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Diabetic foot ulcer and poor compliance: How would you treat?

A 45-year-old Caucasian man, M.N., visits his family physician for a follow-up examination of the ulcer on his right foot. Today the patient reports that his foot feels more swollen. He has no pain, fever, or chills. Nine months ago M.N. began to exhibit a calloused, erythematous area on his right foot that subsequently became edematous and ulcerated. He was treated with cefuroxime (Ceftin) for 10 days and encouraged to stay off his feet. In a subsequent visit it was decided to refer him to a podiatrist and also to help him procure shoe inlays. The appearance of his foot infection improved for a while, then worsened. The patient was on his feet most hours of each day at his job as a baker, and this slowed his healing. His physician then treated him with cephalexin (Keflex), and he began to wear a cam walker. He failed to improve and, in fact, worsened. He was referred to an orthopedist. Plain films of his foot showed soft tissue ulceration without definite evidence of osteomyelitis. He was referred to the wound care clinic and began using Duoderm. He received yet another course of antibiotics. Wound cultures were not obtained.

Other medical history
- Diabetes mellitus type II
- Diabetic retinopathy
- Hypertension
- Erectile dysfunction
- Obesity
- Pes planus

Family history
- Diabetes and hypertension in father and paternal grandmother. Father had 2 myocardial infarctions and died at age 62. Mother is healthy. Sister has borderline diabetes.

Social history
- Nonsmoker
- 4 to 5 beers per week
- Divorced
- Works as a baker

Review of systems
- Negative except for increased swelling of right foot

Physical exam
- Alert male in no distress
- Blood pressure 135/68 mm Hg, temperature 37.5 °C, respiratory rate 14, heart rate 80, weight 236 pounds
- Heart, lung, and abdominal exam unremarkable
- Right 3rd toe has erythema at the metatarsophalangeal joint, with a draining ulcer on the plantar surface. Foot is edematous with erythema spreading proximally toward lower extremity. Erythema is <2 cm from ulcer rim. Pedal pulses are 1+, and capillary refill is <2 seconds. Monofilament testing reveals insensitivity at more than 4 sites.

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Q: What is the differential diagnosis of the patient's symptoms?

A: _____

_____

_____

Important elements of the history and exam

Assess vascular integrity. Arterial insufficiency is suggested by a history of cardiac or cerebrovascular disease, leg claudication, impotence, or pain in the distal foot when the patient is supine. Exam may reveal diminished or absent pulses, pallor on elevation, redness of the foot on lowering the leg, delayed capillary refill in toes, and thickened nails or absence of toe hair. With diabetes or renal impairment, the pulse exam may be unreliable due to arterial calcification.

Helpful studies may include segmental limb pressures, pulse-volume wave form, transcutaneous oxygen pressure, and ankle brachial index (which can be normal with significant calcinosis). Obtain a vascular surgery consultation immediately if you suspect arterial insufficiency, as revascularization may be necessary.[1]

Evaluate for musculoskeletal problems. Examine gait, look for foot deformities, and test joint range of motion. If a mechanical basis of the ulceration is found, eliminate or reduce foot pressure with shoes, inserts, orthoses, etc. Reconstructive foot surgery may be an option for some patients.

Gauge neurologic status. Most foot ulcers develop because of loss of protective sensation; therefore, screen all patients with diabetes annually for loss of protective sensation, using a 10-g nylon monofilament. Press the monofilament against the plantar skin until it buckles, hold it there for 1 second, and remove it.[2] The neurologic exam can also include testing for motor strength, deep-tendon reflexes, and vibratory (128-Hz tuning fork), proprioceptive, and protective sensation.

Measure the wound, watch for infection. When examining an ulcer, assess location, size, and depth. When caring for wounds, document at each visit the length and width of the wound.[3] Note any signs of infection (warmth, redness, pain, tenderness, induration, pus) or gangrene. Observe for fever, chills, and leukocytosis, but do not rely on systemic symptoms as indicators of infection. Assess the severity of infection, and explore the wound for foreign or necrotic material with a sterile metal instrument.

Examine toenails for fungal infection, as this may be a significant contributor to the initiation and continuation of a foot ulcer. Callus formation, especially with hemorrhage, may be evidence of an impending ulcer.[3]

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Test for loss of protective sensation, using a 10-g nylon monofilament

M.N.'s physician was increasingly concerned about the lack of healing of his ulcer. The differential diagnosis for this patient's swollen foot includes cellulitis, osteomyelitis, gout, foreign body, arthritis, trauma, deep venous thrombosis, pseudogout, and venous insufficiency. Many of these were excluded by the physical exam. A bone scan was ordered.

Q: What are the signs and symptoms of a severely infected diabetic foot ulcer?

A: _____

_____

_____

TABLE 1

Risk factors predisposing to foot ulcers and inhibiting healing

Vascular: arterial insufficiency or venous hypertension
Neurologic: sensory, motor, or autonomic neuropathy
Anatomical: altered biomechanics, limited joint mobility, bony deformity
Infections
Trauma
Diabetes

Referral to plastic surgeon

When M.N. returns to the clinic with worsening drainage, edema, and spreading erythema, the decision is made to admit him to the hospital, start intravenous ampicillin/sulbactam (Unasyn) and ciprofloxacin (Cipro), and consult with a plastic surgeon.

Following the examination and review of the bone scan results, which show osteomyelitis, the surgeon recommends surgical therapy of the affected toe. He advocates aggressive debridement, and also thinks that this wound could require a staged surgical approach or amputation.

Q: Are there other laboratory or imaging studies you would like to obtain?

A: _____

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_____

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Debride nonviable, infected tissue to expose healthy, bleeding soft tissue

Further primary care evaluation

Laboratory:

- Complete blood count, normal
- Erythrocyte sedimentation rate (ESR), 38
- C-reactive protein (CRP), 2.1
- Lipid panel: HDL 32 mg/dL, LDL 96 mg/dL, triglycerides 116 mg/dL
- Hemoglobin A1c, 6.0

Details of foot ulcers

Statistics

About 50% to 60% of serious foot infections are complicated by osteomyelitis, and 10% to 20% of mild to moderate infections likely involve the bone. Twenty-five percent of foot infections in persons with diabetes will spread to subcutaneous tissues or bone. Up to 50% of those with a foot infection will experience a recurrence within a few years.[2] Approximately 10% to 30% with a diabetic foot ulcer will eventually require amputation. Infected foot ulcers precede 60% of amputations. Two thirds of patients with a diabetic foot ulcer have peripheral vascular disease, and 80% have lost protective sensation. Infections most commonly involve the forefoot, usually plantar surface.[2]

Pathophysiology

Ulcers develop from breaks in the dermal barrier with subsequent erosion of subcutaneous tissue. Healing is inhibited when wound-repair mechanisms are corrupted by impaired perfusion, infection, or

repeated trauma. Ulceration progresses due to impaired arterial supply, neuropathy, or musculoskeletal deformities.[1]

Risk of ulceration correlates with number of risk factors. The risk is increased by 1.7 in persons with isolated peripheral neuropathy (**TABLE 1**), by 12 in those with neuropathy and foot deformity, and by 36 in those with peripheral neuropathy, deformity, and previous amputation.[1]

Pathology usually mixed. The feet have sensory and motor neuropathies that cause the patient to put abnormal stresses on them, resulting in trauma that may lead to infection. Immunologic impairment due to hyperglycemia also plays a role; this can include reduced function of neutrophils, monocytes, and complement. Skin and nail disorders are more common among persons with diabetes than in the general population, and these may also increase the rate of infection.[2]

TABLE 2

Clinical characteristics of a severe infection

Acute or rapidly progressive
Penetrating to subcutaneous tissues or involving fascia, muscle, joint, bone
Extensive cellulitis (>2 cm around ulcer rim)
Signs of inflammation, crepitus, bullae, necrosis, gangrene
Systemic signs: fever, chills, hypotension, confusion, volume depletion, leukocytosis
Metabolic abnormalities: severe hyperglycemia, acidosis, azotemia, electrolyte abnormalities
Absent pulses

Q: What are the patient's choices for management of his ulcer and osteomyelitis?

A: _____

_____

_____

Management of ulcers

Optimal management should involve a multidisciplinary group of consultants. Mechanical debridement, systemic antibiotic therapy, and measures to reduce weight bearing are the main elements of effective care. Foot soaks and whirlpool therapy may be detrimental and lead to further skin breakdown, but moist dressings on granulating wounds may help.

Debridement a must. Remove nonviable, infected tissue to achieve a border of healthy, bleeding soft tissue and uninfected bone. Debridement improves the outcome of foot ulcers.[3]

When hospitalization is indicated. Determine whether or not the patient requires hospitalization based on the presence of a severe infection (**TABLE 2**) and need for surgical intervention, fluid resuscitation, IV antibiotics, or control of metabolic derangements.[2] Consider hospitalization also if there is concern about the patient's ability or willingness to comply with wound care, antibiotic therapy, or off-loading of the affected area.

Consider need for off-loading. Most diabetic wounds develop because of unperceived trauma, and likely do not heal because of ongoing trauma. Total contact casting, whereby loading levels to a foot ulcer are drastically reduced, has been shown to be effective in healing ulcers in about 6 weeks.[4] This suggests that healing of neuropathic ulcers must include mechanical off-loading of the ulcer. Total contact casting has several limitations, and new modalities are being investigated.[5]

Obtain cultures. Wound culture results can greatly assist in determining appropriate antimicrobials. Gram stain can help direct therapy, and culture results are

TABLE 3

Wagner ulcer grading system

WOUND GRADE	WOUND DEPTH
Grade 0	Intact skin
Grade 1	Superficial ulcer
Grade 2	Deep ulcer to tendon, bone, or joint
Grade 3	Deep ulcer with abscess or osteomyelitis
Grade 4	Forefoot gangrene
Grade 5	Whole foot gangrene

The Wagner ulcer grading system does not identify infectious processes except in Grade 3. Erythema, edema, and pain may be present in foot infections, and may manifest as paronychia, cellulitis, or superficial skin infection.

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Mechanical off-loading hastens healing of neuropathic ulcers

consistent with Gram staining in 95% of cases. Gram-stained smear is 70% sensitive for identifying organisms that grow on culture, and is much better for gram-positive organisms than for gram-negative bacilli.

Deep tissue specimens collected aseptically at surgery contain the true pathogens more often than more superficial samples. Curettage, involving tissue scraping with a scalpel from the base of a debrided ulcer, is more accurate than a wound swab. Wound swabs are likely to miss key pathogens as well as include nonpathogenic bacteria that confuse the antibiotic choice.[2]

When antibiotics are needed. In gross infections and cellulitis, topical antibiotics may reduce bacterial loads, but there are few published data about their efficacy in diabetic foot infections. The Wagner ulcer grading system (**TABLE 3**) is most widely used for tracking diabetic foot ulcers, but it does not allow for identification of superficial infection and has not been validated as an effective tool.[6] An alternate method of classifying foot ulcers, taken from Lipsky et al, is shown in **TABLE 4**.

Currently systemic antibiotics are recommended only for established infection, although one study suggested that antibiotic therapy in clinically uninfected foot ulcers may significantly improve healing.[7]

Optimal duration of antibiotic therapy has not been studied, but convention has found 1 to 2 weeks to be effective for mild to moderate infections, at least 2 weeks for serious infections, and at least 6 weeks for osteomyelitis.[2]

Oral antibiotics are indicated when the ulcer is believed to be infected, and they should cover the usual pathogens, streptococci or staphylococci[7] (**TABLE 5**). Treat severe infections with intravenous broad-spectrum antibiotics, covering for gram-negative and gram-positive aerobes and anaerobes.

Studies have shown similar therapeutic outcomes between high-dose oral fluoroquinolones and intravenous cephalosporin therapy. Oral fluoroquinolones cause fewer side effects and reduce hospitalization-related costs compared with cephalosporins, penicillinase-resistant penicillins, and vancomycin.[8] Clindamycin or metronidazole may be added to fluoroquinolones to cover anaerobic organisms in severe or limb-threatening infections.[9] One study found that patients treated with vancomycin had a greater rate of recurrence.[5]

Staphylococcus aureus is the most important pathogen in diabetic foot infections and may cause disease in isolation or as part of a mixed infection. Gram-negative rods, usually Enterobacteriaceae, are found in patients with chronic or previously treated infections. *Pseudomonas* species may be isolated from wounds that have been soaked or treated with wet dressings. Enterococci are more likely to be cultured from patients previously treated with a cephalosporin. Suspect anaerobes in cases of ischemic necrosis or deep tissue infections.[2]

When a person with diabetes has peripheral vascular disease, therapeutic antibiotic concentrations are often not achieved in infected tissues even with adequate serum levels.[2] Novel methods of antibiotic delivery are being experimented with in an effort to solve this problem.

Surgery. Surgical options may include plastic reconstruction involving debridement and either primary closure or flap coverage. Optimally, vascular-bypass is performed to allow either primary healing or surgical reconstruction. If

TABLE 4

Clinical classification of diabetic foot infections

CLINICAL APPEARANCE	CLASSIFICATION
Wound lacking purulence or any manifestations of inflammation	**Uninfected**
Presence of 2 or more manifestations of inflammation (purulence, erythema, pain, tenderness, warmth, or induration). Any cellulitis/erythema extends 2 or more cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues. No other local complications or systemic illness.	**Mild**
Infection (as above) in a patient who is systematically well and metabolically stable but which has 1 or more of the following characteristics: cellulites extending >2 cm, lymphagitic streaking, spread beneath the superficial fascia, deep-tissue abcess, gangrene, and involvement of muscle, tender, joint or bone	**Moderate**
Infection in a patient with systemic toxicity or metabolic instability (eg, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	**Severe**

Source: Lipsky et al, 2004.[2]

revascularization is not possible, amputation may be required.

If osteomyelitis complicates the picture. No validated or well-accepted guidelines exist for diagnosing or treating diabetic foot osteomyelitis. Factors that may suggest osteomyelitis: long-standing ulcers (>4 weeks), large (>2 cm) or deep ulcers (>3 mm), elevated ESR (>70 mm/h).[2]

Laboratory assays for diagnosing osteomyelitis can include measurements of erythrocyte sedimentation rate or C-reactive protein, though there are insufficient studies to assess their usefulness. One study found that 100% of patients with an ESR >70 mm/hr had osteomyelitis, despite lack of physical signs of inflammation. In diabetic patients with noninflamed foot ulcers, ESR can have a specificity of 100% and sensitivity of 28%. With inflamed ulcers, the sensitivity decreases to 23%.[8] Some believe that the ESR can be used to follow osteomyelitis, and a persistent elevation or rise after initial fall would suggest osteomyelitis. Studies are inadequate to support this, however.[5]

Imaging for osteomyelitis can begin with plain films, which may show soft-tissue swelling, disruption of the bone cortex, and periosteal elevation. The American College of Radiology suggests this in the guidelines.[10] However, 50% of the bone may be destroyed before these changes are evident. Plain films have a sensitivity of 28% to 100% and a specificity of 69% to 92%. If initial films yield normal results, it may be useful to repeat them in 2 to 4 weeks.[9]

MRI is highly sensitive (>90%) and specific (>80%), and may be even better with gadolinium. MRI is more sensitive for forefoot osteomyelitis than a leukocyte scan.[11] Positron-emission tomography (PET) scans and high-resolution ultrasound may be helpful in the future.

Some studies suggest probing of sinuses and deep ulcers may be more sensitive than imaging. Palpable bone found at the base of an ulcer, with no overlying soft tissue, is highly predictive of osteomyelitis.[1] Visible bone in a nontraumatic wound suggests osteomyelitis, with a sensitivity of 32% and specificity of 100%.[12] The gold standard for diagnosis of osteomyelitis is obtaining a specimen of bone for pathology and culture.[9]

Antibiotic choice should be based on

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High-dose oral fluoroquinolones are equivalent to IV cephalosporins and cause fewer side effects

TABLE 5

Selecting antibiotics for diabetic foot infections (from the Sanford Guide)

DIAGNOSIS	ORGANISMS	SUGGESTED ANTIBIOTICS	DURATION OF THERAPY
Mild soft-tissue infection	Aerobic Gram-positive organisms	Oral dicloxacillin, clindamycin, cephalexin, trimethoprim-sulfamethoxazole	1–2 weeks
Mild soft-tissue infection that has failed to respond to initial antibiotics	Aerobic Gram-positive organisms and Gram-negative organisms	Oral amoxicillin-clavulanate, levofloxacin, or addition of ciprofloxacin to original antibiotics	1–2 weeks
Mild soft-tissue infection that has failed to respond to initial antibiotics, and MRSA suspected	Aerobic Gram-positive organisms, Gram-negative organisms, and MRSA	If susceptible, oral clindamycin or trimethoprim-sulfamethoxazole. Linezolid, vancomycin, or daptomycin if not susceptible	1–2 weeks, or longer if slow clinical-response
Moderate soft-tissue infection	Gram-positive, Gram-negative, and anaerobic organisms	Oral amoxicillin-clavulanate, levofloxacin, or combination of ciprofloxacin plus clindamycin	2–4 weeks*
Moderate soft-tissue infection with systemic toxicity, metabolic derangements, or in need of surgical procedures	Gram-positive, Gram-negative, and anaerobic organisms	Ciprofloxacin plus clindamycin, amoxicillin-clavulanate, ampicillin/sulbactam, or piperacillin/tazobactam	2–4 weeks*
Moderate soft-tissue infection with antibiotic-resistant organisms likely	Antibiotic-resistant Gram-positive, Gram-negative, and anaerobic organisms	Vancomycin, linezolid, or daptomycin for Gram-positive coverage plus ceftazidime, aztreonam, or ciprofloxacin for Gram-negative coverage with or without anaerobic coverage with metronidazole	2–4 weeks*
Severe soft-tissue infection	Gram-positive, Gram-negative, and anaerobic organisms	Piperacillin/tazobactam; imipenem; vancomycin, linezolid, or daptomycin plus ceftazidime, aztreonam, or ciprofloxacin with or without anaerobic coverage with metronidazole	2–4 weeks
Osteomyelitis	Gram-positive including *S aureus*, Gram-negative, anaerobes	Parenteral imipenem, meropenem, ticarcillin/clavulanate, piperacillin/tazobactam, ampicillin/sulbactam, cefepime plus metronidazole or aztreonam plus vancomycin plus metronidazole	Duration varies†

*If response to parenteral therapy is good, may be able to complete course with oral.
† 2–5 days if no residual infected tissue (post-surgery), 2–4 weeks if residual infected soft tissue, 4–6 weeks if residual infected viable bone, >3 months if residual dead bone.
Source: Gilbert DN, Moellering RC, Eliopoulos GM, and Sande, AM. *Sanford Guide to Antimicrobial Therapy*, 2004.

Family physician commentary

This case highlights several functions of the family physician and illustrates some of the challenges faced by primary caregivers. The dilemma in this scenario is that the patient ignored medical advice from specialists who had been consulted because of his worsening condition. What is a family physician's responsibility in this circumstance? If you place yourself in this physician's situation, you may experience a variety of emotions and thoughts, including frustration. How do you to provide a high standard of care for a patient who will not accept your recommendations?

Patient autonomy is paramount

As physicians we always need to respect patient autonomy. Though we may need to perform many roles, we always are the patient's advocate. This can be difficult when a patient deviates from what we consider appropriate medical care. We may fear complications arising from lack of cooperation with advised treatment. In this case, the physician was legitimately concerned about worsening bone and skin breakdown, which could ultimately lead to foot or limb loss.

We are trained to evaluate and treat patients within our scope of knowledge and then incorporate the help of specialists as necessary. We are less well trained to deal with patients who refuse recommended medical treatments. In these situations, we must first thoroughly review with patients their options and the risks and benefits of each. We must also assess whether patients are competent to make decisions. If they are competent, then we must allow our patients to choose to do nothing, though it may not be what we would choose. The physician must make a choice of continuing to care for the patient, or begin the process of transferring care. If the patient-physician relationship continues, physician and patient should negotiate responsibility for outcomes and document the patient's understanding.

In the case presented here, the patient continued seeing his physician for follow-up of his ulcer, though he had not followed the physician's treatment recommendation. This required the physician to continue his relationship with the patient despite a major difference of opinion. This is an example of respecting a patient's autonomy while continuing a therapeutic relationship.

This case demonstrates several family physician functions in addition to patient advocate:

Family physician as coordinator… The physician obtained appropriate specialty consultations, and facilitated the patient's visits to the podiatrist, orthopedist, wound care specialist, and plastic surgeon. He remained the central point of contact for the patient and assured that the patient received adequate follow-up.

…as comprehensive caregiver… This patient required management of several chronic diseases, including diabetes, hypertension, and obesity. He also needed health care maintenance. To give good care, the physician had to understand the patient's background, work situation, and personal values. To appropriately treat the patient's foot ulcer, the physician needed to know the patient, his work situation, and his medical history. As family physicians, we are able to build relationships with our patients that allow them to communicate their values, their history, and their wishes to us.

…and as educator. M.N. needed adequate and accurate information to make a final, informed decision concerning the care of his foot ulcer and osteomyelitis. As family physicians, we should be able to summarize for our patients their medical problem and present them with an overall picture of the problem and recommended treatment. This relationship allows the patient to make educated choices with a trusted healthcare provider.

–Jessica Farnsworth, MD

bone culture, as soft-tissue or sinus tract cultures do not accurately predict bone pathogens. When empiric therapy is necessary, coverage should always include *S aureus*. Cure of osteomyelitis has traditionally been thought to require removal of infected bone, but studies are showing that antibiotics may be adequate in two thirds of cases, especially those with good bioavailability. When bone is removed, shorter antibiotic therapy may be sufficient.[2]

Additional treatment options may include revascularization in an ischemic foot, which has been shown to salvage up to 98% of limbs. Hyperbaric oxygen may provide benefit, but data are insufficient to document this measure. Edema control may be beneficial for wound healing. Promising adjuvant therapies include granulocyte colony-stimulating factor (G-CSF), antibiotic-impregnated beads or orthopedic implants, and "biosurgery" with fly larvae.[2]

Case resolution

The family physician and M.N. discuss the options. The specialist recommends surgery, but the patient does not want to undergo this procedure. As his physician explains his concerns about the chronic, nonhealing ulcer and osteomyelitis, M.N. says he will negotiate a change in his work situation that would allow him to decrease the time spent on his feet and thus improve healing.

The patient has small clinical improvement of his ulcer while hospitalized, and a peripherally inserted central catheter (PICC) line is placed to administer long-term antibiotics on an outpatient basis. The ulcer heals gradually in coming weeks and months. Laboratory results show improvement as well, with normalization of the ESR and CRP. Given the clinical improvement and a steady decrease in inflammatory markers, a bone scan is not repeated. The patient now has a job that allows him to sit instead of being on his feet all day. ■

FAST TRACK

Osteomyelitis: select antibiotics based on bone culture, not on soft-tissue or sinus tract cultures

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