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Clinical case

Prospective and descriptive study of adult dengue cases in an emergency department, in Martinique

Étude clinique prospective et descriptive des cas de dengue observés chez l'adulte dans un service d'urgences en Martinique

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Abstract

Objective. – Knowing about the clinical aspects of dengue in endemic zones is essential to implementation of appropriate case management protocols and public health interventions.

Patients and methods. – The authors made a 4-year prospective, observational study of dengue-infected patients admitted to the emergency department of the Fort-de-France University Hospital.

Results. – Two hundred and sixty-three male and 297 female patients were included. The median age was 37 years (range: 14–91). The diagnosis was based on a positive RT-PCR (463 patients) or on the presence of specific IgM (97 patients). Two hundred and seventy-seven patients (49.5%) presented with dengue fever without complications. According to WHO criteria, 95 patients (17%) developed plasma leakage, including 39 patients (7%) diagnosed with DHF, and 10 (1.8%) diagnosed with DSS. Among the other patients without plasma leakage, 84 (15%) had isolated thrombocytopenia, 14 (2.5%) had internal bleeding, and 90 (16%) had unusual manifestations. Seven patients died (1.3%): fulminant hepatitis (two), myocarditis (one), encephalitis (one), acute respiratory failure (one), gangrenous cholecystitis (one), and post-traumatic intracranial hemorrhage (one). The other patients recovered. Seven patients were pregnant (1.3%) from 6 to 27 weeks of amenorrhea and carried their pregnancy to term without complications.

Conclusion. – With this experience, we were able to develop appropriate case management protocols for patients during dengue epidemics.

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Keywords: Dengue; Hemorrhagic fever; Martinique

Résumé

Objectif. – La connaissance des aspects cliniques de la dengue dans les zones d'endémie est indispensable à la mise en place des protocoles de prise en charge et des actions de santé publique.

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Patients et méthodes. – Étude observationnelle prospective des patients adultes admis aux urgences et infectés par un virus de la dengue conduite au CHU de Fort-de-France pendant quatre ans.

Résultats. – Deux cent soixante-trois hommes et 297 femmes ont été inclus. L'âge médian était 37 ans (extrêmes 14–91). Le diagnostic reposait sur un test RT-PCR positif (463 patients) ou sur la présence d'IgM spécifique (97 patients). Deux cent soixante-dix-sept patients (49,5 %) avaient une fièvre dengue non compliquée. Quatre-vingt-quinze patients (17 %) ont présenté un syndrome de type dengue hémorragique défini par l'apparition de signes de fuite plasmatisque. Parmi les autres patients, 84 (15 %) ont eu une thrombopénie isolée, 14 (2,5 %) une hémorragie interne et 90 (16 %) des manifestations atypiques. Sept patients sont décédés : hépatite fulminante (deux), myocardite (un), encéphalite (un), syndrome de détresse respiratoire (un), cholécystite gangréneuse (un), hémorragie cérébrale post traumatique (un). Tous les autres patients ont guéri. Sept femmes étaient enceintes entre six et 27 semaines d'aménorrhée. Leur grossesse a évolué favorablement.

Conclusion. – L'expérience acquise nous a permis de développer des protocoles de prise en charge des patients pendant les épidémies de dengue. © 2009 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Dengue ; Fièvre hémorragique ; Martinique

1. Introduction

Dengue is the most widespread arbovirus in the world. Transmitted by mosquitoes of the *Aedes* species, dengue is prevalent in most tropical and subtropical regions and affects 50 to 100 million people every year [1,2]. The dengue virus (DENV) belongs to the Flaviviridae family and includes four serotypes (DENV-1 to DENV-4). The first infection by one of these four serotypes (primary dengue) is often asymptomatic and results in life-long immunity for this serotype. Infection by another serotype (secondary dengue) has been suggested as one of the factors possibly contributing to the origin of the more severe forms of the disease by a complex immunopathological mechanism [3]. When symptomatic, DENV infection causes a non-specific, acute febrile disease, which lasts for less than 1 week (classic dengue fever). In some cases, a plasma leakage syndrome occurs, between the 4th and 7th day of illness, presenting clinically with the development of hemoconcentration and hypovolemia and/or by serous effusions (pleural, ascites). It is often complicated by hemorrhagic manifestations of variable severity, thrombocytopenia and hepatic cytolysis. In the absence of treatment (based essentially on prompt, adapted restoration of plasma volume [4]), a state of shock can develop and the outcome can be fatal. The clinical presentation is dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) as described in the WHO classification [5]. However, this description was made in Thailand more than 30 years ago on the basis of pediatric observations. It does not seem to fit the currently observed clinical presentation, notably the one observed in adults in Latin America and in the Caribbean [6–8]. The WHO classification suggests that the only severe form of the disease is hemorrhagic and does not mention other forms of dengue complicated by severe organ involvement: encephalitis [9], hepatitis [10], myocarditis [11], cholecystitis [12], pancreatitis [13] and other abdominal syndromes [14], rhabdomyolysis [15], acute respiratory failure [16], ocular diseases [17], lymphoplasmocytic activation syndrome [18], etc. The WHO classification no longer corresponds to reality; an updated description of clinical presentations based on modern diagnostic means is necessary. Knowing about the clinical aspects is essential to the implementation of appropriate case management. Moreover, the evaluation of prevalence and incidence of the severe forms of dengue in endemic zones is essential for the management of epidemics

and for the evaluation of new vaccines, which should soon be available [19].

Martinique is one of three French overseas departments in South-America with a population of around 400 000 inhabitants, for the most part of African ancestry. According to epidemiological reports on the Caribbean between 1975 and 1996 [20], dengue can be said to be endemoepidemic in Martinique [21]. Every year, an increased number of cases are observed during the rainy season with multiplication of mosquitoes (between June and December). Epidemic outbreaks occur every 2 to 4 years. Over the last 10 years, the number of cases recorded during successive epidemics varied: approximately 8000 cases in 1998 (DENV-1 and DENV-2), 24,000 in 2001 (DENV-3), 14,600 in 2005 (DENV-2 and DENV-4), and 17,000 in 2007 (DENV-2) [21]. The endemic cocirculation of all four serotypes was demonstrated [22]. This type of transmission, associated with the emergence of more virulent genotypes, such as the DENV-2 genotype 3 known as “Asian-American” native to Southeast Asia and introduced into the Caribbean in the 1980s, could explain the emergence of severe forms of the disease in the region [22].

Dengue epidemics are responsible for a great number of hospitalizations. The adult emergency department of Fort-de-France University Hospital belongs to the surveillance network set up in Martinique by the Inter-Regional Epidemiology Unit (CIRE Antilles-Guyane), which has for task to evaluate the severity of clinical forms of dengue observed at the hospital. In these settings, a prospective, observational study of patients admitted to the emergency department with acute febrile illnesses was implemented at the end of 2003. This report describes the clinical and evolutive aspects of confirmed cases of dengue observed in adults over the last 4 years.

2. Patients and methods

2.1. Study population and case management

All patients admitted to the adult emergency department, between January 1st, 2005 and December 31st, 2008, with an acute febrile illness (fever ≥ 38.4 °C) lasting for less than 8 days were eligible. The clinical data was recorded in real time in the computerized medical record system (DxCare, Medasys, Gif-sur-Yvette, France) by means of a questionnaire parameterized

for acute febrile illness. The date of fever onset was recorded and defined as the first day of illness (D1). Routine biochemical and hematological tests, hemoculture, and bacteriological examination of urine were carried out on samples taken at admission. A 10 mL serum sample was stored at -70°C for study-related virological and immunological testing. Further examinations (blood gases, lumbar puncture, and medical imagery) were carried out at the physicians' discretion according to the clinical presentation. Pending the results of the examinations carried out at admission, an intravenous drip of an isotonic crystalloid solution was initiated at 50 mL/kg per 24 h. Hospitalization was decided by physicians according to the usual criteria: clinical severity, diagnostic hypotheses, biological abnormalities, co-morbidity, and medico-social environment. Hospitalized patients were monitored daily. After a complete evaluation, patients that did not need hospitalization more than 24 h following admission were followed, either at home by their regular physician or asked to come the next day for in-depth outpatient surveillance in the Department of Infectious and Tropical Diseases. The long-term follow-up of all patients was done by a follow-up phone call at home.

2.2. Inclusion criteria and clinical definitions

Only patients infected by a DENV were included in this study. The diagnosis of dengue was established by the presence of viral RNA by RT-PCR (confirmed cases) or, in case of negative RT-PCR and in the absence of an alternate diagnosis, by the presence of anti-dengue immunoglobulin M (IgM) (probable cases). The illness was later classified on the basis of clinical and biological data collected in the emergency department and throughout the episode. In line with WHO criteria [5], patients who presented a hemoconcentration (hematocrit increasing by 20% or decreasing by 20% after 24 h of rehydration), and/or a proteinemia less than 50 g/L, and/or one or more serous effusions (pleural, ascites) revealed by lung x-ray or ultrasounds, were included in the group "DHF/DSS-like". This group included patients who met all criteria defined by WHO [5] for dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) (i.e., acute febrile illness, plasma leakage, hemorrhagic manifestations, platelet count less or equal to $100 \times 10^9/\text{L}$ with or without signs of shock), and patients who did not present hemorrhagic manifestations and/or thrombocytopenia (incomplete DHF/DSS). Other patients who presented no evidence of plasma leakage during the course of the disease were included in the group "classic dengue fever". Among these, the patients who presented with only fever or fever associated to minor cutaneous bleeding (positive tourniquet test, petechiae) and/or mucosal bleeding (nasal, gums, heavy menses) without other sign of severity were included in the group "uncomplicated dengue fever". The "classic dengue fever" group could also include patients who presented with other signs of severity: internal bleeding (gastro-intestinal, metrorrhagia, hematuria), isolated thrombocytopenia (platelets $< 50 \times 10^9/\text{L}$ without other signs of severity), or unusual manifestations (meningeal signs, mental confusion, syncope, convulsions, symptomatic postural hypotension, pseudo-surgical abdominal syndromes, dyspnea,

metabolic or acido-basic problems, elevated enzyme levels [aminotransaminases greater than 10-fold the upper level of normal, and creatine phosphokinase greater than 20-fold the upper level of normal, troponin I $> 1 \mu\text{g}/\text{L}$]).

2.3. Biological tests

Routine blood analyses (biochemistry, blood and platelet count, coagulation tests) were carried out with automatic analyzers. In the case of severe thrombocytopenia (platelets $< 50 \times 10^9/\text{L}$), the platelet count was controlled manually on a new citrate tube sample. Specific antibodies were measured with Panbio kits (Brisbane, Australia) according to the manufacturers' recommendations [23,24]. The presence of immunoglobulin G (IgG) anti-dengue measured by immunocapture in a sample taken before the sixth day of fever was considered as a symptom of secondary dengue. The absence of IgG anti-dengue by both immunocapture and by indirect ELISA was taken as proof of primary dengue. DENV serotype was determined by RT-PCR using the method described by Lanciotti et al. [25]. Laboratory methods were calibrated based on internal procedures and controlled by external audits.

2.4. Data analysis

Most data was extracted from computerized records with a data extraction tool (DxExtract, Medasys, Gif-sur-Yvette, France). The database was then completed when necessary from archived medical records or from blood test results communicated by the patients or by laboratories located in the city. The data was analyzed with the statistical software StatView (Abacus Concepts, Berkeley, CA, the USA) using the Mann-Whitney test (for continuous data), Fisher's exact test (for categorical data), and the Wald test (for multivariate analysis).

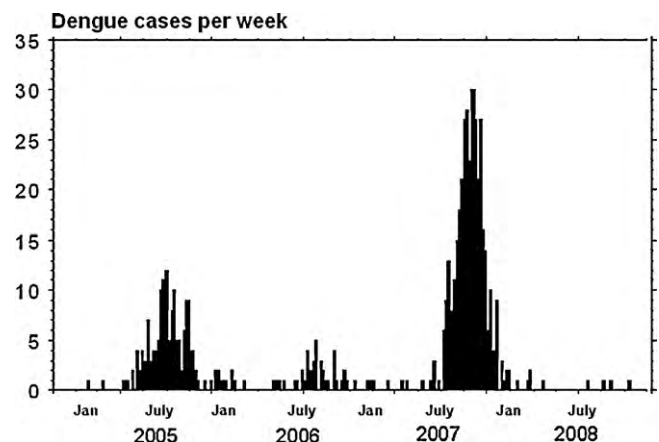


Fig. 1. Weekly distribution of adult dengue cases admitted to the emergency department from January 1st, 2005 to December 31st, 2008. *Distribution hebdomadaire de cas de dengue adulte admis aux urgences du 1^{er} janvier 2005 au 31 décembre 2008.*

3. Results

3.1. Epidemiological and demographic data

During the study period, 560 patients were admitted to the emergency department for dengue, confirmed by RT-PCR ($n = 463$; 82.7%) or by the presence of IgM anti-dengue ($n = 97$; 17.3%). The weekly distribution of cases is shown in Fig. 1. Two epidemics (in 2005 and 2007) and a seasonal outbreak (2006) occurred. The circulation of DENV-2 was considerable throughout the study, with 36.9% of isolates in 2005 (co-epidemic), 41% in 2006, 98.3% in 2007 (epidemic), and 72% in 2008. DENV-4 was dominant in 2005 (co-epidemic) with 61.2% of isolates, and continued to circulate, accounting for approximately 10% of isolates over the period 2006–2008. DENV-3 circulated particularly in 2006 (seasonal outbreak) with 43.6% of isolates, then disappeared in 2007–2008. DENV-1 appeared at the end of 2006, circulated at low levels in 2007 and accounted for 16% of isolates in 2008. Overall, serotypes 1, 2, 3, and 4 were diagnosed in respectively 2, 64.8, 3.4, and 12.5% of the patients. The immunological status was documented for 399 patients: primary dengue for 128 patients (32.1%) and secondary dengue for 271 patients (67.9%). During all the study period, DENV-2 infections were more frequently secondary dengue ($n = 218/280$; 77.9%) and DENV-4 infections more often primary dengue ($n = 52/59$; 88.1%).

The patients consulted the emergency department after a median of 4 days of fever (range: 1–9 days). The median age was 37 years (range: 14–91 years). The male to female ratio

was 263:297 = 0.9. The distributions of ages and sex between the four serotypes and between primary and secondary dengue were not significantly different.

3.2. Comorbidities

Thirty-nine patients (7%) presented with one or several associated chronic diseases. Cardiovascular diseases, often associated with diabetes were the most frequent (15 patients). These patients were very often treated by oral anticoagulants and/or antiplatelet drugs. Several patients were immunosuppressed: current chemotherapy (five patients), corticotherapy (two patients), cyclosporin treatment (one heart transplant patient). Three patients had sequels from stroke including one with complications due to decubitus. Two patients presented with epilepsy, one with hemophilia, one with sickle cell anemia, one with myopathy, one with hypophyseal insufficiency, one with hyperparathyroidism, and one with a chronic undernutrition syndrome (sequel of intestinal resection). Other patients had co-infections: HIV (two patients), pyelonephritis (two patients), acute prostatitis (one patient), *Plasmodium vivax* malaria (one patient), *Proteus* septicemia (one patient). Finally, seven patients were pregnant (one in the first trimester, five in the second, and one in the third trimester) and two women were admitted following childbirth. Following their examination in the emergency room, 182 patients (90 women and 92 men) were admitted and hospitalized for more than 24 h (32.5%). The median duration of the hospitalization was 4 days (range: 2–39).

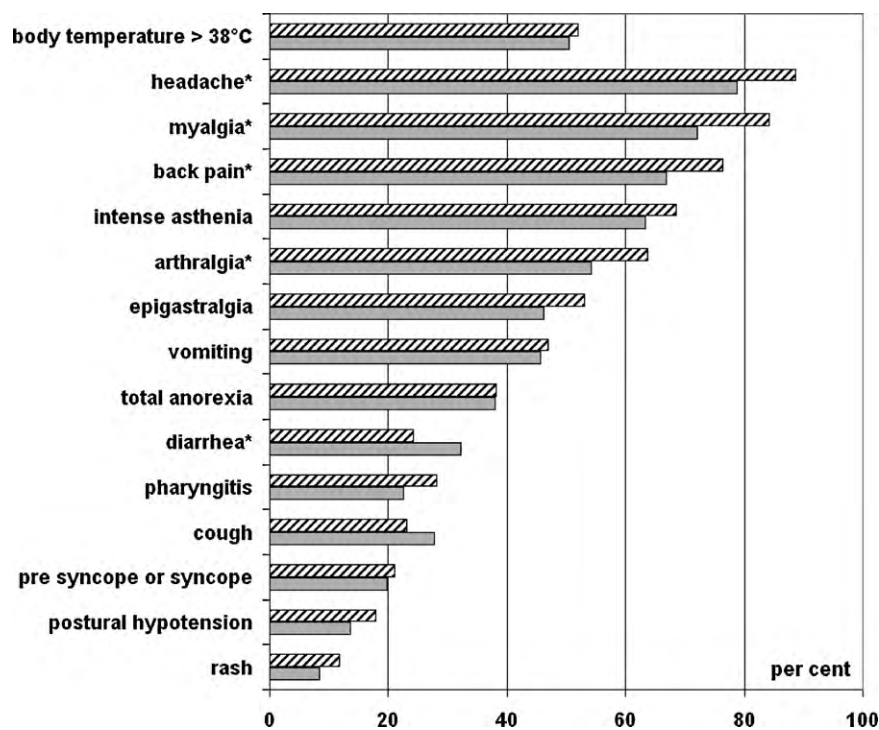


Fig. 2. Basic symptoms recorded in adult dengue patients on admission to the emergency room. Notes: hatched bars, female patients; full bars, male patients; * $p < 0.05$.

Symptômes observés chez les patients adultes atteints de dengue à l'admission aux urgences.

Table 1

Epidemiologic profile and biological data recorded on admission to the emergency department in 560 consecutive adult patients infected by dengue viruses. Profil épidémiologique et biologique enregistré à l'admission aux urgences chez 560 patients consécutifs infectés par les virus de la dengue.

Data (normal limits)	Male (n = 263) Median (range)	Female (n = 297)	P
<i>Epidemiologic profile</i>			
Time from onset to admission (days)	4 (1–9)	3 (1–9)	0.296
Age, (years)	38 (14–91)	35 (15–86)	0.07
DENV-2, n (%)	172/263 (65.4)	191/297 (64.3)	0.657
Secondary infections, n (%)	122/177 (68.9)	149/222 (67.1)	0.747
<i>Biochemistry</i>			
Na, mmol/L (135–145)	136 (121–146)	137 (122–145)	0.055
K, mmol/L (3.5–5.5)	3.9 (2.8–6.4)	3.8 (2.3–5.8)	0.235
Cl, mmol/L (90–105)	97 (78–109)	99 (77–108)	<0.001
RA, mmol/L (22–30)	27 (4.5–36)	26 (4–34)	<0.001
ASAT, U/L (4–37)	69 (13–12770)	57 (13–1159)	0.012
ALAT, U/L (4–50)	47 (4–4340)	38 (6–803)	0.012
Total bilirubin, µmol/L (0–17)	12 (1–94)	8 (2–47)	<0.001
CPK, U/L (20–170)	242 (25–22400)	121 (25–3835)	<0.001
LDH, U/L (219–439)	648 (81–23280)	589 (61–5005)	0.065
CRP, mg/l (0–10)	11.3 (0–387)	12 (0–307)	0.917
Creatininemia, µmol/L (30–115)	96 (43–838)	71 (28–204)	<0.001
Proteinemia, g/L (60–80)	73 (50–101)	74 (50–94)	0.246
<i>Hematology</i>			
Hematocrit, % (36–44)	43 (24–56)	38 (20–49)	<0.001
Hemoglobinemia, g/L (130–170)	150 (87–204)	131 (55–182)	<0.001
Neutrophils, ×10 ⁹ /L (1–7.5)	2.62 (0.25–22.4)	2.26 (0.09–21.8)	0.003
Lymphocytes, ×10 ⁹ /L (1–4)	0.78 (0.03–5.36)	0.77 (0.16–5.18)	0.825
Platelets, ×10 ⁹ /L (140–400)	98.5 (3–351)	120 (8–331)	<0.001
<i>Coagulation</i>			
Prothrombin, % (80–100)	88 (28–100)	87 (38–100)	0.603
APTT, s (24–40)	42 (29–64)	40 (27–63)	<0.001
Fibrinogen, g/L (2–4)	3.2 (1.1–11.3)	3.2 (1.6–8.7)	0.744

3.3. Signs, symptoms, and main biological findings

The frequencies of the basic symptoms recorded on admission to the emergency department are shown in Fig. 2. There was a significant difference between men and women in clinical presentation and in distribution of biological data (Table 1).

3.4. Hemorrhagic manifestations

Various forms of bleeding were observed in 21.3% of men and 19.9% of women ($p=0.68$) (Table 2). Among the patients who bled and who subsequently recovered, bleeding generally stopped before the 9th day following the onset of fever. Hemorrhage was classified as “severe” when it entailed a fall in hemoglobin level of at least 30 g/L or a drop in blood pressure, or brain hemorrhage. Gastro-intestinal hemorrhage included bleeding of gastric origin (duodenal ulcer, one case; Mallory-Weiss syndrome, one case; diffuse gastric hemorrhage, two cases) or of colonic origin (diverticulosis, three cases). The origin was not documented in five cases. Bleeding could be of traumatic origin as wounds or contusion following a fall (three patients), hematuria on a urinary catheter, iatrogenic wound of the femoral artery and vein (hemodialysis catheter), hemorrhagic cerebral contusion, and intraoperative hemorrhage. Nineteen patients received platelet transfusion and five of them a red blood cell transfusion.

However, it should be noted that the guidelines for platelet transfusions were implemented between two epidemics [26].

3.5. Evolution of platelets and other biological variables

Among blood biological abnormalities, platelets, neutrophils, lymphocytes, hepatic transaminases, LDH, and activated partial thromboplastin time (APTT) demonstrated significantly variable kinetics (Fig. 3). Lymphocytopenia developed from day 1 to day 4 (D1–D4). The most important abnormalities of platelet count were observed four to seven days after the onset of fever and resolved during the second week. Monitoring the evolution of severe thrombocytopenia until increase of platelet count in 211 patients determined the median day of the increase to be D7 (range: D4–D12). Platelet counts normalized 2 to 4 days after.

3.6. Plasma leakage syndrome

The retrospective diagnosis of clinical forms depending on the presence of plasma leakage syndrome during the course of the disease is detailed in Table 3. The diagnosis of plasma leakage was based primarily on hemoconcentration (63 cases), hypoproteinemia (13 cases), a pleural effusion and/or ascites (16 cases), or on presentation of pulmonary edema in two patients

Table 2

Hemorrhagic manifestations observed in 560 consecutive adult dengue patients admitted to the emergency department.
Manifestations hémorragiques observées chez 560 patients consécutifs infectés par les virus de la dengue.

Type(s) of bleeding ^a	Localization(s) ^a	Number ^a	Platelet transfusion (n)	RBC ^b transfusion (n)
No bleeding		445	3	
Minor bleeding	Cutaneous (petechiae, ecchymosis)	41	1	
	Mucous (nose, gums, menorrhagia, conjunctival)	78	2	
	Metrorrhagia	27	1	
	Gastrointestinal	7	3	
	Hematuria	4		
	Traumatic (wounds, ecchymosis)	4	2	
Severe bleeding	Gastrointestinal	5	4	3
	Metrorrhagia	2	^c	^c
	Traumatic (wounds, intracranial)	3	3	2

^a Some patients might have several types and/or sites of bleeding.

^b Red blood cells.

^c One patient refused platelet and RBC transfusion.

with cardiac insufficiency. When compared with other patients, patients diagnosed with uncomplicated dengue fever were significantly younger and more often female; the median time from the onset of fever to emergency admission was shorter (2 days [$n = 277$, range: 1–9] against 5 days [$n = 282$, range: 1–8], $p < 0.001$). Patients who subsequently developed a plasma leakage syndrome were older and mostly male and reported more often cough (in 37.6% of patients against 22.7% of patients diag-

nosed with a classic dengue fever; $p = 0.004$). Primary infections were more frequent in the classic dengue fever group than in the DHF/DSS-like group (respectively 118/211 [35.9%] against 10/70 [14.3%], $p < 0.001$). DENV-2 accounted for 75.7% of isolates in the classic dengue fever group and 92.1% of isolates in the DHF/DSS-like group ($p < 0.001$). The multivariate analysis of associations between etiological co-variables (age, sex, serotypes, immune status) and the later onset of a plasma leak-

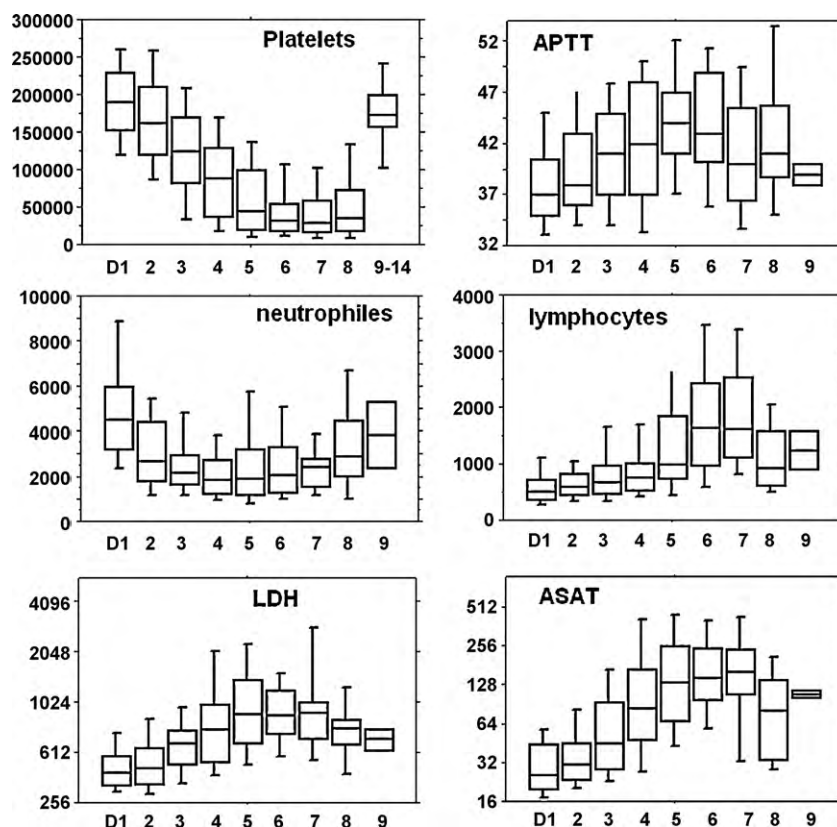


Fig. 3. Distribution of biological data recorded in adult dengue patients according to the time since the onset of fever. Notes: data was recorded on admission to the emergency room, except for platelets which included the follow-up of platelet count in 211 patients. D1 was the day of fever onset. Box plots show median values (horizontal line in the box), 25–75% interquartile range (lower - upper limits of the box), 90% range of data (additional bars).

Distribution de données biologiques enregistrées chez les patients adultes atteints de dengue selon le délai après apparition de la fièvre.

Table 3
Retrospective classification of illnesses and main epidemiologic and biological data recorded on admission time.
Classification rétrospective des maladies et données épidémiologiques et biologiques enregistrées à l'admission.

Illnesses ^a	Age, year, median (range)	M:F ratio	DENV-2, %	Secondary infections, n ^b (%)	Platelets ^c , × 10 ⁹ /L, median (range)	ASAT ^e , U/L, (range)	Time from onset to presentation, day (range)
<i>Plasma leakage^d (DHF/DSS-like), n = 95</i>							
DHF (WHO criteria) ^e , n = 39	43 (17–73)	3.9	79.5	31/32 (96.9)	17 (3–224)	192 (17–12770)	5 (1–8)
DSS (WHO criteria) ^e , n = 10	42 (16–75)	2.3	80	5/7 (71.4)	53 (19–311)	159 (34–2782)	5 (1–8)
Incomplete DHF/DSS ^f , n = 46	45 (16–83)	2.5	67.4	25/32 (78.1)	53 (8–314)	120 (18–1578)	4 (1–7)
<i>No plasma leakage (classic dengue fever), n = 465</i>							
Uncomplicated DF, n = 277	29 (14–78)	0.6	61.7	97/190 (51)	154 (50–351)	33 (13–271)	2 (1–9)
DF with isolated thrombocytopenia ^g , n = 84	44 (16–81)	0.8	66.7	59/62 (95.2)	32 (9–279)	140 (23–439)	5 (1–8)
DF with internal hemorrhage, n = 14	40 (18–76)	0.2 ^h	64.3	9/10 (90)	25 (11–113)	126 (46–572)	5 (3–8)
DF with unusual manifestations, n = 90	42 (15–91)	1	63.3	45/66 (68.2)	110 (8–287)	83 (13–1159)	4 (1–7)

^a Retrospective diagnosis based on data recorded during follow-up.

^b Number of patients with interpretable serology.

^c Data recorded on admission time.

^d Indicated by an hematocrit increased by 20% or decreasing by 20% after 24 h of rehydration and/or a proteinemia less than 50 g/L and/or one or more serous effusions (pleural, ascites) revealed by lung x-ray or in ultrasounds.

^e WHO criteria include acute febrile illness, plasma leakage, hemorrhagic manifestations, platelet count less than 100 × 10⁹/L (DHF) and shock (DSS).

^f Bleeding and/or thrombocytopenia missing.

^g Platelet count less than 50 × 10⁹/L without any other sign of severity.

^h Biased by vaginal bleeding.

age syndrome demonstrated that the DHF/DSS-like group was independently associated with a secondary infection regardless of the infecting serotype (adjusted odds ratio 2.9; 95% confidence interval 1.2–7.2, $p=0.024$). The decrease of platelets below 100 × 10⁹/L and the increase of hepatic transaminases to above five-fold the upper limit of normal were noted to various degrees in all subgroups of patients. Patients included in the DHF/DSS-like group were hospitalized more frequently than patients diagnosed with classic dengue fever (80.6% versus 25%, respectively, $p<0.001$).

3.7. Liver involvement

Acute hepatitis (defined as an increase of aminotransaminases superior to 10-fold the upper limit of normal) was reported in 42 patients (7.9%). The univariate analysis demonstrated that hepatitis was independent of age and sex, and was significantly associated with gastrointestinal symptoms reported at admission time. Among the patients who developed acute hepatitis, 65.9% reported diarrhea, compared to 25.6% in patients without hepatitis ($p<0.001$); in addition, a plasma leakage syndrome was observed more frequently (respectively, 40.5% versus 15.7%, $p<0.001$). Two hundred and eighty-one patients had used self-medication before admission to the emergency room. A maximum dose of acetaminophen greater than 60 mg/kg for at least one day was reported in 31 patients and was more frequently recorded in patients diagnosed with acute hepatitis than in patients without hepatitis (22.6% versus 7.8%, $p=0.006$).

3.8. Patient outcome

Seven patients (1.3%) died from dengue (Table 4). The deaths were mostly related to severe acute organ failure; the organs most often affected were the brain and the liver. The severity of these patients' conditions was clinically visible on admission: seizure and/or coma justifying tracheal intubation and respiratory assistance (Table 4, obs. 1,6,7), massive hepatic cytolysis (Table 4, obs. 3,5), septic shock with multiple organ failure (Table 4, obs. 4), signs of left ventricular failure, diffuse ST-segment abnormalities on EKG, and increased serum troponin-1c levels (Table 4, obs. 2). All the other patients recovered. No death related to DSS was reported. Contrary to other reports [27], we did not observe any death related to co-morbidities in our study. The post dengue syndrome [28] was not studied. All pregnant women carried their pregnancy to term without complications.

4. Discussion

In spite of the endemic presence of all four dengue serotypes, cases of dengue admitted to the emergency department outside of epidemic periods were infrequent. Uncomplicated dengue fever was the most frequent clinical presentation. In comparison with other published results, rash was rarely observed in emergency admissions, probably because of the difficult detection in ethnic melanodermic patients. Plasma leakage syndrome was found in most patients who presented clinical signs of severity. However, the WHO criteria used for the diagnosis of dengue

Table 4
Fatal dengue cases.
Cas fatals de dengue.

Age, sex, date of entry, time from onset to entry	Serotype, immune status	Temp (°C) ^a /AP syst: diast (mmHg)/HR (min)	Platelets ^a × 10 ⁹ /L/fibrinogen (g/L)/prothrombin (%)/ASAT (U/L)	Clinical form	Cause(s) of fatal outcome
Obs. 1, 62 years, F, 9/9/2005, D4 ^b	DENV-2, secondary infection	36/121:95/80	14/2.33/79/453	DHF	Post traumatic intracranial hemorrhage
Obs. 2, 35 years, F, 19/9/2005, D5	Unknown, secondary infection	38.1/102:75/134	134/2.20/83/109	Unusual	Acute myocarditis, refused heart transplant
Obs. 3, 53 years, M, 23/10/2005, D5	DENV-2, secondary infection	39.2/101:54/108	17/2.86/38/12770	DHF	Fulminant hepatitis
Obs. 4, 41 years, F, 17/11/2005, D2	DENV-2, secondary infection	40.1/100:55/130	311/5.98/59/50	DSS	Gangrenous cholecystitis, septic shock
Obs. 5, 63 years, M, 1/8/2007, D4	DENV-1, secondary infection	38.5/125:90/83	4/2.88/68/3203	DHF	Fulminant hepatitis
Obs. 6, 59 years, M, 1/9/2007, D6	DENV-2, unknown	37.7/86:64/110	19/4.37/62/150	DSS	Status epilepticus, inhalation pneumonia
Obs. 7, 65 years, M, 18/10/2007, D6	DENV-2, primary infection	37.9/199:107/106	116/3.51/83/49	DSS	Encephalitis, brain death

Temp, body temperature; AP: arterial pressure; syst: systolic; diast: diastolic; HR: heart rate.

^a Data recorded on admission to the emergency room.

^b Time from the onset of fever (D1) and admission to the emergency room.

hemorrhagic fever were not always present. It should be noted that these criteria were not all systematically screened for. The time-consuming tourniquet test, which is very unpleasant for the patient was not often performed in emergency wards. The specific value of hemoconcentration as a sign associated to a plasma leakage syndrome was not high in patients dehydrated by several days of high fever, uncontrollable vomiting, and food intolerance. The detection of pleural effusion or ascites depended on the sensitivity of the examination used and on its repeated use throughout the course of the disease. As other authors, we were able to observe that ultrasound could sometimes reveal a mild ascites or a small pleural effusion in patients who presented no sign of hemoconcentration [29]. The procedures used to establish the diagnosis of plasma leakage syndrome during dengue and to determine the real incidence of this syndrome in this disease should be validated by prospective multicenter clinical studies [30].

Besides these classical clinical forms, many patients presented with clinical manifestations of variable severity not included in WHO definitions. Sudden syncope usually associated with low orthostatic blood pressure and occurring around the fourth day of fever was a rather frequent motive for emergency admission. Syncope sometimes caused falls and head trauma, all the more worrying that they occurred in thrombocytopenic patients. This scenario was responsible for one death by intracranial hemorrhage. Gastro-intestinal or uterine hemorrhage, sometimes requiring blood transfusion, were observed in patients who presented none of the other WHO criteria for DHF. Severe thrombocytopenia, sometimes lesser than $10 \times 10^9/L$, was confirmed in some patients who presented no other objective clinical sign of severity. Most of the classic and/or atypical

clinical manifestations showed a considerable overlap among the various clinical forms of dengue.

A moderate increase of hepatic enzymes was commonly observed. Two of the seven patients who died presented with fulminant hepatitis. Even if they met all the criteria for DHF, severe acute hepatic insufficiency was responsible for the fatal outcome. Some studies suggested that hepatic damage provoked by the DENV would result more from a direct massive viral infection of hepatocytes and Kupffer cells than from cytokine deregulation [31]. However, emergency physicians observing hepatic cytolysis during dengue should systematically look for an overdose of acetaminophen. A case of reversible fulminant hepatitis due to acetaminophen was observed in a dengue case in Martinique in 1998 (unpublished observation). Warnings about the use of acetaminophen during dengue are given to healthcare professionals and to the Martinique population through information campaigns at the beginning of every epidemic [32]. These recommendations are important since we demonstrated a significant relationship between taking acetaminophen greater than 60 mg/kg per day for at least one day and the later appearance of acute hepatitis in our cohort. A relationship between acetaminophen and hepatic damage during dengue was also reported in French Guyana [33].

Severe acute organ failure was found in every other fatal case: encephalitis, myocarditis, acute respiratory failure, and gangrenous cholecystitis. No deaths were reported in case of DSS according to the WHO definition. However, it is important to underline that these observations were made with adults. DSS remains the most frequent cause of mortality due to dengue in children in Southeast Asia and in Latin America [34,35]. It is also necessary to keep in mind that during the DENV-2 epidemic

in Cuba in 1981, mortality was 15 times higher in children than in adults [36].

Emergency physicians have to triage patients who come to the emergency department with pyrexia. This triage has a critical importance during dengue epidemics when large numbers of febrile and thrombocytopenic patients arrive at the emergency department. During an epidemic, the risk is to attribute any acute febrile illness to dengue and to misjudge bacterial infection (high prevalence of pyelonephritis due to *E. coli* in Martinique), imported malaria (proximity to malaria endemic regions), leptospirosis, even meningitis or pneumonia. Such diagnostic errors can be fatal (unpublished observations).

In case of apparently uncomplicated dengue observed at the onset of the disease, there are no available clinical or biological parameters, which allow predicting a severe form of the disease. The search for reliable predictive signs should be the object of prospective multicenter clinical studies [30]. It was demonstrated a long time ago that thrombocytopenia and an increase in hepatic transaminases were associated with severe forms of the disease [37]. However, clinicians have regularly noticed these abnormalities on the sixth or seventh day of the disease, at a time when most patients begin to feel much better. It is thus very important to correctly assess the chronology of these biological abnormalities in relation to the first day of fever (Fig. 3) and to compare them with other physiological parameters, and to use clinical common sense. The search for early signs of hypo perfusion (decreased pulse pressure, capillary refill time greater than 3 s.) is essential, as well as looking for effusion by ultrasound [38]. If there is any doubt, the patient must be kept in observation, to measure blood lactate, and be reevaluated after a few hours of intravenous rehydration. The systematic use of an isotonic aqueous crystalloid solution drip brought dramatic improvement to the great majority of patients at the emergency department. An early rehydration, oral if possible otherwise intravenous, is recommended in every case (expert consensus), on the condition that the risk of fluid overload and pulmonary edema in patients with increased vascular permeability was assessed [4].

The clinical experience acquired while following this cohort, in particular after the analysis of the 2005 epidemic [8], allowed us to implement specific case management protocols. The study of evolutionary profiles allowed us to elaborate a strategy for patients with severe thrombocytopenia. The indications for platelet transfusion in adults were defined, avoiding unnecessary transfusion and sparing blood bank resources [26]. The number of thrombocytopenic patients hospitalized was limited by the implementation of ambulatory follow-up in the outpatient clinic or at home. Finally, this clinical experience allowed us to define the basis for a descriptive multicentre study of dengue in Guadeloupe, Martinique, and French Guyana. Indeed, it seems necessary to extend the descriptive analysis of clinical forms of dengue to pediatric forms and to assess the incidence of severe forms. During the last 4 years, Martinique was mainly affected by serotypes 2 and 4. The clinical data collected during this period and presented in this study does not allow to predict what might be observed in children and adults in the next epidemic, notably with serotype 1 which features some specificities [39]

and which has rarely circulated in Martinique in the last 10 years [22].

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