Capillary Leak Syndrome—

Desk to Bed Side

Tarun Kumar Dutta, Ratnakar Sahoo, B Karthikeyan

Abstract: Capillary leak syndrome (CLS) is characterized by hypotension with hemoconcentration, hypoalbuminemia without albuminuria and generalized edema, the etiology of which is multiple starting from snake bite and dengue fever to sepsis and drugs. Typically the syndrome manifests in two phases: initial capillary leak phase characterized by generalized edema, serous effusion and hypotension which is followed by phase of volume overload or recruitment phase. Similarly treatment is in form of fluid replacement to vasopressor therapy and inotropic support during capillary leak phase and diuretics during volume overload phase, apart from specific treatment for the cause of CLS. Prognosis, however, is poor in most of the patients. The important parameters of CLS are summarized:

- CLS is due to increased capillary permeability from various etiologies.
- Inflammatory mediators play a key role in CLS.
- Diagnostic features of CLS are hemoconcentration, hypotension, generalized edema and hypoalbuminemia without albuminuria.
- Fluid resuscitation is essential in the initial phase of CLS.
- Clinical signs of volume overload herald the second phase of CLS which require diuretic/ultrafiltration therapy.
- In some specific conditions colloid has been found superior to crystalloids.
- Vasopressor support/vasoconstrictors may be required based on the clinical setting.
- Theophyllines, terbutaline, leucotriene inhibitors have been shown to be of benefit in SCLS. Withdrawal of offending medication usually causes improvement in drug associated CLS. Management of snake bite/sepsis/VHF associated CLS is mainly supportive; steroids may cause some benefit. Toxalbunins have potential to be used in bioterrorism and treatment of manifestations is symptomatic though toxoids are available for pre-exposure prophylaxis.

• Early diagnosis, good supportive care, monitoring of fluid electrolyte status, vasopressor therapy, antibiotics and ventilatory support are essential in management of CLS.

INTRODUCTION

Capillary leak syndrome (CLS) otherwise called as capillary permeability syndrome was first described by Clarkson in 1960. Thus, it is also known as Clarkson’s syndrome. It is characterized by hypotension with hemoconcentration, hypoalbuminemia without albuminuria and generalized edema. This syndrome is due to capillary hyperpermeability with massive extravasation of plasma containing macromolecules smaller than 200kD and sometimes upto 900kD. Capillary leak may occur as a part of the systemic capillary leak syndrome (SCLS) or secondary to the systemic inflammatory response syndrome (SIRS). This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following toxemias, poisoning shock syndromes, low-flow states, or ischemia-reperfusion injuries. It can lead to generalized edema and multiple organ failure.
STRUCTURE OF THE MICROCIRCULATION²

The Capillaries

The smaller arterial branches terminate in networks of vessels, which pervade nearly every tissue of the body. These vessels are termed capillaries. They are interposed between the smallest branches of the arteries and the commencing veins, constituting a network, the branches of which maintain the same diameter throughout; the meshes of the network are more uniform in shape and size than those formed by the anastomoses of the small arteries and veins.

The diameters of the capillaries vary in the different tissues of the body, the usual size being about 8 μ. The smallest are those of the brain and the mucous membrane of the intestines; and the largest those of the skin and the marrow of bone, where they are stated to be as large as 20 μ in diameter. The form of the capillary net varies in the different tissues, the meshes being generally rounded or elongated. Sometimes the capillaries have a looped arrangement, a single vessel projecting from the common network and returning after forming one or more loops, as in the papillae of the tongue and skin.

The number of the capillaries and the size of the meshes determine the degree of vascularity of a part. The closest network and the smallest interspaces are found in the lungs and in the choroid coat of the eye. In these situations the interspaces are smaller than the capillary vessels themselves. In the intertubular plexus of the kidney, in the conjunctiva, and in the cutis, the interspaces are from three to four times as large as the capillaries which form them; and in the brain from eight to ten times as large as the capillaries in their long diameters, and from four to six times as large in their transverse diameters. In the adventitia of arteries the width of the meshes is ten times that of the capillary vessels. As a general rule, the more active the function of the organ, the closer is its capillary net and the larger its supply of blood; the meshes of the network are very narrow in all growing parts, in the glands, and in the mucous membranes, wider in bones and ligaments which are comparatively inactive; blood vessels are nearly altogether absent in tendons, in which very little organic change occurs after their formation. In the liver the capillaries take a more or less radial course toward the intralobular vein, and their walls are incomplete, so that the blood comes into direct contact with the liver cells. These vessels in the liver are not true capillaries but “sinusoids”, they are developed by the growth of columns of liver cells into the blood spaces of the embryonic organ.

Structure

The wall of a capillary consists of a fine transparent endothelial layer, composed of cells joined edge to edge by an interstitial cement substance, and is continuous with the endothelial cells which line the arteries and veins. When stained with nitrate of silver the edges, which bound the epithelial cells, are brought into view. These cells are of large size and of an irregular polygonal or lanceolate shape, each containing an oval nucleus, which may be displayed by carmine or hematoxylin. Between their edges, at various points of their meeting, roundish dark spots are sometimes seen, which have been described as stomata, though they are closed by intercellular substance.

Pathophysiology of CLS

Capillary permeability is influenced by hemodynamic forces, cytokines and inflammatory mediators. The exact mechanism of the capillary leak syndrome is still not elucidated. Various mechanisms for this phenomenon have been postulated for specific etiologies like SCLS, snakebite, hemorrhagic fevers, toxins, graft versus host disease, post chemotherapy and monoclonal gammopathy of IgG class. Components from the sera of patients with active SCLS in contrast to healthy subject sera mediate early and extensive endothelial apoptosis in vitro is
associated with oxidation injury. These data represent compelling initial evidence for oxidation-induced apoptosis as a likely mechanism for endothelial injury leading to SCLS.³

**Etiology of Capillary Leak Syndrome**

The causes of capillary leak are:

1. Primary/idiopathic systemic capillary leak syndrome.
2. Secondary capillary leak syndrome:
   a. Venomous snake bite (ophitoxemia).
   b. Viral hemorrhagic fever (dengue, hantan virus).
   c. Toxin related (abrin, ricin, sanguinarine).
   d. Adverse drug reaction (interleukin-2, interferon β-1b, gemcitabine).
   e. Endocrine (hypothyroidism).
   f. Sepsis related CLS.
   g. Miscellaneous (following cardio-pulmonary bypass, BMT).

**Primary/Idiopathic Systemic Capillary Leak Syndrome**

This type of capillary leak syndrome is a rare idiopathic disorder characterized by recurrent episodes of hypotension and hemoconcentration due to sudden transient extravasation of 10-70% of plasma. More than 50 cases have been reported; of the first 25 patients described, 19 (76%) did not survive beyond 5 years after the diagnosis. Although the morbidity and mortality rates associated with this syndrome are high, the prognosis seems to have improved recently. Clinically, this syndrome presents with a characteristic triad of hypotension, hemoconcentration, and hypoalbuminemia, often with an associated monoclonal gammopathy (without any evidence of multiple myeloma). It has been reported in patients aged 21 to 68 years of age.⁴

Crisis are heralded by abdominal pain, nausea, and vertigo, followed rapidly by severe shock and generalized edema. Normal blood pressure is restored by intravenous fluid administration. The end of the crisis is characterized by rapid polyuria. A monoclonal gammapathy, the only laboratory anomaly between crises, has been described for all but two of the reported cases. The differential diagnosis of SCLS includes C1 esterase inhibitor deficiency, adrenal disease or myeloma. In many of the reported cases, death occurred during severe shock because of lack of vascular access. The pathophysiology of SCLS is still unclear. Leukotriene B4 (LTB4) plays a central role in capillary permeability.⁴ Although capillary permeability can be increased by a number of circulating factors, including histamine, bradykinin, complement derived anaphylatoxins, C5a and C3a, it has been found that complement, kinins, prostaglandin, coagulation factors, histamine and serotonin are all normal in patients with SCLS. A secondary SCLS has been induced by injection with IL-2 and IFN β and has been described in graft vs host disease and infection, suggesting a role for cytokines in the pathogenesis of SCLS. However, cyclosporin A, which decreases IL-2 production, did not prevent crises in patients.

**Venomous Snake Bite (Ophitoxemia)**

Snake venom, is a mixture of enzymatic and non-enzymatic compounds as well as other nontoxic proteins including carbohydrates and metals. There are over 20 different enzymes including phospholipases A2, B, C, D hydrolases, phosphatases (acid as well as alkaline), proteases, esterases, acetyl cholinesterase, transaminase, hyaluronidase, phosphodiesterase, nucleotidase and ATPase and nucleosidases (DNA and RNA). The non-enzymatic components are loosely categorized as neurotoxins and hemorrhagens. These hemorrhagens are zinc containing metalloproteinases which degrade the compact proteins of basement membrane underlying endothelial cells. They also act on endothelial cells causing lysis or drifting apart of vascular endothelium leading to shift of fluid from intravascular to interstitial space.
Two vascular apoptosis inducing proteins VAP1 and VAP2 that damage endothelial cells have been identified. The apoptotic activity of VAP2 is specific for endothelial cells.\(^6\) Snake venom has also been found to produce reactive oxygen species in endothelial cells (ROS) which lead to apoptosis. Serine protease—a capillary permeability increasing enzyme (CPI-2), has been isolated from the venom of snakes.

The pathophysiologic basis for morbidity and mortality is the disruption of normal cellular functions by these enzymes and toxins. Some enzymes such as hyaluronidase disseminate venom by breaking down tissue barriers. The variation of venom composition from species to species explains the clinical diversity of ophitoxemia. There is also considerable variation in the relative proportions of different venom constituents within a single species throughout its geographical distribution, at different seasons of the year and as a result of aging. The various venom constituents have different modes of action. Ophitoxemia leads to increase in the capillary permeability, which may cause loss of blood and plasma volume into the extravascular space. This accumulation of fluid in the interstitial space is responsible for edema. The decrease in the intravascular volume may be severe enough to compromise circulation and lead on to shock. Snake venom also has direct cytolytic action causing local necrosis and secondary infection, a common cause of death in snakebite patients. Hypotension and shock are common in patients bitten by Vipera species (e.g., V. palaestinae and V. berus), some of the North American rattlesnakes (e.g., C. adamanteus, C. atrox and C. scutulatus), Bothrops and Daboia. They may also occur with Echis carinatus (saw-scaled viper) bite. The central venous pressure is usually low and the pulse rate rapid, suggesting hypovolemia, for which the usual cause is extravasation of fluid into the bitten limb. Patients envenomed by Burmese Russell’s vipers show evidence of generally increased vascular permeability.

The pathological changes in the capillary by BaH1, a hemorrhage metalloproteinase isolated from Bothrops asper was studied in mouse gastrocnemius muscle after intravascular injection of the toxin. At the ultrastructural level the earliest change was decrease in the number of pericyte vesicles, cytoplasmic projections into vascular lumen and detachment of the endothelial cell from the surrounding lamina with thinning of the endothelial cell. Capillaries showed gaps in endothelium through which fluid leaks to the interstitial space.

**Viral Hemorrhagic Fever (Including Dengue)**\(^7\)

CLS is a known complication of dengue. It is a principal pathologic event in causation of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

The hematocrit in DHF is usually > 40%, but may be as high as 55-60%. This hemoconcentration is due to plasma leakage, which starts at the end of the febrile stage and continues up to 24-48 hours after defervescence of fever. Increased capillary permeability leading to plasma leakage is by far the most common cause of shock in DHF.

Early diagnosis of capillary leak is essential to start volume replacement and indicates progression to DSS.

**Plasma leakage is manifested by:**
- Rapidly rising hematocrit.
- Hematocrit equal to or greater than 20% of baseline.
  [Caution: This hematocrit criterion is not applicable in patients with prior anemia or significant blood loss at presentation].
- A drop in hematocrit following volume replacement equal to or greater than 20% of hematocrit at presentation.
- Pleural effusion, ascites (serositis).
- Suspect plasma leakage in:
  - males with hematocrit above 47%
  - females with hematocrit above 40%
Management is mainly supportive with fluids and inotropes initially in phase 1 and diuretics in phase 2 of the CLS.

**Clinical Features**

*Figs 4.1 to 4.5*

**Prodromal Phase**

- Irritability, fatigue, myalgia
- Nausea, and abdominal pain
- Thirst, presyncope, syncope

**Initial Phase 1-4 Days (Phase 1)**

- Generalised edema
- Compartment syndromes
- Intestinal edema
- Ascites
- Pleural and pericardial effusion
- Rhabdomyolysis
- Renal failure
- Conjunctival chemosis (*Figs 4.1 and 4.2*)
- Hypotension

**Recruitment Phase (Phase 2)**

- Pulmonary edema
- Polyuria

Myalgias in the extremities frequently occur, possibly as a result of subclinical compartment syndromes.

The clinical presentation of an acute episode consists of **two phases**.

**Initial capillary leak phase (first phase)** may last from 1 to 4 days and is essentially a phase of acute hypovolemia due to marked extravasation of intravascular fluids and macromolecules. The capillaries are unable to retain macromolecules smaller than 200 kDa and, sometimes, ones as large as 900 kDa. Therefore, hemoconcentration, leukocytosis, increase in IgM concentration, and decrease in concentrations of albumin, IgG, C3, and C4 may occur, as well as extravasation of plasma occurs up to 70%. Compartment syndromes, intestinal edema, ascites, pleural and pericardial effusions may occur. Of note, the pulmonary, cerebral, and renal circulations are infrequently involved in this phase. Complications of the capillary leak phase include rhabdomyolysis caused by compartment syndromes. Renal failure can result from acute tubular necrosis due to either hypotensive shock or rhabdomyolysis.

**The recruitment phase (second phase)** is the normalization of the extraordinary vascular leak, resulting in the recruitment of the initially extravasated fluids (native and supplemental) and macromolecules. This may result in severe acute intravascular fluid overload; thus, this period is critical for the patient. Although the patient’s kidneys may function normally, the ensuing diuresis may be unable to keep up with the rapidity of the recruitment. This can result in pulmonary edema, the most frequent cause of death in the systemic capillary leak syndrome. In between episodes, patients are asymptomatic and, except for monoclonal gammopathy, usually do not have significantly abnormal laboratory values.

**Laboratory Diagnosis**

- Hemoconcentration
- Leukocytosis
- Increase in IgM concentration
• Decrease in serum albumin without albuminuria
• Decrease in serum IgG, C3, and C4.

Management of Capillary Leak
The management of capillary leak requires a multi-pronged approach. Early diagnosis of capillary leak is essential to start volume replacement. BP, hematocrit, serum albumin should be monitored to diagnose CLS early. Management consists of supportive care, specific treatment and use of possible disease modifying agents.

Supportive Care
- ICU care indicated whenever available
- Withdraw offending drugs if applicable
- Continuous monitoring of vital signs.
- Subclavian/jugular CVP/peripherally inserted central catheter (PICC)
  Position of the central line to be confirmed as fluid management depends on accurate measurement of CVP.
- Continuous bladder drainage (CBD) measurement of accurate urine output.
- Hematocrit monitoring every 4 to 6 hours or as clinically indicated.
- Renal and liver profile/ABG/DIC screening, and repeat as required.

Volume Replacement
Volume replacement has to be done aggressively to maintain perfusion to vital organs, both colloids and crystalloids can be used. Anectodal reports suggest that colloids may be superior in specific conditions, but the difference is not significant. In cases of snake bite, fresh frozen plasma has been recommended. Colloids and volume expanders at the rate of 20 ml/kg body weight/hourly has been recommended in cases of DSS. Crystalloids are recommended in sepsis. For adult patients who are hypotensive, an isotonic crystalloid solution (sodium chloride 0.9% or Ringer lactate) in boluses of 500 mL (10 mL/kg in children), should be administered with repeat clinical assessments after each bolus. Administer repeated boluses until signs of adequate perfusion are restored. A total of 4-6 L may be required. Monitor patients for signs of volume overload, such as dyspnea, pulmonary crackles, and pulmonary edema, on chest radiograph. Improvement, stabilization, and normalization of the patient’s mental status, heart rate, BP, capillary refill, and urine output indicate adequate volume resuscitation.

Vasopressors and Inotropic Support
When proper fluid resuscitation fails to restore hemodynamic stability and tissue perfusion, therapy should be initiated with vasopressor agents. These agents are dopamine, norepinephrine, epinephrine, and phenylephrine. These vasoconstricting drugs maintain adequate BP during life-threatening hypotension and preserve perfusion pressure for optimizing flow in various organs. The mean BP required for adequate splanchnic and renal perfusion (mean arterial pressure [MAP] of 60 or 65 mm Hg) should be maintained based on clinical indices for organ perfusion. If the patient remains hypotensive despite volume infusion and moderate dose dopamine, a direct vasoconstrictor (e.g. norepinephrine) at a dose of 0.5 mcg/kg/min should be started and titrated to support a systolic BP of 90 mm Hg. While potent vasoconstrictors (e.g. norepinephrine) traditionally have been avoided because of their adverse events on cardiac output and renal perfusion, human data has shown that norepinephrine can reverse septic shock in patients unresponsive to volume and dopamine therapy. These patients require invasive hemodynamic monitoring with arterial lines and pulmonary artery catheters.

Diuresis/Dialysis
During the second phase of capillary leak, there is reaccumulation of extravasated fluid into the intravascular space; patient requires diuretics in this phase to prevent life threatening pulmonary edema. When renal failure complicates the picture as in ophitoxemia, intensive dialysis and ultrafiltration/fluid removal is required for prevention of complications. The second phase is identified by improvement in BP, fall of hematocrit and complication of fluid overload.

Specific Treatment
Specific treatment is directed against the primary disease process like appropriate antibiotics in sepsis, anti-snake venom (ASV) in ophitoxemia, withdrawal of the offending drug and levothyronine in hypothyroidism.

DISEASE MODIFYING AGENTS

- Theophylines
- Terbutaline
- Leucotriene inhibitors
- Monteleukast, Zafarleukast
- Plasmapheresis
- Prostacyclin
- Gingko biloba
- Corticosteroids
- Eicosapentonoic acid.

An algorithm of management is given in Flow Chart 4.1. Leucotriene inhibitors like monteleukast and zafarleukast, have been shown to terminate an acute episode. Plasmapheresis, steroids, prostacyclin, and Gingko biloba have been tried in individual patients with variable success. Corticosteroids have also been tried in patients with variable results.

Experimental Therapies
Endothelial cell apoptosis has been shown to be increased in CLS, and apoptosis is induced by reactive oxygen species (ROS). Studies have shown that antioxidants such as aminothiol protect against endothelial cell apoptosis. A great deal of interest exists in using antioxidants as adjuncts to resuscitation to try to minimize oxidant-mediated contributions to the inflammatory cascade. In particular, mega dose vitamin C infusion during resuscitation has been studied in animals. Endothelium stabilizing agents may have a role in treatment. Inhibitors of nitric oxide, which play a role in IL-2 induced CLS have been shown to ameliorate interleukin-2 therapy-induced capillary leak syndrome in healthy or tumor-bearing mice without compromising the antitumor effects of IL-2 therapy. Antibodies to endotoxin may be helpful in management of sepsis-induced CLS.

Despite best of treatment prognosis is poor in most of the patients.

Experience at JIPMER, Pondicherry
We encountered a total of 15 cases of CLS following viperine bite (viperine bite being very common in this part of the country) over a period of 21 months. Out of 15 cases, 11 were male and four were female patients; and age ranged from 14 years to 55 years. All of them had chemosis of eye at the outset and CVP was always zero. Associated complications were acute renal failure, cellulitis, sepsis, DIC and overt bleeding. Treatment of these patients with ASV, antibiotics, fresh frozen plasma and hemodialysis did not save them except in case of one patient, who was additionally given intravenous hydrocortisone.

REFERENCES
2. Grays Textbook of Anatomy online version.