Hemostatic Changes in Vietnamese Children with Mild Dengue Correlate with the Severity of Vascular Leakage Rather than Bleeding

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Abstract. The mechanisms underlying the bleeding manifestations and coagulopathy associated with dengue remain unclear, in part because of the focus of much previous work on severe disease without an appropriate comparison group. We describe detailed clinical and laboratory profiles for a large group of children with dengue of all severities, and a group with similar non-dengue febrile illnesses, all followed prospectively from early presentation through to recovery. Among the dengue-infected patients but not the controls, thrombocytopenia, increased partial thromboplastin times and reduced fibrinogen concentrations were apparent from an early stage, and these abnormalities correlated strongly with the severity and timing of vascular leakage but not bleeding. There was little evidence of procoagulant activation. The findings do not support a primary diagnosis of disseminated intravascular coagulation to explain the intrinsic coagulopathy. An alternative biologically plausible hypothesis is discussed.

INTRODUCTION

During the latter half of the twentieth century dengue emerged as a major public health problem for the tropical world.1 The frequency of epidemics increased, severe disease became increasingly common, and the virus and its mosquito vectors began spreading to new geographic locations.2,3 Globally, dengue now ranks among the most important viral infections affecting humans. Infection may be asymptomatic or may lead to a spectrum of clinical disease patterns ranging from undifferentiated fever to dengue fever (DF), dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS).4 Although adults may experience serious complications the burden of severe disease falls mainly on children,5,6 and in many countries in Asia dengue ranks among the leading causes of hospitalization and death for the pediatric population. The pathognomonic feature of DHF is an increase in systemic vascular permeability resulting in reduced intravascular plasma volume, with progression to hypovolemic shock in severe cases. However, the pathologic process reverses spontaneously after a few days and most patients recover with appropriate supportive care.5,7 Thrombocytopenia and coagulopathy are also prominent features of symptomatic infection. In children, minor hemorrhagic manifestations are commonly observed but major bleeding is unusual except in association with profound shock.8,9

The pathogenesis of hemorrhage associated with dengue infection remains poorly understood, and there are conflicting opinions as to whether disseminated intravascular coagulation (DIC) occurs, and whether fibrinolysis is activated or impaired.9,14 Most studies to date have enrolled relatively small patient numbers, often focusing on subjects with severe disease in whom secondary dysfunction of multiple organ systems likely confounds results. There have been few studies documenting serial changes in hemostatic parameters across the whole disease spectrum as the clinical manifestations evolve over time. Finally, most groups have used the current World Health Organization (WHO) classification system for assessment of severity. It is becoming increasingly apparent that there is overlap between the various diagnostic categories defined by this system and that classification of individual patients is not always straightforward.15–17 In addition, use of the WHO system precludes examination of potentially important relationships between individual criteria, such as bleeding or vascular leakage, and the parameters of interest. Documentation of the natural history of the disease, together with increased efforts to understand the underlying mechanisms predisposing to hemorrhage, are becoming more important as the significance of dengue increases globally: early development of thrombocytopenia or coagulation disturbances may be predictive of subsequent complications; in certain parts of the world prophylactic platelet transfusions are given, and it is essential that the rationale for such transfusions is assessed critically before this becomes established practice18; and finally, better knowledge of disease pathogenesis may allow the development of novel therapies for patients who do experience severe bleeding. We conducted a systematic study of a large cohort of children with suspected dengue infection, following them prospectively from presentation in the early febrile phase through to recovery. In addition to showing the evolution of the coagulopathy, we focused on studying relationships between hemostatic abnormalities and the severity of vascular leakage and bleeding assessed independently.

METHODS

Patients and clinical methods. Previously healthy children, 2–15 years of age, admitted to one of the infectious disease wards at the Hospital for Tropical Diseases of Ho Chi Minh City with fever of short duration and clinically suspected dengue were eligible for enrollment into the study provided a parent or guardian gave informed consent. The nature of the local healthcare system means that children with relatively mild disease are frequently admitted to the hospital for observation rather than managed at home. Ethical approval for the study was obtained from the Scientific and Ethical Committee of the hospital.

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For confirmation of dengue infection, paired plasma samples were tested using Dengue Duo IgM and IgG Capture ELISA kits (Panbio, Australia), interpreted according to the manufacturer’s instructions. Reverse transcription-polymerase chain reaction (RT–PCR) was also carried out on acute samples from patients with negative or indeterminate serology, according to the method of Lanciotti and others.19

**Statistical analysis.** Data on patient characteristics and laboratory results were compared between different groups using the χ² test for categoric variables and the Kruskal-Wallis test for continuous variables, with Spearman’s correlation and the Cuzick test for trend where appropriate. Data are presented according to the vascular leak category (A–D) and grouped by day of illness into early (Day 1–3), critical leak period (Day 4–6), convalescent (Day 7–10), and follow-up (1 month) values. Comparisons between results obtained from the same patient at different time points were performed using the Wilcoxon signed-rank test. All statistical computations were carried out using SPSS (version 14, SPSS, Inc., Chicago, IL) or STATA (version 8) software.

**RESULTS**

Between August 2002 and January 2004 a total of 431 children with symptoms of a viral syndrome thought likely to be dengue were recruited into the study. All the children recovered completely and 50% attended for follow-up after 1 month. Three hundred seventy-five patients were confirmed serologically to have had acute dengue infection. Forty patients who had exclusively negative serology and PCR, and recovered without antibiotic therapy, were considered to have had prior febrile illnesses (OFI), most likely viral in origin although no further diagnostics were available. The remaining 16 patients had indeterminate serology and negative PCR.

There were limited clinical and/or laboratory data available for eight of the confirmed dengue-infected patients, but all others were classified for the overall severity of vascular leakage, as described previously. Summary data for these patients and the children with OFI were basically similar (Table 1). Children with confirmed dengue who went on to develop shock presented a little later than other patients (P = 0.02). All were identified at an early stage when in compensated shock and recovered rapidly with standard treatment. As expected, patients with shock received considerably more parenteral fluid therapy than other groups, and those without shock received progressively more intravenous fluid as the severity of hemoconcentration increased (P < 0.01). Bleeding was more common (P < 0.001) in the confirmed dengue patients when compared with the OFI group, largely as a result of minor skin bleeding in the dengue group. Bleeding was also more common in the dengue-infected patients with shock than those without (P < 0.001). Only one child experienced clinically significant bleeding, developing melaena and a notable drop in hematocrit after shock resuscitation, but made a good recovery without transfusion. Hemorrhagic manifestations were similar across the three vascular leak categories without shock; mucosal bleeding was relatively infrequent in all three groups and in most cases amounted to minor epistaxis or gum bleeding only.

**Coagulopathy.** Results of the serial coagulation tests for the dengue-infected children are shown in Table 2, showing within-patient changes over time in each leakage category.
Figure 1, shows the differences between the leakage categories within each time period. The APTT results were significantly prolonged during the early febrile period, peaked during the critical period, and were improving by the convalescent period, both within the individual vascular leak categories (Table 2) and with a trend toward higher values with increasingly severe leak (Cuzick test $P < 0.001$ for the critical period and 0.03 for the convalescent period, Figure 1). Fibrinogen concentrations were significantly depressed during the critical period and remained so in convalescence, and also with consistent patterns within (Table 2) and across the vascular leak groups (Cuzick test $P < 0.001$ for the critical period, and 0.01 for the convalescent period, Figure 1). Although patients with more severe vascular leakage received proportionately more parenteral fluid therapy overall, there was no relationship between fibrinogen concentrations and the volume of fluid received each day (data not shown), excluding the possibility of a purely dilutional effect. There were highly significant negative correlations between APTT and fibrinogen (Spearman correlation of 0.2, $P < 0.001$ for the early and critical periods and $< 0.001$, 0.03 for the convalescent period) during the acute illness but not at follow-up.

The PT values were marginally increased during the early febrile period in some but not all leak categories, with a relatively weak trend association (Cuzick test, $P = 0.03$). Overall however, the PT abnormalities demonstrated were minor, and were not distinct from those seen in the OFI group at this time. For the critical period, correlations with percentage haemoconcentration as a continuous variable rather than by leak category confirmed a highly significant association with APTT (Spearman correlation of 0.3, $P < 0.001$) and fibrinogen (Spearman correlation of 0.2, $P < 0.001$), and a weaker association with PT (Spearman correlation of 0.2, $P = 0.01$). In addition, a significant correlation between PT and APTT was apparent for each time period (Spearman correlation of 0.2–0.3, $P < 0.01$), but this relationship was maintained in the follow-up samples (Spearman correlation of 0.2, $P = 0.01$) indicating that at least in part this reflects normal hemostatic balance.

Results for the OFI group were similar for each time period to the follow-up values in both OFI and dengue-infected patients (Figure 1), and corresponded with the expected normal ranges for these parameters. Positive FDPs, in general weakly rather than strongly positive, were noted in up to 10% of follow-up samples and around 20–25% of acute samples, although reaching 45% in dengue group C during the critical period. There were no associations between positive FDPs and either vascular leak or bleeding severity. In addition, no associations or trends were demonstrated between bleeding severity and any of the other coagulation tests at any time.

**Thrombocytopenia.** Thrombocytopenia was evident in all dengue-infected patients, and the serial platelet counts were helpful in differentiating these children from those with OFI (Table 2). In the children with dengue the platelet count dropped progressively from Day 2 onward, with a median (90% range) nadir of 54,000/mm$^3$ (16,000 – 142,000), occurring in most cases on Day 6. By comparison, patients with OFI showed only mild thrombocytopenia, median (90% range) nadir of 169,000/mm$^3$ (52,000 – 296,000), usually on Day 3 of illness, with only minor changes over time. A platelet count of 100,000/mm$^3$ or less was recorded at some point in 311/367 (85%) of the dengue patients compared with 4/40 (10%) of the OFI group, and in 24% of the dengue group the lowest recorded value was 30,000/mm$^3$ or below. No patient received any blood products, and recovery of the platelet count was as rapid as the decline.

A strong association between platelet count and severity of vascular leak is shown in Figure 1. There was an obvious trend to increasing thrombocytopenia with increasing vascular leakage, and this was apparent even in the early febrile phase before the development of hemococoncentration (Cuzick test, $P < 0.001$ for early, critical, and convalescent periods). In contrast, the associations between platelet count and severity of bleeding were much weaker (Cuzick test, $P = 0.03$ for the critical and 0.04 for the convalescent periods). The platelet nadir was 56,000/mm$^3$ on Day 6 in the one child with significant mucosal bleeding, with recovery to 100,000/mm$^3$ by Day 8.

**Tourniquet test.** The tourniquet test was positive in 270/365 (74%) of dengue-infected patients as compared with 13/40 (33%) of children with OFI ($P < 0.001$). In the dengue group, 52% were positive on the first test but 26% required testing for 3 or more days before a positive result was seen. Those who had a positive test at any time were more likely to manifest some other evidence of bleeding ($P < 0.001$), and there was an association with the maximum recorded APTT (median and 90% range of 35 [32–47] seconds in consistently negative patients, versus 36.5 [32–48] seconds in those with a

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**Table 1**

Demographic and selected clinical information for the children with confirmed dengue and those with other febrile illnesses (OFI)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OFI (N = 40)</th>
<th>Group A: no haemoconcentration (N = 112)</th>
<th>Group B: mild haemoconcentration (N = 112)</th>
<th>Group C: significant haemoconcentration (N = 110)</th>
<th>Group D: developed shock (N = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12 (6–14)</td>
<td>11 (7–14)</td>
<td>12 (7–14)</td>
<td>12 (7–14)</td>
<td>12 (7–14)</td>
</tr>
<tr>
<td>Male sex</td>
<td>23 (58)</td>
<td>58 (52)</td>
<td>59 (53)</td>
<td>64 (58)</td>
<td>15 (46)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>30 (20–56)</td>
<td>33 (20–54)</td>
<td>32 (20–51)</td>
<td>34 (21–61)</td>
<td>31 (21–49)</td>
</tr>
<tr>
<td>Day of illness on admission</td>
<td>3 (1–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>35 (90)</td>
<td>44 (39)</td>
<td>53 (48)</td>
<td>47 (43)</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Skin only</td>
<td>2 (5)</td>
<td>57 (52)</td>
<td>46 (41)</td>
<td>45 (41)</td>
<td>18 (56)</td>
</tr>
<tr>
<td>Mucosal (any site)</td>
<td>2 (5)</td>
<td>10 (9)</td>
<td>12 (11)</td>
<td>17 (16)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Severe mucosal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total parenteral fluid volume</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>received (mL/kg)‡</td>
<td>25 (12–98)</td>
<td>26 (11–83)</td>
<td>37 (11–102)</td>
<td>42 (12–127)</td>
<td>160 (91–300)</td>
</tr>
<tr>
<td><strong>Hospital stay (days)</strong></td>
<td>7 (5–11)</td>
<td>6 (4–9)</td>
<td>6 (4–8)</td>
<td>7 (4–9)</td>
<td>7 (5–9)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) or median and 90% range
†Missing data for one patient in each group
‡For those receiving IV fluids: 

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Table 2

Serial coagulation screening tests for 367 children with confirmed dengue infection, presented according to the severity of vascular leakage, and grouped by day from onset of fever at the time of sampling *

<table>
<thead>
<tr>
<th>Dengue group A: no haemoconcentration</th>
<th>Dengue group B: mild haemoconcentration</th>
<th>Dengue group C: significant haemoconcentration</th>
<th>Dengue group D: developed shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1–3</td>
<td>D4–6</td>
<td>D7–10</td>
<td>D1–3</td>
</tr>
<tr>
<td>(N = 56)</td>
<td>(N = 64)</td>
<td>(N = 70)</td>
<td>(N = 58)</td>
</tr>
<tr>
<td>PT – seconds</td>
<td>Median 12.5 ‡ 12.1</td>
<td>Median 12.0 12.2 12.0 12.2</td>
<td>Median 12.0 12.0 12.2</td>
</tr>
<tr>
<td>APTT – seconds</td>
<td>Median 3.0 2.9 ‡ 2.7 § 3.2</td>
<td>Median 3.4 3.4 3.4 3.4 3.4 3.4 3.4</td>
<td>Median 3.1 3.1 § 3.1 3.1 § 3.1</td>
</tr>
<tr>
<td>90% range</td>
<td>2.0–3.8 2.0–3.8 2.0–3.8 2.0–3.8 2.0–3.8</td>
<td>3.0–5.0 3.0–5.0 3.0–5.0 3.0–5.0 3.0–5.0 3.0–5.0</td>
<td>2.0–4.1 2.0–4.1 2.0–4.1 2.0–4.1</td>
</tr>
<tr>
<td>Fibrinogen – g/L</td>
<td>Median 149 § 82 § 107 § 308 146 § 63 § 73 § 308 119 § 51 § 60 § 308 100 20 32 –90% range</td>
<td>Median 148 § 78 § 92 § 248 146 § 61 § 73 § 248 118 § 48 § 60 § 248 90 20 32 –</td>
<td>Median 149 § 78 § 92 § 248 146 § 61 § 73 § 248 118 § 48 § 60 § 248 90 20 32 –</td>
</tr>
<tr>
<td>Negative</td>
<td>44 (79)</td>
<td>50 (85) 50 (85) 50 (85) 50 (85) 50 (85)</td>
<td>47 (81) 47 (81) 47 (81) 47 (81)</td>
</tr>
<tr>
<td>Strongly positive</td>
<td>5 (9)</td>
<td>4 (6) 4 (6) 4 (6) 4 (6) 4 (6)</td>
<td>7 (12) 7 (12) 7 (12) 7 (12) 7 (12)</td>
</tr>
<tr>
<td>Platelet count – 10 × 106/μL</td>
<td>Median 110 § 92 § 72 § 110 110 § 92 § 72 § 110 110 § 92 § 72 § 110 110 § 92 § 72 § 110</td>
<td>Median 110 § 92 § 72 § 110 110 § 92 § 72 § 110 110 § 92 § 72 § 110 110 § 92 § 72 § 110</td>
<td>Median 110 § 92 § 72 § 110 110 § 92 § 72 § 110 110 § 92 § 72 § 110 110 § 92 § 72 § 110</td>
</tr>
<tr>
<td>Negative</td>
<td>29</td>
<td>29 29 29 29 29 29 29 29 29 29 29 29 29 29 29 29</td>
<td></td>
</tr>
<tr>
<td>Strongly positive</td>
<td>12 (2)</td>
<td>12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2) 12 (2)</td>
<td></td>
</tr>
</tbody>
</table>

*   FU = follow up; PT = prothrombin time; APTT = activated partial thromboplastin time; FDP = fibrin degradation products.

**P** < 0.01, ***P** < 0.001.

†   0.01 > *P* > 0.05.

‡   0.001 > **P** > 0.01.

It is known that dengue can directly activate plasminogen in vitro, and that plasminogen cross-reactive antibodies are elicited during infection. The use of ultrasensitive D-dimer testing might have identified low level fibrinolysis, either positive test, *P* = 0.02). There were no associations between a positive test and the other coagulation parameters, the severity of vascular leakage, the overall platelet nadir, or the daily platelet counts.

**DISCUSSION**

This study presents a careful evaluation of clinical bleeding manifestations, vascular leakage, and hemostatic indices in a large group of children with dengue infection, recruited early and followed prospectively from the initial febrile phase through the critical and convalescent phases to full recovery. In addition to documenting the evolution of changes over time, by focusing on relatively mild disease we were able to study the intrinsic nature of the coagulopathy without the confounding effects of hypovolaemia or shock. We were careful to minimize the potential effects of difficult venesection and delayed sample separation on the coagulation profiles, and, by comparing results in the dengue group to those from children with OFI, to allow for possible non-specific effects of fever and mild systemic disturbance.

Spontaneous bleeding was infrequent in the dengue group, with 40% having no bleeding at all throughout the illness. In the remainder only minor skin or mucosal bleeding were seen apart from the one child who experienced gastrointestinal bleeding after the development of shock. Significant thrombocytopenia was universal in the dengue-infected children, and a strong association with the subsequent severity of vascular leakage was apparent from a very early stage. Although mild thrombocytopenia was also noted in the OFI group, counts less than 100,000 were rare and rapidly improved. A mild to moderate increase in the APTT and a reduction in fibrinogen concentration were the two consistent coagulation abnormalities detected in the dengue group and absent in the OFI group. Clear patterns emerged both over time and in relation to the overall severity of vascular leakage, although not in relation to bleeding severity. Minor increases in PT were apparent during the early febrile phase in the dengue group but were not significantly different to the changes seen at a similar time in children with OFI. These findings are in agreement with previous studies involving small numbers of patients with mild disease, but in addition clearly show the temporal association of the APTT and fibrinogen changes with the period of maximal vascular leakage.

Apart from thrombocytopenia the hemostatic changes demonstrated were all relatively minor and unlikely to result in spontaneous bleeding. However, the implications for understanding dengue pathogenesis are important. Production of fibrinogen normally increases during acute infections. If DIC explains the basic dengue coagulopathy, consumption of fibrinogen sufficient to result in the low levels demonstrated here would usually be accompanied by evidence of procoagulant activation. Yet only small increases in PT were observed, primarily in the early febrile phase, and these were similar to the changes noted in the OFI group. Similarly, FDPs were demonstrated in relatively few samples. Independent activation of the fibrinolytic pathway might explain the findings, although the lack of a proportionate increase in FDPs remains puzzling. It is known that dengue can directly activate plasminogen in vitro, and that plasminogen cross-reactive antibodies are elicited during infection. The use of ultrasensitive D-dimer testing might have identified low level fibrinolysis, either
secondary to DIC or to primary activation of fibrinolysis, but these tests are expensive and we were also limited by the volume of samples available. In other studies, measurement of specific coagulation proteins has produced conflicting results with some groups suggesting that the fibrinolytic pathway is activated, whereas others indicate that fibrinolysis is impaired in patients with DHF. \(^{11-13}\) In most of the studies procoagulant markers tended to be increased, although without clear evidence in support of DIC. It must be stressed, however, that these studies were carried out mainly in patients with severe disease and extrapolation of the findings to explain the coagulopathy associated with uncomplicated dengue infections is likely to be misleading.

Elucidating what happens to fibrinogen could be crucial in determining the pathogenesis of the intrinsic dengue associated coagulopathy. In recent years considerable advances have been made toward understanding the mechanisms controlling microvascular permeability. \(^{25}\) Basic ultrafiltration is now thought to be regulated primarily by the endothelial surface glyocalyx rather than by endothelial cells per se. Although fibrinogen is a large molecule (340 kDa), there is evidence from \textit{in vivo} animal studies that it permeates the endothelial surface layer at a very similar rate to albumin (69 kDa). \(^{26}\) During dengue infections the transcapillary filtration of albumin increases markedly. \(^{27}\) It may be that fibrinogen filtration increases in a similar manner and that the low plasma concentrations measured simply reflect loss from the intravascular to the interstitial space. A pathologic process involving the endothelial surface glyocalyx could also offer a potential explanation for the increase in APTT seen in these patients. Glycosaminoglycans, such as heparan sulfate, form an integral part of the bush-like structure that is the backbone of the glyocalyx layer; if minor damage occurred and heparan sulfate were liberated into the circulation this would function as an anticoagulant similar to heparin and would be expected to result in prolongation of the APTT. \(^{28}\) We have demonstrated that the reduction in fibrinogen levels and increases in APTT are strongly associated with vascular leakage both temporally and in terms of severity, and a pathological mechanism that involved a specific capillary structure and linked all three effects would be compelling. Histopathologic studies to date have not shown any obvious vascular abnormalities.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Box and whisker plots presenting the results of the serial coagulation screening tests for children with confirmed dengue infection and those with other febrile illnesses (OFI). Boxes represent the median and interquartile values and whiskers the overall range excluding outliers. See text for definitions of vascular leak categories A, B, C, and D. Within each time-period relationships across the dengue vascular leakage categories were examined using the Cuzick test for trend. * 0.01 > \(P\) < 0.05. ** 0.001 > \(P\) < 0.01. *** \(P\) < 0.001.}
\end{figure}
but have been limited to examination of cellular structures, as the glycocalyx layer is difficult to visualize using conventional methods. However, novel techniques are now available to interrogate both the structure and function of the glycocalyx and will hopefully provide interesting insights into dengue pathogenesis in the future.

The study also confirms the strong association between thrombocytopenia and severity of vascular leakage. This association was apparent from the early febrile phase when absolute counts were still above 100,000/mm³ in most patients, and signs of leakage were not yet apparent. The rate of fall in serial platelet counts at this stage could prove to be a useful predictor for the subsequent development of shock and merits further study in a larger series. The rapid rise in platelet counts during the convalescent period is also noteworthy and indicates that prothrombotic platelet transusions are unlikely to be of any benefit in children. Reports of clinical disease profiles in adults suggest that serious bleeding may be more common than in children but it is of concern that prothrombotic platelet transusions, with all their attendant risks, are becoming commonplace for adult patients in some countries. Similar descriptive series documenting the natural history of the thrombocytopenia and coagulopathy in adults need to be performed, and clear evidence of efficacy obtained, before this practice becomes established.

In summary, thrombocytopenia, prolongation of the APTT, and a reduction in fibrinogen concentration are typical and consistent findings during mild dengue infection, and all three abnormalities are strongly associated with the severity of vascular leakage. Bleeding is unusual but probably arises when tissue integrity is breached for any reason in the presence of these derangements. The pattern of abnormalities seen is not consistent with classic DIC and alternative underlying mechanisms need to be studied.

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