Serious Thrombocytopenia Due to Dengue Hemorrhagic Fever Treated with High Dosages of Immunoglobulin

Sir—During the 2002 dengue hemorrhagic fever (DHF) outbreak in Brazil, we treated 5 patients in Recife with DHF. The patients were white women aged 32, 37, 40, 41, and 67 years in whom DHF had been diagnosed on the basis of clinical and serological (ELISA with a positive IgM result) findings. All of them had positive tourniquet test results. Presence of extensive petechiae, epistaxis, and/or hematemesis was evident. Findings of coagulation tests were normal except for accentuated thrombocytopenia (median platelet count, 20,000 platelets/mm³; range, 18–36,000 platelets/mm³), with no signs of disseminated intravascular coagulation. Bone marrow aspiration revealed normal or hyperplastic megakaryocytes for all patients. Findings of thoracic and abdominal CT scans of all patients were normal. Other viral serological tests (for HIV, cytomegalovirus, rubella virus, hepatitis B virus, and herpes C virus) and collagenosis tests (for antineutrophil cytoplasmatic antibodies, antinuclear antibodies, and antinative DNA) had negative results. Two of our 5 patients underwent hemoconcentration. It should be noted that all patients had received volume replacement therapy before admission to our medical service, which may have affected their hematocrit levels.

All patients were admitted to our hematology unit within 24–48 h after the first bleeding episode, where they received clinical care that included receipt of parenteral hydration, acetaminophen, and third-generation γ-globulin from European donors, which had tested negative for any dengue antibody. The patients received 500 mg/kg per day of intravenously administered immunoglobulin (IVIG) in infusions of 3 h for 5 days. The evaluation of efficacy suggested immediate clinical response and recovery of the platelet level (figure 1 and table 1).

Today there is good evidence that heterologous secondary infection is the main risk factor for DHF, as explained by the immunologic enhancement hypothesis. According to this hypothesis, heterophilic antibodies complex with dengue viruses without neutralizing them, enhancing the efficiency of mononuclear phagocytes and exaggerating the immune reaction. Massive T-cell activation, with release of cytokines and induction of plasma leakage, is a major pathophysiological change that induces more-severe clinical symptoms and, in some cases, shock (dengue shock syndrome). Although the cause of thrombocytopenia is not completely understood, recent studies suggest a role for the immune-mediated destruction of platelets and vasculitis caused by immune complexes [1].

The mechanism by which γ-globulin can abbreviate the course of thrombocytopenia and probably stop the progression to vasculitis, capillary leak syndrome, and shock is not well understood. Blockage of the Fc receptor on phagocytes and modulation of the activity of T and B lymphocytes leading to a more balanced immune response are possible explanations; these mechanisms would be similar to those involved in the successful use of IVIG to treat idiopathic thrombocytopenia.

Figure 1. Recovery of platelet counts for 5 patients with dengue hemorrhagic fever treated with high doses of intravenously administered immunoglobulin (IVIG). Day 0, day IVIG therapy initiated.
nic purpura, vasculitis caused by immune complexes, and other immunity-related disorders [2, 3].

Without treatment, the mortality rate associated with DHF can exceed 20%. With proper care—hydration and supportive care that may include transfusions and treatment in an intensive care unit—the mortality rate can be reduced to <5% [4]. Under these circumstances, without γ-globulin therapy, the platelet counts tend to normalize, on average, in 9 days [5].

Although it is possible that the responses seen in our patients were spontaneous and unrelated to γ-globulin administration, the rapid decrease in bleeding episodes and the immediate recovery of platelet counts suggest a potential therapeutic benefit of γ-globulin in the management of DHF. The cost of gammaglobulin therapy is an economic concern, but we should consider that at least two-thirds of the potential patients are children, who would need lower dosages of γ-globulin than adults. Moreover, the rapid improvement observed suggests a possible shortening of γ-globulin therapy. These findings should stimulate further studies regarding the real efficacy of this new treatment alternative.

Table 1. Platelet counts for 5 patients with dengue hemorrhagic Fever treated with high doses of intravenously administered immunoglobulin (IVIG).

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<tr>
<th>Patient</th>
<th>Platelets × 10^9/mm³, by day of treatment or follow-up</th>
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<tr>
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<td>0</td>
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<tr>
<td>1</td>
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<td>23</td>
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<td>18</td>
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**NOTE.** Day 0 was the first day of treatment with IVIG. There were 60 days of follow-up.

**References**


**Prevalence and Optimal Detection of C. upsaliensis in Stool Specimens**

Sirs—Campylobacter species, particularly those other than Campylobacter jejuni and Campylobacter coli, are frequently under-identified in isolates from clinical specimens. We read with interest the recent report of Labarca et al. [1] that compared the frequency of recovery among 5 Los Angeles County clinical laboratories of Campylobacter species from stool specimens obtained from patients with campylobacteriosis.

We agree with Labarca et al. [1] that Campylobacter upsaliensis is often under-identified and that the true prevalence of infection with this pathogen is unknown. As Labarca et al. [1] suggested, the failure of 1 of the 5 participating laboratories to isolate C. upsaliensis may have been due to the culture medium used and the shorter incubation time, which are critical factors because C. upsaliensis strains are generally more fastidious and slower growing than are C. jejuni strains. However, we also note that this laboratory used Campy-thioglycolate broth (Becton Dickinson) as a transport medium and that this broth contains cephalothin [1], to which C. upsaliensis has been shown to be susceptible [2]. Incubation conditions in this laboratory were not specified and may not have been optimal for efficient growth of some Campylobacter species [3]. Also, 4 of the 5 participating laboratories in the study used isolation and incubation temperatures of 42°C (3 laboratories) or 38°C (1 laboratory), which may be too high for growing some strains of C. upsaliensis and other Campylobacter species.

Our laboratory does not use selective media for Campylobacter isolation but, rather, uses the “Cape Town” protocol of membrane filtration (pore diameter, 0.60 μm) onto antibiotic-free Tryptose blood agar plates (CM 233; Oxoid), with primary incubation at 37°C in an H₂-enriched microaerobic atmosphere (BR38 [Oxoid] or BBL70304 [Becton Dickinson] gaspaks, without catalyst) [3, 4]. When tested against a variety of selective media, this protocol was consistently superior for isolating 17 species or subspecies of Campylobacteraceae from clinical specimens [3, 4]. The use of antibiotic-free plates allows growth of antibiotic-susceptible strains of C. upsaliensis and other Campylobacter species. The H₂-enriched microaerobic atmosphere permits growth of species that have an essential requirement for H₂, such as Campylobacter concisus. Some strains of C. fetus subspp fetus, C. lari, and C. upsaliensis grow poorly, if at all, under conventional microaerobic conditions but flourish in an H₂-enhanced microaerobic atmosphere [4].

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