hospital, Fort-de-France, Martinique; Yannick Brouste, MD, Emergency and Intensive Care Department, University Hospital, Fort-de-France, Martinique; Christophe Deligny, MD, Department of Internal Medicine, University Hospital, Fort-de-France, Martinique; Jean-Marc Dueyme, MD, Department of Nephrology and Hemodialysis, General Hospital, Lamentin, Martinique; Gisèle Elana, MD, Department of Pediatrics, General Hospital, Lamentin, Martinique; Christiane Fonteau, PharmD, Laboratory of Biochemistry, University Hospital, Fort-de-France, Martinique; Yves Hatchuel, MD, Department of Pediatrics, University Hospital, Fort-de-France, Martinique; Patrick Hochedez, MD, Department of Infectious and Tropical Diseases, University Hospital, Fort-de-France, Martinique; Guillaume Hurtrel, MD, Department of Infectious and Tropical Diseases, University Hospital, Fort-de-France, Martinique; Janick Jean-Marie, CCRA, CIC-EC (Inserm CIE 802), University Hospital, Fort-de-France, Martinique; Christian Léonard, MD, Emergency and Intensive Care Department, University Hospital, Fort-de-France, Martinique; Sophie Mainguy, MD, Emergency and Intensive Care Department, University Hospital, Fort-de-France, Martinique; Jenny Martial, MSc, Laboratory of Virology and Immunology, University Hospital, Fort-de-France, Martinique; Hossein Mehdaoui, MD, Emergency and Intensive Care Department, University Hospital, Fort-de-France, Martinique; Harold Merle, MD, Department of Ophthalmology, University Hospital, Fort-de-France, Martinique; Paul Mourlhou, CCRA, CIC-EC (Inserm CIE 802), University Hospital, Fort-de-France, Martinique; Yves Plumelle, PharmD, Laboratory of Hematology and Coagulation, University Hospital, Fort-de-France, Martinique; Dabor Résières, MD, Emergency and Intensive Care Department, University Hospital, Fort-de-France, Martinique; Nicolas Vignier, MD, Department of Infectious and Tropical Diseases, University Hospital, Fort-de-France, Martinique.