Dengue Vascular Permeability Syndrome: What, No T Cells?

To the Editor—Tam et al found that 0.5 or 2.0 mg/kg of prednisolone administered orally for 3 consecutive days early in the course of dengue disease in Vietnamese children or adults failed to reduce subsequent abnormal hemostasis or loss of fluid from capillaries [1]. This result was greeted with dismay because an anticipated accessible and inexpensive ameliorative treatment of the dengue vascular permeability syndrome had failed, but neither the authors nor a published commentary identified the full significance of this audacious clinical trial [2].

The unusual clinical course of severe dengue permits early access to patients as illness begins with the sudden-onset fever that prompts many patients to seek medical attention. However, the abnormal hemostasis and increased vascular permeability that comprise the dengue vascular permeability syndrome occur several days after onset of fever, usually during defervescence. Thus, during dengue illnesses there is a therapeutic window for possible early intervention. The short duration of dengue vascular permeability has led most investigators to entertain the hypothesis of an underlying pharmacological mechanism, with central efforts focused on cytokines released during the elimination of dengue-infected cells [3].

As evidence of some therapeutic effect, in the Vietnam trial prednisolone slightly reversed leukopenia and aspartate aminotransferase levels, but the full immune elimination event was not altered as all patients recovered from their dengue infection uneventfully and on schedule. The steroid doses administered should have been immunosuppressive, so perhaps the dengue vascular permeability syndrome is not T cell mediated. If not, what could be the late-in-illness pathogenic mechanism? The answer may reside in an old suspect—the dengue-soluble complement-fixing antigen, or nonstructural protein 1 (NS1) [4]. Recently, Lin et al have found that during the late stages of dengue disease NS1 circulates as complexes with thrombin [5]. More importantly, NS1 also forms complexes with prothrombin, resulting in a prolongation of activated partial thromboplastin times, values that have been shown to be the strongest correlate of vascular permeability in patients with dengue infection [6]. As its original name implies, NS1 interacts powerfully with the complement system, and complement activation once was recognized as an intrinsic component of the dengue vascular permeability syndrome [7, 8].

Might the release of NS1 from dengue-infected cells contribute to the late onset of the dengue shock syndrome? Studies on the virological course of dengue infections in monkeys found that peak cellular infection occurred at the end of the viremic phase [9]. If this is true for humans, then during defervescence the cell elimination immune process may release a bolus of NS1, which—still biologically active despite circulating as immune complexes—produces a NS1 toxicosis. It is well to recall that NS1 produces a NS1 xing antigen, or nonstructural viral protein NS1 and complements as complexes with thrombin [5]. More importantly, NS1 also forms complexes with prothrombin, resulting in a prolongation of activated partial thromboplastin times, values that have been shown to be the strongest correlate of vascular permeability in patients with dengue infection [6]. As its original name implies, NS1 interacts powerfully with the complement system, and complement activation once was recognized as an intrinsic component of the dengue vascular permeability syndrome [7, 8].

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Scott B. Halstead
Dengue Vaccine Initiative, International Vaccine Institute, Seoul, Korea

Note
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Correspondence: Scott B. Halstead, 5824 Edson Lane, North Bethesda, MD 20852 (halsteads@erols.com).

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