Narrative Review: The Systemic Capillary Leak Syndrome

Kirk M. Druey, MD, and Philip R. Greipp, MD

The systemic capillary leak syndrome (SCLS) is a rare disease of reversible plasma extravasation and vascular collapse accompanied by hemoconcentration and hypoalbuminemia. Its cause is unknown, although it is believed to be a manifestation of transient endothelial dysfunction due to endothelial contraction, apoptosis, injury, or a combination of these. Fewer than 150 cases of SCLS have been reported, but the condition is probably underrecognized because of its nonspecific symptoms and signs and high mortality rate. Patients experience shock and massive edema, often after a nonspecific prodrome of weakness, fatigue, and myalgias, and are at risk for ischemia-induced organ failure, rhabdomyolysis, and muscle compartment syndromes, and venous thromboembolism. Shock and edema reverse almost as quickly as they begin, at which time patients are at risk for death from flash pulmonary edema during rapid fluid remobilization. Diagnosis is made clinically and by exclusion of other diseases that cause similar symptoms and signs, most notably sepsis, anaphylaxis, and angioedema. Acute episodes are treated with vasopressor therapy and judicious fluid replacement, possibly with colloid solutions for their osmotic effects, to prevent the sequelae of underperfusion. Between episodes, patients may be treated with theophylline and terbutaline, which clinical experience suggests may reduce the severity and frequency of acute episodes. Prognosis is uncertain, but patients who survive an initial severe SCLS episode are estimated to have a 10-year survival rate greater than 70%. Much remains to be learned about SCLS, and clinicians should consider the diagnosis in patients with unexplained edema, increased hematocrit, and hypotension.

For author affiliations, see end of text.

Methods

We performed MEDLINE and Scopus searches of articles from 1960 to 2010 by using the search terms systemic capillary leak syndrome, idiopathic capillary leak syndrome, capillary leak, vascular leak, and vascular permeability, retrieving articles in English, French, and Chinese. Most references report findings from 1 patient, and with the exception of the therapeutic experience from the Mayo Clinic (3), none included more than 3 patients. For this reason, we summarize trends from separate reports that describe similar procedures or tests (such as skin biopsies). However, the conclusions from such studies should be interpreted with caution, because most cases varied considerably in disease severity, treatments, and temporal association of sample collection to acute symptoms. Where possible, we compare and contrast published findings with our experience in evaluating and treating 25 patients with SCLS at the Mayo Clinic (3) and 16 patients at the National Institute of Allergy and Infectious Diseases (some were seen at both institutions).

Our research was funded in part by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health. The funding source had no role in the design, analysis, or reporting of this study or in the decision to submit the manuscript for publication.

Epidemiology

One hundred cases of SCLS were reported in the world literature between 1960 and 2006, according to recent reviews (4–6). We identified an additional 26 published cases since 2006 (7–26), which may reflect increased awareness and recognition of the disease. On the basis of these reports and our clinical experience, we believe that SCLS occurs sporadically and is diagnosed most often in previously healthy white adults. Our analysis of 118 cases for which information was available revealed that the median age of onset was 45 years (range, 5 months to 74 years) and 57% of patients were male, including our unpublished cases and those from 23 published studies (4–26). Six of these patients have what we term chronic SCLS, which is characterized by noncyclic peripheral edema and hypoalbuminemia rather than acute, intermittent hypotensive episodes. Because SCLS is so often misdiagnosed, these series probably underestimate its true prevalence. We also believe that some patients may die during their first episode of SCLS, which would further contribute to the underestimation of its prevalence. Recently, a case of familial SCLS was reported (7); however, the clinical histories of affected relatives of the index patient were vague. The syndrome has been described in an infant aged 5 months (10) and in 3 children aged 3 (27) and 6 years (13, 28) who...
presented with recurrent classic acute shock episodes. We also saw a newborn at the Mayo Clinic who experienced an attack shortly after being delivered from a mother with SCLS; however, the infant did not experience any further episodes.

**Cause and Pathophysiology**

**Histologic Studies**

The molecular cause of SCLS is unknown, and systematic research studies are limited because of its rarity. Immune dysregulation may have a function in disease pathogenesis. Two separate case reports documented increased numbers of circulating CD25+ (29) and CD25+ T cells (13), but no further immunophenotyping was performed. Skin biopsies taken during acute SCLS episodes in 4 of 9 patients showed perivascular mononuclear infiltrates, whereas light microscopy showed normal results in the remainder (1, 30–35). The results were normal in 8 of 10 muscle biopsies, including those from 3 patients with cutaneous perivascular infiltrates (1, 31, 33–38). Although immunofluorescence staining for immunoglobulin or complement was performed on most of the biopsy specimens, no immunoglobulin or complement deposits were seen in any of them.

Ultrastructural and functional studies have provided insight into endothelial dysfunction in SCLS. Electron photomicrographs of skeletal muscle endothelial cells from a patient with SCLS suggested apoptosis (cell blebbing) without widening of intercellular gaps (39), and serum from other patients with SCLS induced apoptosis of cultured microvascular endothelial cells derived from healthy donors (40). Serum from patients with sepsis or pancreatitis also induced apoptosis to a similar degree; however, when considered in the context of the time it takes for a capillary leak to reverse in patients with SCLS, these findings suggest that endothelial injury and apoptosis, rather than simply prolonged endothelial contraction or retraction, may be responsible for SCLS. This distinction is important, because many circulating components associated with anaphylaxis and shock typically induce endothelial cell shape change and retraction and decreased intercellular connections rather than outright cell death (41). However, because of the considerable overlap between the signaling pathways associated with contraction and apoptosis, these findings do not exclude a role for endothelial contraction in SCLS. For example, activation of guanosine triphosphatases (such as Rho) and tyrosine kinases (including Src and abl) by growth factors and cytokines may affect endothelial contraction and apoptosis, depending on the cellular context (42–44). Therapeutic compounds that increase intracellular cyclic adenosine monophosphate, which reduces the symptoms of SCLS, may mitigate both endothelial phenotypes through multiple mechanisms (45, 46).

**Soluble Mediators**

No soluble factors have been associated specifically or typically with SCLS. However, we cannot rule out a circulating component that elicits attacks. Most serum analytes are within the normal range in patients with SCLS, including complement and C1 esterase inhibitor (C1-INH) levels (23), and no coagulation abnormalities, elevations in compounds known to induce capillary permeability (such as bradykinin, histamine [33], or prostaglandins), or endocrine dysfunction have been reported, with the exception of increased C3a levels in 1 patient (1, 36, 47). In 2 recent studies (13, 37), 3 patients had elevated levels of serum interleukin (IL)–6 and tumor necrosis factor-α, which suggests a systemic inflammatory response. However, the role of these cytokines in the pathogenesis of SCLS is unclear, because levels varied widely among patients and no baseline levels were reported. In addition, proinflammatory cytokine levels remained elevated long after capillary permeability resolved in 2 of the patients (13).

Recently, 2 patients with SCLS were reported to have high levels of plasma vascular endothelial growth factor (VEGF) during an acute, severe episode, which decreased with symptom resolution (11). We have also found high baseline plasma VEGF in several patients with SCLS (unpublished data). This factor may contribute to endothelial permeability in several disorders, including sepsis (48), the ovarian hyperstimulation syndrome (49), and the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy of undetermined significance [MGUS], and skin changes). The POEMS syndrome and SCLS have considerable overlap, because patients with the POEMS syndrome often show evidence of chronic vascular leakage in the form of peripheral edema, visceral effusions, papilledema, and polycythemia (50). Levels of VEGF are also increased in the plasma cells of patients with myeloma (51). However, we emphasize that the source of VEGF and its function in the pathogenesis of SCLS is not known.

**Monoclonal Gammopathy of Undetermined Significance**

An estimated 79% to 82% of patients with SCLS have MGUS (4, 6), defined as a serum monoclonal immunoglobulin (paraprotein) level less than 0.3 g/L; the presence of less than 10% bone marrow plasma cells; and the absence of end-organ damage, such as lytic bone lesions or renal failure. The condition was present in 19 of 25 (76%) cases of SCLS followed at the Mayo Clinic. In the general population older than 50 years, the prevalence is 3% and the risk for progression to myeloma is approximately 1% per year (52). We have not observed an increased incidence of progression to myeloma in the patients with SCLS and MGUS whom we have followed. The systemic capillary leak syndrome has occasionally been diagnosed in the setting of multiple myeloma (53–56), amyloidosis (53), and plasma cell leukemia (55).
The Systemic Capillary Leak Syndrome

**Figure. Progression of a classic acute SCLS episode.**

- **Prodrome:** weakness, malaise, myalgias, or abdominal pain
- **Hemoconcentration:** presyncope, increased thirst, cool skin, and oliguria
- **Shock:** hypotension and hypoperfusion
- **Leak phase:** hypoalbuminemia and severe edema of face, trunk, and extremities
- **Postleak phase:** restoration of intravascular volume and diuresis
- **Compartment syndromes, rhabdomyolysis, and DVT**
- **Renal failure, stroke, and DVT**
- **Cardiopulmonary failure**

Classic acute prodromal symptoms, which can last hours to days, may precede the rapid development of hemoconcentration and hypovolemia, although symptoms may occasionally develop rapidly in the absence of a prodrome. Hypoalbuminemia and edema due to fluid and protein extravasation characterize the leak phase, which lasts for several days in the classic acute syndrome. The postleak phase comprises restoration of capillary barrier function with recruitment of fluids into the intravascular space and diuresis. Complications associated with each phase are listed. DVT = deep venous thrombosis; SCLS = systemic capillary leak syndrome.

Whether the paraproteins present in SCLS are directly pathogenic or are a secondary phenomenon is unclear. The literature and our clinical experience suggest that paraprotein levels in MGUS do not fluctuate substantially between attacks, and no clear link has been found between serum paraprotein levels and disease symptoms. In vitro experiments have not shown that paraprotein purified from patients with SCLS binds to cultured endothelial cells or induces cytotoxicity (11, 56, 57). Although the amount of paraprotein produced in MGUS is usually small, which indicates few clonal plasma cells, it theoretically could be pathogenic either by aggregating and depositing in tissue, such as in light-chain amyloidosis, or by binding to autologous common antigens (acting as an autoantibody), such as in cold agglutinin disease, mixed cryoglobulinemia, the von Willebrand syndrome, paraproteinemic neuropathy, or the Schnitzler syndrome (intermittent urticaria or fevers and signs of acute inflammation, such as elevated erythrocyte sedimentation rate) (58–61).

We speculate that in SCLS, the paraprotein could bind and inhibit a factor crucial for endothelial barrier function. A classic example of this mechanism is acquired angioedema, which has been diagnosed in the setting of MGUS and other lymphoproliferative disorders (62). An autoantibody against C1-INH leads to C1-INH inactivation, complement pathway activation, and overproduction of permeability factors (such as bradykinin). Paraprotein that reacts with a putative endothelial protective factor could render patients with SCLS more susceptible to inflammation-induced vascular injury. However, we note that the relationship between inflammation and SCLS is not known. Some of our patients cannot identify a clear trigger for attacks and show no signs of systemic inflammation, such as fevers, arthralgias, or myalgias, at the onset of an episode.

**Symptoms and Signs**

Patients with the classic acute form of SCLS rapidly develop shock and edema due to plasma extravasation (up to 70% of total plasma volume). Shock and edema may develop in the absence of preceding symptoms or it may follow a prodrome of generalized weakness; fatigue; myalgias; and occasionally fevers, vomiting, abdominal pain, flushing, and diarrhea (10, 36, 63) (Figure). We term the period of shock and edema the **leak phase**. The hypotension usually lasts for 1 to 3 days and is accompanied by massive third spacing of fluids, mainly in the trunk and extremities. Visceral edema (pleural and pericardial effusions) is not usually found. The symptoms reverse almost as quickly as they begin, with massive fluid recruitment from tissues into circulation and diuresis when capillary barrier function seems to be restored. We term this the **postleak phase**. Patients who die of SCLS most often do so during the postleak phase, of flash pulmonary edema induced by rapid fluid remobilization—which may be exacerbated by the high volume of fluid given to prevent frank shock during the leak phase. However, patients may also die of ischemia-induced organ failure due to hypovolemia during the leak phase, which necessitates a fine balance between administration of sufficient intravenous fluids to prevent organ hypoperfusion and overzealous fluid resuscitation, which can both contribute to pulmonary edema in the postleak phase and lead to muscle compartment syndromes and rhabdomyolysis in the leak phase. Patients are also at risk for venous thromboembolism, due to venous stasis from hypovolemia, and hyperviscosity from severe hemoconcentration.

The severity and frequency of SCLS episodes may vary widely from patient to patient but are usually stereotyped in each patient. Occasionally, the pattern of attacks and the duration of the capillary leakage change unpredictably over time. In the 41 patients we have cared for, intervals between leak phases range from once every 20 years to once every 3 to 4 days. Patients usually feel well between episodes.

**Diagnosis**

The systemic capillary leak syndrome may be difficult to recognize and diagnose on initial presentation. A characteristic triad of hypotension, hemoconcentration (elevated hematocrit, leukocytosis, and thrombocytosis), and hypoalbuminemia in the absence of secondary causes of
shock is typical (3). This singular combination of hypotension and elevated hematocrit reflects the profoundly reduced intravascular volume and endothelial barrier dysfunction that is unique to SCLS. The leak phase is characterized by dramatic, rapidly developing, generalized edema of the face, trunk, and extremities. Although SCLS has no pathognomonic marker, it should be considered in any patient with acute, severe hypotension without obvious cardiac dysfunction—particularly if it is unresponsive to or worsens despite aggressive intravenous fluid resuscitation or vasopressor support and is accompanied by an elevated hematocrit (often >60).

During the episode, we recommend performing a complete blood count to identify hemoconcentration, routine blood and urine cultures to exclude sepsis, and serum immunofixation electrophoresis to determine whether MGUS is present. We also recommend measuring serum albumin level to confirm protein leakage from the intravascular compartment and serum tryptase level to exclude anaphylaxis. Although MGUS supports the diagnosis of SCLS, it is not a primary criterion because it is not uniformly present (4, 6). Chest radiography, electrocardiography, and echocardiography may exclude a primary cardiogenic cause of hypotension and peripheral edema.

Some patients with classic acute SCLS have less frequent life-threatening episodes and more frequent mild episodes, which may be characterized by mild hypotension, hemoconcentration, hypoalbuminemia, and edema and resolve with oral hydration. For this reason, we propose a severity scale that may aid the clinician in charting the course and pattern of disease in patients with SCLS and in evaluating the efficacy of treatment (Appendix Table).

### Differential Diagnosis

Many diseases have features similar to those found in SCLS (Table 1), but SCLS has distinguishing features. Evidence of underlying infection or sepsis, anaphylactic triggers, or other causes of capillary leakage is conspicuously absent. Elevated hematocrit and leukocytosis are often more severe than in sepsis or simple dehydration and can be mistaken for polycythemia vera (37). Unlike anaphylaxis, which usually resolves after administration of subcutaneous epinephrine, the hypotension of SCLS can be resistant even to very high doses of vasopressors. In our experience, urticaria, focal angioedema (for example, peri-oral), and stridor due to laryngospasm, which often accompany anaphylaxis, are usually not observed in classic acute SCLS. Although flushing may be present occasionally at the onset of SCLS episodes and is a symptom common to mastocytosis or neuroendocrine tumors (such as carcinoid tumors or pheochromocytoma), progression to severe hypotension and edema is not characteristic of the latter disorders. Patients with the inferior vena cava syndrome due to inferior vena cava thrombosis may present with rapidly developing hypotension and edema of the extremities, but this syndrome is not typically associated with elevated hematocrit or low serum albumin levels.

As mentioned, a chronic form of SCLS has been described in several patients, which often presents a diagnostic challenge. These patients have persistent (noncyclic), generalized edema rather than acute attacks and, unlike patients with classic acute SCLS, may have visceral (pleural and pericardial) effusions (11, 64, 65). Hypotension and hemoconcentration with hypoalbuminemia may be difficult to demonstrate in such patients and MGUS may not

### Table 1. Differential Diagnosis of SCLS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Similarities to SCLS</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic syndrome</td>
<td>Edema and hypoalbuminemia</td>
<td>Noncyclic edema, proteinuria</td>
</tr>
<tr>
<td>Protein-losing enteropathy</td>
<td>Edema and hypoalbuminemia</td>
<td>Noncyclic edema, diarrhea</td>
</tr>
<tr>
<td>Inferior vena cava syndrome</td>
<td>Lower-extremity edema and hypotension</td>
<td>Progressive, irreversible hypotension and normal albumin levels</td>
</tr>
<tr>
<td>Idiopathic anaphylaxis</td>
<td>Acute hypotension and flushing</td>
<td>Normal albumin levels, hives, laryngeal edema more common, and elevated serum tryptase levels</td>
</tr>
<tr>
<td>Hereditary angioedema</td>
<td>Acute cyclic edema</td>
<td>Normotension, visceral effusions, and decreased C1 esterase inhibitor levels or function</td>
</tr>
<tr>
<td>Carcinoid tumor</td>
<td>Flushing and hypotension</td>
<td>Absence of edema and elevated 5-HT and 5-HT metabolite levels</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Flushing and hypotension</td>
<td>Labile hypertension and elevated norepinephrine and epinephrine metabolite levels</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Flushing and hypotension</td>
<td>Urticaria pigmentosa and elevated serum tryptase levels</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>Severe leukocytosis, erythrocytosis, and thrombocytosis</td>
<td>Normotension, normal albumin levels, and absence of edema</td>
</tr>
<tr>
<td>Gleich syndrome</td>
<td>Cyclic edema</td>
<td>Urticaria, eosinophilia, elevated IgM levels, and normal albumin levels</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Hypotension and hypoalbuminemia</td>
<td>Severe abdominal pain, nausea, and vomiting and elevated amylase levels</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Hypotension and edema</td>
<td>Normal albumin levels and acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome</td>
<td>Hypotension, hypovolemia, and edema</td>
<td>Visceral effusions and a history of ovulation induction</td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>Hypotension</td>
<td>Normal albumin levels, renal failure, desquamatory rash, mucosal hyperemia, and delirium</td>
</tr>
</tbody>
</table>

5-HT = 5-hydroxytryptamine; SCLS = systemic capillary leak syndrome.
be present, which makes the diagnosis of SCLS difficult and uncertain. Many other disorders associated with chronic extremity edema, such as the Gleich syndrome (episodic urticaria, angioedema, and fever with eosinophilia) (66), venous stasis, protein-losing enteropathy, and the nephrotic syndrome, can usually be excluded by careful history and routine laboratory studies and should be considered in these patients.

TREATMENT
Acute Management of a Severe SCLS Episode

Because of the infrequency of SCLS, all treatment strategies are based on single case reports and our clinical experience with 41 patients over 30 years. We have occasionally stopped or minimized the severity of the capillary leakage by using oral corticosteroid therapy to counter the inflammatory triggers of SCLS; this required early patient recognition of signs and symptoms of hypovolemia. However, we believe that steroids do not prevent the attack from progressing in most patients and may be harmful to patients who experience more frequent attacks. Although oral hydration with electrolyte-containing solutions may make intravenous fluids unnecessary in patients who experience milder attacks, which may be self-limited, whether they affect the course of subsequent episodes is uncertain.

Patients who present with signs and symptoms of a severe attack should be treated immediately in an intensive care setting. A recent report (13) demonstrated the efficacy of intravenous theophylline in reducing the duration and intensity of the leak phase of an acute SCLS episode when serum levels of 111 to 139 μmol/L were achieved. We have found that vasopressors and judicious fluid and colloid boluses (for example, 250 mL of a 25% albumin-containing solution, administered over 30 minutes to 1 hour at intervals determined by clinical status) may be more effective in maintaining hemodynamic stability (low normal blood pressure with or without high normal heart rate in patients with normal cardiac function). We prefer colloid (albumin) because it has a reverse oncotic effect and may remain in the intravascular space for a longer period than saline alone. Boluses of 10% pentastarch (molecular weight, 264 kD) were used with some success in 2 patients with refractory hypotension during the leak phase who did not respond to aggressive crystalloid replacement and inotropic agents (14). Conservative fluid replacement to maintain central venous pressure at the minimum level required to prevent underperfusion-related sequelae (approximately 4 to 8 mm Hg, assuming normal pressure to be 8 to 12 mm Hg) may be helpful in preventing such leak phase sequelae as compartment syndromes (which require fasciotomy and increase the risk for infection) and rhabdomyolysis (which increases the risk for renal failure). For these reasons, achieving normotension and normal central venous pressure for their own sakes might be considered suboptimal during the leak phase of SCLS.

Mild lactic acidosis, elevated levels of creatine phosphokinase or liver transaminases, and oliguria are to be expected and may be tolerated to a certain extent, as long as hemodynamic and metabolic parameters do not deteriorate and urine output and urine electrolytes are strictly monitored for signs of acute tubular necrosis. Chronic anticoagulation should be considered in patients with venous thromboembolism during episodes (Figure). Consultation with an orthopedist is recommended to monitor intracompartmental pressure, and fasciotomy and muscle debridement should be considered as clinically indicated by the risk for muscle necrosis (67). The risk increases as compartment pressures exceed mean arterial pressure, but sufficient pressure is needed to prevent underperfusion of muscles. In 1 reported case, fasciotomy during an SCLS attack was complicated by acute cardiac arrest due to rapid release of potassium (serum potassium level, 7.8 mmol/L) with muscle reperfusion (15). Finally, aggressive diuretic therapy is needed during the postleak phase of fluid remobilization.

Many patients who experience even a moderately severe attack maintain adequate cognition and respiration and do not require mechanical ventilation. In more severe attacks, patients may require mechanical ventilation because of flash pulmonary edema.

Maintenance Therapy

Maintenance therapy may reduce the severity and frequency of episodes in patients with SCLS and is largely empirical (Table 2). Compounds that prevent cyclic adenosine monophosphate degradation and increase intracellular cyclic adenosine monophosphate levels, such as β-adrenergic agonists (terbutaline) and phosphodiesterase inhibitors (theophylline), have been used for several years at the Mayo Clinic and elsewhere and are effective in some patients (3, 68, 69). We therefore recommend that patients in whom SCLS has just been diagnosed begin receiving theophylline and terbutaline. The theophylline dosage must be individualized on the basis of peak serum concentrations, but dosages ranging from 400 to 1600 mg/d in adults and 10 to 36 mg/kg of body weight per day in children aged 1 to 9 years are usually necessary to achieve peak serum concentrations between 55.5 and 111 μmol/L. We have found that serum theophylline levels decrease over time, which necessitates regular monitoring to ensure that they are in the therapeutic range. The primary limitations of this therapy are side effects, such as tremor, anxiety or irritability, insomnia, and palpitations. Terbutaline should be given at a total dosage of 20 to 25 mg/d in divided doses as tolerated; cells may become desensitized to β-agonists after prolonged exposure (70).

Other maintenance therapies have been tried sporadically, with varying degrees of effectiveness. We emphasize that all of the following compounds remain unproven.

The anti-VEGF monoclonal antibody bevacizumab has been used successfully to treat patients with the
POEMS syndrome, in which VEGF seems to play a pathogenetic role (71), but was used without success in a patient with the chronic form of SCLS who had generalized edema, visceral effusions, IgA MGUS, and high plasma VEGF levels (11). However, homoconcentration, hypoalbuminemia, and posttreatment VEGF levels were not documented, which makes the diagnosis of SCLS and the ascertainment of treatment efficacy uncertain. No report describes the use of bevacizumab for classic acute SCLS episodes.

Dowden and colleagues (13) recently reported rapid improvement of a patient with classic acute SCLS who received infliximab, the humanized anti–tumor necrosis factor (TNF)-α monoclonal antibody.

Because of the prominence of MGUS in patients with SCLS, treatments that target plasma cells and their products are attractive potential strategies. Two patients with SCLS who had MGUS that evolved into myeloma had complete regression of vascular leak symptoms after receiving combination chemotherapy for myeloma (62). High-dose chemotherapy, followed by autologous peripheral blood stem-cell transplantation, has been successful in treating the POEMS syndrome (72, 73), and a patient with SCLS and plasma cell leukemia had complete resolution of capillary leak symptoms after autologous peripheral blood stem-cell transplantation, even when the leukemia relapsed (54). Given the similarity of SCLS to the POEMS syndrome, we propose that autologous peripheral blood stem-cell transplantation be considered for the treatment of patients with frequent, life-threatening SCLS episodes that are refractory to standard therapy.

Immunomodulatory drugs, such as thalidomide and lenalidomide, are toxic to malignant plasma cells and have been used successfully to treat the POEMS syndrome (74). Thalidomide therapy improved both visual symptoms and ophthalmologic findings in a patient with classic acute SCLS accompanied by macular edema (75). Anakinira, an IL-1 receptor antagonist that blocks the biological activity of IL-1, has induced remission in patients with the Schnitzler syndrome (urticaria, fevers, and acute inflammation) (76, 77) and those with “smoldering” or “indolent” multiple myeloma, but it has not been explored for the treatment of SCLS (78).

Intravenous immunoglobulin (IVIG) has been used successfully for years to treat autoantibody-mediated diseases. Patients with MGUS and acquired von Willebrand disease responded well to IVIG (60), which suggests that it could be effective in SCLS. Lambert and colleagues (8) recently demonstrated the efficacy of IVIG in reversing acute SCLS episodes in 3 patients. Gousseff and Amoura (6) report anecdotal success with IVIG as a prophylactic therapy for SCLS in 3 patients. Although 2 of our patients who had frequent, life-threatening SCLS episodes that are refractory to standard therapy.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Putative Mechanism</th>
<th>Efficacy in SCLS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial signal transduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline plus terbutaline</td>
<td>Phosphodiesterase inhibition and β-receptor stimulation; increases endothelial cAMP levels</td>
<td>Yes, as acute or maintenance therapy</td>
<td>5, 68</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Prostacyclin analogue; increases endothelial cAMP levels and promotes vascular smooth-muscle relaxation</td>
<td>Yes, in acute setting</td>
<td>33</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>Decreases Rho prenylation</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Dasatinib or imatinib</td>
<td>Decreases Src or other tyrosine kinase activity</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Decreases VEGF activity</td>
<td>No (tested with chronic form of SCLS)</td>
<td>15</td>
</tr>
<tr>
<td>Immune modulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory</td>
<td>Indeterminate (tested with chronic form of SCLS)</td>
<td>11, 64–65</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Decreases tumor necrosis factor–α activity</td>
<td>Yes, in acute setting</td>
<td>15</td>
</tr>
<tr>
<td>IMiDs (lenalidomide or thalidomide)</td>
<td>Decreases clonal plasma cells, anti-inflammatory</td>
<td>Yes (thalidomide)</td>
<td>75</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Decreases circulating paraprotein levels</td>
<td>Possible temporary efficacy</td>
<td>58</td>
</tr>
<tr>
<td>IVIG</td>
<td>Anti-inflammatory and anti-idiotypic</td>
<td>Yes, as maintenance therapy</td>
<td>8, 10</td>
</tr>
<tr>
<td>Hematologic intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous peripheral blood cell transplantation</td>
<td>Decreases clonal plasma cells</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Decreases B-cell levels</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Melphalan or prednisone</td>
<td>Decreases clonal plasma cells</td>
<td>Yes, in the setting of myeloma or plasma cell leukemia</td>
<td>54, 56</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Decreases clonal plasma cells</td>
<td>ND</td>
<td>–</td>
</tr>
<tr>
<td>Anakinira</td>
<td>Decreases clonal plasma cells</td>
<td>ND</td>
<td>–</td>
</tr>
</tbody>
</table>

cAMP = cyclic adenosine monophosphate; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IMiDs = immunomodulatory drugs; IVIG = intravenous immunoglobulin; ND = no data; SCLS = systemic capillary leak syndrome; VEGF = vascular endothelial growth factor.
apy (13, 24). At this point, the long-term effectiveness of IVIG for the treatment of SCLS is unknown.

**Prognosis**

The prognosis of SCLS is uncertain; however, Dhir and colleagues (5) estimated the current 5-year survival rate to be 70%. Other studies (4, 6) have placed the overall 10-year mortality rate of SCLS at 25% to 34%. In our experience at the Mayo Clinic, the median survival of patients (counting only SCLS-related deaths) followed over 30 years was approximately 15 years. Complications may include compartment syndromes (67); renal failure from hypoperfusion-induced acute tubular necrosis or myoglobinuria secondary to rhabdomyolysis (67); and venous and arterial thrombosis, including pulmonary embolism (79) (Figure 1). We estimate that most patients who survive an appropriately treated severe SCLS attack do not typically exhibit residual end-organ damage. Regardless, chronic renal failure and long-term extremity sensorimotor deficits do occur as a result of ischemia and compartment syndromes.

**Areas of Uncertainty**

Because the pathophysiology of SCLS is unknown and no valid criteria for diagnosis exist, we stress the importance of demonstrating hypotension, hemoconcentration, and hypoalbuminemia in patients with recurrent episodes of edema to establish the diagnosis. It is unclear whether patients with chronic SCLS, who often lack cyclic leak or postleak phases, frank hypotensive episodes, and a serum paraprotein, have a distinct pathophysiologic basis for their symptoms. In either case, secondary causes of edema must be rigorously excluded until unique diagnostic indicators of SCLS are discovered.

We also emphasize the need for prospective therapeutic studies for SCLS outside of the time-honored regimen of theophylline and terbutaline. The fatal nature of SCLS and the persistent difficulty in treating acute, grave attacks may warrant investigation of newer, evidence-based therapeutic methods. Targeting other endothelial signal transduction pathways may be possible for SCLS. For example, statins may reduce vascular permeability (80–83) by inhibiting Rho prenylation and could either diminish symptoms in patients with chronic SCLS or reduce the severity of acute flare-ups. Src and abl tyrosine kinase inhibitors (such as dasatinib or imatinib), which have been used in part by the Intramural Research Program of the National Institutes of Health, National Institute of Allergy and Infectious Diseases, grant AI001083 LAD (Dr. Druey).

**Conclusion**

The systemic capillary leak syndrome is a multiorgan disease characterized by severe, transient episodes of massive endothelial barrier dysfunction with resulting hypotension, hemoconcentration, and macromolecular extravasation. The syndrome has rarely been reported in the literature, probably because of the high mortality on initial presentation and resulting underdiagnosis. Because little progress has been made in the treatment of SCLS, we feel that it is time for this disease to be reexamined, particularly because it shares many phenotypic similarities with other shock syndromes, such as sepsis, anaphylaxis, and angioedema. The endothelial dysfunction seen in SCLS also typifies a diverse group of disorders, including diabetic retinopathy (87), lupus nephritis (88), and infection with malaria or Ebola or Marburg viruses (89, 90). Clarification of the unique features of SCLS will further our understanding of both the immune system and endothelial cell biology. A succinct description of the signs, symptoms, and treatment of SCLS for both patients and physicians can be found on the National Organization for Rare Disorders Web site (www.rarediseases.org). Additional information and a patient networking community are available on the RareShare Web site (www.rareshare.org/communities/systemic-capillary-leak-syndrome) and the Mayo Clinic Web site (www.mayoclinic.org/systemic-capillary-leak-syndrome/).

From the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, and Mayo Clinic College of Medicine, Rochester, Minnesota.

**Acknowledgment:** The authors thank Omar Rahman, MD, Geisinger Medical Clinic, for his helpful discussions.

**Grant Support:** In part by the Intramural Research Program of the National Institutes of Health, National Institute of Allergy and Infectious Diseases, grant AI001083 LAD (Dr. Druey).

**Potential Conflicts of Interest:** None disclosed. Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-0527.

**Requests for Single Reprints:** Kirk M. Druey, MD, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Room 11N242, Bethesda, MD 20892; e-mail, kdruey@niaid.nih.gov.

Current author addresses and author contributions are available at www.annals.org.

**References**


The Systemic Capillary Leak Syndrome


Current Author Addresses: Dr. Druey: Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Room 11N242, Bethesda, MD 20899. Dr. Greipp: Mayo Clinic College of Medicine, Department of Hematology, 200 First Street SW, Rochester, MN 55905.

Author Contributions: Conception and design: K.M. Druey, P.R. Greipp. Analysis and interpretation of the data: K.M. Druey, P.R. Greipp. Drafting of the article: K.M. Druey. Critical revision of the article for important intellectual content: K.M. Druey, P.R. Greipp. Final approval of the article: K.M. Druey, P.R. Greipp. Administrative, technical, or logistic support: K.M. Druey. Collection and assembly of data: K.M. Druey, P.R. Greipp.

Appendix Table. Proposed SCLS Severity Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Defining Clinical Course</th>
<th>Hemoconcentration</th>
<th>Hypoalbuminemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Oral fluid resuscitation only</td>
<td>Increase in hemoglobin level $\leq 30$ g/L</td>
<td>Decrease in albumin level $\leq 5$ g/L</td>
</tr>
<tr>
<td>1b</td>
<td>Oral fluid resuscitation only</td>
<td>Increase in hemoglobin level $\geq 30$ g/L</td>
<td>Decrease in albumin level $\geq 5$ g/L</td>
</tr>
<tr>
<td>2</td>
<td>IV fluids, no hospitalization</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>IV fluids, ICU monitoring</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>Fatal</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; IV = intravenous; SCLS = systemic capillary leak syndrome.