Acute Ischemic Syndromes of the Peripheral Arteries

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Abstract

Acute ischemic syndrome of the lower extremity can occur in any region of the leg or distal regions of the foot. Previous stent or bypass surgery, increasing age, peripheral artery disease (PAD), and cardiovascular disease all increase the risk of acute ischemic syndrome of the lower extremity and can contribute to poorer outcomes. Acute ischemia is characterized by sudden onset over the course of a few hours and up to 14 days, with darkening and blistering of the skin, altered sensory and motor experience, change in pulse, and other histopathological changes, including tissue injury and death that can lead to systemic metabolic syndromes, organ failure, and death. The condition can progress rapidly in the lower limbs, particularly in the distal extremities, and prevalence of mortality and limb loss due to amputation remain high despite modern technological improvements in diagnostic imaging and percutaneous endovascular treatments. The most common treatments are thrombolysis (embolysis), thrombectomy/embolectomy, and open surgery, though new technologies such as excimer laser photoablation and high-frequency ultrasound have recently become available. To improve patient care, it is essential to understand the underlying pathophysiology of acute ischemic syndrome of the lower extremity, which can result from embolus, thrombus, trauma, aneurysm, and other chronic conditions. There are numerous new technologies that can improve diagnosis and treatment of this condition.

Introduction

Defining Acute Lower Limb Ischemia

Acute lower limb ischemia (ALLI), also known as acute ischemic syndrome of the lower extremity, is a potentially life-threatening condition that results from obstruction of blood flow to the lower limb, most commonly due to embolism or thrombosis. In 2000, representatives from 14 medical and surgical vascular, cardiovascular, vascular radiology, and cardiology societies in Europe and North America collaborated in the Transatlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease to formally define acute limb ischemia, including that of the lower limb (leg), and made recommendations for optimal surgical and endovascular interventions for peripheral arterial occlusive disease (PAOD) (Norgen et al. 2007).

In 2004, a more inclusive group made up of representatives from 16 societies originating in Europe, North America, Australia, South Africa, and Japan came together in the new TASC Working Group along with specialists in health economics, health outcomes, and evidence-based medicine to examine the history, epidemiology, risk factors, and risk management for intermittent claudication, critical limb ischemia, and acute limb ischemia (Norgen et al. 2007). The end result of
this collaboration was the 2007 publication of an update known as TASC II, published in three major medical journals (Norgen et al. 2007; Diehm et al. 2008).

The TASC II definition of acute lower limb ischemia is arguably the most widely accepted and influential definition to date. TASC II defines acute limb ischemia (ALI) as is any sudden decrease in limb perfusion causing a potential threat to limb viability, with presentation normally up to 2 weeks (14 days) following the acute event. These events are characterized by ischemic rest pain, sensory loss, ulcers, and/or gangrene and can ultimately threaten the limb viability and patient survival (Katzen 2002). Acute lower limb ischemia is considered a medical emergency with variable time-course, while presentations extending more than two weeks are considered subacute or chronic limb ischemia (Elsevier 2013).

The TASC II definition and recommendations were also influenced by major works in the field, such as the CoCaLis (coronary (Co) and/or carotid (Ca) artery disease in leg ischemia (Lis)) document (2006) (Clement et al. 2000) and the American College of Cardiology/American Heart Association Guidelines for the Management of Peripheral Arterial Disease (2000) (Hirsch et al. 2006). Most notably, the TASC II diverged from its predecessor by incorporating contemporary diagnostic and interventional strategies, such as revascularization and advanced diagnostic and intraoperative imaging. It also further addressed modifiable risk factors, specifically peripheral artery disease (PAD) and diabetes (Norgen et al. 2007). Unlike many other resources, the TASC II was intentionally designed for an audience of clinical vascular specialists as well as general practitioners and primary health physicians, which has contributed to its wide acceptance.

Epidemiology and Impact of Acute Lower Limb Ischemia

Incidence of Acute Lower Limb Ischemia
Over the past two decades, acute arterial vascular events have consistently remained a leading cause of premature death and disability in the developed world (Murray and Lopez 1997; Fuster 1999). Of acute arterial vascular conditions, acute lower limb ischemia is major public health risk due to its prevalence and high mortality and amputation rates, particularly in older populations. Acute limb claudication caused by occlusions are relatively common, estimated to occur in as many as 14–15 per 100,000 people in the general population, though the majority of these cases are transient and do not develop into full acute ischemic events (Dormandy et al. 1999; Creager et al. 2012). There are relatively little information pertaining to the precise incidence of acute leg ischemia, though the TASC II report estimated that approximately 140 million patients could be affected by acute leg ischemia each year based on national registries and regional surveys (Norgen et al. 2007).

Economic Impact
Acute ischemic syndromes of the lower limb account for as much as 10–16 % of the vascular workload in hospitals (Dormandy et al. 1999; Creager et al. 2012). The cost of treating a single patient with acute lower limb ischemia has been reported to be between $6,000 and $45,000 USD (Singh et al. 1996; Eliason et al. 2003; Hoch et al. 1994; Ouriel et al. 1994). In addition, the true cost of amputations, a relatively common outcome of irreversible acute ischemic syndromes, is difficult to objectively assess because the full cost impact of amputation far exceeds that of the procedure and hospitalization costs, including ongoing care such as rehabilitation therapy, home health aides, adaptations of the patient’s home and workspace, lost incomes and wages, family and well-being impact, and long-term care (Alonso and Garcia 2011). As a result, the lifetime cost of treatment may be much higher than estimates that appear in the literature.
Risk Factors

Peripheral Vascular Disease (PAD) and Cardiac Disease

Acute ischemic syndromes of the lower limb can be caused by underlying vascular conditions, such as peripheral artery disease (PAD). Up to 20% of cases are due to in situ arterial thrombosis associated with PAD (Elsevier 2013). The prevalence of PAD has been reported as 3.1–5.5% in adults over age 40 and as high as 18% in patients over the age 70 years, though these estimations may be misleadingly low due to the large number of patients with asymptomatic PAD (Norgen et al. 2007; Criqui et al. 1985; Selvin and Erlinger 2004). Like PAD, cardiac disease has also been consistently linked to increased risk for acute limb ischemia (Norgen et al. 2007; Steffen et al. 2008). Over 95% of patients with PAD patients have cardiovascular disease risk factors, such as elevated fibrinogen and C-reactive protein levels that have been linked to greater risk of acute lower limb ischemia (Norgen et al. 2007; Selvin and Erlinger 2004).

Age

The risk of acute vascular events rises progressively with age, and individuals age 65 or older have consistently been shown to be at greater risk for acute vascular events in all arterial beds, including those of the lower limbs (Rathwell et al. 2005). The aging population and increasing survival from cerebrovascular, coronary, and arterial conditions are expected to cause an increase in the prevalence of acute limb ischemia worldwide in the coming years (Brooks and Jenkins 2008).

Ethnicity

PAD is strikingly more common in non-white ethnicities, particularly black patients of South African descent who may be more than twofold more likely to be diagnosed with PAD (Norgen et al. 2007). The National Health and Nutrition Examination Survey (NHANES) reported that PAD was most common in non-Hispanic blacks, occurring in 19.5% of the population compared to 11.7% in non-Hispanic whites and 15.6% in Hispanic men and women (Steffen et al. 2008). The link between PAD and risk for acute ischemia of the lower limbs suggests that populations with greater PAD may be at greater risk for development of acute limb ischemia of the lower limb.

Gender

The prevalence of PAD, symptomatic or asymptomatic, is larger in men than women, though this difference becomes smaller with age and has been controversial in some modern studies (Norgen et al. 2007). In a study of 2,756 patients with acute ischemic syndromes conducted by Žaliūnas et al. (2008) in 2008, significant differences were found in atherogenic dyslipidemia in patients with acute ischemic syndrome by gender, with men more frequently exhibiting increased triglyceride concentrations and women exhibiting decreased high-density lipoprotein cholesterol HDL-C concentrations. Such gender-related discrepancies between PAD were confirmed by the Genetic Epidemiology Network of Arteriopathy (GENOA) study clearly indicating gender-related risk not explained solely by classical atherosclerosis (Norgen et al. 2007).

Obesity

Obesity can increase the risk for both chronic and acute vascular disease, accounting up to 4.6 million lost work days in the United States alone and contributing to a large public health burden worldwide (Spentzouris and Labropoulos 2009). Obesity has been linked with increased occurrence of acute ischemic syndromes, particularly those in the lower limb, in part due to increased arterial blockage, elevated cholesterol levels, and other chronic cardiopulmonary conditions (Norgen et al. 2007; Žaliūnas et al. 2008).
Hypertension
Arterial hypertension has been linked with increased incidence of acute ischemic syndromes (Norgen et al. 2007; Zaliūnas et al. 2008). Chronic arterial hypertension can increase the mechanical and biochemical stresses on vessels and contribute to emboli origination and translocation into occluded vessels.

Diabetes Mellitus
Diabetes mellitus has been linked with increased occurrence of acute ischemic syndromes (Norgen et al. 2007; Zaliūnas et al. 2008). Acute ischemic syndromes of the lower limb caused by thrombosis are likely related to dehydration in diabetic patients, though prolonged exposure to extreme weather, infection, and gastroenteritis can have similar effects (Callum and Bradbury 2000).

Dyslipidemia
In a study of 2,756 patients with acute ischemic syndromes conducted by Žaliūnas et al. (2008) in 2008, significant differences were found in atherogenic dyslipidemia in patients with acute ischemic syndrome by gender, with men more frequently exhibiting increased triglyceride concentrations and women exhibiting decreased high-density lipoprotein cholesterol HDL-C concentrations, suggesting increased risk for peripheral acute ischemic syndrome.

Hyperviscosity and Hypercoagulable States
Hyperviscosity, such as that caused by polycythemia and thrombocytosis, and hypercoagulation can increase the risk of acute ischemic syndromes of the lower limbs (Callum and Bradbury 2000).

Chronic Renal Insufficiency and Atherosclerosis
Chronic renal insufficiency is closely related to atherosclerosis, which can encroach on arterial ostia and cause renal insufficiency, hypertension, mesenteric ischemia, secondary aneurysmal formations, and claudication of variant severity (Nayak and Cavendish 2007). Both chronic renal insufficiency and atherosclerosis increase the risk of vascular abnormalities, including acute ischemia of the lower limb (Norgen et al. 2007; Nayak and Cavendish 2007).

HIV Arteriopathy
Human immunodeficiency virus (HIV) patients have compromised immune function and reduced CD4 counts (<250/cm³) that contribute to both upper and lower extremity acute ischemia risk. In HIV patients, the distal arteries may exhibit acute and chronic cellular infiltrates in the vasa vasorum and viral protein in the lymphocytes (Norgen et al. 2007). Furthermore, myositis and compartment syndrome developed secondary to HIV infection can contribute to increased risk (Lam et al. 2003).

Other Risk Factors
Other risk factors for acute ischemic syndromes of the lower limb include prolonged unusual posture, particularly sitting or kneeling; smoking; solid and hematological malignancy; hyperviscosity due to polycythemia and thrombocytosis; and thrombophilia due to Protein C or S and antithrombin III deficiencies, activated protein C resistance, antiphospholipid syndrome, and factor V Leiden (Callum and Bradbury 2000).
Mortality and Lower Limb Loss

Mortality
Despite recent advancements, such as thrombolysis and the Fogarty catheter, mortality from acute lower limb ischemia remains high, with 15–20% mortality rates reported within 1 year of initial presentation even for surviving patients (Creager et al. 2012). Comparably, early mortality due to acute lower extremity ischemia mortality occurs at approximately one third that of acute myocardial infarction at similar timeframes, and nearly three times more than the mortality rate following elective repair surgery for abdominal aortic aneurysm (Eliason et al. 2003). In patients over age 65, the risk of acute vascular events, including acute lower limb ischemia caused by both thrombus and embolism, increases progressively, and the case-fatality rates rise dramatically for patients over age 75 (Rathwell et al. 2005; Brooks and Jenkins 2008). This increase may, in part, be due to the prevalence of comorbid conditions, which can lead to a variety of acute and chronic vascular conditions. In fact, Dormandy et al. (1999) speculated that the lack in improvement in overall mortality rates after acute limb ischemia interventions over the past two decades was reflective of the severity of the high-risk diseases characterizing this patient population. This has implications for successful treatments aimed at reducing post-intervention mortality, including the need to monitor and treat underlying conditions following revascularization therapy.

Lower Limb Loss
A leg affected by embolus is nearly always threatened and requires immediate surgical revascularization. Emboli usually lodge at the common femoral bifurcation or, less commonly, the popliteal trifurcation. Femoral embolus is associated with profound ischemia to the level of the upper thigh because the deep femoral artery is also affected. A femoral pulse does not exclude the diagnosis. Loss of a leg due to amputation within 30 days of hospitalization for acute lower leg ischemia occurs in between 10% and 30% of patients, with the majority of cases amputated above the knee (Norgen et al. 2007; Eliason et al. 2003; Earnshaw et al. 2004). In cases of occlusion in the digits of the foot, amputation may also be conducted at the digit or ankle.

Etiology of Acute Limb Ischemia

Signs and Symptoms
The key signs and symptoms of acute lower limb ischemia include resting pain, increasing pain upon walking or activity, hair loss, thickened brittle nails, smooth or shiny skin, altered skin color (especially digits), muscular atrophy, gangrenous ulcers, numbness, and paralysis, as well as other less common manifestations (Brooks and Jenkins 2008). Acute lower limb ischemia is generally considered to be a surgical emergency when the “five Ps” of pain, pallor, pulselessness, paresthesias, and paralysis are present or severe, and a “6th P” of perishing cold (inability of the ischemic limb to take on ambient temperature) is sometimes considered (Norgen et al. 2007; Brooks and Jenkins 2008). Of these, anesthesia and paralysis are considered the most important prognostic indicators (Callum and Bradbury 2000). In cases of complete ischemia, pain may be absent in severe cases and complete paralysis may be observed (Callum and Bradbury 2000). Notably, pallor and pulselessness are also observed in chronic ischemia of the lower limb and cannot be used as sole indicators of acute ischemia (Callum and Bradbury 2000).
Transient Ischemia

Transient lower limb ischemia occurs in 5–7 % of the general population, though spontaneous resolution often occurs prior to severe acute ischemic events (Brooks and Jenkins 2008). The prevalence of intermittent claudication, a significant risk factor for severe acute ischemic events, has been reported to be about 3 % in patients at 40 and 6 % in patients at age 60, evidencing a significant increased with age (Norgen et al. 2007). In patients with intermittent lower limb claudication, their walking or other strenuous activities result in inadequate limb blood flow and pain due to transient muscle ischemia that can lead to shunting of blood from major muscle groups and peripheral nerves (Brooks and Jenkins 2008). Transient acute lower limb ischemia contributes to more serious chronic vascular conditions and onset of sudden and severe acute ischemic events in a stepwise manner. Examining risk factors, such as claudication and prior surgeries, is particularly important the unexpected onset of severe acute events can limb loss and mortality risks.

Common Etiologies

Acute lower limb ischemia occurs when there is a sudden decrease in the blood flow to the leg or foot, though the specific causes and mechanisms vary between patients. As a result, limb-threatening ischemia occurs due to insufficient local blood flow to meet the metabolic demands of resting muscle or tissues (Neschis and Golden 2012). The most common etiologies of acute lower limb ischemia are acute thrombotic occlusion of a preexisting stenotic arterial segment (approximately 50–60 %) or embolism (approximately 30–40 %), as reported by the TASC II and a recent retrospective study of 440 patients with acute lower limb ischemia conducted by Klonaris et al. (2007). Less common etiologies also exist.

The prevalence of these etiologies has, however, shifted in recent years due, in part, to the wide availability of improved patient monitoring equipment, the decreased prevalence of cardiac valvular disease that is caused by both better medical care and reductions in rheumatic fever incidence, and improved management of atrial fibrillation with anticoagulants (Norgen et al. 2007). As a result, the incidence of acute leg ischemia due to emboli has evidenced a steady decline over the past several decades; conversely, the incidence of thrombotic acute leg ischemia has steadily increased, potentially due to the increasing number of vascular surgeries that raise the risk for subsequent thrombosis formation (Norgen et al. 2007).

The TASC II report cites the combined etiologies of acute limb ischemia described by Berridge et al. (2002) and Campbell et al. (1998), which list the most common etiologies, in order of prevalence, as native thrombosis, embolism, reconstruction/graft thrombosis, trauma (including astrogenic), and peripheral aneurysm with embolus or thrombosis (Norgen et al. 2007). Notably, the widely accepted TASC II document was published in 2007 and cites data from the 1990s and early 2000s. Despite the relatively consistent shift in etiologies and advancement of interventional technologies, few studies have since systematically examined the shift in recent etiologies of acute lower limb ischemia on a large scale.

Risk by Etiology

The risk to patient limbs and life varies predictably based on the underlying etiology of the acute ischemic event as well as modifiable and non-modifiable risk factors. In general, acute lower limb ischemia caused by embolism poses the greatest risk to both the affected limb and the life of the patient because these occlusions are generally not associated to extensive collateral networks. Embolisms generally translocate to the region of occlusion, and thus adequate collateral vessels rarely have time to form in acute patients, though, in rare cases, embolism can also result in more gradually occluded chronic blockages (Schellong et al. 2001). For most patients, acute ischemia
stems from local arterial thrombosis in vessel systems that already exhibit a highly atherosclerotic character and extensive collateral networks due to occlusion. As a result, there is often some degree of physiologic compensation for thrombosis patients due to the effects of perfusion and collateral vessel structures – structures that are readily apparent by angiography (Schellong et al. 2001). Differentiation between embolism, thrombosis, and other less common etiologies, however, remains challenging based on clinical history and examination alone and may be impossible in 10–15 % of cases without specialized angiographic methods (Dormandy et al. 1999).

**Thrombosis: Native, Graft/Stent, Induced, and Trauma Thrombosis**

In Greek, “thrombousthai” literally means clotting. The central distinguishing factor of thrombosis is that a blood vessel clot forms and remains lodged in the blood vessel adjacent to the area of formation, where it occludes normal blood flow and causes variant degrees of ischemia in local tissues. Thrombosis onset occurs relatively slowly, generally over hours or days before the patient is admitted for treatment (Callum and Bradbury 2000). Thrombotic occlusions of the lower limb are most commonly due to native or graft thrombosis, in which thrombosis occurs in either normal blood vessels or vessels treated with graft or stent interventions, respectively.

It is rare that multiple sites are simultaneously affected by thrombotic occlusions, though cases of multiple occlusions have been uncommonly reported in patients with PAD or other degenerative conditions affecting lower limb vascularity (Lebow 2010). Compared to occurrence in the upper limbs, acute lower limb ischemia is tenfold more likely (Callum and Bradbury 2000). In the vast majority of clinical patients, occluded arteries in the lower limb are palpably hard with apparent calcifications, bruits are present, and the contralateral leg pulse is conspicuously absent. Furthermore, previous history of claudication should be considered in patients with thrombotic occlusion; most patients diagnosed with thrombotic occlusions of the lower limb have no previous history of claudication (Callum and Bradbury 2000).

Previous history of cardiac or other arterial surgeries or pathologies is often the underlying cause and most significant risk factor for thrombosis. Over 70 % of thrombotic occlusions of the lower limb occur subsequent to interventions, with about 65 % occurring after bypass grafts and about 5 % occurring after iliac or femoral stent placement; conversely, only about 30 % of cases exhibit native arterial thrombosis (Klonaris et al. 2007). Thrombotic occlusion of the lower limb can be caused by acute plaque rupture, decreased blood volume (hypovolemia), pump failure, or surgical complications, and these occlusions are generally incomplete due to the relatively long period of time for collateral vessels to form compared to other acute ischemic conditions of the lower limb (Callum and Bradbury 2000; Bounameaux 1990).

In rare cases, thrombotic occlusions in the lower limb can also be induced by medications or metabolic deficiencies, such as heparin administration (heparin-induced thrombosis), anti-thrombin II deficiency, protein C and S deficiency, Factor V Leiden, prothrombin 20210 polymorphism, hyperhomocysteinemia, and lupus anticoagulant (antiphospholipid syndrome) (Knoebl 2008). Trauma is also a potential cause of thrombotic occlusion when critical collateral vessels are damaged or severed in the lower limb, as in the case of severe compound tibial, fibular, and femoral fractures in the lower limb as well as, in rare cases, compound patellar damage (Ali et al. 2005).

**Embolism: Cardiac and Noncardiac**

In Greek, “embolus” literally means projectile (Lebow 2010). Embolism of the lower limb can cause acute lower limb ischemia when a clot forms in a distant region, most commonly the heart, and migrates to the vessels of the leg, occluding normal blood flow. Unlike thrombotic occlusions, the onset of symptoms is generally very rapid, occurring over minutes or even seconds (Callum and
Bradbury 2000). Common indicators of acute lower limb embolism include sudden onset of pain at rest, rapid deterioration in claudication, and ulcers or gangrene 18.

The incidence of multiple occlusions due to embolism is high, reported in up to 15 % of patients (Callum and Bradbury 2000). Compared to the arms, the lower limbs are threefold more likely to be affected by acute limb ischemia due to embolism (Callum and Bradbury 2000). The most indicative sign of embolism is the sudden occurrence of multiple lower limb occlusion sites in patients with previously normal limbs, though palpably soft and tender arteries, bruit absence, and a clearly present contralateral leg pulse are also considered valuable clinical indicators of embolism (Callum and Bradbury 2000).

Thrombosis patients with preexisting arterial or cardiac conditions are a greatly elevated risk for sudden and persistent embolic limb-threatening deterioration (“acute-on-chronic ischemia”). These events can result from acute thrombosis of preexisting stenosis, bypass graft occlusion, or occlusion of major collaterals (Ali et al. 2005). If any signs of lower limb embolism are present, factors such as clinical history of atrial fibrillation, intermittent claudication, critical ischemia, or prior bypass graft surgery are generally considered sufficient to confirm a diagnosis of thrombotic lower limb occlusion diagnosis.

Cardiac disease is an important risk factor to thrombotic occlusion of the lower limb, as clots that originate in the heart or adjacent large arteries during abnormal heart rhythms can rapidly travel through the circulatory system into the lower limb and become lodged in the smaller femoral, popliteal, peroneal, and tibial arteries in the leg. As much as 80 % of all peripheral emboli have been reported to originate in the left atrial appendage as a result of atrial fibrillation; however, emboli may also be caused by other abnormal ventricular or valve motion, prosthetic bypass grafts, aneurysmal disease, paradoxical embolism, and atrial myxoma, though these causes are relatively rare (Callum and Bradbury 2000). Morrison (2006) reported that virtually all emboli arise from the left heart, aorta, or iliac vessels and that atrial fibrillation, left ventricular aneurysm, penetrating ulcers, or aneurysms of the aorta and common iliac arteries are, by far, the most common sources of emboli. Emboli typically lodge at the branches where large arteries bifurcate into smaller arteries in the vascular tree, thereby occluding multiple tributaries at once (Morrison 2006).

Noncardiac emboli have been reported to account for only about 13 % of emboli in the lower limb (Klonaris et al. 2007). Furthermore, between 9 % and 15 % of emboli are of unknown origin (Callum and Bradbury 2000; Klonaris et al. 2007). Of these, a significant percentage of occlusions, paradoxically, occur due to venous emboli that are able to pass through an intracardiac shunt (Morrison 2006). The occurrence of noncardiac emboli is, however, relatively low in patients with acute ischemia of the lower limb.

Less Common Causes: Trauma, Blue Toe Syndrome, Popliteal Artery Aneurysms, and Other Causes

Approximately 10 % of acute lower limb ischemia cases are attributable to less common causes, such as iatrogenic and other trauma, vasculitis, and dissection (Klonaris et al. 2007). Though severe lower limb ischemia can result from iatrogenic trauma – generally due to literal severing of major arteries and veins – proper application of modern (post-1990) techniques combined with early intervention and management can dramatically reduce progression and severity of acute ischemia in the lower limb (Melliere et al. 1996). In the case of trauma-induced injury, restoration of blood flow is central to limb salvage.

While occlusion can occur anywhere in the leg, the small vessels of the foot are, in part due to their size, particularly prone to occlusion. Microembolization of the small vessels in the foot from a proximal source, commonly known as blue toe syndrome, is a type of acute digital ischemia of
the foot. Blue toe syndrome is, as its namesake suggests, characterized by the painful cyanotic appearance of the affected region (Lebow 2010). Other key clinical indicators of blue toe syndrome are an audible and palpable Doppler pedal pulse and the progression of skin discoloration (Dolmatch et al. 1989). Matchett et al. (2000) reported that 27% of patients with blue toe syndrome treated with arterial stenting required limb amputation and 20% were deceased at a mean of 18 months after treatment. This condition, along with livedo reticularis and digital gangrene, is a less common cause of acute ischemic syndrome documented since the 1960s (Fukumoto et al. 2003). Though uncommon, this study also reported that up to 7% of patients exhibited progression of embolic occlusion to other areas of the affected lower limb.

Other causes of acute lower limb ischemia include popliteal cysts, popliteal entrapment, ergotism, compartment syndrome, and aneurysms of the popliteal artery (Norgen et al. 2007). Of these, popliteal artery aneurysm (PAA) is particularly prevalent (Dorigo et al. 2002). Popliteal aneurysm can occur in isolated vessels or compound other large vessel aneurysms of the abdominal and femoral arteries, and occurrences effect all layers of the vessel wall (intima, media, adventitia) leading to variable degrees of ischemia and metabolic imbalance in adjacent tissues (Reed 2013). Popliteal artery aneurysms have an incidence rate ranging from 0.1% to 2.8%, making these occurrences the most common type of peripheral arterial aneurysms and a major source of limb- and life-threatening acute ischemia of the lower limbs (Kropman et al. 2010). Thus, the popliteal artery is often the suspect in patients exhibiting incomplete or generalized symptoms of lower leg ischemia.

Pathophysiology of Acute Limb Ischemia

Local Pathophysiology

Tissue Injury and Death

The end result of sustained occlusion of the vessels of the lower limb is tissue injury or death due to ischemia in the muscles and nerves supplied by the occluded arteries. Initially, the lack of blood flow will produce a visibly white area, described as “marble white” by Callum and Bradbury (2000), due to the lack of blood supply (red hemoglobin). Over a period of hours, the initial muscle spasm will relax and the skin will assume a light purple color in progressively larger patches as deoxygenated blood fills the tissue. As stagnant blood coagulates in the ischemic tissue, the color will progressively darken and eventually blister and liquefy. Generally, patients within the first few hours of occlusion that exhibit white tissues are eligible for revascularization, while those with darker tissues must undergo amputation due to the potentially life-threatening effects of reperfusion injury (Callum and Bradbury 2000).

Tissue death in the ischemic region is caused by a complex combination of the effects of altered extracellular calcium levels (altering essential calcium differentials controlling platelet aggregation, clotting, vasospasm, and edema), accumulation of free radicals, mitochondrial dysfunction, lactic acidosis, excitatory neurotransmitters (excitotoxins), neutrophil activation, and ultrastructural change that is itself due to a complex cascade of intracellular effects (Darwin 1995).

Calcium Imbalance

In patients with acute ischemia of the lower limbs, calcium imbalance localized in the tissues supplied by the occluded artery has been reported to raise the risk tissue death during ischemic periods and exacerbate reactive oxygen species formation, plasma membrane damage, tissue edema, and local and systemic inflammatory response, particularly after reperfusion (Piriou et al. 2004).
In healthy tissues, extracellular calcium is maintained at concentrations approximately 10,000 times greater than intracellular concentrations (10,000:1 differential) due to the combined effects of ATP-driven membrane pumps, calcium-sodium exchange at the cell membrane, ATP-driven endoplasmic reticulum intracellular calcium sequestration, and oxidation-dependent calcium sequestration, with the end result that calcium accumulates in the mitochondria (Darwin 1995; Carafoli and Crompton 1978). Elevated intracellular calcium levels can release harmful free fatty acids, activate membrane phospholipases and protein kinases, and ultimately damage the cell membrane during the ischemic episode, as well as contributing to systemic metabolic imbalance (Wolfe 1982).

Furthermore, when revascularization allows oxygen to again reach previously ischemic tissues, rapid restoration of ATP levels can result in sudden and massive calcium overload, resulting in damage or destruction of the mitochondria (Safar 1986). Thus, calcium imbalance is a central risk for localize tissue injury and death during acute ischemic episodes and following revascularization.

**Free Radical Accumulation**

Patients with acute ischemic conditions of the lower limb may present with tissue damage due to accumulation of free radicals in ischemic tissues, particularly after revascularization. Hydrolysis of ATP via AMP during ischemic periods can allow hypoxanthine to accumulate, while increased calcium levels contribute to conversion of xanthine dehydrogenase (XD) to xanthine oxidase (XO) – both of which can generate free radicals upon reoxygenation (Tien and Aust 1982). Some studies have suggested that metal catalyzed Haber-Weiss reaction ($\cdot$O$_2$ + H$_2$O$_2$ $\rightarrow$ $\cdot$OH + OH$^-$ + O$_2$) following ischemia may result in potentially even more damaging free radicals (McCord 1983). During reperfusion and reoxygenation, significantly increased free-radical levels contribute to degradation of the cell and capillary membranes and contribute to increased tissue injury and poorer outcomes following acute ischemia (Darwin 1995). In addition to the localized effects of free radicals, systemic distribution of these species contributes to organ failure and metabolic syndrome.

**Lactic Acidosis**

Lactic acidosis is a physiologic condition that results from lactic acid buildup in the bloodstream that exceeds the rate at which it can be removed, generally occurring when oxygen levels in the body drop (Seifter 2011). Acute lower limb ischemia and revascularization can cause disseminated intravascular coagulation and altered venous efflux as a result of increased lactic acid levels combined with other factors, such as calcium imbalance (Celoria et al. 1990). Resultant pH drops as a consequence of lactic acidosis can cause mitochondrial injury or inactivation, degradation of NADH necessary for ATP synthesis, reduced ATP recovery, and additional catalyzing of ferrous iron that leads to elevated free radicals and subsequent free-radical-mediated injury (Darwin 1995).

**Biomechanical Effects in Occluded Vessels**

Acute limb ischemia of the lower limb results from a sudden obstruction in the arterial flow to the extremity due to an embolism or thrombosis, forming a biomechanical blockage of normal blood flow. The most apparent effect of occlusion caused by thrombosis, embolism, or other etiologies is the reduction or even complete elimination of blood flow to tissues supplied by the affected vessel, and the subsequent insufficient local blood flow to meet the metabolic demands of resting muscle or tissues (Neschis and Golden 2012).

Embolic acute ischemia in the lower limb commonly results in more complete ischemia than thrombosis due to primarily biomechanical factors. Mobile emboli generally lodge at the bifurcation of a large vessel into multiple smaller tributary vessels (Morrison 2006). As a result, both vessels are generally occluded, though the occlusion may be variably complete per vessel. The additional stress...
placed on the bifurcation by the pressure of blood pressing against the lodged emboli can mechanically distort occluded vessels an effect exacerbated by the progressive inflammatory response. Because the vascular bed in which the emboli is lodged is generally “virgin” with no substantial prior collateral expansion, unaccustomed stresses and strains on small collateral vessels may cause distortion or rupture and contribute to occlusion completion and further complicate revascularization (Bannerjee and Dastidar 2010).

Conversely, acute lower limb ischemia caused by in situ thrombosis occurs in vessels that have developed collaterals due to gradual and often asymptomatic disease progression prior to symptom onset. Collaterals act to reduce biomechanical stress and strain on the occluded vessel and surrounding collaterals, thus resulting in less rapid and often less complete occlusion and progression of atherosclerotic narrowing (Bannerjee and Dastidar 2010). Mechanical damage caused to both the occluded vessel and associated collateral vessels can raise the risk of vessel rupture and contribute to inflammation and ischemia if untreated.

**Systemic Effects**

**Metabolic Syndrome**

In approximately 7.5 % of patients with acute arterial occlusion of the extremities, severe and complex metabolic syndromes occur, and these effects are the leading drivers for loss of life and limb amputation (Haimovici 1979). The most common justification for amputation is as a means for controlling potentially life-threatening metabolic complications. Furthermore, these patients are at increased risk for renal, cardiopulmonary, and muscular complications.

Metabolic syndrome occurs in two consecutive phases, including (1) an ischemic or devascularization phase and (2) a phase of revascularization. Severe clinical manifestations such as outstanding limb rigidity (“rigor mortis”) and nephropathic-metabolic changes (oliguria, acidosis, myoglobinuria, azotemia, hyperkalemia) are indicators of metabolic syndrome that must be immediately treated. Identification and correction of early signs of devascularization-induced metabolic syndrome can minimize the adverse effects of revascularization. Conversely, more severe, unmediated, or unresponsive metabolic complications are more likely to threaten the viability of the limb and patient survival (Haimovici 1979). Another central element of metabolic syndrome is the altered systemic acid-base and electrolyte balance that results from limb hypoperfusion (Bannerjee and Dastidar 2010). Notably, the rate of systemic acid-base balance abnormalities has been reported to be significantly higher in patients that died in the postoperative period after acute arterial occlusion of the lower extremities (Zimon et al. 1992).

**Rhabdomyolysis and Renal Dysfunction**

Ischemic rhabdomyolysis is the breakdown of muscle fibers caused by damage to skeletal muscle lacking oxygen. Extensive rhabdomyolysis leads to the release of muscle fiber contents (myoglobin) into the bloodstream, which is then filtered from the blood by the kidneys. Notably, ischemic rhabdomyolysis is considered to be an initiating event with the capacity to lead to further biochemical and metabolic alterations that can ultimately be the central determinants of both limb and life prognosis in patients with acute ischemia of the lower limb (Haimovici 1979). Rhabdomyolysis causes renal dysfunction leading to renal vasoconstriction, tubular toxicity, and luminal obstruction, which can ultimately lead to kidney failure (Holt and Moore 2000). Holt and Moore (2000) identified several key mechanisms by which rhabdomyolysis could cause renal dysfunction or failure, including lipid peroxidation initiated by the heme center of myoglobin, even without free iron, due to redox cycling of the heme group from ferrous to ferric and to ferryl oxidation states.
Notably, this condition is preventable if appropriate alkaline conditions are established early enough to prevent myoglobin-induced lipid peroxidation by stabilizing the reactive ferryl myoglobin complex. Because skeletal muscle damage extent and subsequent rhabdomyolysis are progressive over time if acute ischemia remains untreated, early treatment is central to ensuring good outcome by minimizing myoglobin distribution into the systemic circulation and preserving renal integrity function.

Microvascular Permeability (Platelet-Vascular Wall Interactions)
Both ischemia and revascularization impact the permeability of blood vessels throughout the body by altering the normal regulation of platelets with vascular walls. Ischemia stimulates synthesis of thromboxanes (Tx), a potent vasoconstrictive and hypertensive agent belonging to the family of lipids known as eicosanoids, that is central to platelet aggregation and blood clot formation. Thromboxane acts by binding to any of the thromboxane receptors, G-protein-coupled receptors coupled to the G-protein Gq thromboxane (Yokoyama 2005).

Both thromboxane A2 (TXA2) and the related compound prostacyclin (PGI2) are major products formed in the cyclooxygenase-catalyzed arachidonic acid metabolic pathways in vascular endothelium and platelet, respectively (Rossi et al. 1996a). These two compounds play central roles in the pathophysiology of various cardiovascular diseases due to their role in maintaining normal regulation of the interactions between platelets and the vessel wall in vivo. In the circulatory system, there is normally a dynamic homeostatic balance between these two pathways. When the balance is shifted toward the thromboxane pathway in vivo, the pathophysiological implication is the promotion of prothrombotic state in the blood vessels.

In patients with acute lower limb ischemia, however, both PGI2 and TXA2 synthesis have been shown to increase by nearly twofold compared to patients with chronic ischemic conditions of the lower limb, though PGI2/TXA2 ratios remained relatively constant in both types of patients (Rossi et al. 1996b). Furthermore, patients with acute lower limb ischemia caused by thrombotic occlusion have been shown to consistently have PGI2/TXA2 ratios nearly twofold those of patients with acute lower limb ischemia caused by embolism, which may be indicative of systemic arterial conditions (Rossi et al. 1996b). Thus, some researchers suspect that elevation of PGI2 and TXA2 synthesis in acute lower limb ischemia may be indicative of increased platelet-vascular wall interactions, which could potentially impact long-term cardiopulmonary outcomes and be used as an indicator of the occlusion etiology.

Cardiopulmonary Dysfunction and Sepsis
While the most apparent effects of acute limb ischemia are local, there have been an increasing number of reports since the 1980s that examined the systemic effects of lower extremity ischemia on the inflammatory response, specifically on the potential detrimental effects of such imbalance on cardiopulmonary function (Anner et al. 1987). One potential impact of altered platelet-wall interactions during and immediately after interventions for an ischemic event of the lower limb is increased microvascular permeability in the lungs and other tissues (Anner et al. 1988). This condition, when severe, can lead to sepsis syndrome and acute lung injury following lower limb ischemia-reperfusion, wherein the sterile inflammatory response rapidly escalates to lethal sepsis syndrome that can be localized in the lower torso or systemic (Harkin et al. 2001).

Plitas et al. (2003) reported that hindlimb ischemia (HI) in mice increased neutrophil-mediated matrix metalloproteinase activity in the lungs, including pulmonary metalloproteinases (MMP) proMMP-9, active MMP-9, and active MMP-2 levels, that is generally blocked by neutrophil depletion under normal metabolic conditions. These findings suggest that acute limb ischemia
leads to pulmonary polymorphonuclear leukocyte-mediated changes in metalloproteinases activity. Thus, altered metalloproteinases activity may also contribute to pulmonary dysfunction following ischemic events in the lower limbs.

Localized neutrophil activation and oxygen radical generation have been implicated in the pathogenesis of acute ischemia and are central to lung damage following revascularization (Cohen et al. 1997). Zimon et al. (1992) reported that pulmonary abnormalities were reported in 66% of patients with acute arterial occlusion of the lower extremities that died immediately following surgery, most commonly with patients exhibiting signs of “shock lung,” also known as adult respiratory distress syndrome. With this extremely high mortality rate and close correlation with pulmonary abnormalities, the systemic effects of acute ischemia in the lower limbs on cardiopulmonary function cannot be ignored.

Acute limb ischemia events can initiate the release of greater number of polymorphonuclear leukocytes, which then progressively become sequestered in the lungs potentially causing cardio-pulmonary dysfunction (Anner et al. 1987). Lung injury is partly attributed to release by PMNs of the extracellular matrix (ECM) modifying metalloproteinases (MMPs) (Plitas et al. 2003). Even successful reperfusion may result in the release of such highly toxic free radicals that have the potential to further compromise these critically ill patients (Bannerjee and Dastidar 2010).

Postthrombotic Syndrome
Postthrombotic syndrome (PTS) can broadly refer to a wide range of postthrombotic chronic venous diseases attributable to venous hypertension and stasis after occlusion of the deep veins of the lower limb. The spectrum of PTS encompasses several combinations of symptoms in various degrees of severity. These include chronic leg heaviness, leg aching, and venous claudication, edema, venous varicosities, and chronic trophic skin changes that exhibit a variety of hyperpigmentation to frank nonhealing ulceration or fibrotic scarring. It is often difficult to fully differentiate PTS from other primary varicose veins and other causes of chronic venous insufficiency, for example, valvular agenesis, that are not related to the acute ischemic event. The “heavy leg syndrome” (with or without accompanying edema or varicosities) is probably the most common symptomatology related to chronic venous insufficiency (Sharafuddin et al. 2003).

Skin Microcirculation
The unique nature of skin microcirculation is critical to fully understand the pathophysiology of acute ischemic events, particularly as the condition of the skin (color and appearance) is one of the most evident and commonly applied clinical indicators of acute ischemia in the limbs – and it is often employed first, prior to diagnostic imaging. The nutritional capillary blood flow to the skin in the distal limbs, particularly in the foot, represents a small fraction (~15%) of the total blood flow. Thus, nearly 85% of blood flow to the distal limbs serves a primarily thermoregulatory function (Norgen et al. 2007). As a result, the effects of acute but severe ischemia on the skin are extremely heterogeneous in nature and display a wide gambit of characteristics.

Though more common in patients with chronic incomplete ischemia or claudication, some patients with can develop localized microcirculatory defects in the skin, such as endothelial dysfunction, altered hemorheology, neutrophil activation, and inflammation that disturb microcapillary flow in small patches (Norgen et al. 2007). Thus, ischemic skin tends to exhibit complex local microcirculatory responses that can cause both rest pain and trophic changes with the ability to interfere with the tissue’s normal defense mechanisms. Hjortdal et al. (1994) reported that venous ischemic tissues evidenced significantly elevated hematocrit and higher post-collection clotting than normal blood. These tissues also exhibited red blood cell extravasation, activated
fibrin, excessive platelets, distended red blood cell shapes, and partly disrupted capillaries when examined by scanning electron microscopy (SEM). Thus, the histopathology of the skin during ischemic periods varies greatly from that of the underlying muscle and connective and nervous tissues, where ischemic damage and reperfusion injury may proceed at very different rates and uniformity.

**Ischemia-Reperfusion Injury**

Ischemia-reperfusion injury is a general name for the condition that results from the complex combination of local tissue damage and systemic effects caused when blood supply returns after an ischemic period. This condition encompasses many of the individual systemic and localized pathophysiological elements previously discussed. Ischemia-reperfusion injury is a central concern in patients with severe or advanced acute lower limb ischemia, as attempts to revascularized limbs in advanced stages can be life threatening due to its impact (Callum and Bradbury 2000). Callum and Bradbury (2000) recommended that small fasciotomy incision and observational techniques be used to determine the severity of tissue damage and inferred risk of ischemia-reperfusion injury is revascularization is performed. Because of the heterogeneous nature of ischemic injury, it is often difficult to predict the risk and severity of reperfusion injury, making close clinical observation and rapid laboratory analysis of key metabolic markers important in ischemia-reperfusion injury prevention and care.

**Clinical Diagnosis and Management**

**Diagnosis of Acute Ischemic Events of the Lower Leg**

The type of medical intervention is generally dependent on the type of occlusion, with interventional strategies well-defined for both embolism and thrombosis. For all acute ischemic events that occur in the lower limbs, however, contrast angiography remains the gold standard for diagnosis, though computed tomography angiography (CTA) and magnetic resonance angiography (MRA) also provide good results with lower toxicity (Lebow 2010).

**Contrast Angiography**

Contrast angiography is a form of diagnostic imaging that uses X-ray to examine blood vessels after the injection of water-soluble ionic or nonionic X-ray contrast media into the blood stream through target arteries (arteriography) or veins (venography). As in peripheral artery disease (PAD), contrast angiography remains the gold standard for diagnosis of acute ischemia of the lower limbs. In most modern clinical settings, angiographic images are attained primarily using preoperative and intraoperative digital subtraction angiography (DSA), though single-shot and cine digital video recordings are visible on using many contemporary device flat panel or image intensifier screens. The diagnostic results of contrast angiography are generally sufficient to provide a decision of normal insignificant stenosis, equivocal stenosis, significant stenosis, occlusion, or aneurysm, as well as to provide information about the extent of occlusion, if present (Tins et al. 2001).

Contrast is injected into the arteries or veins using needles or percutaneous polyethylene, polyurethane, or nylon catheters, and complications can arise due to adverse reactions to contrast agents or damage from the catheter. Angiographic studies are routinely performed under local anesthesia. After infiltration of the skin and the tissue around the artery or vein to be punctured, a small skin incision is made, and the artery is punctured with an angiographic needle. For
percutaneous catheter insertion, the Seldinger technique is used (GE Healthcare (GEHC) 2010). Power injection is used in some cases.

Carbon dioxide (CO$_2$) angiography with electronic injection proved to be less comfortable than iodinated angiography. CO$_2$ arteriography is equivalent to iodinated arteriography for imaging the iliac arteries, but imaging performance progressively degrades in the more distal arteries of the legs (Rolland et al. 1998). Thus, appropriate contrast agents should be carefully selected when high contrast images of the distal extremities, such as the foot, are required.

**Computed Tomography Angiography (CTA)**

Both standard computed tomography angiography (s-CTA) and contemporary dynamic computed tomography angiography (dyn-CTA) have been shown to have good diagnostic accuracy for detection of stenosis and occlusions leading to pain and ischemia in the lower leg. Sommer et al. (2012) reported that dyn-CTA increased the diagnostic confidence compared to s-CTA and also improved the arterial contrast enhancement and overall diagnostic accuracy. Thus, contemporary CTA technologies may be more useful than their predecessors in diagnosing acute ischemia of the lower limbs. Additionally, Fleischmann et al. (2006) reported that CTA is useful in differential diagnosis of embolism from thrombus in cases where the differential diagnosis is not clear from angiography alone. Due to the increasing importance of this technical in clinical practice, major review articles have been compiled to guide modern clinical use of CTA and examine recent advancements, such as the widely cited work prepared by Funaki (2010) in 2006.

**Magnetic Resonance Angiography (MRA)**

Magnetic resonance angiography (MRA) technologies have advanced rapidly in the past decade. Like other magnetic resonance technologies, the key benefit to patients is the use of magnetic field and radiofrequency rather than potentially harmful ionizing radiation, such as the potentially carcinogenic X-ray radiation used in computed tomography and conventional X-ray imaging. Compared to CTA, the results of MRA are quite comparable, with similar ability to visualize vessel abnormalities and provide diagnostic information pertaining to the lower-extremity arteries (Chahin and Cho 2013). Furthermore, both technologies produce images very similar to those attained by conventional gold standard angiography. In a prospective study comparing CTA, MRA, and digital subtraction angiography (DSA), all three diagnostic modalities exhibited similar diagnostic accuracy (Chahin and Cho 2013).

**Doppler Ultrasound**

Ultrasound technologies have become more affordable and portable in the past decade. In many cases, portable ultrasound may be more readily available than conventional devices and has been considered as an additional prehospital emergency response tool due to its ability to provide information on arterial condition within a smaller time window and without the need to move patients (Hölscher 2012). Doppler ultrasonography has become a routine second-line diagnostic tool for assessing lower-extremity arterial disease due to its ability to provide rapid and generally acceptable information about the anatomy and physiology of both small and large vessels of the leg. Spectral Doppler ultrasonography and color-flow vascular imaging technologies have also recently appeared and undergone rapid technological advancement, allowing modern ultrasound to identify blood vessels, confirm blood flow direction, and detect vascular stenosis or occlusion with improved accuracy (Chahin and Cho 2013; Lindner et al. 2008; Polak et al. 1991). Furthermore, microbubble contrast agents for ultrasound, such as vascular endothelial growth factor-loaded microbubbles, have been developed. These contrast agents control the impact of disruption to tissues...
and membranes during ultrasound, which may lead to future specialized diagnostic and therapeutic applications of ultrasound for patients with lower limb vascular diseases (Hu et al. 2009).

**Diagnosis: Special Considerations for Thrombosis**

Generally, stable chronic ischemia will not progress to thrombotic occlusion of the lower limbs unless additional iatrogenic or non-iatrogenic deterioration occurs, such as that caused by cardiac treatments, malignancy, cardiac infarction, or trauma (Callum and Bradbury 2000). Thrombosis generally requires angiographic diagnosis and can be treated by medical bypass and thrombolysis (Callum and Bradbury 2000).

Due to the progressive nature of the arterial conditions that most commonly lead to thrombotic occlusions, both thrombotic vessels and their collaterals often exhibit significant abnormalities that are readily apparent by conventional angiographic examination. Angiographic techniques can reveal information about the entire arterial tree of the affected limb, thus allowing clinicians to make an effective determination of perioperative risk (Schellong et al. 2001). The presence of distinct collaterals surrounding a single occlusive site is indicative of thrombotic occlusion.

Because about 80 % of thrombotic occlusions occur at the site of previous grafts rather than at the native arteries, previous clinical history and knowledge of grafts and prior graft complications can also play an important role in the diagnosis; native vessel thrombosis, however, can be much more difficult to treat and require much more elaborate operations (Lebow 2010). Similarly, heparin-induced thrombosis can appear between 3 and 10 days after heparin administration and is characterized by a twofold decrease in platelet counts, which may not be readily apparent by diagnostic imaging alone and will require laboratory tests (Lebow 2010). Other congenital conditions and metabolic disorders can also contribute to a differential diagnosis of thrombotic occlusion of the lower limb. Thus, knowledge of a patient’s clinical history is a requisite for the diagnosis of acute thrombosis.

**Diagnosis: Special Considerations for Embolism**

Embolisms can generally be clinically diagnosed, but radiography may be required to determine the size (macroemboli vs. microemboli) and content (e.g., fibrinoplatelet clumps, cholesterol) of the emboli, which can play a role in determining treatment and prognosis (Lebow 2010). When multiple occlusions are observed by clinical exams or diagnostic imaging, differential diagnosis clearly points to embolism, as mobile emboli can be readily transported to different regions by the circulatory system and lodged in multiple different vessels. In fact, multiple occlusions have been reported in up to 15 % of patients (Callum and Bradbury 2000). Furthermore, embolisms may be more difficult to detect by diagnostic imaging due to the lack of extensive collateral vessels and indicators of chronic vessel damage.

**Limb Viability and Clinical Management**

The initial management of patients and determination of limb viability influence both long- and short-term outcomes in patients with acute ischemic event of the lower limb, in part because of the rapid progression of the disease. Unlike acute ischemia of the upper limb, lower limb occlusion poses the notably greater risk of limb amputation and early mortality and generally requires more swift management. Acute limb ischemia is dependent primarily on whether occlusion occurs in the upper or lower limbs and whether sensation and movement are absent or present (Callum and
Bradbury 2000). Because of the significance of sensation, epidural or spinal anesthesia can complicate diagnosis (Callum and Bradbury 2000).

Strategies have been developed to better categorize the severity of acute ischemia based on viability and symptoms in the lower limbs, thus allowing practitioners to improve treatment by increasing the speed of patient care and management. Rapid response is critical in maximizing the chance of good outcomes and limiting risk factors. While these strategies are by no means fully mature and are often criticized for overgeneralizing the varied pathophysiology of acute ischemic manifestations, they provide a critical tool for rapid diagnostic assessment and management decisions in clinical settings.

**Limb Viability**

For the purposes of determining clinical management, acute limb ischemia is categorized by severity as viable, threatened marginally, threatened immediately, and irreversible, as described in the widely accepted definitions provided by the *Journal of Vascular Surgery* and numerous published manuscripts (Katzen 2002; 2000; Rutherford et al. 1997). This system is commonly known as the “Rutherford Criteria” (Class 1, 2A, 2B, and 3, respectively) (Lebow 2010). The central signs and symptoms that vary between these categories are sensory loss, muscle weakness, arterial Doppler signals, and venous Doppler signal, though skin color and appearance may also be considered. Notably, these categorizations of viability and severity fail to fully represent the etiology and pathophysiology of lower limb acute ischemic syndromes but provide essential clinical indicators that enable rapid diagnosis and subsequent interventions for patients requiring emergency treatment to salvage limbs or even preserve life.

**Viable (Rutherford Class 1)**

In viable acute lower limb ischemia, there is not an immediate threat to the limb, and there is generally no sensory loss or muscle weakness. Additionally, both arterial and venous Doppler signals are clearly audible in the pedal arteries. Furthermore, there is generally no continuing ischemic pain or neurologic deficit, and skin color is relatively normal due to adequate capillary circulation (Rutherford et al. 1997). Patients with viable lower limbs are generally eligible for conservative treatments and sometimes can evidence spontaneous resolution, though generally treatments, such as anticoagulants, are recommended to prevent progression or formation of additional occlusions in more distal regions of the lower limb.

**Limb Threatened Marginally (Rutherford Class 2A)**

In acute lower limb ischemia where limbs are threatened marginally, limbs are generally considered salvageable with prompt treatment. Sensory loss in these cases is limited to the distal digits and does not generally appear in higher regions of the leg. In these cases muscle and motor functions remain normal, though the patient may report minor pain or sensory loss in the immediate region of the occlusion. The arterial Doppler signal is, however, often obscured in these patients, though venous Doppler signals remain audible, particularly in the pedal arteries (Rutherford et al. 1997). Because these occlusions occur in the most distal regions of the lower limb, there is minimal chance that the thrombi from the occlusion will become mobile and potentially occlude other downstream vessels. Treatment is generally required to present the conditions from becoming more severe. Patients with marginally threatened limbs commonly seek out treatment due to unusual and progressive symptoms.
Limb Threatened Immediately (Rutherford Class 2B)
In acute lower limb ischemia where limbs are threatened immediately, emergency revascularization treatment is necessary for limb salvage and the metabolic effects of revascularization must be considered. Like patients with marginally threatened limbs, the pedal arterial Doppler signal is often inaudible. Sensory loss is more profound in these patients, and muscle weakness may be mild to moderate and can affect large regions of the lower limb. These patients may experience progressive pain or sensory loss that is not alleviated by rest, and notable discoloration of tissues is apparent (Rutherford et al. 1997). Surgical interventions are usually necessary to restore blood flow to ischemic tissues, and the metabolic effects of revascularization should be considered during and immediately following successful revascularization operations.

Irreversible (Rutherford Class 3)
When capillary skin flow is absent and major tissue loss or nerve damage is observed, acute lower limb ischemia is considered to be irreversible. Generally, both the arterial and venous pedal Doppler signals are inaudible, and the patient generally experiences profound paralysis (rigor), anesthetic sensory loss, and extreme pain in adjacent tissues. In these cases, amputation may be required to preserve the patient’s life (Rutherford et al. 1997). Tissue death is often readily apparent due to darkening and variably severe blistering and liquefaction of the affected tissues. Sepsis and metabolic syndromes are major mortality risks, and multiple organ failure, particularly of the pulmonary and renal systems, is possible without immediate and appropriate interventions.

Anticoagulant Treatments
Following diagnosis and determination of sensation and movement impairment, patients are generally evaluated clinically and admitted to the hospital for treatment with intravenous anticoagulants such as heparin or warfarin to prevent further thrombi from forming and, in theory, to potentially reduce subsequent clotting due to mobilization of additional emboli (Callum and Bradbury 2000). The value of early anticoagulant therapy has, however, been challenged by studies that claim that there is no significant short-term benefit in the majority of acute lower limb ischemia patients. These critics site that up to 15 % more patients will experience bleeding complications and many may go on to have surgical interventions despite attempted conservative treatment, thus increasing the duration of ischemia and revascularization surgery (Jivegård et al. 1991).

Long-term anticoagulant therapy is sometimes administered after thromboembolectomy in patients with acute limb ischemia. This treatment is designed to mediate preventable future arterial occlusive events, particularly in patients with atrial fibrillation or cardiac thrombus. This treatment has, however, been challenged by studies that indicated minimal benefit in some patient groups (Forbes et al. 2002).

Initial Management: Special Considerations for Thrombosis
It is considered a medical emergency when a patient presents with apparent signs of ischemia in any region of the lower limb without or with significantly impaired sensation or movement (Callum and Bradbury 2000). It is widely recommended that these patients should be immediately treated with intravenous heparin and fluids, and a catheter is commonly placed to ensure good urine output and maintained renal function. Urgent operative interventions are generally required for these patients, most commonly bypass, thrombectomy, or thrombolysis. When thrombotic occlusion is caused by non-iatrogenic injury such as limb fractures, blunt injury, and dislocations, often as a result of automobile accidents, ligation of collaterals can contribute to thrombotic occlusion severity and progression (Callum and Bradbury 2000).
Initial Management: Special Considerations for Embolism
Early recognition and anticoagulation treatment is essential in acute ischemia of the lower limb due to embolism because such treatment minimizes the risk of recurrent embolic occlusions and distal propagation (Lebow 2010).

Laboratory Testing
Diagnostic imaging and clinical examination may not always reveal a complete situation regarding systemic toxicity and metabolic abnormalities that can impair limb salvage efforts and eventually threaten the life of patients with acute ischemic syndromes of the lower limb. It is recommended that the metabolic parameters, renal function, blood count, prothrombin, partial thromboplastin, fibrinogen, and fibrin degradation products be assessed prior to, as well as during and after, treatment of acute ischemia. Furthermore, patient blood type should be recorded prior to any intervention, even thrombolysis, in the event that surgery becomes required and infusion is needed (Fleischmann et al. 2006). Thus, it is important that a full battery of appropriate examinations is performed to ensure good outcomes and prevent rapid and potentially detrimental changes in patient condition during and after acute ischemic events of the lower limbs.

Treatment Interventions and Outcomes of Acute Ischemia of the Lower Limb
The treatments and interventions for acute ischemic syndrome of the lower limbs are commonly based on a variety of factors, including presumed etiology (which can be determined in only about 85 % of cases), lesion morphology, lesion location, extremity viability, physiologic state of the patient, and availability of venous conduits for bypass grafting (Lebow 2010). Both conservative and surgical treatments are available, and appropriate treatment plan should be commensurate with the severity of occlusion.

Treatments and Interventions
At this time, the widely accepted treatments for acute ischemic events of the lower limb include systemic thrombolysis (emboleysis), percutaneous endovascular embolectomy/thrombectomy, and open surgical embolectomy/thrombectomy. There are also a number of less widely accepted treatments with great potential for future research use and clinical applications, including advanced excimer laser ablation and high-frequency ultrasound therapies.

Systemic Thrombolysis (Embolysis)
Systemic thrombolysis, also commonly referred to as embolysis for embolism patients, refers to the dissolution of a thrombus, especially one caused by a blood clot. In the lower extremities, arterial thrombolysis is a demonstrated safe and effective intervention for acute limb ischemia patients, particularly those presenting with in situ thrombosis or embolic occlusion. There are, however, contraindications for thrombolysis, including nonviable limbs (indicated by absent motor or sensory function) and severe or persistent bleeding. Fleischmann et al. (2006) stated in his 2010 article, the most important thing to understand about thrombolysis is that it merely restores the baseline condition and does not treat the underlying pathology. Thus, determination of patient eligibility is critical for successful thrombolysis intervention in patients with lower extremity occlusions.

Patients are generally only eligible for thrombolysis within the first 7 days of symptom onset and while the limb is still viable. Thrombolysis has similar limb salvage rates as surgery for eligible
patients, but mortality rate is lower for thrombolysis due to the lower risk of cardiopulmonary complications (Fleischmann et al. 2006). The thrombolysis procedure consists of accessing target artery, conducting preoperative planning imaging (most commonly angiography) to understand relevant anatomy, inserting the sheath and catheter, and conducting the thrombolytic infusion (most commonly tissue plasminogen activator combined with low-dose heparin) (Fleischmann et al. 2006). In addition to tissue plasminogen activator, widely available thrombolytic agents include urokinase, natural streptokinase, anistreplase, alteplase, reteplase, and tenecteplase (Vorwerk 2003). The outcomes of these procedures are generally good when employed by experienced practitioners in properly eligible patients with viable limbs.

For treatment of occlusion of the lower limb, the Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial is one of the most well-known comparisons of thrombolysis versus open surgery (The STILE Trial 1994). The study examined 393 patients undergoing revascularization for lower limb ischemia due to grafts or native occlusions to evaluate intra-arterial thrombolytic therapy and surgery, concluding that although chronic ischemia patients responded well to open surgery, thrombolysis improved amputation-free survival and reduced hospital stays in patients with acute lower limb ischemia. Some critics, however, have challenged these findings based on the methodology and criteria for defining acute ischemia, suggesting that the study underestimated the population of patients that could benefit from open surgeries, such as patching, bypass, and re-bypass (Rutherford et al. 1997; Lebow 2010).

**Percutaneous Endovascular Embolectomy/Thrombectomy**

Embolectomy/thrombectomy can be done under local, regional, or general anesthesia (Callum and Bradbury 2000). Treatment of acute lower limb ischemia was revolutionized in 1961 with the advent of the Fogarty embolectomy (named for its inventor Thomas J. Fogarty), a type of catheter embolectomy in which a catheter with an inflatable balloon at the tip is inserted into the affected artery to a point just beyond the clot (Fogarty and Cranley 1965). The balloon is then inflated, and the clot is removed by withdrawing the catheter. Since the 1960s, many other strategies have been developed that leverage the use of computerization and advanced materials. One such balloon novel catheter is the PolarCath™ balloon cryoplasty system (Boston Scientific, Natick, Mass) (Rogers and Laird 2007).

Though many variations exist in both methods and catheterization devices, the two broad classifications of percutaneous endovascular embolectomy/thrombectomy procedures are balloon and aspiration-based catheterization procedures. Percutaneous aspiration thrombectomy (PAT) is an alternative method for percutaneous catheter-guided thrombus removal. The benefits of this treatment are its relative ease, low cost, and speed as well as the ability to selectively use large-lumen catheters (6- to 8-F) or small-lumen catheters (5-F) to forcefully aspirate vessels of different sizes (Karnabatidis et al. 2011). One such aspiration catheter is the Pronto V3™ aspiration extraction catheter (Vascular Solutions) (Rogers and Laird 2007). There are also reactivity recent additional strategies that employ hydromechanical shredding to dislodge occlusive clots, which have shown high success and good patency for treatment of acute lower-limb ischemia (Höpfner et al. 1999). The function of these treatments is primarily mechanical, acting by breaking down and removing the arterial occlusions. Furthermore, these treatments may be used as alternatives to thrombolysis or in combination with thrombolysis, and research is ongoing for novel and minimally invasive methods to reduce limb loss and mortality.

A retrospective review conducted by Ansel et al. (2008) in 2008 demonstrated that percutaneous mechanical thrombectomy (PMT) achieved complete or substantial clot removal in about 63 % of patients, partial clot removal in about 28.0 % of patients, and minimal clot removal in about 8.8 % of
patients, with a 5-year amputation-free survival rate near 95%. Similarly, Oguzkurt et al. (2010) reported that PMT resulted in complete removal of thrombus occlusions in 90% of patients with lower extremity thromboembolic acute occlusions, and 1-month, 1-year, and 2-year amputation-free survival rates of 100%, 93%, and 93%, respectively.

As Rogers and Laird (2007) described in depth in their article review of device for lower extremity revascularization, there are numerous contemporary thrombectomy devices, including AngioJet® and AngioJet® Ultra Thrombectomy System (Possis Medical), XCOrT™ (NexGen), Export XT™ catheter (Medtronic), minimal clogging Rio™ Catheter (Boston Scientific) and the Diver CE™ (Ev3 Inc), FrontRunner™ XP chronic total occlusion catheter (Cordis), CROSSER® chronic total occlusion recanalization system (FlowCardia), OutBack® LTD reentry catheter (Cordis), and others that possess unique benefits and limitations.

Pharmacomechanical Thrombolysis-Thrombectomy
For acute and subacute ischemia, isolated pharmacomechanical thrombolysis-thrombectomy (IPMT), often followed by balloon dilation, leverages the benefits of a hybrid catheter device capable of uniquely isolating the thrombolytic agent between two balloons inflated proximal and distal to the thrombotic lesion, enhancing mechanical agitation of the clot and thrombolytic agent. This procedure is often followed by aspiration of the thrombosed material to reduce systemic distribution of the thrombolytic agent and thus achieve rapid revascularization without the risks of prolonged systemic thrombolytic exposure (Gupta et al. 2011). The Trellis™ (Coviden) system is an example of a dual-balloon peripheral infusion device.

Open Surgery
Severe acute ischemic limbs can be treated with open surgical techniques designed to salvage the limb. These techniques allow for more reconstructive options than their less invasive endovascular counterparts, providing a means for stabilization of damages or ruptured vessels and redirection of blood beyond occluded vessels that cannot be revascularized by endovascular methods. The primary types of open surgery are balloon catheter thrombectomy, bypass procedures to direct blood flow beyond the occlusion, endarterectomy with or without patch angioplasty, and intraoperative isolated limb thrombolysis (Kasirajan). Three large clinical trials of acute limb ischemia have indicated that there is still a role for aggressive surgical intervention, demonstrating that open surgery produces a higher limb salvage rate and that approximately 25% and 9% of patients will be required with either immediate open surgery or surgery within 30 days of performing Fogarty thrombectomy or embolectomy (Campbell et al. 1998; Nypaver et al. 1998; Pemberton et al. 1999). Furthermore, these studies suggest that surgical revascularization may allow for more rapid and complete revascularization, though the risk of cardiopulmonary events may be elevated by open surgery.

Because a large number of patients with femoropopliteal occlusions exhibit an underlying thrombotic occlusion with irregular blood vessel damage, intraoperative stent placement is also possible during surgery and may be used more frequently than generally reported (Vorwerk 2003).

Therapeutic Ultrasound
Therapeutic applications of high-frequency ultrasound, such as that produced by Omnisonics system (Omnisonics), have also recently appeared. Ultrasound therapies can achieve thrombus removal in two ways: (1) ultrasound energy can be applied to break fibrin bonds and thus accelerate thrombolysis or (2) ultrasound energy can be used directly as a tool for thrombus destruction. Notably, the very small catheters required by such systems make them particularly suitable for small arteries of the distal lower limb and foot, where small size is necessary (Vorwerk 2003). Ultrasound
contrast agents can also have therapeutic effects for treating peripheral vascular diseases, particularly in the case of thrombotic and angiogenic diseases. A combination of targeted contrast agent and drug-carrying contrast agent may be safe and effective for treating thrombosis compared with surgery. Current research provides compelling evidence that vascular endothelial growth factor-loaded microbubbles can be expected to become effective as safe treatments for neovascular diseases such as severe limb ischemia and other diseases in the near future (Hu et al. 2009). Although there remain notable limitations for the use of high-frequency ultrasound and therapeutic ultrasound microbubble contrast agents for acute ischemia of the lower limb, these therapies are rapidly advancing and may offer new hope for reductions in amputation rates and mortality for these patients in the future.

**Therapeutic Excimer Lasers**

Excimer lasers are a promising new technology that can be employed for clinical removal and debulking of thrombotic occlusions by delivering targeted laser energy to the occlusive site, which transforms clots into a gaseous state through photochemical molecular bond breakage (Laird et al. 2004). Laser procedures produce minimal heat and damage to surrounding tissues (low disruption and thermal effects). Furthermore, 308-nm lasers, such as the commercial Spectranetics CVX-300® excimer laser photoablation system (Spectranetics), are capable of ablating calcified tissues (Laird et al. 2004).

Arterial occlusions in the femoropopliteal and infragenicular arteries have been successfully treated using excimer laser-assisted methods, prompting renewed interest in this promising field (Laird et al. 2004). A prospective study of 78 patients with lower limb occlusions conducted by Visonà et al. (1998) examined the effects of treatment with excimer laser angioplasty, resulting in an immediate post-procedural success rate of 97 %, and only 8 % of patients exhibited reocclusion. Patency was 47 % at 12 months and 40 % at 12 months, suggesting that excimer laser angioplasty may be an effective procedure for eliminating occlusion in patients showing less than 10 cm occlusions and good runoff (Visonà et al. 1998). Excimer laser-assisted angioplasty has also demonstrated success in the treatment of long occlusions in the superficial femoral artery, and the Laser Angioplasty for Critical Limb Ischemia Phase 2 Trial (LACI) results provided further evidence on the viability of laser for treating patients with occlusions of the lower limb who are otherwise not good candidates for bypass surgeries (Laird et al. 2004). Furthermore, though percutaneous endovascular therapies can range from 30 % to 50 %, more cost-effective than comparable open surgeries, laser therapies may be even more cost-effective for treating lower limb occlusions (Hunink et al. 1994; Jansen et al. 1998; Laurila et al. 2000).

**Interventions: Special Considerations for Thrombosis**

For thrombotic occlusions of the lower limb that occur subsequent to other interventions, as in the case of graft thrombosis, the duration of time between the original intervention and diagnosis of thrombosis can be used as an indicator of appropriate intervention. For patients with early thrombosis (approximately 14–30 days) following these interventions, the technical defect may be repairable, and on-table twists, kinks, and stenosis should be examined (Lebow 2010). When the thrombosis occurs later, it is important to examine the duration and severity of ischemia. Lytic therapy may be required to unmask lesions and stenosis, and open or endoscopic repair of the vessel may be required. Because additional emboli can form from both the source of the original clot and dislodged sections of occlusive clots, the initial treatment following clinical diagnosis of embolism
are anticoagulants like warfarin and heparin (Callum and Bradbury 2000). Immediate anticoagulant treatment may be necessary to ensure that acute ischemia does not develop due to embolic occlusions in other areas of the body and in the more distal regions of the affected lower limb.

**Interventions: Special Considerations for Embolism**

Special precautions should be taken to avoid dislodge emboli that may translocate to other distal vessels and cause secondary occlusions (Lebow 2010). During surgery for acute ischemia of the upper regions of the lower limb, particularly for cases of multiple embolisms and extreme vessel damage, it may be necessary to place compressive cuffs around the distal lower limb to prevent migration of thrombi (Vorwerk 2003). In general, open surgery with or without compressive cuffs may be required when vessel condition is poor, incomplete, or collapsed due to conditions such as aneurysm or trauma. Certain types of catheters have been developed to optimally prevent distal embolization, including the Rotarex® and Aspirex® contemporary over-the-wire rotational thrombectomy catheters that combine mechanical clot fragmentation and active negative-pressure removal (Horsch et al. 2009).

**Interventions: Special Considerations for Popliteal Artery Aneurysms (PAA) s**

The consequences of acute thrombosis of a PAA can be both limb- and life-threatening. Because thromboembolization most commonly occurs at the runoff arteries, amputation risks are greatly increased in these patients (Kropman et al. 2010). In previous decades, the treatment of choice was surgical thrombectomy of crural arteries and femoropopliteal/femorocrural bypass grafts. More recently, beginning in the 1980s, intra-arterial catheter-directed thrombolysis was successfully employed and rapidly accepted for reducing the arterial runoff prior to surgical revascularization, thus increasing bypass patency in the lower limbs (Schwarz et al. 1984). Only in recent years has endovascular treatment (thrombolysis and stent grafting) become a reliable alternative to open surgery for PAA, and optimal PAA treatment remains controversial (Kropman et al. 2010).

A review conducted by Kropman et al. (2010) in 2010 examined 25 studies comprised of 895 patients presenting with acute leg ischemia due to thrombosed popliteal artery aneurysm, demonstrating that preoperative and intraoperative thrombolysis notably improved graft patency rates after 1 year, but did not reduce amputations. Thus, popliteal aneurysm remains a notable cause of poor outcomes in acute ischemic syndrome of the leg, meriting immediate surgical treatment if suspected.

**Adverse Events Following Acute Ischemia of the Lower Limb**

The relative prevalence of adverse events following acute ischemia of the lower limb is a central challenge in improving patient short- and long-term outcomes.

**Intimal Lesions and Secondary Thrombosis**

Arterial intimal lesions can result from improper vessel closure, improper catheter advancement, and suturing during endovascular and open surgical procedures, and these occurrences raise the risk of infection and recurrent thrombosis (Siani et al. 2006). Following balloon embolectomy for lower limb ischemia, intimal lesions have been reported to lead to secondary thrombosis of the vessel and contribute to dissection or rupture by causing cholesterol embolisms to dislodge from existent atherosclerotic plaques (Fleischmann et al. 2006).
Early Failing
When stents are used or grafts are restored during an acute ischemic event, there is always some risk of future graft failure. Bypass grafts can also occlude during the early postoperative period due to technical or poor quality vein graft, and neither of these treatments responds well to percutaneous thrombolysis (Fleischmann et al. 2006). These conditions can necessitate open surgery rather than more conservative treatment and potentially extend the time until surgical completion, potentially increasing reperfusion injury and infection risk.

Site Bleeding
Following thrombolysis treatment for acute lower-leg ischemia, the incidence of major bleeding complications has been reported to vary from about 7 % to (Hull et al. 2006). After thrombectomy and open surgery, bleeding may be even more prevalent, occurring in up to 15 % of the patients, due to the more invasive nature of these procedures (Jivegård et al. 1991). Furthermore, prolonged administration of anticoagulants, such as heparin, can raise bleeding risks. Localized bleeding can usually be mediated by an application of compression to the local region, and infusion, cryoprecipitate, and discontinuation of heparin can be employed for persistent bleeding at the discretion of the physician (Fleischmann et al. 2006).

Decreased Fibrinogen
It is common practice to monitor fibrinogen levels on a case-by-case basis and potentially consider ceasing thrombolysis treatment and give fresh plasma when levels decrease to 100 mg/dL or less (Fleischmann et al. 2006). Though the STILE trial indicated a correlation between fibrinogen levels and bleeding complications (The STILE Trial 1994), there is limited prospective evidence that fibrinogen and bleeding risk are linked, making monitoring of fibrinogen levels controversial. Fibrinogen level can be artificially high or normal in rtPA infusion due to accumulation of fragment X, one of several fibrin degradation products (Morrison 2006).

Leg Pain
Elevated pain is commonplace during thrombolysis and may be considered a normal indicator of treatment progression. When pain is reported either locally or in other areas of the body, clinicians should carefully consider the motor and sensory characteristics of the affected area and the possibility of systemic and of reperfusion injury, such as compartment syndrome and reperfusion injury. Pain can be managed with intravenous morphine administered every 1–2 h, as needed (Fleischmann et al. 2006). Pain can indicate rare and severe adverse events, such as organ failure; major cardiopulmonary events, renal failure or injury, and intracranial hemorrhage are rare following thrombolytic therapies (Fleischmann et al. 2006). Thus, careful consideration should be given to all aspects of patient when abnormal pain levels are reported.

Summary and Recommendations
To improve overall outcomes of limb loss and mortality, which remain relatively high in patients with acute ischemia of the lower limb, it is crucial to employ appropriate and timely management. Improved diagnostic and interventional technologies can assist in identifying the underlying pathology, either thrombus or embolus, and determining the presence of chronic or native vessel abnormalities. Furthermore, intraoperative imaging has greatly improved, allowing increased control over minimally invasive percutaneous endovascular techniques for thrombectomy and
Embolectomy. Appropriate treatment requires careful consideration of all available evidence and rapid clinical response. Improved therapeutics, such as novel contemporary catheters, laser technologies, and therapeutic high-frequency ultrasound merit further study and wider clinical implementation, as maturation of technologies may be central to improving care for these patients in the future.

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References

Kasirajan K Current options in the diagnosis and management of acute limb ischemia. MedScape MultiSpecialty


