Diabetic Foot: Addressing Problems Seen in the Pharmacy Clinic

by Nicole Van Hoey

Upon successful completion of this article, the pharmacist should be able to:

1. Discuss clinical indicators of diabetes that reflect increased diabetic foot morbidity risks, with a focus on neurologic and microvascular complications.
2. Describe how peripheral nerve disease develops in diabetes and identify some evaluation techniques that can prevent complications.
3. Distinguish between wound care and infection care, particularly differentiating the roles of dressings and empiric antibiotic therapy selection and timing.
4. Provide proactive measures to maintain circulation and foot health that reduces infection and re-infection risks.

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DIABETIC FOOT

Overview

Approximately 6 percent of the U.S. population has type 2 diabetes mellitus type 2 (T2DM, or DM), a 6-fold increase in numbers over the last 4 decades. Diabetes is now the fourth leading cause of death worldwide, predominantly as a result of secondary complications involving nerve and vascular damage. The morbidity of lower-limb complications from this damage is commonly referred to as diabetic foot. Its unique foot pathology involves changes in tissues, vasculature, and nerves. Despite available preventive lifestyle and disease care measures available, 15 percent of people with diabetes or an approximately 3 percent annual incidence, will experience diabetic foot ulcers.

The three major disorders of diabetic foot are neuropathy, ulceration, and vascular disease. Neuropathy both results from and causes foot deformities and plantar pressure changes. These changes can be irreversible and often instigate ulcer formation. Ulceration begins with minor wounds and often culminates in acute or chronic infection. Ischemia or peripheral vascular disease greatly increases the likelihood of severe infection and amputation in an already-formed ulcer.

Lifestyle and Disease Causes

Why do people with diabetes experience foot complications? The reasons involve a complex interplay of primary disease control, lifestyle choices, and more. Studies and clinical observations support the connections among blood sugar, sole pressure, and limb neuropathy that contribute to ulcer manifestations and long-term damage.

Uncontrolled diabetes sets the body up for underlying damage and poor response to normal foot trauma and pressure. Glycosylation in soft tissues of the foot...
change the structure of fatty pads, joints, bones, and tendons and predicate changes to the skin barrier. Damage by elevated blood sugar in tissues decreases skin thickness, increases skin hardness, increases muscle atrophy, reduces tendon and joint mobility, and reduces protective pads on feet. These foot changes result from friction, poor weight distribution across soles, and skin cracks. Structural changes such as a bunion are also a contributing factor to tissue damage. Blood sugar damage to the ends of nerves and blood vessels in lower limbs also impair sensation and blood flow.

Additionally, people with diabetes appear to walk more slowly and have slower reaction times to foot trauma overall. Stiff, glycosylated muscles and tendons instigate these lifestyle changes and reduce rates of walking for exercise. Poor physical activity habits also increase the likelihood of vascular edema and unnoticed nerve or skin changes to encourage a cycle of damage.

**Risk Factors and Reducers**

According to the International Working Group on Diabetic Foot (IWGDF), patients at high risk of developing foot complications can be identified well before larger complications manifest. Disease and lifestyle indicators of risk for diabetic foot include diabetes for more than 10 years, positive tobacco and alcohol use, and poor blood sugar control (e.g., A1c >7% repeatedly). Vascular and nerve damage elsewhere in the body reflect a greater risk of diabetic foot morbidity as well; symptoms of such damage include kidney dysfunction and poor visual acuity.

Poor footwear is one of the most common contributors to early diabetic foot development. Poorly fitted shoes, whether too tight or too loose, cause abnormal foot pressures, friction, and bunions. Pharmacists can reinforce podiatrist guidelines for proper footwear or fit and sell therapeutic footwear. Avoid recommendations that encourage specialized stockings or orthotic shoes but are too general for patients to apply toward overall prevention. Easy-to-implement, specific recommendations instead are to buy shoes in the evening when feet are swollen; to buy shoes that are leather and that use Velcro or laces; to buy shoes that have nonslip rubber soles; to buy shoes that have 2- to 3-cm–wide heels, and to buy shoes that do not have seams in the soles. Note: shift workers, especially the overnight shift, should buy shoes after their shift which may not be in the evening. Shoes with these guidelines help disperse pressure and reduce blisters, deformities, and nerve changes.

Similarly, many individuals at risk of foot ulcers or infections can prevent early initiation of damage through daily patient foot care. Self checks each day that include washing, drying, nail clipping, and emollient use, are essential to maintaining foot health. Patients should be advised against going barefoot or wearing compression stockings or socks with tight elastic.

**Etiology**

Nearly 1 million people globally who have diabetes lose a leg each year from diabetic foot complications. Peripheral nerve damage, of which patients are often unaware, allows even a small wound to go unnoticed. The sequence of complications starts innocuously when a minor skin crack or pressure blister introduces a problem. Without direct examination, such small skin changes progress to larger wounds and develop into ulcers. Untreated, an ulcer can become infected with or without ischemia and result in amputation in as many as one third of occurrences. This damaging sequence of changes is one of the most serious impacts on quality of life and morbidity in patients with diabetes.

**Prevention**

According to the IWGDF, multidisciplinary team foot care strategies are effective for ulcer and infection prevention. Close, evidence-based monitoring and education can lower amputation rates by 85 percent. Team care, with every specialist engaging patients, helps continually inform patients of the seriousness of diabetic foot conditions.

Professional screening in primary care settings for preliminary foot damage supplement common sense guidance for self care and treatment of early wounds and acute ulcers. Exams traditionally involve visual, neurologic, and vascular evaluations; they may incorporate plantar pressure measurements as necessary. Bunions, hammertoes, and calluses are signs of undue pressure. Lesions or fissures reflect...
Nerve Morbidity Defined and Classified
Peripheral neuropathy can be defined most simply as changes in the endings of nerve fibers in the skin that result in dysfunction of nerve sensation. Damage occurs in part when hyperglycemia changes the way nerve endings respond to stimulation, causing spontaneous or responsive pain, sensation loss, or both.

Symptomatic neuropathy develops slowly. As nerve changes minimize joint movement, emphasized by the inability to notice shoe discomforts, the damage builds. In addition, nerve changes inhibit protective sweating that moistens feet to prevent cracks and fissures.

A formal classification of diabetic neuropathy, called the Dyck scale, stages neuropathy by symptoms and their effects. At stage 0, no symptoms are present and sensation is normal; at stage 3, diabetic neuropathy symptoms have contributed to new ulcers and structural deformities. Stages 1 and 2 represent subclinical and clinical disease, respectively. In subclinical disease, no pain symptoms are present, but sensation exams are abnormal; in clinical disease, pain is possible and early sensation loss is already present.

Symptom Interplay
Common pain symptoms include burning, numbness, tingling, and limb fatigue. These can be spontaneous or provoked; can change over time; and can worsen in the evening. Nerve pain is a large quality-of-life concern; up to one fourth of patients with diabetic neuropathy experience daily chronic pain.

Treatment to control pain improves symptoms only, not the nerve damage itself. Tricyclic antidepressants are common first-line agents, although they have high rates of adverse effects and low ranges of effective doses. Antiepileptic drugs, particularly carbamazepine, gabapentin, and pregabalin are second-line choices. Capsaicin topical cream on unbroken skin and oral opiates like tramadol or oxycodone (a last-resort drug) can minimize some painful sensations. Selection can rely on the predominant symptom: Numbness responds best to carbamazepine, then lidocaine or topiramate. Paroxysmal spasms respond better to pregabalin. Burning sensations are relieved best by capsaicin and pregabalin, followed by tricyclics and then opiates. Hypersensitive responses are minimized with topical drugs; all sleep symptoms respond to pregabalin treatment.
Continued attention to symptom changes during this phase of neuropathy is crucial to identify additional, more severe sensation changes. Loss of protective sensation, or LOPS, is untreatable, irreversible nerve fiber damage that is more dangerous than nerve pain or tingling. LOPS is a predominant early contributor to diabetic foot ulcers. Early warning signs include low sensitivity to pain and heat as well as poor balance and increased falls resulting from impaired proprioception. As sensory impairment progresses from tingling to full LOPS, foot injury can go unnoticed.

When LOPS begins, the surrounding muscle structure also weakens and changes gait. Deformities that result from nerve and muscle dysfunction include claw toe, collapsed arch, and bunions. These deformities and the changes in gait and mobility increase pressure and friction on soles. Simple repeated stress—from as little as a daily walk—frequently starts an open wound.

Development of a diabetic foot ulcer from unnoticed trauma is the primary cause of diabetic foot ulcers and is often the first symptom of diabetic neuropathy as well. Up to 60 percent of all diabetic foot ulcers are considered entirely the result of this peripheral neuropathy path.

**Screening**

To identify diabetic neuropathy before it leads to LOPS-related ulceration, regular screening is recommended by the American Diabetes Association. Exams determine health by evaluating nerve function, skin changes, reflexes, temperature response, and pressure changes. The goal is to identify patients at greatest risk for unnoticed ulcers in order to establish self-care measures and routine preventive screening.

Peripheral neuropathy screening is performed at shorter intervals as time with diabetes lengthens. All patients, even asymptomatic patients with controlled diabetes, should be screened at diabetes diagnosis and again every year, starting at age 30 years. In younger patients who are diagnosed with type 1 diabetes, screening should occur initially at five years after diagnosis, and annual screening should begin at age 30.

Clinical recommendations agree that patients with neuropathy should undergo more frequent neuropathy testing; every three to six months instead of annually is reasonable for patients with some clinical or subclinical diagnosed neuropathy (eg, some abnormal sensations or pain symptoms but without LOPS); patients with high risks of sensation loss should be checked every one to three months. High-risk patients include those with a history of foot ulcer, physical deformities, or known vascular damage. They warrant intense education about proactive skin care between each screening.

Peripheral neuropathy examination uses touch and vibration testing with cotton wool, 10-g monofilaments, and tuning forks. These tests can identify sensory loss before skin breaks or ulcers develop. The 10-g monofilament test is the most common evaluation for protective sensation, seconded by vibratory fork testing. Both have a role: tuning forks best reflect changes to the foot and toe joints; flexible filament thread can detect pressure changes across the sole.

Repeat monofilament testing is not useful on fully insensate feet. Once LOPS is diagnosed on clinical exam, such as when a patient fails to feel any of the four diagnostic pressure points on a 10-g nylon monofilament test, patients require a variation of diabetic neuropathy testing and goals. Goals may have a particular focus on gait and pressure. Patients with LOPS require podiatrist referral and an even greater educational effort to prevent ulcers through avoidance of trauma and foot stress. In patients with LOPS, plantar pressure and more intense visual exams assist ulcer and deformity prevention. When available, Harris pressure mats or computer software programs identify abnormal pressure points while patients are standing still. These aids identify vulnerable areas prone to ulceration and suggest a need for footwear or gait re-evaluation by a podiatrist. Even without technologic tools, though, a detailed visual exam will note calluses that develop from improper pressure on the foot. Such early changes can be indicative of developing fissures, cracks, or ingrown nails. Addressing foot changes, even after LOPS, that initiate ulcers greatly reduces the likelihood of later complications.

**Case Resolution**

H.G. tested positive on the 10-g monofilament test for full loss of protective sensation (LOPS) and has an open but superficial wound. Moving forward, evaluations should not include the
monofilament test but instead should focus on more frequent checks for abnormal pressures and broken skin barriers that could go unnoticed without nerve sensation.

H.G. was unaware of the skin injury, which is at risk for ulceration and bacterial colonization. He requires appropriate and immediate wound care and daily self checks. Pharmacist S.W. schedules a podiatrist checkup, and instructs the patient on how to manage the injury to ensure healing, including coverage of moisture, daily cleansing, emollient lubrication, and correct footwear. Finally, S.W. emphasizes the importance of a daily foot check at this stage in particular to prevent wound infection now and reduce amputation risk for the long term. H.G. plans to return in one month for another disease state evaluation and foot exam.

ULCER WOUNDS AND INFECTIONS
Case Presentation II: Ulcer Infections
H.G. returns to the pharmacy six weeks later, after missing the last monthly clinic. He is in a boot to disperse plantar pressure and has a prescription for antibiotics, as well as instructions to S.W. from his endocrinologist to monitor response to the antibiotics at the monthly clinic in two weeks. What is the likely antibiotic regimen (including duration) he received? What should S.W. observe to determine if treatment is effective? What are indications that the infection has worsened? While he waits for his medication, S.W. takes the opportunity to measure blood pressure (140/85 mmHg) and blood glucose (168 mg/dL). H.G. admits to going days without checking glucose or remembering medications for blood pressure or “sugar.” How does S.W. more emphatically counsel H.G. about the connection between glucose control and his foot infection?

Ulcer Etiology
Ulcers are skin defects that extend into tissues, muscle, joints, and even bone. Dorsal toe and plantar surfaces are the most frequent ulcer sites, especially with a superficial start. Not every skin crack or callus will develop into an ulcer, and not every ulcer or wound will become infected. Diabetes disease control plays a large role. Uncontrolled blood sugar increases bacterial flora at skin wounds and promotes edema through fluid imbalance.

In 2006, Medicare-reported costs for diabetes patients with ulcers were three times greater than general patient costs. Even uninfected ulcers can take months to heal completely; in one study, just under 25 percent of wounds healed after 12 weeks of good care, especially with shorter ulcer duration; Within 20 weeks of good care, 30.9 percent of ulcers healed. An important consideration and reason to prevent ulcers and infections at all is the high rate of recurrence. At 5 years after an index ulcer, 70 percent of patients experience another, usually at the same weakened location.

Ulcer Risk Factors
Independent risk factors for ulcers include foot deformities like bunions, increased time with diabetes, living alone, age older than 70 years, and poor footwear that increases plantar pressure and friction. Large fluctuations of blood sugar or continually high glucose levels impair the body’s ability to heal skin damage before ulceration occurs and cause vascular or neurologic changes that limit patient awareness of damage.

Lifestyle factors that increase ulcer risk include reduced mobility, lack of physical activity, poor nutrition, depression, obesity, and smoking. Smoking constricts vessels in the limbs and reduces oxygen in the blood that reaches peripheral tissues. The reduced circulation increases the risk of both ulcers and their infections.

Ulcer Grading Options
Ulcers defy a standard global classification, and even infected ulcers are characterized by clinical symptoms. Ulcer severity can be described by depth, ischemic component, and level of infection. An old but still-used classification of foot lesions is the Wagner ulcer scale. It provides a measured description of ulcer infections, without ischemic characterization, to guide clinical evaluation and treatment. On the scale, 0 indicates no lesions and some minor skin or pressure changes; 1, superficial skin ulcers; 2, deep ulcers into the fat or tendon but not into joint or bone; 3, abscessed and infected ulcers; 4, local gangrene; and 5, extensive gangrene requiring amputation.

Newer scales like the IWGDF PEDIS also grade infected and noninfected ulcers by clinical presentation
but include vascular changes as a component and use stages that incorporate signs and symptoms. However, PEDIS is used in research or hospitalization scenarios more often than in outpatient community settings. On PEDIS, 1 represents no infection, and 4 represents severe infection with systemic toxicity. Grade 2 is indicated by cellulitis at or less than 2 cm with redness at ulcer site; grade 3, greater than 2 cm cellulitis and symptoms beyond superficial areas, into joint or abscesses.

Ulcerated Wound Care

Even low-grade, uninfected ulcers warrant prompt wound care to ensure complete healing and minimize infection. The primary goal of ulcer care is to close the wound quickly. Wound care is distinct from infection care and is essential for every ulcer. Successful treatment at this stage, before infection, avoids antibiotic overuse, prevents amputation, and increases quality of life. No evidence yet supports antibiotic prophylaxis; antibiotics are only warranted if the ulcer becomes infected, because prophylaxis increases costs, adverse effects, and resistance. Appropriate wound care involves cleansing, debridement, offloading, and dressing, per IWGDF 2011 guidelines.

Debridement. Debridement and drainage remove necrotic, or dead, tissue and pus from the local area. Surgical debridement is the recommended debridement method. Removing the extra skin, dead tissue, and particulate matter along the base and margins of an ulcer is the first step to reducing infection rates and providing a healing environment that lowers acute inflammation.

Debridement is an ongoing part of ulcer care that should be repeated as necessary to keep the wound clean and free of dead tissue. All ulcers should be inspected and drained of pus daily for best care.

Offloading. To maintain healing in a clean wound, offloading is crucial. Any method that removes weight from the ulcerated foot is supported as long as the wound can be accessed for daily cleansing, dressing, and inspection. Recent indications are that pressure offloading might be the best way to facilitate healing of a cleansed, uninfected ulcer. Through casts or boots, offloading disperses normal stress on the foot to minimize calluses, reduce pressure, and improve blood flow throughout the limb.

Dressings. Maintaining moisture at a wound also has been a breakthrough for successful diabetic foot care. Wounds heal best when kept moist, often with 0.5 percent normal saline in dressings, because moisture speeds up formation of skin at wound sites. Dressings offer protection and promote healing, but they must be removable, easy to change, and nonadherent to allow inspection for early signs and symptoms of infection. Absorbent, protective dressings are easy to use and provide a vehicle for moisture and potentially more treatment options. Simple, passively protective gauze and saline/emollient-immersed covers are easy to change and effective for cleanliness. More complex dressing options, also known as active or interactive dressings, change the wound itself with cell stimulation or growth factors, or with absorbed collagen as a matrix to prevent tissue destruction.

Common options are fibrous hydrocolloids, hydrogels, foams, alginates, and iodinated colloids. Hydrocolloids (such as, DuoDERM®, Te gaderm®, Restore® dressings) are useful protective coverings and might prevent infection; however, data on preventive efficacy are controversial. Hydrogels (eg, AquaForm® gel; Hy draGel® and FlexiGel® dressings) are similar to hydrocolloids but also provide moisture as part of the dressing. They are most effective for necrotic, debrided tissue. Foams (such as, Al lvyn®, Mepilex® dressing) are absorbent and thermal, providing an insulating effect. Alginates (eg, Restore®, Aq ucel® dressings, Sorbsan™ dressing or rope) are similarly absorbent and also easy to change. They can be packed into open cavities that are actively infected. Iodinated or silver dressings, conversely, have little evidence to support anti-infective or healing benefits, but they remain popular.

Dressings have had few advances over the years; newer, complex options use growth factors or biological advances to actively treat wounds, not just moisture and shield them. Growth factor dressings (such as, Regranex® gel) stimulate a cellular response for healing. Another product, Apligraf®, is a disc of living cells
bioengineered to substitute normal cell healing and blood vessel building to increase rapid wound closure in addition to passive protection.

Despite a handful of recent case reports of success at reducing infection or amputation with newer dressings, there are still not substantial data to support advanced options like hyperbaric oxygen, topical growth factors, or human dermal cultures administered via dressings. Thus, these are not yet considered routine care.

In some recent investigations, hydrogels and foams appear more beneficial than basic wound care, though hydrocolloids have not. However, differences in cost and antibacterial components have not been associated with efficacy differences. In addition, two 21st century reviews of dressings, one through 2006 and one covering 2006 through 2010, identified no superiority of dressing types.

The overall platform of ulcer care remains a challenge, with little evidence for wound care durations and infection prevention measures. Although dressings are integral and standard to diabetic foot care, their selection is based on experience more than on clinical data. Dressing recommendation remains an area of great uncertainty, even for health professionals who frequently treat diabetic foot conditions. Wound care, and in particular diabetic foot ulcers, can provide a gateway for pharmacists to contribute to diabetic foot team care, via patient education and dressing guidance.

Ulcer Infections

Ulcer infections, also known as diabetic foot infections or DFIs, cause nearly 25 percent of all U.S. diabetes-related hospital admissions each year; DFIs are the most common diabetes-related hospitalization. Infections start when normal skin bacteria colonize wounds that are not aggressively addressed in developing stages. Infections range from superficial wounds with local inflammation, or cellulitis, to extensive, often chronic, soft tissue necrosis or bone involvement (known as osteomyelitis). DFIs occur in more than 50 percent of people who develop an ulcer; 25 percent of the infections reach deep tissue and increase amputation risk.

Ulcers are most likely to develop an infection when they remain unhealed for more than 30 days, have abscessed down to the bone, are traumatic, are recurring, or involve arterial disease. Like ulcers, DFIs start insidiously but can develop rapidly when untended. Symptoms, treatment, and prognoses vary widely and depend on multiple factors. Frequency of ulceration, presence of ischemia or vascular damage, poor blood sugar control, and neuropathy contribute to poorer outcomes. Some normally innocuous bacteria or fungi thrive on high blood glucose and promote infection in the extremities. The progression, if not observed early, can be rapid and dire. Identifying and halting infection at superficial levels protects the dermal and subcutaneous tissues, especially when protective nerve sensations are gone.

Despite the high prevalence and costs of DFIs, there are still no standard definitions or treatment algorithms for diagnosis and care. Each occurrence is unique, and antibiotic delivery to limbs can be complicated by poor blood flow or edema.

Clinical diagnosis of DFI. Infections are diagnosed clinically, not by culture, in part because bacterial culprits are flora normally present on the skin without pathologic consequences. In fact, cultures of infected surface tissue rarely describe causal infectious bacteria in full. Rather, swabs or scrapes deep into the cleansed tissue base, or a biopsy of wound tissue, is necessary for an accurate picture. Diagnosis instead relies on the patient’s health, not just the wound appearance. Cultures are supportive after diagnosis, to confirm or adjust initial antibiotic selections.

Signs and symptoms of DFI. Markers of wound infection include purulent discharge, foul odor, extensive necrosis, and signs of a local inflammatory response that activates the immune system. Inflammation causes swelling, redness, and pain; in addition, systemic constitutional symptoms (such as, malaise, fever) indicate immune system activity. An accepted standard for clinically defining or diagnosing most DFIs that are uncomplicated by ischemia is the presence of pus as well as two or more signs and symptoms of inflammation.

However, signs and symptoms can be variable and even absent during an active infection in patients with
uncontrolled blood sugar. The systemic response, including fever, can be blunted, especially at blood sugar levels at or greater than 150 mg/dL. Clinically, diagnosis then depends on secondary signs of infection. Poor healing despite good wound care is a predominant indicator.

**DFI grading.** Like uninfected ulcers, infections can be graded on the Wagner or PEDIS scale. In addition, the Infectious Disease Society of America (IDSA) provides a standard description of an infected ulcer to match the numerical PEDIS scale that is simple and effective at guiding treatment. The IDSA diagnostic scale of 0 to 5 uses pus and two or more inflammatory markers but also incorporates evaluation of major contributing factors, including local skin changes, foul odor, and history of blood sugar control, for a better picture of infection and risks. Regardless of grade, successful infection care remains a challenge. Multiple pathologies contribute to developing infections, and patients with DFIs often present atypically because of their coexisting neuropathy and lower extremity glycosylation damage.

**Antibiotic Treatment of DFI**

Pharmacologic treatment is warranted when clinical signs and symptoms of infection develop locally, not when cultures report bacterial growth without evidence of illness. Upon identification, any wound warrants full assessment to address each contributing factor: cleansing, debridement, depth assessment, neuropathy checks, and ischemia checks complement infection evaluation. Dressing changes and debridement to reduce bacteria-laden pus and necrotic tissue and offloading to reduce stress. Because infection is so greatly associated with hospitalization and amputation, immediate treatment is warranted. The antibiotic treatment goal is to eliminate infection, not to heal the wound. Antibiotic selection is guided by clinical decision making, more than by evidence-based medicine, according to severity and duration of the infection.

**Mild Infections.** The IDSA definition of mild disease includes 2 or more signs of pus, tenderness, pain, or warmth; cellulitis 2 cm or less around the ulcer; no complications (such as, recurrence, LOPS); and no deep tissue or systemic infection. These acute infections frequently present with subcutaneous manifestations only, so stable outpatient care is sufficient.

Acute, uncomplicated, tissue infections are most often colonized by only one bacterium, namely gram positive cocci. *Staphylococcus aureus* and beta-hemolytic streptococcus are the most frequent invaders; group B strep appears more common in patients with diabetes than in patients without. *S. epidermidis* is possible.

**Treatment selection and duration**—Initial antibiotic treatment for mild infection should be directed at gram positive cocci and confirmed by culture. Empiric treatment of acute, uncomplicated infection optimally involves oral treatment with synthetic penicillins like dicloxacillin; cephalosporins like cephalexin or cefdinir; or clindamycin to provide sufficient antimicrobial activity. No one antibiotic regimen appears best for every patient.

Most cases of mild infection respond to empiric antibiotic care within three to five days of treatment initiation. Even a mildly infected wound should be reassessed by culture and clinical symptoms at two to three days after treatment to determine antibiotic efficacy and measure the healing progress. Empiric gram-positive coverage for mild infection then can be broadened to cover potential resistance or complication scenarios. A slow response to antibiotics suggests inadequate coverage, a more severe disease, or unusual flora. Culture at the wound base at this point can determine the level of gram negative bacilli involvement; Klebsiella and Bacteroides are possible in some long-lasting mild infections.

Even when treating mild infections, complications can arise through allergies, intolerances, or resistance scenarios. Amoxicillin/clavulanate is a common empiric option that unnecessarily covers gram negative bacilli and anaerobes for simple mild infections. However, this coverage is useful for slow-healing infections with resistant bacteria. Clindamycin is a recommended drug of choice for gram positive coverage in patients with penicillin allergy. Fluoroquinolones can replace penicillins as well; levofloxacin has better gram positive coverage than ciprofloxacin orally. When community-as-
sociated methicillin-resistant *S. aureus* (MRSA) is a factor, a tetracycline or sulfamethoxazole/tri-methoprim might counter the resistant bacteria.

Any antibiotic treatment for mild tissue infection should last at least one to two weeks, and two to four weeks is better for borderline moderate infections. Wound care should continue after any antibiotic ends.

**Moderate Infections.** Infections that are not efficiently diagnosed, or those that do not respond to initial treatment and progress further into tissues, become more complex in pathology and treatment. Even with proper care of mild DFIs, numerous factors can lead to more severe infection. A history of antibiotic use, MRSA in the hospital or community, poor wound care, and regularly high blood sugar worsen infection depth and duration.

Moderate disease is characterized by cellulitis greater than 2 cm from the wound or by involvement of deep tissues like tendons or fascia. Lymph symptoms are often present, including increased white blood cells. Constitutional symptoms of fever and edema also are seen in at least half of patients. In addition to the broadened spread of cellulitis, moderate disease involves abscess and localized joint gangrene. Untreated, these complex infections can lead to severe gangrene or osteomyelitis, which occurs in at least 20 percent of patients with DFIs. Severe disease also can involve systemic symptoms of sepsis (eg, fever, acidosis, and hypotension).

Unlike acute infections by one bacterial strain, these complex infections are polymicrobial, especially in patients with a history of DFIs. Typical microbes extend from gram positive skin flora to include gram negative rods like *Escherichia Coli*, *Klebsiella*, or *Proteus* as well as anaerobes like *Bacteroides*. Deep tissue infections often have more gram negative rods than gram positive bacterial flora. Anaerobes contribute most often in chronic infections and when tissue becomes gangrenous from vascular damage and a lack of oxygen delivery.

**Treatment differences**—As with mild disease, no standard exists for antibiotic selection or duration of moderate-to-severe infection. Empiric selection must cover gram positive cocci, resistant gram positive organisms, gram negative bacilli, and anaerobes, particularly as disease duration increases and the variety of colonized bacteria grows. Within these parameters, options are wide; they can be tweaked as needed according to culture results. Combination of a beta-lactam and a fluoroquinolone often provides gram negative rod coverage; ampicillin/sulbactam (which covers *Bacteroides*), piperacillin/tazobactam, and ticarcillin/clavulanate are commonly prescribed. Additional options for intravenous administration include cephalosporins like ceftazidime or cefotaxime plus clindamycin; ciprofloxacin plus clindamycin, and vancomycin, levofloxacin, and metronidazole. Oral treatment options for severe infection include dicloxacillin 500 mg plus cephalaxin 500 mg four times daily; amoxicillin/clavulanate 875 mg twice daily; doxycycline 100 mg twice daily; and sulfamethoxazole/trimethoprim 800/160 mg twice daily.

Most often, osteomyelitis or severe, chronic tissue disease requires intravenous administration and hospitalization followed by aggressively monitored outpatient oral therapy to completely quell infections. Treatment after discharge still requires up to three months of wound care until skin heals completely. Hospitalization allows careful observation and frequent debridement of infected tissue to prevent additional complications or amputation. Hospitalization is particularly warranted for patients who have health barriers to good wound care, for those who have known adherence concerns, for patients who require aggressive offloading, and for non-independent patients (such as, elderly, multiple comorbid diseases). Moderate and severe diseases should have longer durations of antibiotic care as well, at least two to four weeks, and potentially four to six weeks. IDSA guidelines suggest a minimum of two to six weeks of antibiotics for residual, deep infections, but the duration depends solely on positive patient response. Moderate to severe infection can require two to four weeks of inpatient IV treatment followed by four to six weeks of outpatient oral therapy, especially when osteomyelitis is likely. Follow-up is required daily in the hospital setting and should continue every two to five days after discharge to outpatient care. Re-evaluation at day two to five after treatment.
initiation and again at one to two weeks is important as patients transition to outpatient care and risk developing chronic infection with complications.

The infection response is measured by reduction of signs and symptoms of disease, or clinical improvement. Non-healing wounds can get stuck in the inflammatory phase of healing, at which fever and white blood cell responses are dulled but pathologic bacteria remain in the non-healing wound.

**Resistance and treatment failure**—The role of resistance, especially MRSA, has increased greatly in the past decade. MRSA prevalence has increased from 11.6 percent in 2003 to 21.9 percent in 2007, and rates of MRSA in DFIs in 2012 range from 12 percent to 32 percent. Its presence is associated with significant treatment failure, regardless of infection severity.

Resistance is likely when treated infection lasts more than one month, when ulcers are greater than 4 cm across or deep, and when osteomyelitis develops. Other risks include prior hospitalization, prior antibiotic use, nasal MRSA colonization, and chronic renal disease. In addition, MRSA should be covered by antibiotic selection if the community rates exceed 10 percent to 15 percent.

MRSA is not the only concern, though. Multidrug-resistant disease and rarer bacterial infections develop when ulcers occur repeatedly or remain not fully healed. Treatment becomes more complicated as more complex microbial infestation begins. Enterococci, Enterobacteriaceae, and Pseudomonas can thrive; up to five infective microbes in one severe ulcer becomes common.

Clindamycin and levofloxacin in combination cover some MRSA infections, and carbapenems can be added to regimens to cover Enterobacteriaceae. Imipenem/cilastatin and the newer IV ertapenem are broad-spectrum options for complicated, non-bone, non-MRSA DFIs. Newer antibiotics can be useful for moderate to severe bone or gangrenous tissue infections such as these. Moxifloxacin, a fourth-generation fluoroquinolone, provides activity against gram positive and gram negative bacteria as well as anaerobes. Moxifloxacin is orally bioavailable with once daily dosing, and it is considered safe for patients who have chronic renal disease.

Only some drugs—tigecycline, vancomycin, linezolid, and daptomycin—cover resistant strains with some reliability. Of these, vancomycin is still most often used. However, it requires combination therapy with a beta-lactam compound or a carbapenem to cover gram negative rods and anaerobes. The standard vancomycin dose for MRSA infection is 15 to 20 mg/kg every 8 to 12 hours. The first two cases of vancomycin-resistant S. aureus (VRSA) in the United States were in patients with DFIs. Linezolid, a 100 percent bioavailable oral option, is a great outpatient step-down treatment for post-IV MRSA care. In addition to gram positive and MRSA coverage, linezolid is active against VRSA. However, it too requires combination therapy for gram negative rod coverage. Compared with linezolid, daptomycin is less likely to be used because it is available by IV, is more expensive that linezolid, and is not more effective than vancomycin or penicillins.

**Amputation: Risks and Prevention**—Infection contributes to increased amputation rates proportional to severity of disease; osteomyelitis and abscessed gangrene are most often associated with limb loss. Amputation at this stage is often unavoidable. Amputation is performed to preserve the remaining limb and prevent systemic disease, including sepsis. The five-year survival rate after amputation is as low as 30 percent.

Amputations are most common at toes; in men 50 percent more often than in women; and in Hispanic, Blacks, or Native American people (at a 1.5- to 2-fold increase over Caucasians). Larger-limb amputation is more frequent in people with chronic renal disease. Amputation is also more likely when blood sugar is uncontrolled, because the irreversible tissue damage from infectious, neuropathic, and vascular assault is more pronounced.

**Case Resolution**

S.W. anticipates two weeks of a penicillin for H.G.’s first ulcer infection. H.G. presented a prescription for dicloxacillin orally twice daily for three weeks to cover typical gram-positive bacteria. S.W. counsels in lay language that controlled blood glucose helps the infection heal, because high amounts of sugar in the foot’s nerve endings and wound encourage bacterial growth, stop him from feeling pain from the infection that signals a problem, and stop skin from healing properly. In addition to continued wound care
and cleansing instructions, S.W. also emphasizes the importance of adherence to all three weeks of antibiotics to prevent drug resistance and fully heal the infection. Signs of healing include reduced local redness and systemic fever, lack of drainage or odor, and decreased wound size. Signs of ongoing infection include continued pus and possible necrotic skin in wound. S.W. requests a check-in by H.G. in one week at most, but H.G. will be out of town. At the clinic check-up in two weeks, H.G. exhibits signs of ongoing infection despite adherence to antibiotics, indicating that polymicrobial or resistant infection is likely. S.W. refers him back to the physician with this report and waits for the next team care instruction or clinic meeting.

VASCULAR COMPLICATIONS AND LONG-TERM PATIENT CARE

Case Presentation
It has been six months since H.G.’s first ulcer has healed. He again presents to the monthly diabetes clinic at S.W.’s pharmacy. H.G. has well-controlled blood glucose (today, 130 mg/dL; last A1c per physician chart, 7.2 percent) and no skin breaks on either foot. However, on foot exam, you notice some unusual changes on the skin. H.G.’s normally healthy large toenail is now thickened; more important, the skin near the nailbed and past the joint was blue-gray at rest and after applying pressure. Finally, his ankle and toes on the same limb reveal hair loss. How should S.W. treat H.G. today, and how does this exam change the course of his future lower-extremity and diabetes self care?

Vascular Disease Defined
Poor circulation, like nerve impairment, results from lasting uncontrolled blood sugar, because glycosylation damages both small and large blood vessels and hinders blood flow to the foot. Peripheral vascular disease (PVD) is defined as damage to large blood vessels in the lower limbs. The reduced circulation increases leg pain and prohibits sufficient tissue and skin health.

Peripheral artery disease (PAD), a type of vascular disease, is two times more common in patients with diabetes than without. It is present in 8 percent of people with diabetes at diagnosis and in 45 percent of them after 20 years with the disease. Vascular diseases like PAD are associated with the poorest infection outcomes. Although neuropathy is the primary contributor to ulcer development, one third of ulcers have ischemic components as well; vascular disease can increase the risk of infection in these ulcers up to fivefold.

Vascular Effects on Ulcerated Tissue
Vascular damage in diabetes negatively impacts outcomes and complicates care at any stage of wound or infection development. Early microvascular damage changes blood flow to lower-limb skin and reduces oil and sweat gland function in the extremities, thus increasing the rates of dry cracks and fissures that trigger ulcers.

Circulatory impairment at insufficiently vascularized limbs results in diminished delivery of oxygen and nutrients to tissues, so skin weakens and tissues become ischemic. Poor arterial perfusion mutes local infection symptoms, like redness and warmth, and increases the propensity of gangrenous spread. In addition, poor circulation prevents immune cells and antibiotics from reaching infected ulcers to complicate healing and spread infection to surrounding tissue. In severe cases of PVD, antibiotics and wound care are only effective after revascularization bypass surgery in the diseased limb.

Symptoms and Screening
Vascular insufficiency is reflected by a lack of foot pulses upon examination. However, the absence of a pulse only suggests, not diagnoses, damage; in addition, pulses and more thorough ankle pressures, including the ankle brachial index (that compares pressures along the lower limb) are difficult to obtain even for some podiatry clinicians. Circulation problems can be suggested clinically by edema and confirmed by ultrasound, not typically available in the pharmacy clinic. Similarly, toe pressures that deviate from a baseline normal of 70 mmHg identify ulcer risks, especially at pressures less than 45 mmHg, but also are performed by podiatrists.

Therefore, assessment for vascular damage in the outpatient pharmacy clinic incorporates pulse checks but relies most heavily on a visual exam, on which subtle indications of poor circulation can be reflected by seemingly minor skin changes, and on assessment of changeable risk factors.
Lower limb skin pallor upon foot elevation, lack of hair on the extremities, nail atrophy or dystrophy, and coolness and fissured skin on the foot are four common signs of vascular concern. Similarly, wrinkled and thin or blue skin, redness, and edema are abnormal symptoms to note. When circulation is impaired, skin of that extremity suffers and weakens as well; dry, scaly, and cracking skin on soles or between toes are common symptoms and also are ulceration risks. Hypertension, hyperlipidemia, and smoking all contribute to blood vessel damage that extends the risk of lower limb vascular disease as well.

All patients older than 50 should be examined every five years for vascular signs, even if circulation appears healthy. In patients younger than 50, screening is most critical for patients with high risks of vascular damage in diabetes. These risk factors include smoking, hypertension, high cholesterol, and a more than 10 year history of diabetes. Because of the widespread morbidity of vascular disease from infection to amputation, patients with symptoms of vascular problems require even more frequent and aggressive monitoring and prevention efforts.

Case Resolution
H.G.’s long history of diabetes increases his vascular morbidity risk, as does today’s visual exam with indicators of poor circulation. Control of diabetes-related metrics like glucose and blood pressure are now essential to preserve H.G.’s limb. Daily foot exams at home should be supplemented with more frequent checks by professionals. Because of his LOPS diagnosis, H.G. should undergo professional diabetic foot evaluation every month, and visual vascular exam at the same time or at least annually would certainly be justified. Similarly, weekly visits for counseling with S.W. as his most accessible health professional on the management team will only help maintain disease control and prevent infection, ulceration, and amputation in the future. With a concerted team effort and consistent self care, H.G. should maintain a good quality of life despite these manifestations of diabetic foot morbidity.

SUMMARY AND CONCLUSIONS
Summary
More than 50 percent of diabetic foot ulcers become infected, and 20 percent of these are amputated. Treatment of ulcers on an outpatient basis before they become infected will reduce amputation and ultimately increase survival.

Continued follow-up and frequent screening are essential in patients with history of ulcer and positive neuropathy or vascular damage. Prevention care essentials for patients include controlling blood sugar to maintain healthy tissue as well as limiting smoking to promote better circulation. Optimal blood sugar (ie, A1c <7 percent optimally) and cardiovascular parameters (eg, well-controlled blood pressure and lipid profiles) can reduce the risk of diabetic foot.

A problem with preventive care guidance is the generality of the recommendations—for better footwear, for more activity, and for regular health professional visits. Promotion of specific self-care behaviors is more important and more useful. Patients should wash, dry, clip, and inspect skin on feet each day; apply an emollient moisturizer and change socks daily; and avoid bare feet and cuts. Limiting hot temperatures on the feet prevents sole damage, and using loose socks and snug shoes reduces blisters. Close partnership with health professionals can reduce amputations by up to 85 percent, according to the IWGDF. Patients must be encouraged to request a foot exam whenever they are concerns about even small foot changes.

Rapid patient and clinician response to any newly developing foot difficulties is just as important as preventive care. One third of patients develop a second ulcer within one year of an index healing, and up to 70 percent of patients do so within five years. Teams of health professionals working together with a patient can reduce this frequency and increase the quality of life.

Annual foot checks require nerve and vascular evaluation at least; though optimal frequency over time remains unclear and unspecified, screenings should increase when complications develop. Skin changes, temperature responsiveness, and pressure changes are useful indicators. Foot emergencies in patients with prior ulcers involve new wounds, swelling, or discoloration (red, blue, or black). Patients require immediate referral to a foot care team for such an emergency. Best practice care for this or any ulcer scenario involves wound management,
vascular care, debridement, dressing, antibiotics when infected, and pressure offloading. Team management is essential for such complex care.

Conclusions
Diabetic foot is a complicated, chronic disorder that is common in patients with diabetes. Its multifaceted contributors all must be addressed to successfully prevent foot damage, potentially severe infections, and limb loss.

Pharmacists are often not cited in medical literature as a traditional team member for diabetic foot care. Patient education, though, is a pharmacist domain that plays a crucial role in disease care. Any pharmacist—and especially a CDE pharmacist or independent outpatient pharmacy educator—can play a vital role on a health care team in disseminating knowledge to patients about the connections of blood glucose, pressure, numbness, and edema to wounds, infections, and vascular disease in diabetic foot. In addition to their counseling roles and ubiquitous presence in the community, pharmacists encourage patients to develop a diabetic care relationship, at best, or to obtain trusted advice quickly between visits with their specialists, at least.

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CONTINUING EDUCATION QUIZ
Select the correct answer.

1. ___ percent of US patients with diabetes develop foot ulcers annually, for ___ percent of hospitalizations.
   a. 3; 25
   b. 3; 50
   c. 15; 25
   d. 15; 50

2. Basic offloading incorporates which of the following to adjust plantar pressure?
   a. Reduced stress through limb immobility
   b. Reduced friction at stressor sites through pressure-dispersive boot footwear
   c. Solid limb casting to entirely remove pressure on ulcer sites
   d. Elevation of lower limb with wheelchair use

3. Top risks for developing an index ulcer include ____.
   a. Increased physical activity stress on soles
   b. Reduced circulation from smoking
   c. Increased age and time with diabetes
   d. Both B and C

4. Which are valid sensory evaluations for peripheral neuropathy in the outpatient clinic?
   a. Monofilament test to monitor LOPS progression
   b. Temperature response evaluation alone as the first peripheral neuropathy check
   c. Pressure mat, if available, to monitor any neuropathic pain
   d. Visual exam and monofilament test as first neuropathy check

5. What are specific recommendations for smart footwear purchases?
   a. Bare feet whenever possible to reduce shoe-induced blisters
   b. Flexible cotton shoes that slip on and off easily
   c. Seamless rubber soles to avoid points of excess pressure
   d. Elastic compression stockings purchased over the counter

Editor’s Note: For the list of references used in this article, please contact America’s Pharmacist Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.
12. Causative bacteria in moderate to severe infection often include ___.
   a. Resistant gram-positive cocci
   b. Gram-negative rod like Klebsiella
   c. Anaerobes when circulation is impaired
   d. All of the above

13. Reasons for blunted systemic response to infection include ___.
   a. High blood sugar dulling the nervous system
   b. Hypertension constricting large blood vessels
   c. High blood sugar lowering the number of white blood cells to the limbs
   d. Allergies moving the inflammatory response to other parts of the body

14. Moderate to severe infection requires ___ weeks of therapy, according to IDSA.
   a. 1-2
   b. 2-4
   c. 2-6
   d. 12 or more

15. Hospitalization is justified for infection care when ___.
   a. Patients cannot independently care for their own wound during infection
   b. Patients have good adherence histories
   c. Patients require boot offloading
   d. Patients require debridement

16. Which of the following is most likely to lead to amputation?
   a. Index ulcer on heel with 2-cm cellulitis and hydrogel dressing care twice daily
   b. Nonhealing ulcer with poor response to antibiotic coverage and continued deep tissue necrosis
   c. Repeat dermal ulcer on the sole treated with coverage of gram-positive and gram-negative bacteria
   d. Edema and fever associated with an index ulcer on the big toe
17. Vascular disease increases the risk of infection in diabetic foot ulcers by ___.
   a. Twofold
   b. Threefold
   c. Fourfold
   d. Fivefold

18. Outpatient pharmacy assessment of vascular disease includes visual observation for ___.
   a. Extra skin redness with foot elevation
   b. Cracked and thin skin on the extremity
   c. Excessive hair growth on affected limb
   d. All of the above

19. Otherwise healthy middle-aged adults with diabetes should undergo which preventive evaluations?
   a. Vascular checks each year and peripheral neuropathy checks each month
   b. Vascular checks every four years and peripheral neuropathy checks every six months
   c. Peripheral neuropathy checks every year and vascular checks every five years
   d. Peripheral neuropathy checks every three months and vascular checks every two years

20. At what cutoff does blood glucose begin to blunt the immune system infection response?
   a. Glucose > 130 mg/dL
   b. Glucose > 150 mg/dL
   c. Glucose > 180 mg/dL
   d. Glucose > 210 mg/dL

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21. Is this program used to meet your mandatory C.E. requirements?  
   a. Yes b. No  
23. Age group: a. 21–30 b. 31–40 c. 41–50 d. 51–60 e. Over 60  
24. Did this article achieve its stated objectives?  
   a. Yes b. No  
25. How much of this program can you apply in practice?  
   a. All b. Some c. Very little d. None  

How long did it take you to complete both the reading and the quiz? ______ minutes

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