

### Cholesterol embolism

Cholesterol embolism (CE), also known as atheroembolism, is a condition that is often unrecognized in medicine. It is defined by the occlusion of small- and medium-caliber arteries (100-200  $\mu$  m in diameter) by cholesterol crystals (see the image below). Although it was first reported by Panum nearly 150 years ago, clinicians have only recently become aware of its potentially devastating and rather frequent consequences. Too often, the diagnosis of cholesterol embolism is missed or overlooked, with its nonspecific symptoms misattributed to other, more common entities. In 1987, Fine et al described recognizable skin findings in patients with cholesterol embolism, thereby linking cholesterol embolism to conclusive, conspicuous signs and symptoms. In 1999, Belenfant et al described a successful treatment regimen, unleashing breakthrough advances for a disease that has troubled clinicians for more than a

century

Despite these advances, cholesterol embolism is still a troublesome entity to clinically diagnose and effectively treat. Fine's description of livedo reticularis or blue toes (as shown below) in the presence of good peripheral pulses remains invaluable in recognizing cholesterol embolism. However, a high index of suspicion is imperative because symptoms of cholesterol embolism are often atypical, unrecognized, not temporally correlated with the onset of physical findings, or not reported by the patient. Additionally, laboratory test results are not specific for cholesterol embolism. More importantly, although biopsy results demonstrating the needle-shaped cholesterol clefts and intravascular microthrombi are the most specific findings, histologic diagnosis does not always correlate with clinical disease.

# **Pathophysiology**

Despite its often inconspicuous presence on magnetic resonance angiography, atherosclerosis is a necessary prerequisite for cholesterol embolism. However, its mere existence is not always sufficient to cause clinically significant disease. Instead, cholesterol embolism is often triggered by events or procedures that disrupt unstable atherosclerotic plaques, most frequently during invasive vascular radiographic or surgical procedures and the administration of anticoagulants or thrombolytics. Although rare, reports describe spontaneous cholesterol embolism in patients with predisposing risk factors and unstable plaques. 3,4,5

Regardless of proximate cause, the rupture of atheromatous plaques in major arteries releases a shower of cholesterol crystals into the bloodstream. These crystals migrate distally until they lodge in small arterioles, where they provoke an acute inflammatory response. This response triggers a cascade of events, eventually causing intravascular thrombus formation, endothelial proliferation, and, finally, fibrosis of the vessel. Microvascular ischemia leads to tissue loss by segmental infarction, organ dysfunction, and, rarely, catastrophic organ failure. The end result may be devastating ischemia, infarction, and necrosis of the organs supplied by the affected vessels.

In any given patient, the precise clinical syndrome depends on the location of the source of embolism and the pattern and distribution of flow downstream. The most common sites for severe atheromatous disease are in the abdominal aorta and the iliac and femoral arteries; accordingly, signs and symptoms more commonly result from embolism to the lower half of the

body. In fact, 80% of cases are associated with aortoiliac atheromatous plaques. Patients with cholesterol embolism frequently present with lower limb ischemia (blue or purple toe syndrome), abdominal pain, melena, and a stepwise decline in creatinine clearance levels resulting from focal underperfusion of the intestine and the kidneys. When the source of crystals is in the aortic arch, signs and symptoms of embolization may occur in the eyes and the CNS.<sup>6</sup>

Clinical manifestations may be immediate, or a delay of several months may occur after the inciting event. A 1999 study by Belenfant et al of patients with cholesterol emboli found that the likely precipitating event occurred an average of 2 months before their admittance to the ICU with fulminant disease

Once termed the great masquerader for its clinical similarity to several other important systemic diseases (eg, polyarteritis nodosa), cholesterol embolism syndrome is often misdiagnosed. Thus, a high suspicion is needed, especially in the setting of a history of preexisting atherosclerotic disease and specific precipitating events. The classic triad of excruciating lower extremity pain, livedo reticularis, and good peripheral pulses in a person older than 50 years should be considered to be due to cholesterol embolization until proven otherwise.

# **Physical**

The onset of physical findings may be delayed by days to months. Cutaneous manifestations are the most common physical findings in patients with cholesterol embolism (on average, 35% of patients) and the most helpful in establishing a diagnosis. Jucgla et al revealed skin findings in 88% of patients with known disease,<sup>8</sup> and a 2004 report by Manganoni indicated that 50 of 52 patients had recognizable skin findings, often marked erythema of the toes.

On average, when using postmortem findings as the criterion standard for diagnosis, dermatologic findings were associated with a 3-fold increased likelihood of establishing a premortem diagnosis of cholesterol embolism. The following percentages represent all skin lesions found in cholesterol embolism in multiple studies; the total exceeds 100% because more than one manifestation is usually present in an individual.

- Livedo reticularis: This is the most common dermatologic manifestation of cholesterol embolism, comprising 50-74% of cholesterol embolism–related skin lesions.

8 This blue-red

mottling of the skin in a netlike pattern usually affects the feet, the legs, the buttocks, and the thighs and can extend to the trunk and the upper extremities. Occasionally, livedo reticularis may be noted only while the patient is standing; therefore, examining patients in both the supine position and the standing position is important. Livedo occurs with any process that increases the visibility of the venous plexus. See the image below

- Gangrene: Occurring in 35% of patients, gangrene is the loss of tissue due to ischemia. In cholesterol embolism, it may develop in preexisting acrocyanosis or livedo reticularis. Gangrene is almost always dry and confined to the toes (bilaterally in 50% of patients), but rarely it involves the scrotal area. It usually demarcates within weeks and eventually requires surgical debridement. See the image below.

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Acrocyanosis or blue toe syndrome: Occurring in 28% of patients, this is a characteristic blue-black or violaceous discoloration of the distal extremities. The lesions are painful, discolored, or even necrotic from ischemia. Blue toe syndrome, a term coined by Karmody et al,

refers to acute digital ischemia caused by microembolism from the distal aorta, iliac artery, or femoral artery

- Ulceration: This occurs in 17-39% of patients<sup>8</sup> and is typically unilateral and located on the toes and the feet. Unusual presentations, refractory and recurrent ulcers of the digits and the lower extremities, have also been reported.
- Nodules or indurated papules: These are present in 10% of patients and are firm, violaceous, and painful. They can appear on the legs, thighs, toes, or feet as a result of an inflammatory reaction surrounding cholesterol crystals.
- Purpura: Occurring in 9% of patients, this is most commonly seen on the legs and the feet. The lesions resemble those of vasculitis, but, unlike other features in cholesterol embolism, they typically spare the toes.
- Petechiae: Small, pinpoint, purpuric spots, petechiae do not blanch on diascopy and may rarely appear in persons with cholesterol embolism (4%).
  - Balanitis and necrosis of the penile foreskin, perineal area, and scrotum: This has been

reported with cholesterol embolism, reflecting a distal aortic or iliofemoral source.

- Cholesterol clefts: Isolated case reports describe cholesterol clefts in solitary lesions in unusual locations (eg, a nodule on an ear, red and painful swelling on the chest) with microscopic findings of hemorrhagic panniculitis.
  - Punctiform subungual hemorrhages: These may occur.
- Full-thickness cutaneous infarcts mimicking heparin necrosis: These have been reported in patients with cholesterol embolism.

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Extracutaneous manifestations of cholesterol embolism are multifarious. These include constitutional symptoms, such as fever and weight loss, as well as the following:

- Renal manifestations (34%): The frequency of localization to viscera is suggested to roughly correspond to the amount of blood flow delivered. Receiving 20-25% of the cardiac output, all distal to atherosclerotic lesions in the abdominal aorta, renal cholesterol embolism is the best marker for visceral involvement. While the skin has an extensive network of collateral circulation, the blood supply to the renal cortex consists of predominantly end-arterioles. Therefore, embolic events in the kidneys often result in an irreversible loss of glomerular function. The clinical diagnosis of cholesterol embolism can be made when stepwise loss of glomerular function is accompanied by other nonrenal manifestations of cholesterol embolism. The 2 most common renal manifestations of cholesterol embolism are hypertension and loss of glomerular function.
- Hypertension resulting from cholesterol embolism can be accelerated and intractable. In cholesterol embolism, hypertension is thought to be associated with high circulating plasma renin and angiotensin levels. Renin is released by the juxtaglomerular cells of the afferent arterioles in response to decreased blood flow, in this case caused by the obstruction resulting from cholesterol emboli.
- Acute renal failure is common in cholesterol embolism, and one study estimated it to account for 5-10% of all cases of acute renal failure. Loss of glomerular function in cholesterol embolism is a progressive process, occurring over 4-6 weeks. It results from periodic showering of emboli and causes renal insufficiency in approximately 30-50% of patients. A delay of as long as 2-6 weeks may occur between precipitating events and the onset of renal dysfunction. In fact, if renal impairment occurs immediately after an invasive procedure, the clinician must rule out other causes, including contrast-induced nephropathy.
- Also regarding renal failure, a 2007 study of 354 patients by Scolari et al demonstrated that patients with iatrogenically acquired cholesterol embolism were more likely to develop acute or subacute renal failure and have a worse outcome than patients with spontaneous forms. 

  12 In this study, 32.7% of patients required dialysis after the development of cholesterol embolism, with the largest risk occurring within the first 6 months of the event. They also found that the time course to renal insufficiency was a fairly accurate prognostic factor in predicting outcomes for renal and patient death.
- Other features of renal cholesterol embolism may include flank or back pain, gross or microscopic hematuria, pyuria, and/or urinary casts.
- Risk factors for renal insufficiency are the presence of heart failure, lower limb or GI tract involvement, and age older than 70 years. The exact nature of the reversible component to the

acute renal failure is unknown.

- Visualization of cholesterol crystal clefts in a renal biopsy specimen is pathognomonic for cholesterol embolism. The crystals embolize in the arcuate and interlobular arteries of the kidneys, producing an acute inflammatory reaction with endothelial proliferation and occlusion of the lumen, leading to infarction and forming a wedge-shaped scar in the kidney.
- Pulses: Pedal pulses are palpable in 60% of patients, bilaterally decreased in approximately 40%, and absent on the side of the cutaneous lesions in less than 5% of patients. Pulses are purported to be present in cholesterol embolism, even in patients at risk for peripheral vascular disease, because emboli and microthrombi travel to the most distal vessels, sparing the dorsal pedalis and posterior tibial arcades.
  - GI manifestations (30%)
- Cholesterol embolism causes ischemia or infarction of the bowel. Unfortunately, most GI symptoms are nonspecific and, thus, are often misattributed to other conditions.
- Symptoms include abdominal pain, diarrhea, and GI bleeding. Jucgla et al<sup>8</sup> noted that all patients with GI manifestations in their study had concomitant renal involvement. Indeed, patients with bowel disease frequently have concurrent evidence of embolism to other sites, including the spleen (57%), the liver (15%), and the gallbladder (8%).
- Ischemic cholecystitis has been reported, along with perforation of the gallbladder after cholesterol embolism. <sup>13</sup>
- Of patients with GI involvement, 10-30% have hemorrhage, which was found to be the cause of death in at least 1% of patients with fatal cholesterol embolism.
- Digestive involvement is known to be associated with a poor outcome. A 2007 study demonstrated that the hazard ratio indicating risk for both renal and patient death was considerably elevated at 2.57 in patients with any degree of GI involvement.

  12 This high degree of tragic complication is thought to be due to nonspecific presentation and diagnostic delay, coupled with the catastrophic effects of ischemic GI injury.
- Ophthalmic manifestations (6%): Retinal cholesterol crystals (Hollenhorst plaques) are bright-yellow, glittering intravascular plaques situated at the bifurcation of the narrow arterioles of the retina. These are often readily apparent on funduscopic examination and are refractile on fluorescein angiography. Patients may be asymptomatic, with microvascular disease occurring distal to the macula, or they may report intermittent monocular blindness or amaurosis fugax (transient blindness). Retinal infarction resulting from complete occlusion of the vasculature also may occur. Patients with carotid or vertebrobasilar atherosclerosis who undergo endarterectomy are at high risk.
  - Musculoskeletal manifestations
- Cholesterol embolism to arterioles in muscles can cause intense myalgia at rest or muscle tenderness and/or weakness with exertion. Involvement of lower extremity muscles with upper limb sparing is characteristic in cholesterol embolism. Muscle infarcts have also been described.

- Development of rhabdomyolysis after cholesterol embolism is uncommon; however, reports describe this disastrous complication, underscored by Sarwar et al. 

  14 In this report, researchers identified a patient with extensive myonecrosis, rapidly leading to rhabdomyolysis and compartment syndrome. Ultimately, the tissue ischemia progressed despite therapy, and the outcome was gangrene and bilateral below-the-knee amputations.
- CNS manifestations: CNS cholesterol embolism may occur after vascular procedures such as carotid angiography or endarterectomy. The most frequent sources of emboli are the carotid arteries, the thoracic aorta, or the aortic trunk. Manifestations may include transient ischemic attack and stroke from involvement of the cerebral arteries. Case reports have described delirium and dementia attributable to cholesterol embolism.

  15 Case reports also describe spinal cord infarction following cholesterol embolism, as well as other symptoms resulting from anterior spinal artery involvement.
- Pulmonary manifestations: Alveolar hemorrhage, presumably resulting from cholesterol embolism, has been rarely reported. One patient with severe atherosclerosis was noted to develop hemoptysis, renal failure, and purpura after vascular surgery. Another case report documented pulmonary-renal syndrome in a patient with hemoptysis, respiratory distress, and radiographic alveolar shadowing.

  16 Renal and skin biopsies revealed cholesterol embolism. Although pulmonary symptoms have been considered rare in the past, Jucgla et al

reported 57% of patients had pulmonary edema secondary to cardiac failure.

- Endocrine manifestations: Postmortem examination of adrenal glands has demonstrated cholesterol embolism.

  8 One study reported the presumed death of a patient with visceral cholesterol embolism resulting from necrosis of the adrenals.
- Reproductive manifestations: Cholesterol embolism has also been demonstrated in postmortem examinations of the prostate, apparently asymptomatic in the patient.
- Hematopoietic manifestations: Reuter et al reported a case of spontaneous cholesterol crystal embolization to the bone marrow diagnosed in a 77-year-old woman with fever, anemia (hemoglobin value, 10.2 g/dL), and leukocytosis.

  17 Bone marrow biopsy was performed to evaluate the etiology of her anemia. No abnormalities were discovered, with the exception of the presence of cholesterol crystals. Pierce reported the presence of cholesterol embolism to bone marrow in a premortem patient with anemia and other clinical findings.

Muretto also reported a case of cholesterol embolism to bone marrow.

Although his patient was quite ill, anemia was not reported. However, it is now known that anemia is frequently a nonspecific finding in cholesterol embolism.

#### Causes

Cholesterol embolism occurs spontaneously in patients with atherosclerosis, but a trigger is usually required for full expression of cholesterol embolism syndrome. Precipitating factors include the following:

- Anticoagulation and thrombolytic therapy: A history of antecedent therapy with anticoagulants is present in approximately 30-35% of patients. 

  20,21,22 These therapies are thought to predispose to cholesterol embolism by 2 distinct mechanisms. First, anticoagulation and thrombolytics strip away the protective layer of fibrin isolating the subintimal deposits of cholesterol from the bloodstream. Second, hemorrhage into a plaque after therapy undermines the stability of the plaque and may lead to lysis of fibrin cap thrombi, causing cholesterol crystals to dislodge and enter the circulation.
- Interventional vascular techniques: Various surgical or radiologic vascular procedures precede cholesterol embolism in nearly 65% of patients. 

  23 The introduction of a foreign object into the vessel can cause intimal trauma, exposing the underlying cholesterol-rich extracellular matrix to the arterial circulation. This risk is proportionally increased with increased sheath size of the catheter.
- An Italian study of 354 patients demonstrated the most common precipitating factor to be coronary angiography via the femoral artery.
- Additional risk factors for developing cholesterol embolism after cardiac catheterization include hypertension, a history of smoking, and elevated preprocedural C-reactive protein levels.
- Although most reports of cholesterol embolism are noted to occur with endovascular procedures involving the large vessels, it is important for the clinician to be aware that this complication may occur after manipulation of any vascular bed.
- Cholesterol embolism has been reported after peripheral stenting procedures for claudication. 14
- Mere passage of the catheter into the luminal space is now thought to place the patient at risk for cholesterol embolism, disrupting and exposing the soft cholesterol core to the arterial circulation.
- Trauma: This includes cardiopulmonary resuscitation or sudden deceleration injury, and it may also result in cholesterol embolism

# **Laboratory Studies**

- Laboratory abnormalities in cholesterol embolism are nonspecific. However, the basic

metabolic panel, a complete blood cell count with differential, a urinalysis with microscopic evaluation of the sediment, an erythrocyte sedimentation rate, and a C-reactive protein level may all prove helpful in diagnosing cholesterol embolism. Other laboratory studies should be ordered based on the patient's underlying disease and the clinical picture.

- Eosinophilia (>300 cells/ $\mu$ L or 3-18% total WBCs) develops within 3 days of embolization in 70-80% of patients and may remain elevated for up to 1 month after a new diagnosis of cholesterol embolism. Cholesterol crystals in tissue initiate a cascade of reactions, including the systemic release of interleukin 5. T lymphocytes are thought to release interleukin 5 in order to induce eosinophil production, chemotaxis, and maturation.
- Eosinophiluria may indicate cholesterol embolism when identified in patients with other findings of cholesterol embolism. One study found that 8 of 9 patients with biopsy-proven cholesterol embolism had positive Hansel staining for eosinophiluria. However, like many other findings in cholesterol embolism, eosinophiluria is nonspecific. In addition to cholesterol embolism, the differential diagnosis of eosinophiluria includes acute interstitial nephritis.
  - Leukocytosis is found in 50% of patients.
- The presence of elevated blood urea nitrogen levels, creatinine levels, proteinuria, pyuria, hematuria, and various urinary casts (in order of descending frequency: granular, hyaline, white blood cell, red blood cell, and oval fat bodies) are further indications that glomerular damage is occurring.
- The erythrocyte sedimentation rate is often elevated (>30 mm/h) in persons with cholesterol embolism.
- Elevated preprocedural plasma levels of C-reactive protein are associated with subsequent cholesterol embolism in patients who undergo vascular procedures, according to Fukumoto et al. 24
- Hypocomplementemia and antineutrophil cytoplasmic antibody positivity are also reported in persons with cholesterol embolism.
- Because pancreatitis may be a complication of cholesterol embolism, any patient with symptoms of abdominal pain should have his or her amylase level checked. Similarly, transaminase levels should be monitored because of the potential for hepatic involvement.
- Fecal occult blood and digital rectal examination should also be performed in a patient with symptoms of cholesterol embolism and severe abdominal pain.

# **Imaging Studies**

Establishing the source of cholesterol emboli remains a formidable challenge, especially in patients with diffuse atherosclerotic disease. Noninvasive procedures should be performed first, if possible.

- A transthoracic echocardiography may aid in excluding an intracardiac source of embolism.
- Transesophageal studies are required to exclude very small valvular thrombi, which may be below the resolution capacity of transthoracic ultrasonography.
  - Use Doppler ultrasonography of the aorta to exclude aortic aneurysm.
- Magnetic resonance imaging and CT scanning offer alternative means to effectively evaluate thoracic and abdominal aortic sources of embolism. The image below shows a CT scan of the abdomen, demonstrating the infrarenal aorta with an aneurysm and a mural thrombus
- Unfortunately, angiography is necessary in most patients before surgical intervention can be performed, despite the risk of exacerbating cholesterol embolism by mechanical trauma. Peripheral angiography is the best test for establishing a diagnosis of atheroembolism involving the abdominal aorta and the lower extremity arteries. **Procedures**

Definitive diagnosis of the presence of cholesterol embolism is made by performing a biopsy on affected tissue. Skin and muscle are the most accessible sites for obtaining a biopsy specimen and seem to offer excellent specificity (approximately 90%) and favorable sensitivity.<sup>25</sup>

- Include symptomatic skin or muscle in the biopsy site whenever possible, but even asymptomatic extremities in patients with visceral disease may yield positive biopsy results.
- Biopsy incisions should probe to subcutaneous fat, if possible, to sample the small vessels, in which cholesterol embolism commonly occurs.
- Instruct the laboratory to cut sections at multiple levels through the tissue block because changes may be present in only short segments of affected arteries. In one instructive case report, premortem diagnosis of cholesterol embolism was missed when the first sections of a muscle biopsy were interpreted as being consistent with vasculitis. Cholesterol clefts were found in the tissue at postmortem examination, and further sectioning of the original muscle biopsy sample revealed cholesterol crystals amid the vasculitic lesions.

In evaluating a patient with suspected cholesterol embolism, the consulting dermatologist is often faced with the daunting prospect of performing a skin biopsy on an already compromised extremity. Biopsy should be selectively performed. In unfavorable circumstances, biopsy is recommended only if one or more of the following criteria for diagnosis is lacking:

- A patient with documented diffuse atherosclerosis has a history of exposure to a known cholesterol embolism—precipitating factor or factors.
- The patient has acute renal failure with an increase in creatinine levels of more than 150% of the baseline.
  - The patient has characteristic cutaneous lesions or retinal embolism.

## **Histologic Findings**

An understanding of cholesterol embolism is predicated on recognizing the relationship with atherosclerosis. Atherosclerotic lesions develop in the walls of vasculature that has undergone diffuse intimal thickening, a process carried out by smooth muscle cells and involving elastin and proteoglycans. Earliest lesions are thought to be apolipoprotein B–containing lipids in macrophages, known as foam cells, in the outer layers of these thickened vessel walls. <sup>26</sup> Grossl y, these can be identified as fatty streaks.

As the lesion progresses, lipids continuously accumulate and deposit, forming a lipid core. Fibrous, collagenous caps, as shown below, cover these lesions, which usually conceal denuded, friable endothelium. When the fibrin caps rupture, cholesterol embolization may occur

Cholesterol embolism is histologically defined by the presence of birefringent crystals with plane polarized light or biconvex needle-shaped ghostly clefts within the arterial lumen, corresponding to cholesterol crystals dissolved during the fixation process. On frozen sections, the Schultz test stains the acicular (ie, needle shaped) cholesterol crystals green within a few minutes and brown within 30 minutes; however, in the clinical setting, demonstration of the characteristic biconvex cholesterol clefts suffices to establish a diagnosis of cholesterol embolism. In the skin, the artery is usually located at the dermal-subcutaneous junction. In the muscle, the findings occur in small arteries adjacent to areas of patchy myocyte atrophy and necrosis with surrounding infiltrate.

Lesions in different stages of evolution may be found in the same patient, and this is considered evidence of recurrent showers of emboli. The earliest lesions typically reveal the cholesterol clefts surrounded by nonagglutinated red blood cells, reflecting partial occlusion of the arterial lumen. The cutaneous livedo reticularis pattern is believed to be secondary to this local incomplete disturbance of circulation. Macrophages and foreign body giant cells may surround the cholesterol clefts, usually within 24-48 hours. Later, a more complete occlusion may occur as encasement of clefts by intimal proliferation and fibrosis ensues. This final stage most likely underlies tissue necrosis and gangrene. Even in late disease and with recanalization, cholesterol crystals may still be found in affected tissue

### **Medical Care**

Cholesterol embolization has a serious prognosis; unfortunately, treatment options remain limited. However, both conservative medical care and surgical therapy are available. In 1999, Belenfant et all published a prospective study of 67 patients with cholesterol embolism using therapies targeted at the most common causes of death in cholesterol embolism.<sup>2</sup> This approach reduced the 1-year mortality rate to as low as 23%. The treatment includes the following:

- Remove precipitating factors, as follows:
- Discontinue all forms of anticoagulants.
- Avoid invasive vascular procedures normally indicated by underlying disease.
- Modify risk factors, as follows:
- Manage blood pressure (goal blood pressure <140/80 mm Hg) using vasodilators (eg, ACE inhibitors, calcium channel blockers, nitrates).
  - Use statin lipid-lowering medications.
- Use prednisolone in patients with laboratory evidence of inflammation (ie, elevation of C-reactive protein and fibrinogen levels, increased erythrocyte sedimentation rate, a change in serum complement levels).
  - Institute supportive care, as follows:
  - Use high-dose loop diuretics and/or ultrafiltration in some patients with pulmonary edema.
  - Avoid or minimize anticoagulation in patients who require hemodialysis.
  - Provide enteral or parenteral nutritional support.

It must be emphasized that management principles for cholesterol embolism are often conflicting because therapeutic vascular procedures and/or dialysis can also aggravate the disorder and because many of the patients with cholesterol embolism are considered high risk for surgery.

Given that caveat, Wakabayahi et al resumed anticoagulation in an 81-year-old patient with cholesterol embolism due to the development of ischemic stroke. <sup>28</sup> The patient was given heparin therapy for 14 days, followed by warfarin. The result was improvement in the patient's renal function, skin lesions, and hemiparesis. Her level of peripheral eosinophilia also dropped from 756 to 82 cells/µL one day after starting heparin.

Possible success with use of anticoagulation, specifically heparin, was reported in another case.

The efficacy of the antithrombin III—enhancing drug is postulated to be based on the principle that cholesterol embolism is not the result of embolization of solely cholesterol crystals, but the clinical picture of thrombosis and vessel obstruction that occur concomitantly.

Many published anecdotal reports describe other therapeutic approaches to cholesterol embolism. None has been studied critically; however, these methods may be of some value if surgical intervention cannot be performed or must be delayed.

- Case reports exist of spontaneously healing cutaneous lesions.
- Individual case reports show benefit from high-dose corticosteroids. Dahlberg et al,<sup>30</sup> Vach er-Coponat et al,

Belenfant et al,

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and others detailed the potential use of steroid therapy for advanced disease, including those with acute renal failure or in those with pronounced cutaneous manifestations. Steroids may limit the inflammatory effects of ischemia and resultant vascular occlusion. Further study is needed to clearly define the role of corticosteroids in the management of cholesterol embolism. Doses have included prednisone at 60 mg/d and methylprednisolone at 80 mg/d, with therapy lasting from 5 days to months, depending on the patient's response.

- Multiple case reports have found that low-density lipoprotein (LDL) apheresis with the concomitant administration of other medications has produced favorable clinical outcomes. Simvastatin or alprostadil with LDL apheresis reportedly improves livedo reticularis. 31,32 LD L apheresis with corticosteroids and/or an angiotensin receptor blocker has been found to decrease skin and brain manifestations, decrease eosinophilia, and improve kidney function.
- The 2003 and 2007 studies by Scolari et al $^{9,12}$  underscored the theory that statin therapy may be beneficial in patients with known atheroembolic renal disease. In these patients, statin therapy was associated with a better prognosis ( P
- <.001), even when initiated well after diagnosis. The favorable outcomes associated with statin therapy may be secondary to both the anti-inflammatory and lipid-lowering properties of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, contributing to plaque stabilization and regression, perhaps initiating recanalization.
- Successful pain relief and the improvement of purpura, livedo reticularis, and severe cyanosis on the lower extremities have been reported after treatment with intravenous iloprost in 4 cases.
  - Success has been reported in one case using oral pentoxifylline.34
- The use of vasodilators, sympathetic blockers, and low molecular weight dextran has not been convincingly effective.
- Isolated case reports exist of successful management of cholesterol embolism with combination corticosteroid and cyclophosphamide therapy. 

  35 Yucel et al reported the

treatment of a 53-year-old man with corticosteroid and cyclophosphamide combination therapy, leading to subsequent rapid improvement. This report also documents a 74-year-old man treated with the same regimen.

The outcome was appreciable improvement in skin lesions, but ultimately the patient was lost to follow up and succumbed to complications associated with infection.

- Filip and Dillon reported successful therapy for cholesterol embolism using circulator boot therapy. <sup>37</sup> A circulator boot is a compression boot designed to restore blood flow to areas of ischemia. In the study, 41 legs were treated. Of these, 81% healed completely, 15% improved, and only 2 required amputation. Levels of evidence were not reported. The circulator boot is thought to function by expelling venous and lymphatic columns from the leg, thereby increasing the arterial-to-venous pressure ratio and providing force substantial enough to reperfuse areas of ischemia.

## **Surgical Care**

The principal goal of surgical treatment of cholesterol embolism is to promptly identify and eradicate the embolic source and to restore arterial continuity. Carefully weigh the risks versus benefits of the surgical therapies described below. Unfortunately, too often, both the required preoperative arteriography and the surgery itself become factors that may exacerbate this syndrome. However, reports indicate a 75% 3-year survival rate in patients treated surgically, making it a favorable option in select cases.

- Amputation or resection of infarcted or symptomatic tissues is often required in severe cases. Blue toe syndrome is usually an indication for limb salvage surgery.
- Identification of the embolic source and removal of the atheromatous lesions by endarterectomy, a bypass graft, stent grafting, or excision and replacement of the involved segment of aorta are important in preventing recurrent showers of emboli. In one study of endovascular stent-graft repair of an abdominal aortic aneurysm, resolution of cholesterol embolism was noted in only 2 of 19 patients at 30-day postoperative follow-up. At 1 year, 8 of 9 patients had complete resolution of their ischemic symptoms.
- For small uncomplicated aneurysms, intraluminal grafts inserted on a balloon catheter via the transferoral route may offer an alternative to open surgery.
- The role of lumbar sympathectomy to relieve symptoms from ischemic lower extremities in selected patients with blue toe syndrome remains controversial.

## Medication

The goals of pharmacotherapy are to reduce morbidity and to prevent complications.

# **Blood viscosity reducing agents**

These agents increase the fluid characteristics of blood.

## **Pentoxifylline (Trental)**

Methylxanthine derivative that reduces blood viscosity and improves erythrocyte flexibility.

- Dosing
- Interactions
- Contraindications
- Precautions

#### Adult

400 mg PO tid with meals

#### **Pediatric**

Not established

- Dosing
- Interactions
- Contraindications
- Precautions

Coadministration with cimetidine or theophylline increases effects; increases effect of antihypertensives

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity to pentoxifylline or methylxanthines (caffeine, theophylline,

theobromine); recent surgery; cerebral or retinal hemorrhage or coagulation defects; bleeding diathesis

- Dosing
- Interactions
- Contraindications
- Precautions

#### **Pregnancy**

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

#### **Precautions**

Caution in renal impairment; primarily causes GI tract (eg, nausea, vomiting, dyspepsia) and CNS adverse effects (eg, headache, dizziness); do not crush or chew tab

### **HMG-CoA** reductase inhibitors

These agents usually lower LDL cholesterol levels and sometimes lower triglyceride levels, and they may modestly elevate high-density lipoprotein cholesterol levels. These agents may be of value to patients with hypercholesterolemia.

### Simvastatin (Zocor)

Inhibits HMG-CoA reductase, which, in turn, inhibits cholesterol synthesis and increases cholesterol metabolism.

- Dosing
- Interactions
- Contraindications
- Precautions

#### Adult

10-40 mg PO qd

#### **Pediatric**

#### Not established

- Dosing
- Interactions
- Contraindications
- Precautions

Rifampin and nicotinic acid may decrease effects; clofibrate, itraconazole, erythromycin, cyclosporine, and niacin increase toxicity; coadministration with either niacin or erythromycin associated with rhabdomyolysis; atorvastatin increases toxicity of anticoagulants and levothyroxine

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; active liver disease; unexplained elevations of serum transaminases levels; breastfeeding

- Dosing
- Interactions
- Contraindications
- Precautions

### **Pregnancy**

X - Contraindicated; benefit does not outweigh risk

#### **Precautions**

Discontinue if symptoms of myopathy or renal failure develop; caution in history of liver disease and in patients who consume excessive amounts of alcohol

# Prostaglandin analogs

These agents inhibit the cyclooxygenase system, decreasing the level of thromboxane  $A_2$ , which is a potent platelet activator.

## **lloprost (llomedin)**

Chemically stable analog of prostacyclin (epoprostenol) and effective inhibitor of platelet aggregation by increasing intracellular levels of cyclic adenosine monophosphate. Clinical benefit has been observed in occlusive peripheral vascular disease and Raynaud phenomenon, although further clinical trials are needed to assess its place in therapy in these conditions.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

<2 ng/kg/min IV qd

**Pediatric** 

Not established