Peripheral Arterial Disease: Diagnosis and Management

FAISAL A. ARAIN, MD, AND LESLIE T. COOPER JR, MD

On completion of this article, you should be able to: (1) identify patients at risk of developing peripheral arterial disease, (2) apply current medical literature to the management of patients with peripheral arterial disease, and (3) recognize the indications for referring a patient with peripheral arterial disease to a vascular specialist.

Peripheral arterial disease is a common but underdiagnosed and undertreated disorder with substantial morbidity and mortality. The pathophysiology of peripheral arterial disease and the risk factors for developing it are similar to those for atherosclerotic disease occurring at other sites. Peripheral arterial disease can be diagnosed accurately with simple, noninvasive, office-based tests that measure the severity of the disease and provide valuable prognostic information. Optimal medical therapy includes a supervised exercise program, tobacco cessation, and modification of treatable risk factors. Cilostazol can improve pain-free and peak walking distances in patients with intermittent claudication. As a general rule, patients with lifestyle-limiting claudication who do not respond to medical management or those with critical limb ischemia should be referred to a vascular specialist for consideration of revascularization.

Mayo Clin Proc. **2008;83(8):944-950**

ABI = ankle-brachial index; ACE = angiotensin-converting enzyme; ASA = aspirin; CAD = coronary artery disease; CLI = critical limb ischemia; CRP = C-reactive protein; CTA = computed tomographic angiography; DM = diabetes mellitus; DP = dorsalis pedis; GFR = glomerular filtration rate; IC = intermittent claudication; MRA = magnetic resonance angiography; OR = odds ratio; PAD = peripheral arterial disease; PT = posterior tibial

Approximately 8 million Americans are affected by peripheral arterial disease (PAD).[1] The estimated prevalence of PAD in people older than 70 years is between 14% and 29%.[2,3] In the Framingham Heart Study, the annual incidence of intermittent claudication (IC) in people younger than 44 years was 6 cases per 10,000 person-years in males and 3 cases per 10,000 person-years in females.[4] In people older than 65 years, the annual incidence increased 10-fold, to 61 cases per 10,000 person-years in males and 54 cases per 10,000 person-years in females.[4] Intermittent claudication, the classical PAD symptom, is present in only 10% of patients. Approximately 50% of patients with PAD have atypical lower-extremity symptoms; another 40% are asymptomatic.[2,5] The heterogeneity of clinical presentations may explain why PAD is diagnosed and treated in only 25% of affected patients.[6]

Peripheral arterial disease is a strong predictor of systemic atherosclerosis and is considered a coronary artery disease (CAD) risk equivalent.[7,8] The 10-year risk of death in people diagnosed as having PAD is 40% and has remained largely unchanged since 1950.[9] Criqui et al[10] showed that, after multivariate adjustment for age, sex, and other risk factors for cardiovascular disease, patients with PAD had a 3-fold higher risk of all-cause death and a 6-fold higher risk of cardiovascular-related death than patients without PAD. Patients with an ankle-brachial index (ABI) of less than 0.9 were found to have hazard ratios of 1.7 and 2.5 for all-cause and cardiovascular mortality, respectively.[11] In the same study, patients with an ABI greater than 1.4 (indicative of poorly compressible vessels) had hazard ratios of 1.8 and 2.1 for all-cause and cardiovascular mortality, respectively.

RISK FACTORS

In the third National Health and Nutrition Examination Survey,[3] the adjusted odds ratio (OR) for PAD prevalence was significantly greater with tobacco use (OR, 4.2), African American ethnicity (OR, 2.4), glomerular filtration rate (GFR) of less than 60 mL/min (OR, 2.2), diabetes mellitus (DM) (OR, 2.1), and hypercholesterolemia (OR, 1.7). The risk of PAD progressing to critical limb ischemia (CLI) is increased with DM (OR, 4.0), tobacco use (OR, 3.0), ABI less than 0.7 (OR, 2.0), ABI less than 0.5 (OR, 2.5), age greater than 65 years (OR, 2.0), and hypercholesterolemia (OR, 2.0).[12,13]

A number of novel biomarkers, including C-reactive protein (CRP), lipoprotein(a), homocysteine, and D-dimer, have been associated with the development of systemic atherosclerosis.[14-16] Elevated CRP levels are associated with higher all-cause mortality and adverse cardiovascular outcomes in patients with[17-19] or without[20,21] known atherosclerotic vascular disease. High levels of some inflammatory biomarkers are also predictive of high short-term mortality.[22,23] Additionally, CRP levels may be reduced by statin use; using high-dose statin to achieve lower CRP levels yields better clinical outcomes than using statins to reduce cholesterol levels only.[24]

From the Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN.

Individual reprints of this article are not available. Address correspondence to Leslie T. Cooper Jr, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (cooper.leslie@mayo.edu).

CLINICAL FEATURES

Clinicians should have a high index of suspicion for PAD, especially in patients who report lower-extremity pain and have hair loss, cool extremities, or poorly palpable pulses. A diagnosis of PAD should be considered in patients who report muscular pain in legs, especially if they belong to known high-risk groups, such as people older than 70 years, African Americans, people with DM, smokers, and people with hyperlipidemia and/or impaired renal function.[12] Elevation pallor (skin pallor within 60 seconds of passive elevation of the feet at 60°) and/or dependent rubor (the onset of erythema after more than 15 seconds of sitting upright after leg elevation) are other signs suggestive of PAD. An algorithm for evaluation of patients suspected of having PAD or at risk of developing PAD is given in the Figure.[5]

INTERMITTENT CLAUDICATION

Intermittent claudication is defined as fatigue, discomfort, or pain that involves specific limb muscle groups during exertion due to exercise-induced ischemia.[13] Other features of IC worth remembering are (1) progression (over time, PAD involves adjacent muscle groups in the same arterial territory), (2) functional decline (pain occurs earlier and/or is more severe with the same activity as the disease progresses), (3) anatomic correlation (certain risk factors correlate with PAD in specific segments of the arterial tree, as for example smoking/hypertension with aortoiliac vessels, DM with isolated infrapopliteal vessels, and small-vessel vasculitis or atheroemboli with microvascular/terminal vessels), and (4) the level of arterial involvement (usually a level above the area of pain, as for example buttock/hip pain with aortoiliac artery disease, thigh pain with iliofemoral artery disease, pain in upper two-thirds of calf with superficial femoral artery disease, pain in lower third of calf with popliteal artery disease, and foot claudication with tibial or peroneal artery disease). Health care professionals should also be aware that the diagnosis of PAD can be missed in up to 90% of patients by relying only on classical symptoms of claudication.[2]

CRITICAL LIMB ISCHEMIA

Patients with CLI have ischemic pain at rest that may be accompanied by tissue loss (ischemic ulcer or gangrene). The pain associated with CLI often improves when the leg is in a dependent position and is exacerbated when it is elevated. A resting ABI value less than 0.4 and a transcutaneous oxygen measurement that is near zero (normal, >40) strongly support the diagnosis. Critical limb ischemia can be caused by a number of other disease entities, such as thromboembolism and vasculitis.[13] Because CLI usually requires mechanical revascularization, an urgent referral to a vascular specialist should be made promptly.

DIAGNOSIS

Ankle-Brachial Index

An abnormal ABI suggests a diagnosis of PAD. This simple, inexpensive, and noninvasive test can quantify the severity of PAD and also predict the risk of future cardiovascular events.[2] Doppler ultrasonography is used to measure systolic blood pressures in bilateral brachial, dorsalis pedis (DP), and posterior tibial (PT) arteries. The higher of the 2 brachial artery systolic pressures is used as the denominator. The right and left ABI values are determined by dividing the higher of DP or PT pressure in each leg by the higher brachial artery pressure. An ABI greater than 0.9 is normal. Patients with claudication typically have ABI values ranging from 0.50 to 0.90 (Table). Those with CLI have values of 0.40 or less. A ratio greater than 1.30 suggests poorly compressible, calcified arteries. When the resting ABI is combined with exercise treadmill testing, functional capacity can also be assessed. The distance walked can then serve as a baseline functional capacity measure that can assist with future comparisons after either conservative or invasive treatments of PAD.

Computed Tomographic Angiography and Magnetic Resonance Angiography

Both computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are useful noninvasive tests that can localize and quantify arterial stenosis in patients being considered for revascularization.[25,26] In general, CTA is considered to have a better spatial resolution than MRA.[26,27] However, as experience with MRA increases, its accuracy may approach that of CTA or contrast angiography.[28] Computed tomographic angiography exposes the patient to radiation, whereas the more expensive MRA, which uses no iodinated contrast material, does not. Because of the risk of contrast-induced nephrotoxicity, CTA is relatively contraindicated in patients with decreased renal function.[28] In general, MRA cannot be performed in patients with implanted devices such as pacemakers, defibrillators, and metal aneurysm clips. Gadolinium, the contrast agent used for MRA scans, recently has been linked to development of nephrogenic systemic fibrosis, especially in patients with a GFR less than 30 mL/min or those receiving long-term dialysis.[29] The risk of using gadolinium in patients with a GFR between 30 and 60 mL/min is unknown,[29] and caution is advised. At our center, CTA is

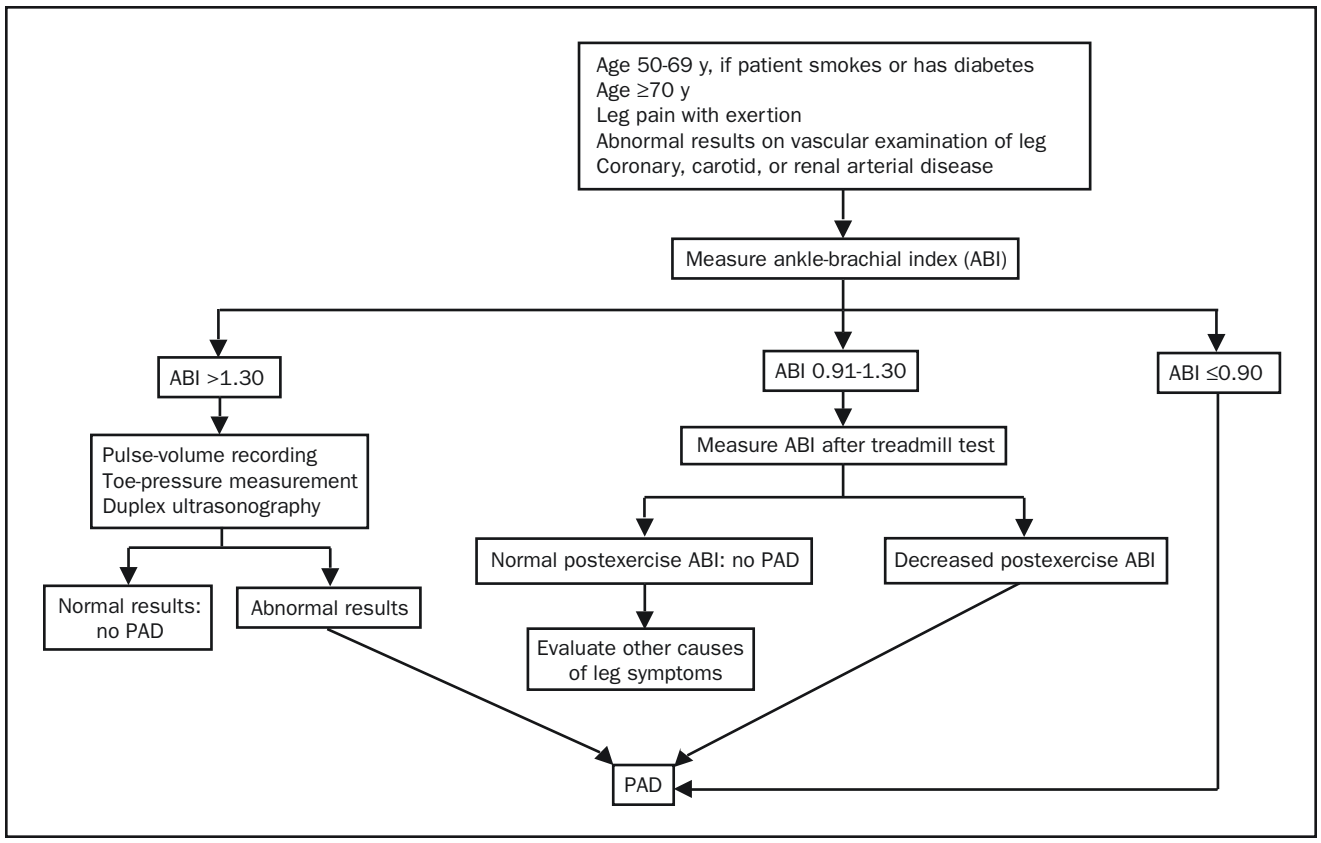

FIGURE. Algorithm for evaluating patients in whom peripheral arterial disease (PAD) is suspected. From *N Engl J Med*,[5] with permission of the Massachusetts Medical Society. Copyright © 2001. All rights reserved.

the preferred noninvasive method; MRA is used as a second-line agent if CTA is contraindicated.

Contrast Angiography

Historically, contrast angiography has been the criterion standard for the diagnosis of PAD.[26] Angiography can determine the location and severity of stenotic lesions and estimate calcification. If the stenosis is amenable to percutaneous revascularization, such procedures often can be performed in the same setting. However, the risks of conventional angiography include bleeding, arterial dissection, infection, and contrast-induced nephropathy.

TREATMENT

Risk Factor Modification

Tobacco Cessation. Tobacco cessation slows the progression of PAD in CLI and reduces the risk of death due to vascular causes.[5,30,31] Multiple modalities, such as behavioral therapy, nicotine replacement, and medications (bupropion and varenicline), are often more effective than a single modality.[32] Although tobacco cessation may not increase walking distance,[31] it decreases the risk of cardiovascular events and reduces the risk of progression to CLI.[30]

Treatment of Hyperlipidemia. Peripheral arterial disease is a strong predictor of systemic atherosclerosis and is considered a CAD risk equivalent.[7,8] Therefore, the target goal for low-density lipoprotein cholesterol should be less than 100 mg/dL (to convert to mmol/L, multiply by 0.0259). Aggressive lipid lowering not only improves cardiovascular outcomes in patients with atherosclerotic vascular disease[33,34] but also improves pain-free walking distance and community-based physical activity in patients with IC.[35] The mechanism of statin benefit is an area of active investigation. In addition to lowering lipid levels,

TABLE. **Disease Severity and Ankle-Brachial Index (ABI) (Mayo Clinic Vascular Laboratory Criteria)**

Disease severity	ABI	
	At rest	After exercise
Normal	>0.9	>0.9
Mild	0.8-0.9	0.5-0.9
Moderate	0.5-0.79	0.15-0.49
Severe	<0.5	<0.15

statins may decrease inflammation, as reflected by lower CRP levels.[36] Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of low-density lipoprotein cholesterol.[24] This finding suggests that statins may provide cardiovascular benefit by modulating the inflammatory pathway in addition to lowering cholesterol levels.

Treatment of DM. Poor glycemic control is closely linked to the development of microvascular complications[37,38]; however, its effect on macrovascular complications is less certain. Recent studies indicate that DM is strongly associated with progression of PAD in smaller, subsegmental, or terminal arteries.[39] It is hypothesized that for every 1% increase in glycated hemoglobin A_{1c}, there is a 26% increase in PAD risk. In patients with DM, a hemoglobin A_{1c} level of less than 7.0% and as close to 6.0% as possible should be targeted.[12] No controlled trials have directly evaluated the effects of antidiabetic therapy on the natural history of PAD.[12,13,37,38]

Treatment of Hypertension. Hypertension, like DM, is linked to the development of atherosclerosis and is a major risk factor for PAD. Angiotensin-converting enzyme (ACE) inhibitors have an important role in management of hypertension in patients with PAD. The Heart Outcomes Prevention Evaluation (HOPE) trial showed that ramipril protected against cardiovascular events beyond the extent expected from blood pressure lowering alone.[40] There is also evidence that ACE inhibition may increase pain-free and maximum walking time in patients with symptomatic PAD.[41] Because β-adrenergic blockers do not worsen PAD symptoms, they should be used in patients with cardiovascular disease as otherwise indicated.[42] The recommended blood pressure goal for patients with PAD is less than 140/90 mm Hg. If the patient also has DM, then the blood pressure goal should be less than 130/80 mm Hg.[12,13]

Antiplatelet Therapy

Antiplatelet therapy reduces the risk of adverse cardiovascular outcomes and death in patients with cardiovascular disease by approximately 25%.[43] Aspirin (ASA) is the most widely used and studied drug in this class. Low-dose ASA (81 mg) is as effective as, and probably safer than, standard-dose ASA (325 mg). Current recommendations are to use low-dose ASA in patients with cardiovascular disease.[43] In the subgroup of patients with symptomatic PAD in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE)[44] trial, the average event rate of myocardial infarction, stroke, or vascular death per year in the clopidogrel group was 3.71% compared with 4.86% in the ASA group (absolute risk reduction, 1.15; relative risk reduction, 23.8%). In the American College of Cardiology/American Heart Association guidelines for management of patients with PAD,[13] clopidogrel is recommended as an alternative therapy to ASA to reduce risk of myocardial infarction, stroke, or vascular death.

Specific Drug Therapy for PAD

Pentoxifylline. Pentoxifylline was the first drug approved for treatment of PAD. Its proposed mechanism of action is to lower blood viscosity and improve erythrocyte flexibility, thereby improving oxygen delivery to tissues. After several subsequent studies showed pentoxifylline to increase walking time only slightly, if at all, when compared with placebo, its use in the management of IC declined.[5,31]

Cilostazol. Cilostazol received Food and Drug Administration approval in 1999 and is currently the only drug other than pentoxifylline to receive such approval for the treatment of claudication.[5] Cilostazol increases intracellular cyclic adenosine monophosphate levels by inhibiting phosphodiesterase type 3, leading to vasodilatation and decreased platelet aggregation, arterial thrombus formation, and vascular smooth muscle proliferation. In one trial, cilostazol increased maximal and pain-free walking distances by 50% and 67%, respectively.[5] Cilostazol is contraindicated in patients with chronic heart failure. Some commonly used drugs that interfere with the metabolism of cilostazol include the "azole" class of antifungals, macrolide antibiotics, nonsteroidal anti-inflammatory drugs, omeprazole, and calcium channel blockers. If concurrent use of any of these drugs is necessary, the standard dose of 100 mg twice daily may be reduced to 50 mg twice daily, or cilostazol may be discontinued temporarily. Patients should avoid concurrent ingestion of grapefruit juice, as it inhibits the major drug metabolic enzyme, cytochrome P450 3A4.

Nonpharmacological/Exercise Therapy for PAD

In patients with claudication, multiple randomized controlled trials have shown that supervised exercise programs are more effective at increasing walking distance than unsupervised ones.[45] Supervised exercise programs improve walking distance by 100% to 150% from baseline, a level of improvement comparable to that achieved with peripheral bypass surgery and potentially better than that achieved with angioplasty.[46,47] Because Medicare does not currently cover the cost of supervised exercise programs in the PAD population, cost issues should be discussed with patients before a referral is made. Rather than empirically choosing a prespecified speed, the clinician should choose the initial workload to elicit claudication of moderate severity within

3 to 5 minutes. After claudication develops, patients may rest or slow down; once the symptoms decrease or resolve, they can begin walking again. The total walking time (not counting the rest periods) should be 30 minutes per day. A minimum of 3 sessions per week is required to improve IC symptoms. On the basis of findings of randomized controlled trials, the duration of the exercise program should be 3 to 6 months.

Revascularization

Referral for mechanical revascularization procedures, which include endovascular procedures and open surgical (bypass) procedures, should be made in the following clinical scenarios: (1) pain at rest due to ischemia, (2) nonhealing ischemic ulceration, and (3) lifestyle-limiting claudication despite risk factor modification, antiplatelet treatment, and an appropriate exercise program.

The choice of a procedure depends on a number of factors, including the location, type, and characteristics of the lesion and comorbid conditions that affect surgical risks. The ongoing Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial compares the outcomes of 2 groups of patients with aortoiliac artery disease: those participating in a supervised exercise program and receiving pharmacotherapy vs those undergoing aortoiliac stenting and receiving pharmacotherapy (www.clinicaltrials.gov/ct2/show/NCT00132743?term=Clever&rank=1). The results from this trial should help physicians identify patients who would benefit from revascularization procedures early in the course of the disease.

CONCLUSION

Peripheral arterial disease is a major component of the overall burden of cardiovascular disease in the United States. The social and economic burden of PAD is expected to increase as the population ages. The mainstay of therapy is simple: lifestyle adjustment, tobacco cessation, and a supervised exercise program; however, long-term adherence is challenging. Early recognition of PAD is pivotal to initiation of these measures. Optimal treatment of hypercholesterolemia, DM, and hypertension in conjunction with antiplatelet therapy improves cardiovascular outcomes in these patients. Cilostazol can alleviate the symptoms of IC and improves walking distance. Mechanical revascularization should be reserved for a select group of patient with CLI or lifestyle-limiting claudication. Educational programs, directed toward health care professionals and patients with cardiovascular risk factors, can help in early diagnosis and proper management of patients with PAD and will ultimately result in decreased cardiovascular morbidity and mortality.

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CME Questions About Peripheral Arterial Disease

1. Which <u>one</u> of the following cardiovascular risk factors is <u>most</u> strongly linked to progression of peripheral arterial disease (PAD) to critical limb ischemia (CLI)?
   a. Hypertension
   b. Family history
   c. Tobacco use
   d. Diabetes mellitus (DM)
   e. Age >65 years

2. Which <u>one</u> of the following clinical scenarios is <u>least</u> likely to be related to PAD?
   a. 65-year-old male smoker with hypertension and hyperlipidemia who is unable to keep up with his wife in the grocery store because of aches in his legs
   b. 60-year-old woman with well-controlled hypertension who has discomfort in both calves at night
   c. 45-year-old man with DM who has an extremely painful ulcer on the big toe
   d. 55-year-old man with long-standing DM and hyperlipidemia who presents with constant pain in his left foot and painful ulcers on his left shin and who has poorly palpable pulses in his left foot
   e. 48-year-old man with hypertension and DM who has almost constant pain in his right foot. The pain becomes worse when he puts his feet up at night to sleep and is relieved when he hangs the foot by the side of the bed

3. A 70-year-old man with coronary artery disease (CAD), hypertension, and hyperlipidemia presents with pain in his left thigh and leg that develops after he walks 3 blocks. Pain resolves at rest. On examination, his pulse intensity (0 = absent, 1 = diminished, 2 = normal, and 3 = bounding; right/left) is 2/1 femoral, 2/1 popliteal, 1/0 dorsalis pedis (DP), and 1/1 posterior tibial (PT). Which *one* of the following diagnostic tests should be ordered *next*?
   a. Digital subtraction angiography
   b. Computed tomographic angiography (CTA)
   c. Magnetic resonance angiography (MRA)
   d. Resting ankle-brachial index (ABI)
   e. Resting and exercise ABI
4. The patient described in question 3 undergoes the proper diagnostic test, the results of which reveal that he has substantial iliofemoral stenosis. The patient is taking a β-blocker, an angiotensin-converting enzyme (ACE) inhibitor, a statin, and aspirin. Which *one* of the following should be the *next* step in the management of this patient?
   a. Referral to a vascular specialist for lower-extremity and coronary angiography
   b. Discontinuation of the β-blocker because it may be causing peripheral vasoconstriction and aggravating claudication
   c. Referral to a supervised exercise program and possible addition of cilostazol
   d. Immediate referral to a vascular surgeon to be considered for a bypass operation
   e. Referral to an interventional radiologist for lower-extremity angiography and percutaneous intervention
5. The patient described in questions 3 and 4 returns after 6 months. He has been unable to finish the exercise program because the pain in his left leg has worsened and is now constant. Examination reveals pulse intensity (right/left) to be 2/1 femoral, 2/0 popliteal, 1/0 DP, and 1/0 PT. The patient's left foot is cold to the touch; there are 2 painful ulcers on the dorsum of the foot. Which *one* of the following is the *next* best step in management of this patient?
   a. Addition of a vasodilator such as amlodipine to the medical regimen
   b. Addition of pentoxifylline to the medical regimen
   c. Referral to a vascular specialist to be considered for a revascularization procedure
   d. Referral to a dermatologist for biopsy of the skin ulcer to exclude vasculitis
   e. Referral to an orthopedic surgeon for transmetatarsal amputation

This activity was designated for 1 AMA PRA Category 1 Credit(s).™

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