BRIEF OBSERVATION

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High-dose Intravenous Immunoglobulin Therapy for Systemic Capillary Leak Syndrome (Clarkson Disease)

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ABSTRACT

BACKGROUND: Systemic capillary leak syndrome is a highly rare disorder of unknown cause. The disease is characterized by episodes of transient vascular collapse, which leads to hypotensive shock and anasarca. Previous treatment of this potentially devastating condition has been largely ineffective. We evaluated intravenous immunoglobulin prophylactic therapy in a cohort of 29 patients with systemic capillary leak syndrome in a longitudinal follow-up study.

METHODS: All patients received treatments at the discretion of their primary providers and retrospectively via questionnaire-recorded symptoms beginning with their first documented episode of systemic capillary leak syndrome to May 31, 2014.

RESULTS: A total of 22 of 29 patients responded to the questionnaire, and 18 of the 22 respondents received monthly prophylaxis with intravenous immunoglobulin during the study period for a median interval of 32 months. The median annual attack frequency was 2.6 per patient before intravenous immunoglobulin therapy and 0 per patient after initiation of intravenous immunoglobulin prophylaxis ($P = .0001$). A total of 15 of 18 subjects with a history of 1 or more acute systemic capillary leak syndrome episodes experienced no further symptoms while taking intravenous immunoglobulin therapy.

CONCLUSIONS: Intravenous immunoglobulin prophylaxis is associated with a dramatic reduction in the occurrence of systemic capillary leak syndrome attacks in most patients, with minimal side effects. A prospective, randomized trial may be necessary to fully assess the benefits of intravenous immunoglobulin for systemic capillary leak syndrome and to determine the optimal dosage and duration of therapy.

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KEYWORDS: Intravenous immunoglobulin; Systemic capillary leak syndrome; Vascular leak

First described in 1960 by Clarkson et al,[1] systemic capillary leak syndrome is a rare disorder diagnosed on the basis of unexplained hypotension and edema, which is accompanied by hemoconcentration and hypoproteinemia as a result of the loss of plasma into the extravascular space.[2-4] Less than 300 cases of systemic capillary leak syndrome have been reported since 1960, and the 5-year mortality has been estimated to be 20% to 35%.[2,3]

Because of the rarity of the disease, prospective therapeutic studies are challenging. In a report by the Mayo Clinic, treatment of 8 patients over a period of 18 years with oral theophylline and terbutaline was associated with a 30-fold reduction in the frequency and severity of systemic capillary leak syndrome episodes[5]; however, many patients continued to experience acute attacks, and the regimen was difficult to tolerate. A European registry of 28 patients studied over 15 years demonstrated a significant survival advantage in patients receiving prophylactic therapies (including intravenous immunoglobulin or theophylline/terbutaline) compared with untreated subjects.[4] We evaluated the efficacy of

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intravenous immunoglobulin as prophylactic therapy in a cohort of patients with systemic capillary leak syndrome.

MATERIALS AND METHODS

Study Population and Design

Subjects were included in the study if they were aged more than 16 years and met the criteria for systemic capillary leak syndrome as described by Gousseff et al.[4] We obtained written informed consent from each patient, and the protocol (09-I-0184) was approved by the institutional review board of the National Institute of Allergy and Infectious Diseases. A voluntary, retrospective questionnaire was approved by the institutional review board and provided to all adult patients who signed the original study protocol consent.

Data Analysis and Statistics

In Figure 1, hemoglobin measurements were obtained by automated analysis (patient 1) or a HemoCue hemoglobin analyzer photomer (patient 2). Statistical analysis was performed using GraphPad Prism software (GraphPad Software Inc, La Jolla, Calif). Nonparametric tests (Mann-Whitney for 2 groups, Kruskal-Wallis for multiple groups) were used; P values $<.05$ were considered significant.

CLINICAL SIGNIFICANCE

- Systemic capillary leak syndrome is associated with substantial morbidity, including chronic sensorimotor defects of the extremities.
- Theophylline-based therapy of systemic capillary leak syndrome was frequently associated with breakthrough symptoms and substantial side effects.
- Monthly prophylaxis with high-dose intravenous immunoglobulin was associated with a sharp reduction in the number of acute systemic capillary leak syndrome attacks with few side effects.

RESULTS

Demographics and Disease Characteristics

Of 29 adult subjects with classic acute systemic capillary leak syndrome who were enrolled in the protocol from 2008 to May 31, 2014, 22 completed and returned the questionnaire. One patient with atypical disease features, who experiences near weekly, stereotyped episodes consisting of hypotension but no edema, was excluded from analysis of treatments because of the uncertain diagnosis[6] and incomplete documentation of symptoms. All but 2 patients are white (1 African American and 1 of Middle Eastern origin), and 82% are male, which reflects the overall demographics of our cohort (77% are male) but is

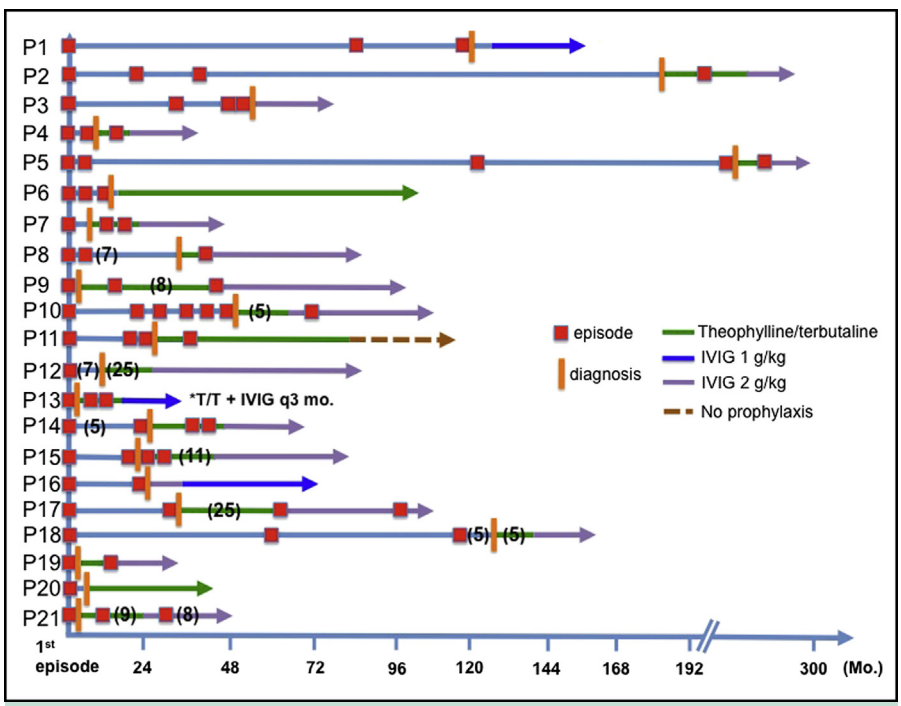

Figure 1 Longitudinal follow-up of 21 adults with classic acute systemic capillary leak syndrome. Clinical course, date of formal diagnosis of the systemic capillary leak syndrome, and treatments were recorded after the initial presenting episode over the time periods indicated as denoted by each symbol. IVIG = intravenous immunoglobulin.