I. Definition: Shift of intravascular fluid and plasma into the extravascular space (Fardet et al., 2004)

II. Physiology/Pathophysiology (Fishel, Are, & Barbul, 2003; Marx, 2003)
   A. Normal: Small blood vessels carrying blood and forming the capillary system. Capillaries connect the smallest arteries (arterioles) with the smallest veins (venules).
   B. Pathophysiology
      1. Generalized capillary endothelial cell injury in multiple organs is responsible for the development of capillary leak syndrome (CLS).
      2. Endothelial cell damage may occur because of endotoxin exposure, ischemia, vessel injury with platelet deposition, or mechanical injury.
      3. Cytokines such as interleukin (IL)-2, tumor necrosis factor (TNF)-alpha, anti IL-1 B, and CD8-positive lymphocytes are present and may have a role in triggering CLS.
      4. Platelet-activating factor and vascular endothelial growth factor increase vascular permeability.
      5. Inflammatory reactions occur and cause microvascular permeability, capillary leak, loss of protein, tissue edema, and hypoalbuminemia.
      6. A shift of fluid and albumin into body tissues occurs.
      7. An associated decreased peripheral vascular resistance, hypotension, and intravascular volume compound the fluid shift.

III. Clinical features (Cahill, Spitzer, & Mazumder, 1996; Nurnberger, Willers, Burdach, & Gobel, 1997)
   A. Risk factors
      1. Blood and marrow stem cell transplant
         a) During preparative regimen
         b) During time of engraftment along with abnormalities in liver and renal function
         c) During rapid steroid tapers
         d) During infection or graft-versus-host disease
         e) During infusion of donor white blood cells (WBCs)
         f) During infusion of marrow/blood stem cells
         g) Human leukocyte antigen mismatched bone marrow transplant recipient
         h) Oxygen toxicity
      2. Kidney transplant
      3. Liver transplant
      4. Biotherapy (especially IL and TNF)
      5. Chemotherapy
   B. History
      1. History of cancer and cancer treatment
      2. Current medications: Prescribed and over-the-counter
      3. History of presenting symptom(s): Precipitating factors, onset, location, and duration
      4. Changes in activities of daily living
   C. Signs and symptoms
      1. Ascites
      2. Weight gain
      3. Edema and/or anasarca (generalized total-body edema)
      4. Chest pain
      5. Shortness of breath
      6. Productive or nonproductive cough
      7. Tachypnea
      8. Decreased urine output
      9. Fever
      10. Lethargy, malaise, or obtundation
      11. Confusion and restlessness
      12. Cyanosis and pallor of skin, lips, and nail beds
   D. Physical exam
      1. Vital signs: Weight (signs of gain), blood pressure (hypotension), pulse (tachycardia)
      2. Pulmonary exam: Presence of rales and rhonchi on auscultation; dullness on percussion over consolidated areas
      3. Cardiac exam: Presence of S3, S4, murmur, or gallop; tachycardia; peripheral edema
4. Abdomen exam: Ascites, tenderness, distention, softness or firmness, hepatomegaly, splenomegaly, presence or absence of bowel sounds
5. Dermatologic: Presence of purpuric lesions, flesh-colored or erythematous lesions (Fardet et al., 2004)

IV. Diagnostic tests
A. Laboratory
   1. Complete blood count with differential
      a) Elevated WBC count may increase suspicion of infection.
      b) Hemoconcentration may occur with an increased WBC count and hematocrit.
   2. Urinalysis
      a) Presence of leukocytes may be caused by infection.
      b) Presence of protein or casts may indicate renal failure or disease.
   3. Liver function tests, including total and direct bilirubin, to rule out hepatobiliary disease
   4. Renal function tests, including urea and creatinine, to evaluate renal function
   5. Serum albumin: May be decreased, leading to decreased oncotic pressure and edema
B. Radiology: Chest x-ray: To rule out noncardiogenic pulmonary edema, pleural effusion, pulmonary venous hypertension, interstitial infiltrates, and pericardial effusions
C. Other
   1. Bronchoscopy, with or without lung biopsy, can rule out infection, hemorrhage, or other causes of respiratory distress.
   2. Arterial blood gases may show hypoxia and CO2 retention.
   3. Pulmonary function tests reveal decreased pulmonary compliance.
   4. Hemodynamic monitoring including pulmonary capillary wedge pressure (PCWP) and cardiac output to measure fluid status (normal PCWP = 6–12 mm Hg; normal cardiac output = 4–8 liters/minute)
      a) Decreased PCWP may indicate hypovolemia.
      b) Increased PCWP may indicate left ventricular failure or cardiac insufficiency.
      c) Cardiac output may be increased early in CLS, then decreased later in the syndrome.
   5. Skin biopsy: Mild perivascular, nonspecific dermal mononuclear infiltrates; mucinous deposits; mild lymphocytic infiltration (Fardet et al., 2004)

V. Differential diagnosis (Fardet et al., 2004)
A. Paraproteinemias or diseases/conditions with low protein levels
B. Lymphoma
C. Psoriasis
D. Drug-induced, such as IV cyclosporine or amphotericin-B, biotherapy
E. Viral syndrome, such as cytomegalovirus
F. Pneumonitis
G. Sepsis (see Chapter 140)
H. Disseminated intravascular coagulation (see Chapter 118)
I. Cytokine reaction

VI. Treatment: Supportive care until CLS resolves (Amoura et al., 1997; Fardet et al., 2004; Fishel et al., 2003; Marx, 2005)
A. Treat the underlying cause.
B. Administer glucocorticoids at high doses, then taper quickly as tolerated.
C. Provide IV fluid replacement.
   1. Infusion of colloids rather than crystalloids, such as blood or albumin
   2. Infusion of albumin
D. Administration of diuretics is controversial because intravascular hypovolemia is present and acute renal failure may develop.
E. Restrict oral fluids to 500–1,000 ml per day. Gradually increase fluids as condition improves.
F. Hemodialysis may be necessary if acute renal failure occurs.
G. Mechanical ventilation may be indicated if respiratory distress or failure occurs.
H. Prophylactic antibiotics may promote growth of organisms and are not recommended.
I. Administer vasopressors as needed for management of hypotension.
J. Provide nutritional support, such as enteral feedings or total parenteral nutrition, to maintain high caloric intake because of increased energy expenditure.
K. Clinical studies using antibodies to IL-1, IL-6, TNF-alpha, angiopoietin-1, and endothelin A receptor antagonist blocks or reduces capillary leak in animal models (Fishel et al., 2003).

VII. Follow-up
A. Inpatient hospitalization is necessary to manage the signs, symptoms, and complications of CLS.
B. Perform daily monitoring of intake, output, weight, and renal and liver function.
C. Perform frequent chest radiographs to monitor pulmonary edema.

VIII. Referrals
A. Nephrologist: To evaluate acute renal failure and recommend management
B. Pulmonologist: To evaluate lung function, perform bronchoscopy, and recommend management

References