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The clinical presentation of peripheral arterial disease and guidance for early recognition

ABSTRACT

Most patients with lower extremity peripheral arterial disease (PAD) are asymptomatic. Although intermittent claudication is the classic presenting symptom in those who are symptomatic, PAD often presents atypically as a result of associated comorbidities. The differential diagnosis involves consideration of many nonvascular and nonatherosclerotic causes of exercise-associated leg pain. Weak or absent pulses are the hallmark physical finding of PAD, and the ankle-brachial index is the most efficient objective test for documenting it. PAD may progress to acute limb ischemia (acute deterioration of limb flow) or critical limb ischemia (chronic compromise in limb perfusion resulting in rest pain and tissue loss), both of which can lead to limb loss without timely treatment.

Peripheral arterial disease (PAD) is common but grossly underrecognized and undertreated. Several factors contribute to its underrecognition. Notably, the majority of patients with lower extremity PAD are asymptomatic.[1,2] Other patients incorrectly attribute the symptoms of PAD to normal aging pains. Moreover, those who are symptomatic often do not present with the classic symptoms of intermittent claudication (IC) as defined in the Rose questionnaire of IC (ie, exertional leg pain) but instead report other exertional leg symptoms or present with progressive functional decline.[3]

Recognizing PAD is important because even its asymptomatic form is a strong marker for future cardiovascular events (stroke and myocardial infarction) and for functional impairment. Establishing the diagnosis identifies individuals who need more aggressive risk-factor modification and who may need other interventions targeted at improving their future cardiovascular outcomes and quality of life.[4–7] Such identification is particularly important in populations with a markedly elevated prevalence of PAD—the elderly, patients with diabetes, and current or past smokers.[1,8,9]

This article reviews the presentation of PAD and considerations in its evaluation and diagnosis, which Figure 1 summarizes in algorithmic form. Special attention is given to the differential diagnosis and signs of progression to acute limb ischemia and critical limb ischemia.

COURSE AND SEQUELAE OF PAD

The progression of PAD in an extremity usually is slow and follows a stepwise pattern. In cases in which rest pain or tissue loss (nonhealing ulcers or gangrene) is evident, the condition is termed *critical limb ischemia*. Sometimes an acute occlusive event in a vessel leads to rapid deterioration of a limb, termed *acute limb ischemia*, which requires emergent treatment.

Most patients with IC do not progress to critical limb ischemia but remain stable or suffer gradual worsening of symptoms over time. For instance, early findings from the Framingham Study showed that less than 2% of patients with PAD required major amputation.[3] A more recent study among a large series of men with IC found the cumulative 10-year rates of progression to ischemic ulceration and rest pain to be 23% and 30%, respectively.[10] A low ankle-brachial index (ABI) and diabetes were risk factors associated with development of ischemic ulcers and rest pain.[10] The cumulative 10-year rate of minor or major amputation in this population was less than 10%.[11]

In addition to the risk of these devastating limb outcomes, patients with IC have an annual mortality rate of approximately 12%, with death usually resulting from ischemic cardiovascular events.[11] Advanced age, a low ABI, diabetes requiring medication, and a history of stroke are independent predictors of death in patients with IC without rest pain or ischemic ulceration.[11]

EVALUATION FOR SUSPECTED PAD

History-taking

An accurate history is the key to the diagnosis of PAD. Eliciting atherosclerotic risk factors in the history may

*Both authors reported that they have no financial relationships that pose a potential conflict of interest with this article.

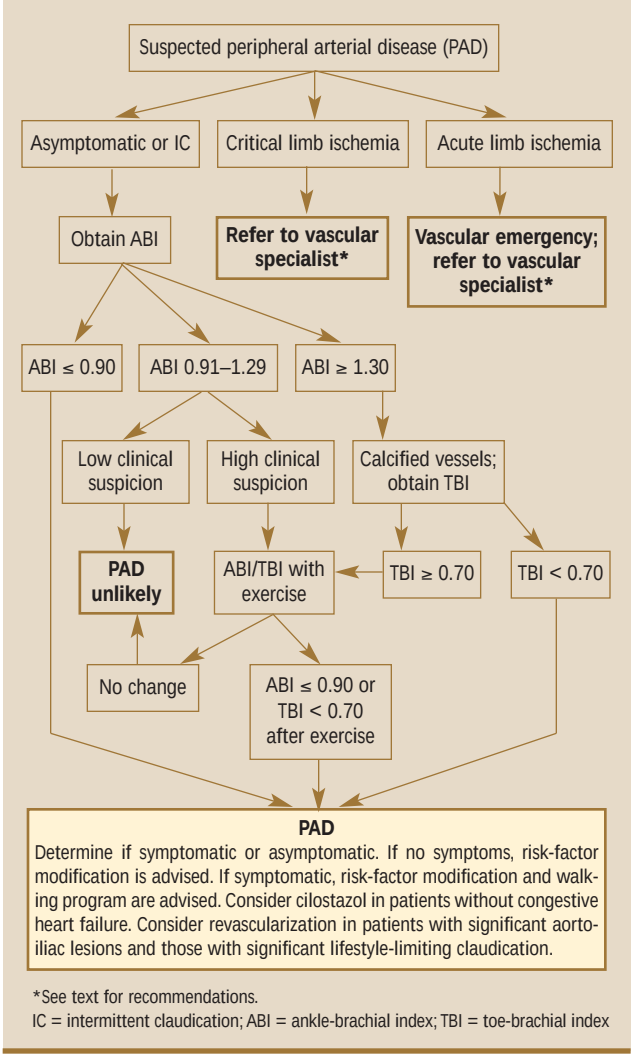


FIGURE 1. Algorithm for the evaluation and diagnosis of suspected peripheral arterial disease.

help to identify patients who, although asymptomatic, have evidence of PAD on physical examination or noninvasive testing. Risk factors for PAD include advanced age, current or past tobacco use, diabetes, hypertension, hyperlipidemia, and (less frequently) certain hypercoagulable states (see the preceding article in this supplement for a detailed discussion of risk factors for PAD).

Classic IC occurs after a defined amount of ambulation—ie, the distance required for symptoms to begin and to limit activity is reproducible. Symptom relief typically occurs within 10 minutes of rest or standing still and, notably, does not require sitting or lying down.

Symptoms correspond with diseased arterial level

Arterial disease in the lower extremity is generally broken down into three levels: aortoiliac disease, femoropopliteal disease, and tibial artery (crural, below-the-knee, or infrageniculate) disease. The location of symptoms can help pinpoint the anatomic area of disease. The diseased arterial segment is typically proximal to the affected muscle group, although multilevel PAD can cause symptoms throughout the leg. Thus, a patient with aortoiliac disease may experience pain in the hip, buttock, or thigh; femoropopliteal disease may result in calf pain; and tibial disease may result in foot claudication. Patients presenting with IC symptoms generally have single-level disease, whereas those presenting with rest pain or ulceration generally have multilevel disease.

Differential diagnosis

Although leg pain associated with exercise and relieved by rest is suggestive of IC, it is not sufficient for diagnosis. IC must be differentiated from lower extremity pain with nonvascular etiologies (Table 1).

Many concomitant disease processes can complicate the diagnosis of PAD. Both neurologic and musculoskeletal and venous pathology can cause leg pain or coexist with leg pain from PAD, confounding the diagnosis. False-positive diagnosis rates of up to 44% and false-negative rates of up to 19% have been reported after findings obtained by clinical evaluation were verified by noninvasive tests.[12] Calf claudication is commonly confused with pain from venous disease, nerve root compression, or spinal cord stenosis. Hip and buttock claudication is commonly confused with osteoarthritis of the hip or with spinal canal narrowing due to osteoarthritis. The nonatherosclerotic conditions that mimic IC and that should be considered in the differential diagnosis are discussed individually below.

Venous claudication occurs in patients with chronic venous insufficiency and those who develop post-thrombotic syndrome after deep venous thrombosis. The baseline venous hypertension in the obstructed veins worsens with exercise and produces a tight bursting pressure in the limb, usually worse in the thigh and uncommonly in the calf.[13] It usually is associated with evidence of venous edema in the leg. Venous claudication tends to improve with cessation of exercise, but total resolution takes much longer than resolution of IC and may require leg elevation.

Chronic compartment syndrome is an uncommon cause of exercise-induced leg pain. It tends to occur in young athletes, who develop increased pressure within a fixed compartment, compromising perfusion and function of the tissues within that space. It results from tight thickened fascia, from muscular hypertrophy, or

when external pressure is applied to the leg (as with casting or taping). The presentation is one of tight bursting pressure in the calf or foot following participation in endurance sports or other robust exercise. The pain subsides slowly with rest, but intracompartmental pressure testing before and after exercise is the diagnostic test of choice.

Peripheral nerve pain is usually attributable to nerve root compression by herniated disks or osteophytes and typically follows the dermatome of the affected root. Pain typically begins immediately upon walking and may be felt in the calf or lower leg. The pain is not quickly relieved by rest and may even be present at rest. There may be a sensation of pain running down the back of the leg as well as a history of back problems.

Spinal cord compression from narrowing secondary to lumbar spine osteoarthritis. In patients with cauda equina syndrome, upright positioning aggravates the narrowing of the spinal canal, thereby causing symptoms. Although symptoms may be associated with walking, upright standing also may produce pain, weakness, or discomfort in the hips, thighs, and buttocks, and even a sensation of numbness and paresthesias. Symptoms are alleviated by sitting or flexing the lumbar spine forward as opposed to standing, which alleviates pain in IC. Patients with spinal cord compression typically have pain on physical examination during a straight leg-raise test.

Hip and knee osteoarthritis. Osteoarthritis in joints is typically worse in the morning or at the initiation of movement. The degree of pain may vary from day to day, and the pain does not cease promptly upon stopping exercise or standing. The pain typically improves after sitting, lying down, or leaning against an object to alleviate weight-bearing on the joint. It may be affected by weather change and may be present at rest.

Nonatherosclerotic etiologies of arterial disease. Thromboangiitis obliterans, popliteal artery entrapment syndrome, cystic adventitial disease, fibromuscular dysplasia, and exercise-induced endofibrosis of the iliac arteries are other arterial causes of IC or critical limb ischemia. All of these conditions typically produce a decrease in the exercise or resting ABI; they are usually differentiated from atherosclerotic etiologies by the history and physical examination.

TABLE 1
Differential diagnosis of intermittent claudication

- Atherosclerotic intermittent claudication
- Venous claudication
- Chronic compartment syndrome
- Hip or knee osteoarthritis
- Peripheral nerve pain (diabetic neuropathy)
- Spinal cord compression or cauda equina syndrome
- Nonatherosclerotic etiologies with similar presentation
  - Thromboangiitis obliterans (Buerger disease)
  - Popliteal artery entrapment syndrome
  - Cystic adventitial disease
  - Fibromuscular dysplasia
  - Exercise-induced endofibrosis of the iliac arteries

Comorbidities complicate symptom detection

Because the prevalence of PAD increases with advancing age, the patients most likely to have PAD are likely to have other age-related conditions that may contribute to lower extremity symptoms or may make such symptoms harder to detect.[14] In many elderly patients, comorbidity-related limitations in physical activity can cause lower extremity symptoms to be overlooked or missed, delaying the diagnosis of PAD. For example, patients with severe coronary artery disease or chronic obstructive pulmonary disease may be unable to walk far enough to experience the typical symptoms of IC until the disease progresses to critical limb ischemia. PAD itself can cause patients to slowly and unwittingly adapt and limit their lifestyles to avoid symptoms.

Physical examination

Physical examination of a patient with exercise-associated leg pain should include palpation of the abdominal aortic and bilateral femoral, popliteal, dorsalis pedis, and posterior tibial pulses; documentation of any iliac, femoral, or popliteal bruits; and inspection of the peripheral skin.

Pulses should be noted on a scale from 0 to 2, for absent, diminished, or normal.[8] Weak or absent pulses are the hallmark physical finding of PAD. Absence of the dorsalis pedis pulse alone does not imply PAD since congenital absence of this artery occurs in up to 10% of the population.[15] Enlarged or widened arteries may signify aneurysmal disease, commonly found in the aorta and popliteal arteries, which can be sources of atheroemboli or thromboemboli occluding the distal arterial tree.

Khan et al recently conducted a systematic literature review to evaluate the accuracy of the physical examination in predicting the presence or absence of PAD.[16] They concluded that physical examination findings are not sufficient alone and must be considered in the con-

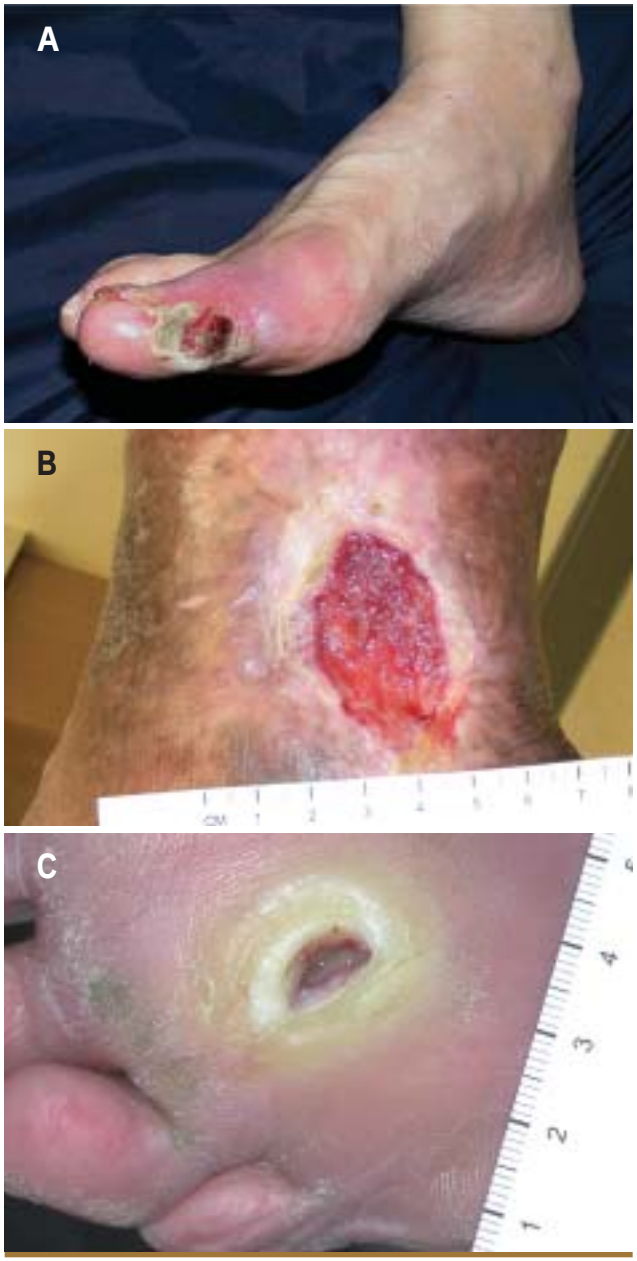
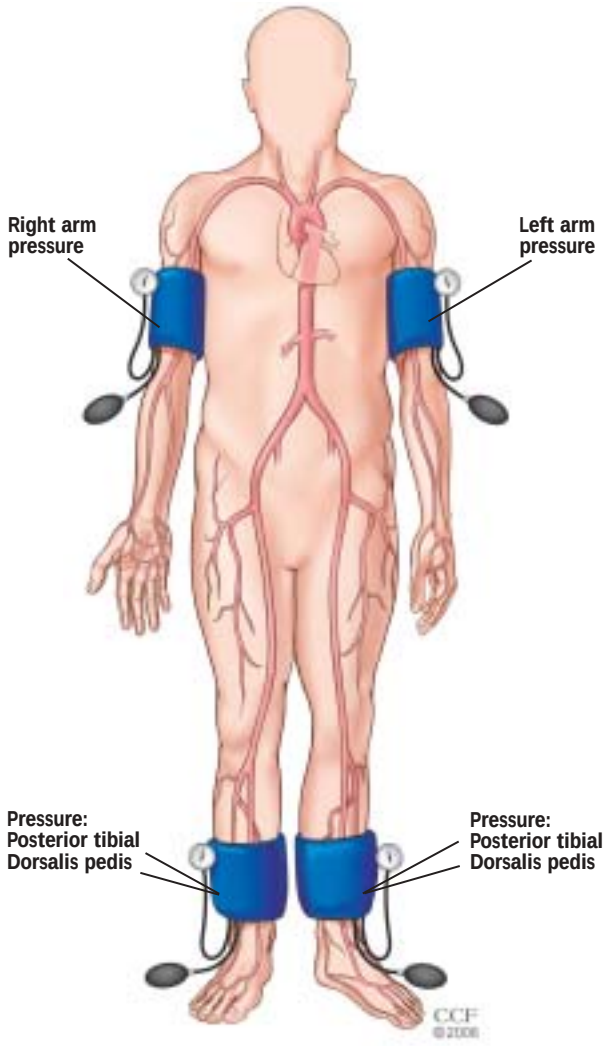


FIGURE 2. An ischemic ulcer in a patient with peripheral arterial disease that has progressed to critical limb ischemia (A), in contrast with a venous stasis ulcer (B) and a neurotrophic ulcer in a patient with diabetes (C).



$$\text{ABI} = \frac{\text{Lower extremity systolic pressure}}{\text{Brachial artery systolic pressure}}$$

FIGURE 3. The ankle-brachial index (ABI) is determined using a Doppler probe and blood pressure cuffs to measure the systolic pressure at both brachial arteries and at the dorsalis pedis and posterior tibial arteries of both legs. The highest pressure in each lower extremity is divided by the highest brachial pressure to establish the ABI.

text of risk factors for atherosclerosis to improve diagnostic accuracy. They noted that a PAD screening score derived from pulse readings using a handheld Doppler probe was particularly helpful for determining which patients should undergo further studies.[16]

Although not specific to PAD, thinning of the skin, atrophy or loss of the sweat glands, alopecia of the limb, and thickening of the nails are common findings. Besides short-distance IC and rest pain, signs of severe disease include dependent rubor, pallor on elevation, and ischemic ulceration over the affected segments. Dependent rubor often coincides with secondary edema due to maintaining the leg in a dependent position to alleviate symptoms of rest pain.

Arterial ulcers (Figure 2A) typically begin after trauma or injury to the limb and appear as pale-to-black, punctate, well-circumscribed lesions. They can be differentiated from venous stasis ulcers (Figure 2B), which

TABLE 2
Rutherford categories of acute limb ischemia

Category	Description/prognosis	Findings		Doppler signals	
		Sensory loss	Muscle weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	None to minimal (toes)	None	Inaudible	Audible
b. Immediately	Salvageable only with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound anesthesia	Profound paralysis	Inaudible	Inaudible

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typically are located in the medial lower calf ("gaiter distribution") and are characterized by thickened, brawny skin with hyperpigmentation from hemosiderin deposition. Diabetic ulcers (Figure 2C) are differentiated from arterial lesions in that they typically occur over weight-bearing areas, have hypertrophic callus formation around the edges, and commonly have associated infection.

Ankle-brachial index

The ABI is the most efficient objective test for documenting PAD in the lower extremity. It is performed using a handheld continuous-wave Doppler probe and blood pressure cuff to assess systolic pressures in both brachial arteries and in the dorsalis pedis and posterior tibial arteries of both legs (Figure 3). The highest ankle pressure in each leg is divided by the highest brachial pressure (for more detail on methods of calculating the ABI, see the article by McDermott at the beginning of this supplement).

In a well-rested supine patient, a normal ABI is 0.91 to 1.29, with values from 0.91 through 0.99 considered borderline normal.[17] An ABI of 0.90 or less is considered evidence of lower extremity PAD in epidemiologic studies. Patients with single-level PAD typically have an ABI from 0.50 to 0.90, whereas patients with severe multilevel disease typically have an ABI of less than 0.50.[18]

An ABI of 1.30 or greater suggests noncompressible or partially noncompressible vessels, which are the result of medial artery calcification (often associated with diabetes mellitus or chronic kidney disease). In such cases, a toe-brachial index should be obtained, since calcification rarely involves digital vessels. In an individual without PAD, the toe pressure is expected to be greater than 70% of the brachial pressure.[18]

A normal resting ABI does not exclude PAD. In patients with mild or very proximal occlusive lesions, pulses may be palpable at rest. Exercise testing increases the sensitivity of the ABI and is conventionally performed on a treadmill at a 12% incline at 2 mph for 5 minutes or until symptoms prohibit continuation of the test.

ACUTE LIMB ISCHEMIA

Acute limb ischemia is a clinical syndrome caused by an acute arterial occlusion, typically by a thrombus overlying a substantial plaque and less frequently by an atheroembolus or thromboembolus. Acute limb ischemia is classically described by the six "P's":

- Pulselessness
- Pain
- Pallor
- Poikilothermy (coldness)
- Paresthesia
- Paralysis.

Rutherford et al have defined three categories of acute limb ischemia to help clinicians risk-stratify these patients and determine the urgency of restoring flow to the affected limb (Table 2).[19]

Category I: Evaluate over ensuing days

A patient presenting with category I (viable) acute limb ischemia should be evaluated for possible thrombolysis, peripheral intervention, or bypass surgery over the ensuing several days. While the patient is evaluated, care must be taken to prevent further injury to an acutely threatened limb; this should include consideration of the use of heel protectors and methods to ensure limb warmth. Prompt initiation of platelet inhibition with aspirin, clopidogrel, or both is impor-

TABLE 3
Clinical criteria for categories of critical limb ischemia

Grade*	Category	Clinical description	Noninvasive laboratory description
0	0	Asymptomatic—no hemodynamically significant occlusive disease	Normal results of treadmill/stress test (5 min at 2 mph on 12% incline)
	1	Mild claudication	Treadmill exercise completed; postexercise ankle pressure > 50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Symptoms between those of categories 1 and 3
	3	Severe claudication	Treadmill exe rcise cannot be completed and postexercise ankle pressure < 50 mm Hg
II	4	Ischemic rest pain	Resting ankle pressure ≤ 40 mm Hg, flat or barely pulsatile ankle or metatarsal plethysmographic tracing, toe pressure < 30 mm Hg
III	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting ankle pressure ≤ 60 mm Hg, ankle or metatarsal plethysmographic tracing flat or barely pulsatile, toe pressure < 40 mm Hg
	6	Major tissue loss—extending above transmetatarsal level, functional foot no longer salvageable	Same as for category 5

* Fontaine classification

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tant, along with consideration of systemic anticoagulation with heparin to prevent propagation of the thrombosis. The patient should be frequently evaluated for changes in the pulse examination or for new signs and symptoms that may place him or her in a more urgent category. In addition to conventional angiography, arterial duplex ultrasonography or magnetic resonance or computed tomographic angiography may help to further characterize the extent and level of disease and to plan for therapy.

Category II: Salvageable with prompt obstruction reversal

The second category of acute limb ischemia is threatened viability, in which the limb is salvageable without major amputation if the arterial obstruction is reversed quickly. Patients with this category of limb ischemia require emergent admission to the hospital with immediate consultation of a vascular specialist.

The category is subdivided into limbs under marginal (IIa) and immediate (IIb) threat. Differentiating between classes IIa and IIb is important because restoration of flow may be delayed without sequelae in some patients, whereas immediate flow restoration is required in other patients. Patients with class IIa acute limb ischemia generally have absent pedal Doppler signals with transient sensory loss limited to the toes and no loss of motor function. These patients typically are considered for intra-arterial thrombolysis, as they may tolerate the time required to perform this therapy. Thrombolysis usually takes more than 24 hours to dissolve an acute thrombus but allows identification of underlying lesions, permitting less invasive treatment.[20] In contrast, class IIb patients have more marked sensory deficits, commonly associated with motor weakness, and need immediate restoration of blood flow by endovascular or open surgical means to avoid major amputation and permanent nerve damage.

Category III: Irreversible ischemia requiring amputation

Category III denotes irreversible ischemia. These patients have absent Doppler signals with marked motor and sensory deficits and muscle rigor. They suffer permanent neuromuscular damage and require major amputation regardless of therapy.

CRITICAL LIMB ISCHEMIA

Critical limb ischemia is a clinical term to describe chronic and severe compromise in limb perfusion that results in failure to meet the basal metabolic needs. It is usually caused by atherosclerotic occlusive PAD and manifests as rest pain and/or tissue loss (ulcers or gangrene). Rutherford et al developed a detailed grading system for critical limb ischemia that is commonly used (Table 3).[19]

The first sign is rest pain

Rest pain is the earliest sign of critical limb ischemia and typically worsens with leg elevation at night, due

to loss of the supplemental effects of gravity on blood flow. Further progression of tissue hypoxia ultimately leads to tissue ulceration and gangrene. Differentiation from venous and diabetic ulcers is important (Figure 2), as previously described. In some PAD patients with venous disease or long-standing diabetes, ulcers can be attributed to two or three etiologies concomitantly.

In contrast to patients with IC, those with critical limb ischemia progress to limb loss in the absence of intervention to treat PAD and improve limb blood flow. In one study, 12.2% of patients with critical limb ischemia progressed to major amputation within 3 months and 20% died within 1 year.[21] A long-term study of 1,244 men with claudication found that diabetes mellitus and low ABI predicted the development of ischemic rest pain.[10] Patients with diabetes, neuropathy, infection, and chronic kidney disease are more likely to progress to limb loss.

Prompt referral indicated

Any patient with foot ulceration, rest pain, and an abnormal ABI or noncompressible vessels should be referred to a vascular specialist for evaluation of the level and extent of arterial blockages and to consider endovascular and open revascularization options.

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