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Review

Neuropathic ulcers: a focused review

Brittany Urso[1], MD, Mondana Ghias[2], MD, Anan John[3], MD and Amor Khachemoune[4,5], MD, FAAD, FACMS

[1]Department of Dermatology, University of California, Irvine, Irvine, CA, USA, [2]Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA, [3]Department of Dermatology, Riga Stradina University, Latvia, Riga 1st Hospital, Riga, Latvia, [4]Department of Dermatology, State University of New York Downstate, Brooklyn, NY, USA, and [5]Department of Dermatology, Veterans Health Administration, Brooklyn, NY, USA

Correspondence
Amor Khachemoune, MD, FAAD, FACMS
Veterans Affairs Hospital & SUNY Downstate
Dermatology Service
800 Poly Place
Brooklyn, NY 11209
USA
E-mail: amorkh@gmail.com

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Abstract

Neuropathic ulcers or diabetic foot ulcers are preventable ulcers associated with diabetes mellitus. These ulcers occur in the setting of unrecognized trauma, peripheral neuropathy, and foot deformities; however, they are often complicated by peripheral arterial disease and infection. Approximately 15% of individuals with a neuropathic ulcer require limb amputation as a result of infection. Not only are neuropathic ulcers a burden to the patient but also to the economy. The cost of diabetic foot ulcer care is approximately $1.38 billion per year. This makes neuropathic ulcers an important therapeutic target. This review presents the pathophysiology, clinical presentation, evaluation, management, and prevention of neuropathic ulcers.

Introduction

Neuropathic ulcers (NUs), also known as diabetic foot or mal perforans ulcer, affect approximately 19-35% of individuals with diabetes mellitus (DM).[1] The rate of NU formation is only increasing with the incidence of type 2 DM increasing annually.[2] NUs are related to underlying diabetic peripheral neuropathy (DPN), a disorder which impairs the sensory and autonomic function of skin, making it more prone to unrecognized trauma, ulceration, and infection.[1] Many NUs are also complicated by peripheral arterial disease (PAD), which is important to diagnose as these lesions require revascularization for proper treatment.[3,4] Prevention is the best management of NUs; however, few guidelines exist to help clinicians determine screening frequency or risk stratify patients at risk of developing NUs. This is surprising as NUs pose a significant burden to both the patient and the economy. NUs are the leading cause of non-traumatic limb amputation in the United States (US), with 15% of individuals with NUs requiring limb amputation.[1,5] Additionally, NU wound care between 2005 and 2010 cost the US approximately $1.38 billion per year.[6]

NUs are an important treatment target given the rising incidence of DM annually, as well as the significant patient and economic burden. This review presents the pathophysiology, clinical presentation, evaluation, preventative care, and management of NUs.

Pathophysiology

DPN and unrecognized injury are inciting factors in the development of NUs.[3,4] DPN can be broken into sensory, motor, and autonomic neuropathy, all of which contribute to ulcer formation.[3,4,7] Autonomic neuropathy is characterized by decreased cutaneous perfusion and sweating of the lower extremity.[8] It signifies early microvascular damage and increases an individual's likelihood of developing a skin infection owing to poor oxygenation and xerosis of the lower extremity.[8] Following development of autonomic neuropathy, individuals progressively lose their

protective sensory perception of pain, touch, deep pressure, and temperature which leads to unrecognized trauma.[3,4] This is further complicated by motor neuropathy, a condition which causes atrophy of the muscles of the foot, foot and joint deformities, and gait and biomechanical disturbances.[4,7] These changes result in abnormal stress on weight bearing surfaces of the foot, such as the heel and metatarsal head of the foot, thus provoking callus formation.[4] With continued stress, these calluses thicken, compress underlying soft tissue, and ulcerate, giving rise to NUs.[7]

NUs may also arise in the setting of PAD or macrovascular wall damage complicating its diagnosis and management.[9] These ulcers are termed "neuroischemic." It is estimated that approximately 50% of NUs are actually neuroischemic.[4] It is important to distinguish the etiology of an ulcer because most NUs heal with standard of care therapeutics, whereas neuroischemic ulcers will not heal without revascularization. Neuroischemic ulcers portend a poor prognosis, often leading to chronic wounds and severe infections as a result of decreased lower extremity perfusion and impaired immune response.[4] Together, NUs and neuroischemic ulcers are the leading cause of non-traumatic amputation.[7]

Clinical Presentation

NUs predominantly affect the metatarsal heads, great toes, and heels of the feet (Fig. 1a), whereas neuroischemic ulcers most frequently involve the foot margin (Fig. 1b).[4,10] Clinically, NUs appear as painless ulcers within the macerated or hyperkeratotic plaques of calluses.[10] They are associated with normal capillary refill, palpable pulses, xerosis, and decreased sensation to the foot.[4,10] Individuals with neuroischemic ulcers typically have decreased pulses and perfusion to the lower leg but have retained sensation of the foot.[10]

Most patients who present with NUs have type 2 DM; however, these ulcers may also occur in patients with type 1 DM, end-stage renal disease (ESRD), alcohol abuse, vitamin deficiency, leprosy, pernicious anemia, spinal cord injury, syringomyelia, and tabes dorsalis.[3]

Evaluation and management

When evaluating an NU, it is important to determine other comorbidities which may contribute to wound development or delay wound healing. Work-up should include history, physical exam, laboratories, nutrition evaluation, and vascular assessment.

History and physical exam

History relevant to the ulcer would include wound duration, recurrence, attempted treatments, previous ulcers at other sites, previous difficulty with wound healing, and history of limb amputation.[3,4,11] Additionally, it is important to review the patient's other health conditions, including history of DM, lung disease, or cardiovascular disease, as these conditions may contribute to poor wound healing. A social history, including smoking and alcohol use, may also be useful.

On initial and each follow-up visit, measurements and photos of the ulcer should be taken to help with wound assessment. It should also be noted if the patient has palpable pedal pulses and pink tissue color, as unpalpable pedal pulses and bluish coloration would suggest concomitant vascular disease.[11] Unlike most patients with PAD who feel pain associated with claudication, those with concurrent neuropathy have "noiseless" claudication owing to sensory loss.[4] If physical exam suggests vascular disease, the ankle-brachial index (ABI) should be determined. An ABI < 0.90 suggests PAD.[4] Referral to vascular surgery may be necessary for revascularization of the limb as this is the definitive treatment. Sensory testing of the bilateral lower extremities should also be completed with the 10g monofilament test and pinprick or vibratory sensation testing as sensory loss is common in neuropathic ulcers and as a complication of uncontrolled diabetes.[4,11]

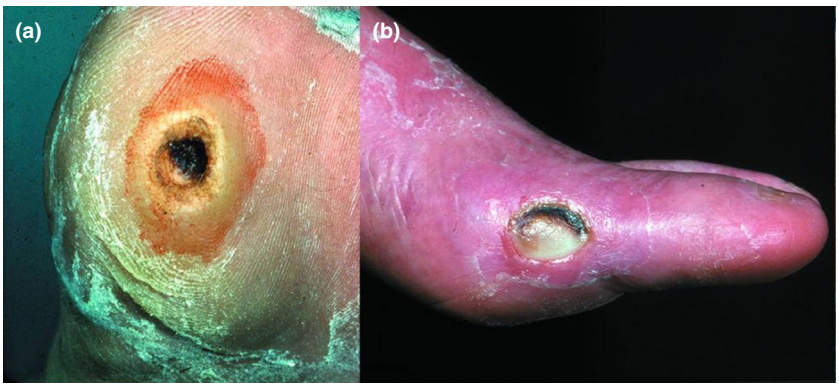

Figure 1 (a) Neuropathic foot with plantar ulcer surrounded by callus. (b) Neuroischemic foot with ulcer on medial aspect of first metatarsophalangeal joint. (Reproduced from *Diabetic foot ulcers*, Edmonds ME, Foster VM, 332:407, 2020 with permission from BMJ Publishing Group Ltd)

Classification systems for NUs

There are multiple systems which are helpful in the evaluation of NUs over time. The Wagner system (Table 1) was one of the first scoring systems used to monitor NUs. It is a five-point scoring system used for grading neuropathic ulcer depth; however, it does not take into consideration infection, ischemia, or presence of neuropathy, which limits its utility.[3,12,13] The SINBAD system for classifying and scoring foot ulcers takes into consideration the ulcer site, ischemia, neuropathy, presence of bacterial infection, and size and depth of the ulcer in a six-point grading system. Neither grading system encompasses comorbidities, such as presence of end-stage renal disease or ulcer recurrence; however, the *International Working Group of the Diabetic Foot (IWGDF)* recommends the SINBAD tool (Table 2) as the universal system for clinicians in classifying NUs.[11] Currently, no scoring system has been developed to determine patient prognosis or risk of adverse outcomes, so these scoring systems are primarily recommended for routine monitoring NUs.

Laboratory screening and nutritional evaluation

As routine laboratory screening for NUs, it is useful to order a complete blood count and a basic metabolic panel as both anemia and renal disease may delay wound healing.[3,5] Also, if a leukocytosis is present, this may suggest infection. If suspicious for osteomyelitis, a deep infection of the bone, then erythrocyte sedimentation rate or C-reactive protein will be elevated.[3] If elevated, then imaging by MRI or bone biopsy may be required.[4,5]

Additionally, a lipid profile is useful in the evaluation of NU, as cardiovascular disease is a risk factor for poor wound healing and underlying ischemic disease.[3] Lastly, a hemoglobin A1C may be ordered to determine the patient's glycemic control. Though poor glycemic control has not been shown to correlate with delayed wound healing, it is a marker for increased cardiovascular and renal disease risk.[3]

It is also important to evaluate a patient for malnutrition as this can impair wound healing. Prealbumin is useful in evaluating short-term protein deficiency, whereas albumin is the gold standard for evaluating long-term nutritional health.[3] If suspicious for nutritional deficiency, then referral to a dietitian or nutritionist may be useful.

Table 1 Wagner classification system

Ulcer grade	Lesion description
0	Foot deformity or redness of skin; no erosions/ulceration
1	Superficial erosion
2	Deep ulcer, involving tendon or joint capsule
3	Deep ulcer, with drainage, joint sepsis, or osteomyelitis
4	Local gangrene, involving forefoot or heel
5	Gangrene of foot

Adapted from Wagner FW. The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle*. 1981;2:64–122.

Table 2 The SINBAD system for classifying and scoring foot ulcers

Category	Definition	SINBAD score
Site	Forefoot	0
	Midfoot or hindfoot	1
Ischemia	At least one pedal pulse palpable	0
	Clinical evidence of decreased pedal circulation	1
Neuropathy	Protective sensation intact	0
	Loss of protective sensation	1
Bacterial infection	None	0
	Present	1
Area	Ulcer < 1 cm^2	0
	Ulcer > 1 cm^2	1
Depth	Ulcer confined to skin and subcutaneous tissue	0
	Ulcer reaching muscle, tendon, or deeper tissue	1
Total score		

Treatment

NU treatment relies on preventing external trauma, offloading pressure, and managing infection. It is key to distinguish a neuropathic from a neuroischemic ulcer as management varies. We will discuss the various NU management strategies.

Wound care and debridement

NUs and neuroischemic ulcers, like other chronic wounds, must be maintained in the right environment to allow healing. Chronic wounds contain necrotic tissue and harbor higher bacterial loads.[3,4] These changes elicit a proinflammatory response which potentiates poor wound healing through the recruitment of matrix metalloproteinases and cytokines.[3,5] This results in poor keratinocyte migration as well as metabolic disruptions in protein and collagen synthesis.[5]

To encourage NU wound healing, it is important to remove dead tissue, exudate, biofilms, and fibrin deposition through proper wound care and debridement every 7 to 14 days. Surgical debridement is the gold standard method of wound debridement (Fig. 2a,b).[5] Through this method, dead tissue is excised from the wound; however, mechanical debridement with wet-to-dry dressings, enzymatic debridement with use of collagenase, or autolytic debridement with use of occlusive dressings also prove useful.[3] The goal of debridement is to reduce the inflammatory response at the site of the wound so the tissue can promote healing and formation of granulation tissue.

NUs are polymicrobial and colonized by many organisms, including *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Peptostreptococcus species*.[5] Wound debridement helps to decrease bacterial load.[3] It has been shown that patients who undergo weekly wound debridement have better outcomes than those who rarely or never undergo wound debridement.[3] Though debridement decreases wound bacterial load, it is important to acknowledge that all NUs are colonized by bacteria; however, not all NUs are infected or require antibiotic therapy.[4] Signs of infection are purulent wound drainage, swelling, erythema, and pain. If these signs are present, then empiric antibiotics should be initiated, in addition to bacterial culture. For bacterial culture, tissue culture is favored over traditional swab cultures because of improved efficacy in identifying the pathogenic, and not just the colonizing, bacteria.[5] Empiric treatment for mild-to-moderate skin infection is amoxicillin/clavulanate, clindamycin, cephalexin, or dicloxacillin. For moderate skin infection, vancomycin and ampicillin/sulbactam, moxifloxacin, cefoxitin, or cefotetan are recommended.[7] Severe cases, where osteomyelitis is suspected, an MRI should be ordered and empiric treatment with vancomycin and piperacillin/tazobactam, imipenem/cilastatin, meropenem, or doripenem is recommended.[7] If osteomyelitis is found, the patient will require IV antibiotics and debridement of bone. Recognizing this complication is imperative as osteomyelitis often leads to limb amputation.[4]

Offloading

Offloading devices refer to devices which redistribute pressure from the wound over the entire plantar foot. In general, offloading devices are worn over a 4- to 6-week period to aid in wound healing.[7] Individuals with NUs have different biomechanics than the general population as they cannot feel the ground as they step. This results in higher pressure applied to the foot as individuals do not decelerate the foot as it hits the ground. This increases the pressure and strain applied to the foot, making the individual more likely to cause deep tissue trauma to the foot. Offloading devices prevent this increased force from being applied to pressure points on the foot.

Total contact casting (TCC), a non-removable offloading device, is reported to be the gold standard method of offloading for neuropathic ulcers.[7] TCCs are molded to an individual's foot to redistribute pressure across the entire plantar surface while walking, in order to decrease any pressure points. TCCs are applied and removed weekly by trained professionals to allow proper wound care as the ulcer heals. Only trained professionals should prepare and apply the cast as improper application may cause formation of iatrogenic ulcers.[14] These casts are not recommended in patients with gait instability or neuroischemic ulcers, as individuals may be more likely to fall while wearing the cast, and patients are more likely to develop unrecognized soft tissue infections in the setting of weekly cast changing.[14]

Removable cast walkers are offloading devices which decrease forefoot pressure by keeping the ankle bent at a 90-degree angle.[14] Patients tend to tolerate these casts better as they can remove the cast for sleeping or bathing; however, patient non-compliance is a barrier to proper wound healing.[7] Additionally, these casts are not molded to the individual; therefore, they may not fit every patient and may lead to the iatrogenic ulcers.[14] These casts can be made irremovable through use of cohesive bandage or fiberglass tape to help with patient adherence.[14] When made irremovable, the devices have similar wound healing rates as TCCs.

Hyperbaric oxygen therapy (HBOT) is used to increase the oxygen delivery to the wound to improve wound healing and correct for the local tissue hypoxia associated with chronic

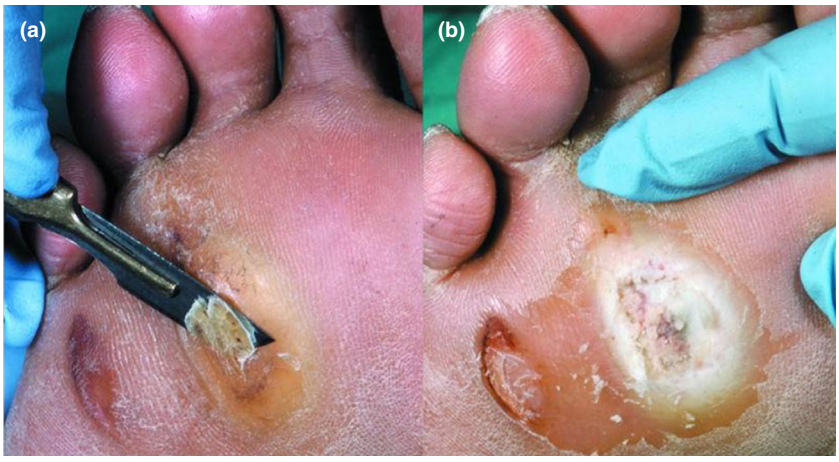

Figure 2 (a) Surgical debridement of callus. (b) White, macerated, moist tissue underlying callus, indicating imminent ulceration. (Reproduced from *Diabetic foot ulcers*, Edmonds ME, Foster VM, 332:407, 2020 with permission from BMJ Publishing Group Ltd)

wounds. Patients sit in a hyperbaric chamber where the patient breathes 100% oxygen at an atmospheric pressure greater than sea-level, multiple times per week over several weeks.[15] HBOT's efficacy is controversial; however, there are studies reporting decreased rates of major amputation in those treated with HBOT.[3,5,11] HBOT is approved by Medicare if the following criteria are met: (i) patient has type I or type II DM and their ulcer is secondary to their disease; (ii) patient has a Wagner grade 3 or higher classified wound; and (iii) patient failed standard wound therapy after a 30-day period. Standard wound care involves optimizing the patient's glycemic control and nutritional status, evaluating and correcting for any contributing vascular disease, wound debridement, proper application of wound care, offloading, and treatment of any underlying infection.[16]

Skin grafting or the application of a tissue or a tissue substitute to a debrided ulcer may offer slight benefit in wound healing; however, evidence is weak. When compared to TCC, which helped most ulcers heal by 6 weeks, grafting helped ulcers heal by 12 weeks.[4] Additionally, there was no evidence to support one type of skin graft over another when examining autografts, allografts, xenografts, and bioengineered or artificial skin.[17]

Prevention

NUs are preventable through patient education, adequate screening, and patient compliance. *The International Working Group on the Diabetic Foot* developed a risk stratification system to help clinicians identify individuals at risk of developing an NU (Table 3).[11] This risk stratification system helps provide a foot screening frequency based on patient symptomology, such as loss of protective sensation (LOPS), and history of PAD, foot deformity, prior foot ulcer, lower extremity amputation, or end-stage renal disease.[11] About 40% of individuals develop a recurrent NU within 1 year of their initial NU resolution, and approximately 65% of patients develop a recurrent NU within 5 years.[5] This shows the importance of initial screening, as once individuals develop an NU, it typically becomes a chronic issue.

To prevent NU formation, it is important to have diabetic patients undergo diabetic footwear and orthotic fitting. Improper fitting shoes, especially in the setting of DPN and foot deformities, are a leading cause of unrecognized trauma and ultimately NU formation.[11] If possible, patients and their family members and caregivers should be recruited to monitor the individual's feet. Many patients with NUs are older and have limited mobility and poor vision, so they often require assistance checking their feet.[11] They should be counseled to keep their feet dry and also watch for signs of pre-ulceration, which include callus formation, edema, blister formation, and evidence of trauma.[11]

Differential diagnoses

Arterial, venous, and pressure ulcers must also be considered when evaluating NUs.[18] As mentioned previously, arterial ulcers, or ulcers occurring in the setting of PAD, often overlap with NUs and delay wound healing. When arterial ulcers occur independently, they usually involve the dorsal toes and foot.[18] Arterial ulcers often have a "punched out" appearance and tend not to bleed easily.[18] Venous ulcers occur secondary to venous insufficiency and typically involve the lower third of the leg, especially the medial malleolus.[18] They appear as irregularly shaped, shallow erosions, with granulation tissue or fibrin deposition centrally.[18] It is a less common reason of foot ulceration. Pressure ulcers commonly occur on the heels of bedridden individuals caused by prolonged tissue compression, shear force, and friction. Initially, these sores present as erythematous patches at the site of skin-surface contact however may progress to full thickness skin necrosis, revealing bone or tendon. Another rare but reported mimicker of NU is pyoderma gangrenosum (PG).[19] Classically, PGs present with an undermined violaceous border and central fibrin deposition.[18] This should be considered if the ulcer is rapidly worsening, despite standard of care NU management, especially debridement.[19] Lastly, a Marjolin's ulcer, or squamous cell carcinoma within the ulcer, should be considered in all chronic, non-healing wounds.[18] These ulcers usually present with friable, exophytic granulation tissue.[18]

Table 3 Neuropathic ulcer risk stratification system

Ulcer risk	Characteristics	Visit frequency
Very low	No LOPS, no PAD	Annually
Low	LOPS or PAD present	Every 6–12 months
Moderate	LOPS and PAD present; or LOPS and foot deformity; or PAD and foot deformity	Every 3–6 months
High	LOPS or PAD and history of one of the following: (i) foot ulcer, (ii) lower extremity amputation, and (iii) ESRD	Every 1–3 months

Loss of protective sensation (LOPS), peripheral arterial disease (PAD), end-stage renal disease (ESRD).
Adapted from the 2019 International Working Group on the Diabetic Foot Risk Stratification System and corresponding foot screening frequency.

Discussion

NUs are a significant burden to both patient and the economy. Patient and physician education are important to help prevent ulcer formation; however, once the ulcer has developed, it is often difficult to heal. Also, once healed about 40% of patients develop a recurrent neuropathic ulcer within 1 year of complete wound healing.[5,15] Unfortunately, many of these ulcers result in limb amputation caused by secondary infection. This highlights the importance of aggressive prevention, management, and evaluation of neuropathic ulcers.

Diabetic patients should be carefully screened to determine their risk of developing an NU. If an NU can be prevented through proper footwear, education, and skin care, that is ideal; however, once an ulcer has developed, it is key to regularly monitor and treat the site. The standard of care of neuropathic ulcers involves offloading, treatment of concurrent infection, and debridement. To track wound response, the clinician should monitor the wound through photos as well as wound measurements. If the wound is not responding to standard of care, then the clinician must take into consideration other problems which impair healing. For example, chronically infected wounds, wounds in nutrient deficient individuals, and wounds subjected to the same persistent trauma will not heal unless the offending agent has been corrected or removed. Additionally, if an ulcer is neuroischemic, it will not heal unless revascularization of the lower extremity has been completed. If standard of care therapies fail, other treatment options include HBOT or skin grafting; however, evidence is limited.

Overall, NUs are a common and preventable condition with significant morbidity to the patient. With DM on the rise, it is important to routinely screen individuals to prevent NU development as well as aggressively manage these wounds to ensure wound healing and prevent limb amputation.

Review Questions (answers provided after references)

1 What percentage of individuals with a neuropathic ulcer require limb amputation?
a 5%
b 10%
c 15%
d 20%

2 True/False: Neuropathic ulcers predominantly affect the foot margin.

3 True/False: The SINBAD system for classifying and scoring foot ulcers does not take into consideration comorbidities, such as end-stage renal disease.

4 True/False: Surgical debridement of a neuropathic ulcer every 7-14 days results in poor wound healing and further ulcer progression.

5 True/False: Total contact casting results in most ulcers healing by 6 weeks.

6 What percentage of patients develop a second neuropathic ulcer within one year of healing from their first neuropathic ulcer?
a 10%
b 20%
c 30%
d 40%

7 True/False: Hyperbaric oxygen therapy decreases rate of amputation in individuals with neuroischemic ulcers.

8 True/False: Neuroischemic and neuropathic ulcers rarely coexist.

9 True/False: Patients with diabetes should be screened at least annually for neuropathic ulcers.

10 True/False: Radiograph is the most sensitive test for diagnosis of osteomyelitis.

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Review Questions: Answer Key

1 C. 15% of neuropathic ulcers result in limb amputation.
2 False. Neuropathic ulcers predominantly affect the metatarsal heads, great toes, and heels of the feet.
3 True. The SINBAD system only takes into consideration ulcer site, ischemia, neuropathy, presence of bacterial infection, and ulcer size and depth. It does not take into consideration other comorbidities, such as end-stage renal disease, or history of recurrent ulcers.
4 False. Surgical debridement of a neuropathic ulcer should occur every 7-14 days to decrease the biofilm, dead tissue, exudate, and fibrin deposition on the ulcer which delay healing.
5 True. Total contact casting results in most neuropathic ulcers healing by 6 weeks.
6 D. 40% of patients develop their second neuropathic ulcer within one year of healing their original ulcer.
7 False. Hyperbaric oxygen therapy is believed to decrease the rates of amputation in those with neuropathic ulcers.
8 False. About 50% of neuropathic ulcers are neuroischemic, with signs of peripheral arterial disease.
9 True. All patients with diabetes should be counseled on and screened for neuropathic ulcers on an annual basis. The International Working Group on the Diabetic Foot encourages increased screening if individuals also have loss of protective sensation, peripheral arterial disease, foot deformity, history of lower extremity amputation, or end-stage renal disease.
10 False. MRI is the most sensitive test for diagnosis of osteomyelitis.