PERIPHERAL ARTERIAL DISEASE
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SUMMARY

The major cause of peripheral arterial disease (PAD) is atherosclerosis. It may present with typical ischemic pain, atypical pain, or with no symptoms. The risk factors for the development of peripheral arterial atherosclerosis are diabetes mellitus, hyperlipidemia, hypertension, and cigarette smoking. The symptoms of peripheral arterial disease can be typical (claudication) or atypical. Intermittent claudication is defined as a reproducible discomfort of a defined group of muscles, which is induced by exercise and relieved with rest. The severity of symptoms of claudication depends on the amount of stenosis, the collateral circulation and the vigor of exercise. Atypical symptoms are often the result of comorbidities, physical inactivity and alterations in pain perception. Detection of asymptomatic PAD is important because it identifies patients at an increased risk of atherosclerosis at other sites. Noninvasive tests include the ankle-to-brachial index, exercise treadmill test, segmental limb pressures, ultrasonography and segmental volume plethysmography. Therapy of patients with claudication involves risk modification including exercise program and medical, percutaneous and/or surgical approaches. The evidence of benefit is convincing only for antiplatelet agents, usually aspirin, and cilostazol. Two important criteria for revascularization, either percutaneous intervention or surgery, are severe disability that limits the patient’s ability to work or to perform other activities that are important to the patient, and failure (or predicted failure) to respond to exercise rehabilitation and pharmacological therapy. About 25 percent of patients with critical limb ischemia undergo amputation within one year. The vast majority of patients presenting with even critical ischemia can be offered a reasonable attempt for limb salvage.

INTRODUCTION

The major cause of peripheral arterial disease (PAD) is atherosclerosis. Patients with compromise of blood flow to the extremities as a consequence of peripheral arterial disease may present with typical ischemic pain, atypical pain, or with no symptoms. Intermittent
claudication is defined as a reproducible discomfort of a defined group of muscles, which is induced by exercise and relieved with rest.

**ETIOLOGY**

The etiology of leg pain can be divided into categories that include vascular, neurogenic and musculoskeletal causes. Vascular pain includes classic claudication, atypical claudication and rest pain. The main cause of intermittent claudication is peripheral atherosclerosis. Neurologic pain is predominantly due to neurospinal (e.g., disk disease, spinal stenosis, tumor) or neuropathic causes (e.g., diabetes, alcohol abuse). Musculoskeletal pain derives from the bones, joints, ligaments, tendons and fascial elements of lower extremities.

The clinical history can help distinguish some of the less common causes of this disorder. Nonarterial pathologic conditions should also be considered on differential diagnosis of limb discomfort: deep venous thrombosis, musculoskeletal disorders, peripheral neuropathy, and spinal stenosis (pseudoclaudication) (Table 1).

**RISK FACTORS**

The risk factors for the development of peripheral arterial atherosclerosis are diabetes mellitus, hyperlipidemia, hypertension, and cigarette smoking. Data from Framingham Heart Study (1) and NHANES (2) analysis confirm that PAD was significantly increased in current smokers and patients with diabetes, hypertension or hypercholesterolemia. Diabetic patients have worse arterial disease and a poorer outcome than nondiabetics (3).

Patients at risk of lower extremity PAD (based upon the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on PAD 2005) are: age ≥70; age 50-69 with a history of smoking or diabetes; age 40-49 with diabetes and at least one other risk factor for atherosclerosis; leg symptoms suggestive of claudication on exertion or ischemic pain at rest; and abnormal lower extremity pulse examination or known atherosclerosis at other sites (e.g., coronary, carotid or renal arterial disease). Current cigarette smoking, the ratio of total to HDL cholesterol, hs-CRP and Lp(a) were statistically important predictors for the largest fall in ankle-to-brachial index (ABI) (large vessel cohort), whereas diabetes was the only significant predictor of progression among patients with the largest fall in toe to brachial index (TBI), small vessel disease (4).

**CLINICAL PRESENTATION**

Patients with PAD may present with typical symptoms such as pain, atypical symptoms, or may be asymptomatic. The 2005 ACC/AHA guidelines on PAD suggest the following distribution of clinical presentation of PAD in patients aged ≥50: asymptomatic – 20%-50%, atypical leg pain – 40%-50%, classic claudication – 10%-35%, and critical limb ischemia 1%-2% (5). Two classification systems, Fontaine’s stages and Rutherford’s categories, have been used for lower extremity PAD based upon the severity of symptoms and the presence of markers for severe disease such as ulceration and gangrene (6) (Table 2).
SYMPTOMATIC DISEASE

Symptoms of peripheral arterial disease can be typical (claudication) or atypical. The severity of symptoms of claudication depends upon the amount of stenosis, the collateral circulation and the vigor of exercise. Patients with claudication can present with buttock and hip, thigh, calf or foot pain, single or in combination. Patients with aortoiliac occlusive disease (Leriche syndrome) present with buttock, hip and sometimes thigh claudication and may be associated with weakness of the hip and thigh on walking. Bilateral aortoiliac disease can cause erectile dysfunction in men. Physical examination reveals bilateral diminished or absent pulses at the level of the groin, occasionally with bruits over the iliac and femoral arteries and muscle atrophy and slow wound healing in legs. Atherosclerotic occlusion of the common femoral artery may include claudication in the thigh, calf or both. These patients have normal groin pulses but decreased pulses distally. Calf claudication is the most common complaint. It is described as cramping pain that is consistently reproduced with exercise and relieved with rest. Cramping in the upper-third of the calf is usually due to superficial femoral artery stenosis, whereas cramping in the lower third of the calf is due to popliteal disease. Foot claudication is often accompanied by occlusive disease of the tibial and peroneal vessels. Isolated foot claudication is rarely seen with atherosclerotic occlusive disease, but is commonly seen with thromboangiitis obliterans (Buerger’s disease). Ischemic rest pain is the result of severe decrease in limb perfusion. It typically occurs at night and involves the digits and foot.

ATYPICAL SYMPTOMS

Some patients have atypical symptoms as the result of comorbidities, physical inactivity and alterations in pain perception. In a study (7) of 460 men and women with known PAD, symptoms were classified as follows: 1) classic claudication: exertional calf pain that does not begin at rest, causes the patient to stop walking, and resolves within 10 minutes of rest (33%); 2) atypical exertional leg pain type I: pain similar to that of classic claudication, but does not cause the patient to stop walking (9%); 3) atypical exertional leg pain type II: pain similar to that of classic claudication, but does not cause the patient to stop walking (9%); 4) leg pain on both exertion and at rest (19%); 5) no exertional leg pain, physically active (14%); and 6) no exertional leg pain, physically inactive (6%). Compared to patients with classic claudication, those with leg pain on both exertion and at rest were more likely to have diabetes, neuropathy or spinal stenosis in addition to PAD. Functional capacity varied among groups, being best among those with type I atypical exertional leg pain and worst among those with pain at both rest and exertion.
ASYMPTOMATIC DISEASE

The PARTNERS program (8) detected PAD by the ABI or by history in 29%. Among patients with a new diagnosis of PAD, approximately 45% had no history of leg symptoms and only 5.5% had classic claudication. Another study showed that in 14% the ABI was abnormal (ABI <0.90) and most of these patients did not report exertional leg symptoms but they were not able to walk as far in six minutes as the group of patients without PAD. The presence of any bruit, pulse abnormality or cool skin increases the likelihood of PAD. Detection of asymptomatic PAD is important because it identifies patients at an increased risk of atherosclerosis at other sites. For example, as many as 50% of patients with PAD have at least a 50% stenosis in one renal artery (9).

Functional capacity is diminished in some patients with PAD even in the absence of claudication (10,11). A gradual decline in activity level may mask the symptoms and lead to underestimation of disease severity. Patients with ABI <0.50 had a significantly greater annual decline in six-minute walk distance than those with ABI of 0.50 to 0.90 and those with ABI of 0.90 to 1.50 (73 versus 59 and 13 feet). Patients with no exertional pain had a greater annual decline in six-minute walk distance than those with typical intermittent claudication (77 versus 36 feet).

These findings suggest that activity level is an important factor in the evaluation of patients with PAD. Patients with the evidence of PAD who report no or few symptoms should be asked about functional capacity and decline in activity over time.

Acute limb ischemia is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers and/or gangrene) in patients that present within two weeks of the acute event. Patients with similar manifestations who present later than two weeks are considered to have critical limb ischemia, which is by definition chronic. The signs of severe PAD on noninvasive testing include ABI <0.40, flat waveform on pulse volume recording and absent pedal flow on duplex ultrasonography.

NONINVASIVE VASCULAR DIAGNOSIS OF LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE

There is a high prevalence of lower extremity PAD in patients over age 70 and in patients aged 50-69 with atherosclerotic risk factors, particularly smoking and/or diabetes.

The review of symptoms should include a history of walking impairment, symptoms of claudication, ischemic rest pain or nonhealing wounds in patients aged ≥70, in those aged ≥50 with a history of smoking and/or diabetes. Measurement of resting ABI should be performed in patients with one or more of these findings. An ABI of ≤0.90 has a high degree of sensitivity and specificity for the diagnosis, using arteriography as the gold standard.

Noninvasive tests include the ABI, exercise treadmill test, segmental limb pressures, ultrasonography and segmental volume plethysmography.

Ankle-brachial index (ABI) is a relatively simple and inexpensive method to confirm the clinical suspicion of arterial occlusive disease by measuring resting and post-exercise systolic blood pressures in the ankle and arm. This measurement is referred to as the ankle-brachial (or ankle-arm) index or ratio, and provides a measure of the severity of peripheral arterial disease (12). The calculation of ABI is performed by measuring systolic blood pressure (by Doppler probe) in the brachial, posterior tibial, and dorsalis pedis arteries (13,14). The highest of the four measurements in the ankles and feet is divided by the higher of the two brachial measurements. The ABI should be measured in both legs in all new patients with suspected PAD, both to confirm the diagnosis and to establish the baseline. If ABIs are normal at rest but symptoms strongly suggest claudication, ABIs and segmental pressures should be obtained before and after exercise on a treadmill or using active pedal plantar flexion, which involves repeatedly standing up on the toes (15). A low ABI has been associated with a higher risk of coronary heart disease, stroke, transient ischemic attack, progressive renal insufficiency, and
All-cause mortality (16-20). An abnormally high ABI (>1.4) is also associated with higher rates of leg pain and of cardiovascular risk.

**Exercise treadmill testing** is a sensitive method for evaluating patients with typical symptoms of claudication in whom resting ABI is normal. The standard exercise test is a treadmill test for five minutes at 2 mph on a 12 percent incline. Severe claudication can be defined as an inability to complete the treadmill exercise due to leg symptoms and ankle systolic pressures below 50 mm Hg.

**Segmental limb pressures** – Once the presence of arterial occlusive disease has been verified using ABI measurements at rest or during exercise, the level and extent of PAD is routinely assessed by segmental limb pressures. A 20 mm Hg or greater reduction in pressure is considered significant if such a gradient is present either between segments along the same leg or when compared to the same level in the opposite leg. Several blood pressure cuff positions are employed to detect the level of peripheral arterial disease (21). As examples, a significant reduction in pressure between the brachial artery and the upper thigh reflects aortoiliac disease; between the upper and lower thigh reflects superficial femoral artery disease; between the lower thigh and upper calf reflects distal superficial femoral artery or popliteal disease; and between the upper and lower calf reflects infrapopliteal disease. In a patient with possible upper extremity peripheral arterial disease, a difference of ≥10 mm Hg between brachial pressures suggests innominate, subclavian, axillary, or proximal brachial arterial occlusion.

Duplex ultrasonography is currently used to depict anatomy, hemodynamics, and lesion morphology; ultrasonographic equipment used for these tasks includes B-mode imaging, pulse wave Doppler, continuous wave Doppler, and color Doppler display. Lower extremity examinations using duplex Doppler begins at the common femoral artery and proceeds distally to the popliteal artery. An area of stenosis is localized with color Doppler and assessed by measuring Doppler velocities at several arterial sites. With progressive peripheral arterial disease, there is elimination of the reverse flow, a decrease in systolic peak and an increase in flow in diastole.

**MEDICAL MANAGEMENT OF CLAUDICATION**

Therapy of patients with claudication involves risk modification including exercise program, the use of antiplatelet agents, and possibly medical therapy for symptom improvement.

**Risk factor modification**

The risk factors for the development of PAD, i.e. cigarette smoking, diabetes mellitus, hypertension and hyperlipidemia, are similar to those for other forms of atherosclerotic vascular disease, so PAD is associated with an increased risk of coronary, cerebrovascular and renovascular disease. PAD is considered a coronary heart disease equivalent, thus being evaluated as a highest risk category (22). Cigarette smoking is the most important factor (23). In contrast, moderate alcohol consumption reduces the risk of PAD and intermittent claudication. A consensus document on the management of PAD recommends smoking cessation, lipid lowering with statin therapy, and treatment of diabetes and hypertension.

**MEDICAL VERSUS INTERVENTIONAL THERAPY**

Therapy for intermittent claudication may involve medical, percutaneous and/or surgical approaches. Most patients, except for those with critical limb ischemia, are treated initially with medical therapy. The medical management of moderate to severe intermittent claudication secondary to PAD, in addition to risk factor modification, involves exercise training or rehabilitation and pharmacological therapy.

Two important criteria for revascularization, either percutaneous intervention or surgery, are severe disability that limits the patient’s ability to work or to perform other activities that are important to him, and failure (or predicted failure) to respond to exercise rehabilitation and pharmacological therapy.
Exercise rehabilitation

A supervised exercise program is recommended as part of the initial treatment regimen. It is recommended for a minimum of 30 to 45 minutes at least three times per week for a minimum of 12 weeks. During each session, exercise of sufficient intensity to elicit claudication is recommended. The value of unsupervised exercise program is less well studied but is recommended for patients who cannot participate in supervised programs.

Pharmacological therapy

Pharmacological therapy is aimed at symptomatic relief or slowing progression of the natural disease. The evidence of benefit is convincing only for antiplatelet agents, usually aspirin, and cilostazol (24).

Aspirin alone does not suggest a statistically significant benefit in the broad PAD population, including asymptomatic patients (25). The Physicians Health Study, a primary prevention study, found that 325 mg of aspirin every other day decreased the need for peripheral artery surgery; however, no difference was noted between the aspirin and placebo groups in the development of claudication (26). The combination of aspirin and dipyridamole was found to increase the pain-free walking distance and resting limb blood flow in a study of 54 patients with intermittent claudication (27). Another study found an improved coagulation profile and ABI with this therapy but does not report if walking distance improved with combined therapy (28).

Ticlopidine, an inhibitor of platelet aggregation, appears to modestly increase walking distance in patients with intermittent claudication, however, because of a substational risk of leukopenia and thrombocytopenia it is rarely used (29). Clopidogrel is a similar but safer drug. The CAPRIE trial (30) found that clopidogrel had a modest, but significant advantage over aspirin (325 mg/day) for prevention of stroke, myocardial infarction (MI) and PAD in 19185 patients with a recent stroke, MI or PAD.

All symptomatic and asymptomatic patients with evidence for atherosclerosis in other circulatory beds should be prescribed an antiplatelet drug. Asymptomatic patients without evidence for atherosclerotic disease elsewhere may be considered for antiplatelet therapy. Nevertheless, aspirin is generally considered the antiplatelet drug of choice because of the high incidence of comorbid coronary disease, the benefits of aspirin in preventing MI, and its lower cost. Clopidogrel may be used if aspirin cannot be tolerated or in the subgroup of patients with symptomatic PAD.

Warfarin has not been shown to improve cardiovascular outcomes in patients with PAD.

Cilostazol is a phosphodiesterase inhibitor approved by the FDA for the treatment of intermittent claudication. It suppresses platelet aggregation and is a direct arterial vasodilator. In a meta-analysis, treatment with 100 mg twice daily for 12 to 24 weeks increased maximal and pain-free walking distance by 50 and 67 percent, respectively (31). Because other oral phosphodiesterase inhibitors used for inotropic therapy caused increased mortality in patients with advanced heart failure, cilostazol is contraindicated in heart failure of any severity. Cilostazol is recommended (in the absence of heart failure) to improve symptoms and increase walking distance in patients with lifestyle-limiting claudication, particularly if antiplatelet agents and exercise rehabilitation are ineffective and revascularization cannot be offered or is declined by the patients. It can be taken safely with aspirin and/or clopidogrel without an additional increase in bleeding time.

Pentoxifylline is a rheologic modifier approved by the FDA for symptomatic relief of claudication. Its mechanism of action includes an increase in red blood cell deformity and decrease in fibrinogen concentration, platelet adhesiveness and whole-blood viscosity. Pentoxifylline is less effective than cilostazol (32). The data available indicate that the benefit of pentoxifylline is marginal and not well established.
INDICATIONS FOR SURGERY IN PATIENTS WITH CLAUDICATION

The prognosis for both limb loss and survival is significantly worse in diabetic patients and those who continue to smoke (33).

Percutaneous transluminal angioplasty (PTA) results in ‘controlled’ dissection of the arterial media. Wolf et al. (34) and the authors of the BASIL trial (35) conclude that PTA should be offered first to patients with significant comorbidities who are not expected to live more than one or two years. For patients expected to live longer who are relatively fit, the reduced intervention rate and possible improved durability with bypass surgery could outweigh the short-term increase in morbidity. Percutaneous intentional extraluminal recanalization (PIER), also called subintimal angioplasty or subintimal recanalization of the lower extremity, is a technique for limb salvage in the setting of critical limb ischemia.

The ACC/AHA and other guidelines suggest the following issues to be addressed when considering either percutaneous or surgical revascularization in patients with intermittent claudication: 1) patients who have not had or are not predicted to have an adequate response to exercise rehabilitation and pharmacological therapy; 2) patients that are significantly disabled by claudication, resulting in the inability to perform normal work or other activities that are important to them; 3) patients that are able to benefit from the improvement of claudication (i.e. exercise is not limited by another cause such as angina, heart failure, chronic obstructive pulmonary disease or orthopedic problems); 4) the projected natural history; and 5) patient prognosis and lesion characteristics permit appropriate intervention at low risk with a high likelihood of initial and long-term success.

Initial revascularization with surgery is recommended only when the arterial anatomy is not favorable for percutaneous approach. Patients who benefit most from elective surgical revascularization are generally under 70 years of age, nondiabetic and have little evidence of disease distal to the primary lesion (36).

Vascular surgery is considered as a high-risk surgical procedure. It is important that preoperative risk stratification is performed in all patients. Peripheral arterial disease presents differently depending on the atherosclerotic lesion localization. There is a general association between the site of claudication and the site of the atherosclerotic lesion. The surgical procedures, complications and success rate of surgery depend on the area affected. Aortoiliac disease is called inflow disease and infrainguinal disease is called outflow disease. The ACC/AHA guidelines recommend that inflow lesions be addressed first, whether surgery or percutaneous intervention is performed. After it has been accomplished, revascularization of outflow disease is warranted if there is persistent infection, ischemic ulcers or gangrenous lesions and ABI is less than 0.8. The procedures for aortoiliac disease, including aortobifemoral bypass, tend to be quite durable, so the threshold for inflow disease is generally lower than that for the infrainguinal disease (outflow disease).

AORTOILIAC OCCLUSIVE DISEASE

Recommendations for surgery in patients with aortoiliac disease are: 1) in patients with unilateral disease with acceptable aortic inflow, iliac endarterectomy and aortoiliac or iliofemoral bypass; 2) these procedures should be performed in conjugation with femorofemoral bypass in bilateral iliac artery occlusive disease if the patient is not suitable candidate for bilateral aortofemoral bypass grafting; and 3) axillofemoral bypass should not be used for the treatment of intermittent claudication except for very limited settings such as chronic infrarenal occlusion associated with severe symptoms in a patient who is not a candidate for aortobifemoral bypass. An important determinant of long-term patency was the initial severity of disease (37). Aortofemoral bypass has become the preferred method of treatment for symptomatic aortoiliac occlusive disease in low-risk patients. Most procedures are performed for severe claudication, but approximately 30%-40% are done for limb salvage. Femorofemoral bypass is a useful option in patients with unilateral iliac occlusive disease whose aorta and contralateral
iliac artery are free from disease. Axillofemoral bypass grafting offers a reasonable alternative in high-risk patients with limb-threatening ischemia. It is not performed for routine claudication. Atherosclerotic lesions in the aortoiliac location generally begin at the bifurcation of the aorta or common iliac artery and can progress in either direction. Patients complaining of claudication due to isolated aortoiliac disease tend to be younger than those in whom claudication is due to a more distal disease. Lesions of aortoiliac system are less likely to cause symptoms compared to the distal lower extremity arteries since there is an extensive collateral system in this area. On the other hand, claudication as the result of aortoiliac disease may result in greater disability due to a larger number of muscle groups directly perfused by these vessels. There is a greater risk of distal embolization with lesions in this area. It is for these reasons as well as for the excellent long-term surgical results obtained in these patients that more aggressive approach to claudication as the result of aortoiliac disease is taken.

FEMOROPoplITEAL AND INFRAINGUINAL OCCLUSIVE DISEASE

For infrainguinal (outflow) disease: 1) bypasses to the popliteal artery above or below the knee should be constructed with an autogenous vein; 2) it is reasonable to use a synthetic graft to the popliteal artery below the knee only if no autogenous vein is available; and 3) the evidence is less well established for femorotibial artery bypasses with autogenous vein and for synthetic grafts to the popliteal artery above the knee. Femorotibial bypasses with synthetic grafts should not be performed because the prosthetic graft crosses the knee joint and is subjected to bending. Femoropopliteal bypass grafts are categorized as either above knee or below knee as determined by the location of the distal graft to artery anastomosis.

An infrapopliteal bypass should be performed only in situations of lower extremity ischemia in which femoropopliteal bypass is not feasible or does not allow for graft flow into patent runoff vessels. Important factors on choosing an outflow vessel for distal anastomosis of infrapopliteal bypass is the overall quality of the vessel and the vessel with the greatest degree of direct continuity with the foot.

The recommendations for postoperative follow-up are that patients with aortobifemoral bypass should have periodic evaluations that note any return or progression of symptoms of claudication, the presence of femoral pulses and measurement of ABI at both rest and after exercise. Patients with lower extremity bypass with an autogenous vein should have periodic evaluation for at least two years that note any claudication symptoms, including physical examination and pulse examination of proximal, graft and outflow vessels, and duplex imaging of the entire length of the graft measurement of peak systolic velocity and calculation of velocity across all lesions.

Patients with lower extremity bypasses with a synthetic graft should have periodic evaluation for at least two years that note any return or progression or symptoms of claudication, a pulse examination of the proximal, graft, and outflow vessels and measurement of ABI at both rest and after exercise.

The predictors of long-term outcome after surgical therapy for atherosclerotic occlusive disease of the terminal aorta and its branches were evaluated in a study by DeBackey and Glaeser (38) and included age, male sex, diabetes mellitus and systemic hypertension. Diabetes mellitus was the only predictor of the recurrence of symptoms or progression of disease. Venous grafts are prone to the development of stenosis, which can reduce blood flow, precipitate thrombosis and lead to limb amputation. Compared to vein grafts, synthetic grafts have a higher rate of thrombosis and graft failure, which may occur more rapidly. The criteria for at-risk grafts were: a fall in ABI of $≤0.1$; peak systolic velocity $<45$ cm/sec; increase in peak systolic velocity at the site of stenosis to $150$ cm/sec; and peak systolic velocity ratio across stenosis $>2.0$. Duplex sonography is considered the best method for such lesions. Only antiplatelet therapy or antithrombotic therapy appears to prevent graft failure. It is recommended that aspirin therapy (75 to 100 mg/day) should begin preoperatively and be continued indefinitely in all patients undergoing infrainguinal bypass or arterial reconstruction.
Warfarin or other vitamin K antagonist was not to be recommended in patients undergoing infrainguinal arterial reconstruction or bypass except for those at high risk of bypass occlusion and limb loss.

**PRIMARY AMPUTATION**

About 25 percent of patients with critical limb ischemia undergo amputation within one year. The vast majority of patients presenting with even critical ischemia can be offered a reasonable attempt for limb salvage. The ACC/AHA guidelines identify the following risk factors for amputation in patients with critical limb ischemia: 1) significant necrosis of weight-bearing parts of the foot in ambulatory patients; 2) an uncorrectable flexion contracture; 3) paresis of the extremity; 4) ischemic rest pain; 5) sepsis; and 6) limited life expectancy due to comorbid disease. The functional outcome following below-knee amputation is by far better than that following amputation at the ankle.

The main indication for thrombolytic therapy is acute limb ischemia of less than 14-day duration in patients with a viable extremity.

It would seem wise to attempt revascularization in patients with advanced renal disease before extensive gangrene is presented. Primary amputation should be considered in those with an infected, gangrenous foot.

**REFERENCES**


