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Background. Dengue, although endemic in Puerto Rico, is often not mentioned in the death certificates of decedents with laboratory results positive for dengue. Because confirmatory results are usually not available during hospitalization, we examined the utility of 2 instruments for diagnosis on the basis of clinical findings: the definition of dengue hemorrhagic fever (DHF) and the publicized (but unevaluated) clinical alarm signals for impending dengue shock.

Methods. We studied data from all patients with laboratory test results positive for dengue who died (23 patients) and from the 8 patients whose death certificates listed dengue as a cause of death but whose laboratory test results were negative for dengue in Puerto Rico from 1992 through 1996. We examined hospital records to determine whether the clinical criteria for DHF were fulfilled and evaluated the incidence and timing of clinical alarm signals (intense, sustained abdominal pain; persistent vomiting; sudden change from fever to hypothermia; and marked restlessness or lethargy) and the hematocrit/hemoglobin ratio as an indicator of hemoconcentration.

Results. A similar proportion of patients with laboratory test results positive for dengue (18 [78%] of 23) and negative for dengue (6 [75%] of 8) fulfilled the criteria for DHF. Clinical alarm signals were found only among patients with laboratory test results positive for dengue and were usually noted on the day that the patient’s condition deteriorated. The hematocrit/hemoglobin ratio identified 1 (6%) of 16 patients with dengue who had significant hemoconcentration. Important comorbidities were present in 16 (70%) of the patients with laboratory test results positive for dengue and in 4 (50%) of the patients with dengue-related deaths with laboratory test results negative for dengue.

Conclusions. Dengue-related deaths in Puerto Rico often occur in patients with comorbidities. Among such patients, the DHF definition and the hematocrit/hemoglobin ratio were not useful in identifying patients with laboratory test results positive for dengue. In contrast, the clinical alarm signals for shock supported the dengue diagnosis and should alert clinicians to the severity of the disease.
nderstand the discrepancy between physician and laboratory diagnoses, we conducted a review of the clinical information available for dengue-associated deaths with laboratory test results positive for dengue and selected suspected dengue-related deaths with laboratory test results negative for dengue from 1992 through 1996. In addition, we evaluated the 4 alarm signals for impending DSS developed from clinical experience in epidemics in the Americas (intense, sustained abdominal pain; persistent vomiting; sudden change from fever to hypothermia; and marked restlessness or lethargy) and the utility of the hematocrit/hemoglobin ratio as an indicator of hemoconcentration, proposed as the result of experiences reported from Venezuela [4, 5]. The widespread use of these signals indicating the need for prompt therapy (i.e., the aggressive use of intravenous fluids to rapidly improve blood pressure and tissue perfusion) would presumably help in the reduction of dengue-related mortality; however, there is no published evaluation of their utility.

METHODS

Laboratory-based surveillance. The Dengue Branch of the CDC receives blood samples for dengue diagnosis from throughout Puerto Rico [6]. The laboratory methods used for dengue virus isolation and anti-dengue IgM and IgG antibody detection have been described elsewhere [1, 6–11]. The measurement of IgM antibody may fail to diagnose ∼5% of secondary dengue infections, so specimens with borderline results by IgM antibody capture ELISA were tested by IgG ELISA in an attempt to confirm the diagnosis by detection of an amnestic antidengue antibody response [12]. Specimens from which a dengue virus was isolated were also evaluated with IgG ELISA to determine whether the patient’s infection was primary (i.e., the first dengue infection) or secondary (i.e., a new infection with a different serotype) on the basis of the presence of IgG antibody in the acute-phase serum sample or high IgG titers in the convalescent-phase serum specimen, as specified below.

Laboratory confirmation of a current dengue virus infection was based on dengue virus isolation from serum or autopsy tissue samples or on demonstration of dengue antigen in autopsy tissue samples by immunofluorescence or immunohistochemical analysis (IHC) [13, 14]. Patients with probable cases of dengue were defined as those individuals from whom a single serum sample was submitted which was IgM positive or had who an antibody titer by IgG ELISA of ≥163,840. These cases were only considered to be probable, because the patients may have had dengue within the past 3 months (IgM may be detectable for ≥90 days after infection), and the symptoms at the time of blood sample collection may have been due to an illness other than dengue [12]. Unless otherwise stated, patients with probable and confirmed cases are considered together as patients with laboratory test results positive for dengue. For specimens collected ≥6 days after onset of symptoms, the absence of IgM antibodies ruled out the diagnosis of dengue, and the patient was considered to have laboratory test results negative for dengue. Single acute-phase serum specimens negative for dengue virus and for IgM were considered to be nondiagnostic, and the patient was categorized as having indeterminate laboratory test results.

Clinical case classification. A reported case of dengue was defined as occurring in a person with an illness that prompted a health care provider to submit a specimen for dengue diagnosis. The vital status of the patients was obtained from the form that accompanied diagnostic samples and from the report on hospitalized patients with suspected dengue provided through the voluntary collaboration of many infection-control nurses at hospitals throughout Puerto Rico. Death certificates that list dengue as a cause of death are routinely provided by the Vital Statistics Office (Registro Demográfico and Oficina de Desarrollo de Sistemas de Información, Puerto Rico Department of Health) as part of its procedures for confirmation of rare causes of death. A suspected dengue-related death refers to a fatal outcome notified through any of the 3 mechanisms (case form, infection-control nurse report, and death certificate). Dengue-attributed death refers to a fatal case in which dengue was identified as a cause of death on the death certificate.

A case of DHF was identified according to strict application of the World Health Organization and Pan American Health Organization guidelines and fulfilled all of the following criteria: fever (or recent history of acute fever), any hemorrhagic manifestation, thrombocytopenia (≤100,000 platelets/mm³), and evidence of plasma leakage due to increased vascular permeability. The latter was documented by hemoconcentration (hematocrit increased above baseline by ≥20% or decreased an equivalent amount after receipt of intravenous fluid therapy), pleural or abdominal effusion (by radiography or other imaging method), or hypoalbuminemia or hypoproteinemia [15]. The World Health Organization and Pan American Health Organization definition requires that cases of DSS meet all of the DHF criteria, “plus evidence of circulatory failure manifested by rapid and weak pulse, and narrow pulse pressure (≤20 mm Hg) or hypotension for age, cold, clammy skin and altered mental status” [15, p. 40]. To use objective measures in our record review, we defined cases of DSS as meeting all DHF criteria and showing hypotension, narrow pulse pressure (≤20 mm Hg), or frank shock.

Record review. We reviewed the hospitalization records for all patients who died with laboratory test results positive for dengue and all patients with dengue-attributed deaths who had laboratory test results negative for dengue. Because the records belonged to deceased individuals, the research was exempt from

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in institutional review regarding human subject participation in research. We extracted information on clinical and laboratory test results and the course of illness, especially the terminal events. We considered any coexisting disease or disability that could affect the development and outcome of the illness episode by debilitating the patient, producing additional symptoms, or enhancing the usual manifestations of dengue to be a clinically significant comorbid condition. The utility of hematocrit/hemoglobin ratio as determined from a single blood sample for confirming significant hemoconcentration was established by comparing that ratio to the relative magnitude of hematocrit change. We calculated the hematocrit/hemoglobin ratio for samples obtained at admission and at maximum and minimum hematocrit (if the maximum or minimum hematocrit occurred at a point other than at admission). A ratio of samples obtained at admission and at maximum and minimum change. We calculated the hematocrit/hemoglobin ratio for confirming significant hemoconcentration was established by comparing that ratio to the relative magnitude of hematocrit change. We calculated the relative magnitude of change in hematocrit by the formula (maximum hematocrit − minimum hematocrit) × 100/minimum hematocrit. A change of ≥20% was considered to be significant. Clinical alarm signals were noted as present if the hospital record noted intense abdominal pain, repeated vomiting, marked change in temperature within a 24-hour period, or an abnormal mental status. The interval to deterioration was defined as the number of days from the first mention of the alarm signal to hypotension, respiratory failure, or onset of coma.

**RESULTS**

We documented 104 suspected dengue-related deaths in Puerto Rico for the 5-year period from 1992 through 1996. Laboratory test results were positive in 23 (22%) of the cases, negative in 31 (30%), and indeterminate in 31 (30%), and no sample was submitted in 19 (18%). The case-fatality ratio over the 5-year period was 1.6 deaths per 1000 cases with laboratory test results positive for dengue (23 deaths among 14,478 cases). The patients with positive laboratory test results included 13 female subjects and 10 male subjects with a median age of 21 years (range, 7 months to 80 years). The cause of death given on the death certificate was stated as dengue for 1 patient and DHF for 10 patients (i.e., 11 deaths were attributed to dengue). Non-dengue diagnoses were given for 12 patients, of which only 2 involved specific etiologies (meningococcemia and staphylococcal bacteremia); the rest of the diagnoses were clinical syndromes, including hepatic or respiratory failure, sepsis, or cerebral infarction. The cases of 10 (43%) of the patients who died who had laboratory test results positive for dengue were documented during the 1994–1995 epidemic. Eight dengue-attributed deaths with negative laboratory test results were identified (4 in female subjects and 4 in male subjects). The median age among these 8 patients was 44 years (range, 21–77 years), and all had dengue (5 patients) or DHF (3) listed as a cause of death on the death certificate. Eight (35%) of the 23 patients with positive test results and 2 (25%) of the 8 patients with negative test results underwent autopsy. In all autopsies, gross findings were consistent with the clinical diagnoses given on the death certificate (e.g., pulmonary hemorrhage) without providing etiologic diagnosis (except for the bacterial culture results noted below).

**Dengue diagnoses.** Seven (30%) of the 23 patients with laboratory test results positive for dengue were confirmed to have dengue infection (3 with dengue virus serotype 1 [DEN-1], 2 with DEN-2, 1 with DEN-4, and 1 with positive results by IHC). All DEN-1 infections were primary, both DEN-2 infections were secondary, serological testing did not clarify whether the DEN-4 infection was primary or secondary, and only autopsy tissue was available for testing for the patient whose case was confirmed by IHC. There were 16 probable cases of dengue, which were diagnosed because of clear elevations of IgM antibody. The standard for positive results in our laboratory is an optical density reading of >0.20 U, and the range of optical density results for these 16 patients was 0.22–1.76 U. Three patients had optical density readings of <0.40 U and had samples obtained on days 1–3 after onset of symptoms, so that the low positive readings must be considered to be a rapid antibody response, given the early time of sample collection.

**Record review.** Among the 23 patients with positive laboratory test results, 16 (70%) had clinically significant comorbid conditions (table 1). Four fatal laboratory-confirmed cases (documented during the 1994–1995 epidemic) were associated with the following additional medical conditions: receipt of a bone marrow transplant (DEN-4 infection), head trauma after onset of dengue symptoms (DEN-2 infection), newly diagnosed diabetes with ketoacidosis (in a patient with positive IHC results), and a history of idiopathic thrombocytopenic purpura 8 years before the final admission to the hospital (DEN-1 infection). The first 3 patients underwent autopsy. Seven patients with probable cases of dengue had other severe, well-documented acute diagnoses or laboratory results positive for the following conditions: perimyocarditis diagnosed by electrocardiogram and doppler echocardiography, acute cerebrovascular accident (sudden left hemiplegia, possibly due to, but not specifically identified as, a hemorrhagic manifestation of DHF), newly diagnosed diabetes with ketoacidosis, *Salmonella*-related gastroenteritis, *Neisseria meningitidis* in CSF samples, *Staphylococcus aureus* bacteremia, and group C β-hemolytic *Streptococcus* bacteremia in a patient with chronic obstructive pulmonary disease, alcoholic hepatitis, and pneumonia. In an additional 5 patients with probable cases of dengue, the medical record indicated the following severe underlying conditions: gastritis; being bed-
ridden for 2 years because of arthritis; arrhythmia and mental retardation; nephrotic syndrome, asthma, and mental retardation; and trisomy 21. One-half (6) of the patients with probable cases of dengue who had comorbidities were detected during the 1994–1995 epidemic. The 7 patients with laboratory test results positive for dengue who had no comorbidities included all 4 infants (age, <1 year) and 3 adults. The median interval from hospitalization to death for patients with laboratory test results positive for dengue was 3 days (range, 0–21 days). Seven (30%) of the patients died within 24 h after admission to the hospital.

Eight dengue-attributed deaths in patients with negative laboratory test results were identified. Seven of these patients were febrile, and all had low platelet counts at admission to the hospital (range, 16,000–85,000 platelets/mm$^3$; median platelet count, 60,000 platelets/mm$^3$). Four patients had jaundice and renal failure (2 of them had pulmonary hemorrhage documented by autopsy, and in 2 others, pulmonary hemorrhage was clinically suspected), 1 patient had bleeding esophageal varices, and 1 patient had uncompensated congestive heart failure. Four patients had clinically-significant comorbid conditions; these were alcohol abuse, heart disease and epilepsy, systemic lupus, and hypertension. The median interval from hospitalization to death was 4.5 days (range, 0–10 days). One (12%) of these patients died within 24 h after admission to the hospital.

The proportion of patients with DHF listed on the death certificate was similar in the group with positive laboratory test results (10 [44%] of 23) and in the group with negative laboratory test results (3 [38%] of 8), whereas hospital record data showed that similar proportions of patients with positive laboratory test results (18 [78%] of 23 patients, including 8 with DHF and 10 with DSS) and negative laboratory test results (6 [75%] of 8 patients, including 5 with DHF and 1 with DSS) fulfilled the clinical criteria for DHF.

Of the 31 patients, 29 had ≥2 hematocrit and hemoglobin measurements reported in the hospital record, and 23 patients (16 of 23 with positive laboratory test results and 7 of 8 with negative laboratory test results) had an increase or decrease in the hematocrit (after intravenous fluid administration) of ≥20%. Only 2 patients had a hematocrit/hemoglobin ratio that was considered to be suggestive of hemoconcentration; these included a patient with DEN-4 infection, with a change in the hematocrit of 29% and a hematocrit/hemoglobin ratio of 3.21 for the sample obtained at admission to the hospital, and a dengue-negative patient with a change in the hematocrit of 76% and a hematocrit/hemoglobin ratio of 3.41 for the sample obtained at admission to the hospital. Therefore, the hematocrit/hemoglobin ratio identified only 1 (6%) of the 16 patients with dengue who had significant hemoconcentration (defined by hematocrit change).

**Clinical alarm signals.** The clinical alarm signals of impending DSS were found only among patients with positive laboratory test results and, when present, were usually noted on the day that the patient’s condition deteriorated (table 2). Although abnormal mental status shortly before death was documented with equal frequency among dengue-positive and dengue-negative patients (~60% in each group), it was present at admission to the hospital only among patients with laboratory test results positive for dengue infection. One patient had a change in temperature from 38.6°C to 36.1°C in a <8-h period (between nursing shifts). Two patients had both severe abdominal pain and vomiting, and 1 patient had severe abdominal pain and abnormal mental status at admission to the hospital. Eleven (48%; 95% CI, 27%–69%) of the 23 patients with laboratory test results positive for dengue infection showed any of these signals, and 5 of these patient had confirmed cases of dengue (3 had DEN-1 infection, 1 had DEN-4 infection, and 1 had infection confirmed by IHC).

### Table 1. Diagnostic laboratory test results for dengue, presence of comorbidities, and attribution of dengue as a cause of death on the death certificate, Puerto Rico, 1992–1996.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Laboratory test results positive for dengue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirmed dengue (n = 7)</td>
</tr>
<tr>
<td>Attributed to dengue</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>No. of patients</td>
<td>4</td>
</tr>
<tr>
<td>Age range</td>
<td>41–77 years</td>
</tr>
</tbody>
</table>

| Unattributed to dengue* | Comorbidities | No comorbidities |
| No. of patients | ... | ... |
| Age range | 6–21 years | ... |
| Total no. of patients | 4 | 4 | 4 | 3 | 12 | 4 | 31 |

* Death certificates that do not mention dengue are not forwarded to the dengue surveillance system for verification.
Table 2. Frequency and onset of clinical alarm signals for impending dengue shock in patients with fatal cases of dengue, Puerto Rico, 1992–1996.

<table>
<thead>
<tr>
<th>Clinical alarm signal</th>
<th>Patients with clinical alarm signal, by laboratory test results for dengue</th>
<th>Time from clinical alarm signal to deterioration of the patient’s condition, median days (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion of patients</td>
<td>Percentage (95% CI)</td>
</tr>
<tr>
<td>Severe abdominal pain</td>
<td>0/8</td>
<td>0 (0–37)</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>0/8</td>
<td>0 (0–37)</td>
</tr>
<tr>
<td>Abrupt change in temperature</td>
<td>0/8</td>
<td>0 (0–37)</td>
</tr>
<tr>
<td>Abnormal mental status⁴</td>
<td>At admission</td>
<td>0/8</td>
</tr>
<tr>
<td></td>
<td>Shortly before death</td>
<td>5/8</td>
</tr>
</tbody>
</table>

⁴ Disoriented, combative, or obtunded.
⁵ One patient was sedated for mechanical ventilation, and mental status was not evaluable.

**DISCUSSION**

Dengue case series reported from other countries have previously identified severe concurrent infections, and we have also reported fatalities in Puerto Rico among patients with laboratory test results positive for both dengue and leptospirosis [1, 16–20]. Our study revealed, in addition, that after infancy, dengue is often present simultaneously with other life-threatening conditions. Seventy percent of dengue-related deaths among patients with laboratory test results positive for dengue were associated with clinically significant comorbidities. The small proportion of fatalities (30%) due exclusively to dengue may in part be explained by the health care infrastructure of Puerto Rico (with abundant hospital beds throughout the island) and by the efforts to educate medical professionals concerning dengue diagnosis and management that have been performed since the 1980s, but this may also be attributable to the age distribution of patients with dengue in Puerto Rico (whose median age is 21–22 years) [1, 3, 6].

It is likely that more deaths due to dengue occurred during the period of our study than are included in this analysis. Previous reports have underscored the difficulty of obtaining a confirmatory diagnosis for fatal cases of dengue and for fatal cases due to other infectious causes [21–24]. A microbiologic diagnosis of dengue can usually be obtained through virus detection or IgM antibody measurement, because tissue examinations and titer comparisons in paired serum samples, although possible, are not performed in most reference laboratories. A diagnosis of dengue can only be ruled out by serologic test results obtained (if the patient survives) at least 6 days after onset of illness.

Clinicians must struggle at the patient’s bedside with the reality that the clinical presentation of dengue may mimic that of other diseases and that the diagnosis of dengue does not exclude other conditions. Most patients recover (and some die) before a definitive dengue diagnosis can be provided by the laboratory (28 [90%] of the 31 patients studied here were hospitalized ≤7 days before death). A recent analysis of risk factors for concurrent bacteremia in adults with DHF recognized acute renal failure and temperature >38°C for >5 days as independent risk factors for dual infection [19]. An accurate determination of the primary cause of death in these cases will depend on the diagnostic skills and medical resources available for patient testing and pathologic investigation [25]. These social and infrastructural requirements affect patient management, disease survival, and the health statistics of countries in which dengue is endemic.

In that context, it is important to evaluate the symptoms, signs, and laboratory data that are proposed as useful in the diagnosis of severe dengue. Among patients with fatal cases, ∼75% fulfilled the criteria for DHF (even among the patients with negative laboratory test results). This suggests limited utility in providing diagnosis for patients with near-terminal cases or in the presence of competing diagnoses with similar manifestations. The hematocrit/hemoglobin ratio identified only 1 (6%) of the 16 patients with dengue who had significant hemoconcentration. A large cross-sectional study of pediatric patients with dengue in Colombia also found that the hematocrit/hemoglobin ratio was not a useful indicator of significant hemoconcentration [26]. Our evaluation of the 4 alarm signals for DSS by comparing patients who had dengue with patients who did not have dengue showed that the signals were only noted in patients with laboratory test results positive for dengue, and at least 1 signal was noted in 11 (48%) of these patients. Severe abdominal pain and an abnormal mental status at admission to the hospital were the 2 signals most frequently observed (in 26% and 17% of patients, respectively). This is consistent with findings from pediatric populations in Cuba and Colombia [23, 26].
The prominence of clinical alarm signals detected in this small study of only the most-severe cases of dengue suggests that they are common findings. Their presence was documented late in the course of the disease, but through this retrospective review, we were unable to determine whether the timing of the identification of these alarm signals could affect the outcome of severe dengue disease. A prospective study is required to evaluate the sensitivity, specificity, and utility of these signals, not only among patients with fatal cases (rare in any hospital or country in the Americas), but also among patients with positive and with negative laboratory test results for dengue who have cases of varying severity.

Our evaluation found that dengue-related deaths in Puerto Rico may have a complex clinical history with associated comorbidities, a pattern that may also apply to other countries in the Americas that have a broad age distribution among patients with dengue. Clinicians must be alert to the possibility of concurrent illnesses, especially when patients are elderly or when antibiotic therapy may be beneficial [19, 27]. Although only fatal cases were included in this study, our findings suggest that, among patients with suspected cases of dengue, the clinical alarm signals support a dengue diagnosis and should alert health care providers of the severity of the disease and the potential for fatal outcome.

Acknowledgments


References