Supplement to:

DIABETIC FOOT DISORDERS:
A CLINICAL PRACTICE GUIDELINE (2006 revision)

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ABSTRACT: *The prevalence of diabetes mellitus is growing at epidemic proportions in the United States and worldwide. Most alarming is the steady increase in type 2 diabetes, especially among young and obese people. An estimated 7% of the US population has diabetes, and because of the increased longevity of this population, dia - betes-associated complications are expected to rise in prevalence.*

Foot ulcerations, infections, Charcot neuroarthropathy, and peripheral arterial disease frequently result in gan - grene and lower limb amputation. Consequently, foot disorders are leading causes of hospitalization for persons with diabetes and account for billion-dollar expenditures annually in the US. Although not all foot complications can be prevented, dramatic reductions in frequency have been achieved by taking a multidisciplinary approach to patient management. Using this concept, the authors present a clinical practice guideline for diabetic foot disor - ders based on currently available evidence, committee consensus, and current clinical practice. The pathophysiol - ogy and treatment of diabetic foot ulcers, infections, and the diabetic Charcot foot are reviewed. While these guide - lines cannot and should not dictate the care of all affected patients, they provide evidence-based guidance for gen - eral patterns of practice. If these concepts are embraced and incorporated into patient management protocols, a major reduction in diabetic limb amputations is certainly an attainable goal.

This clinical practice guideline (CPG) is based on the consensus of current clinical practice and review of the clin - ical literature. This guideline was developed by the Clinical Practice Guideline Diabetes Panel of the American College of Foot and Ankle Surgeons.

INTRODUCTION

The prevalence of diabetes mellitus is growing at epidem - ic proportions in the United States and worldwide (1). Most alarming is the steady increase in type 2 diabetes, especial - ly among young and obese persons. An estimated 7% of Americans are afflicted with diabetes, and with the longevi - ty of this population increasing, the prevalence of diabetes- related complications will continue to rise.

Foot disorders are a major source of morbidity and a lead - ing cause of hospitalization for persons with diabetes. Ulceration, infection, gangrene, and amputation are signifi - cant complications of the disease, estimated to cost billions of dollars each year. Charcot foot, which of itself can lead to limb-threatening disorders, is another serious complica - tion of long-standing diabetes. In addition to improving the management of ulcers—the leading precursor to lower extremity amputation in diabetic patients (2)—clinicians

must determine how to more effectively *prevent* ulceration. Although not all diabetic foot disorders can be prevented, it is possible to effect dramatic reductions in their incidence and morbidity through appropriate evidence-based preven - tion and management protocols.

Taking a multidisciplinary approach to diabetic foot dis - orders, many centers from around the world have noted consistent improvement in limb salvage rates. With this premise as our central theme, the authors present this clini - cal practice guideline based on currently available evidence. Three major pedal complications of diabetes are reviewed: diabetic foot ulcers, diabetic foot infections, and the diabet - ic Charcot foot. These guidelines are intended to provide evidence-based guidance for general patterns of practice and do not necessarily dictate the care of a particular patient.

EPIDEMIOLOGY OF DIABETIC FOOT DISORDERS

Diabetes is one of the foremost causes of death in many countries and a leading cause of blindness, renal failure, and nontraumatic amputation. Global prevalence of diabetes in 2003 was estimated to be 194 million (3). By 2030, this figure is predicted to rise to 366 million due to longer life expectancy and changing dietary habits (4).

The estimated incidence of diabetes in the US exceeds 1.5 million new cases annually, with an overall prevalence of 20.8 million people or 7% of the nation's population (5). An estimated 14.6 million persons are currently diagnosed with the disease, while an additional 6.2 million people who have diabetes remain undiagnosed; this represents a sixfold increase in the number of persons with diabetes over the past four decades (6). A higher incidence of diabetes occurs among non-Hispanic blacks, Hispanic/Latino Americans, and Native Americans compared with non-Hispanic whites (7). Diagnosed diabetes is most prevalent in middle-aged and elderly populations, with the highest rates occurring in persons aged 65 years and older (8-10). As the sixth leading cause of death in the US, diabetes contributes to more than 224,000 deaths per year (5).

Table 1   Classification of Diabetes Mellitus *

Type 1 diabetes - absolute insulin deficiency
Type 2 diabetes - insulin resistant +/- insulin deficiency
Other types - genetic defects of ß-cell function or insulin action
          endocrinopathies
          drug or chemical
          infections
Gestational diabetes

* adapted from: *Therapy for Diabetes Mellitus and Related Disorders*, 3rd edition, American Diabetes Association, 1998.

Four categories of diabetes are recognized (Table 1). Type 1, formerly insulin-dependent diabetes mellitus (IDDM), is an autoimmune disease affecting the pancreas. Individuals with type 1 diabetes are prone to ketosis and unable to produce endogenous insulin. Type 2, formerly non-insulin dependent diabetes mellitus (NIDDM), accounts for 90% to 95% of cases diagnosed. Type 2 diabetes is characterized by hyperglycemia in the presence of hyperinsulinemia due to peripheral insulin resistance. Gestational as well as genetic defects and endocrinopathies are recognized as other types of diabetes (11). Diabetes is associated with numerous complications related to microvascular, macrovascular, and metabolic etiologies. These include cerebrovascular, cardiovascular, and peripheral arterial disease; retinopathy; neuropathy; and nephropathy. Currently, cardiovascular complications are the most common cause of premature death among patients with diabetes (9, 12). Rates of heart disease and stroke are 2 to 4 times higher among diabetic adults compared with nondiabetic adults, accounting for about 65% of deaths in people with diabetes (5). Estimated total (direct and indirect) annual expenditures for diabetes management in 2002 was $132 billion, representing 1 of every 10 health care dollars spent in the US (13).

One of the most common complications of diabetes in the lower extremity is the diabetic foot ulcer. An estimated 15% of patients with diabetes will develop a lower extremity ulcer during the course of their disease (14-17). Several population-based studies indicate a 0.5% to 3% annual cumulative incidence of diabetic foot ulcers (18-21). According to one large British study of neuropathic patients, the 1-year incidence of initial foot ulcer was 7% (22). The prevalence of foot ulcers reported for a variety of populations ranges from 2% to 10% (16, 18, 22, 23). Neuropathy, deformity, high plantar pressure, poor glucose control, duration of diabetes, and male gender are all contributory factors for foot ulceration (see the following section: "Risk for Ulceration") (24-27). National hospital discharge data indicate that the average hospital length of stay (LOS) for diabetic patients with ulcer diagnoses was 59% longer than for diabetic patients without ulcers (16). While 7% to 20% of patients with foot ulcers will subsequently require an amputation, foot ulceration is the precursor to approximately 85% of lower extremity of amputations in persons with diabetes (28-31).

Diabetes continues to be the most common underlying cause of nontraumatic lower extremity amputations (LEAs) in the US and Europe (1, 32). More than 60% of LEAs in the US occur in people with diabetes, averaging 82,000 per year (5, 10). While the number of diabetes-related hospital discharges has progressively increased from 33,000 in 1980 to 84,000 in 1997, this number seems to have leveled off during the present decade. In 2002, there were 82,000 diabetes-related LEA discharges, accounting for 911,000 days of hospital stay with an average LOS of 11.2 days (10). The age-adjusted rate of amputation for that year was 5.2 per 1,000 persons with diabetes, a notable decrease from the highest rate of 8.1 per 1,000 in 1996.

In terms of level of diabetes-related lower limb amputations, toe amputations comprise the majority of procedures. The age-adjusted LEA rate in 2002 among persons with diabetes was highest for toe LEA (2.6 per 1,000 persons), followed by below-knee LEA (1.6 per 1,000 persons). For foot LEA and above-knee LEA, the age-adjusted rate was 0.8 per 1,000 persons. These trends in amputation level have essentially remained the same since 1993 (10). Generally, the LEA rate is 15 to 40 times higher in the diabetic versus

nondiabetic populations, and the rate is at least 50% higher in men versus women (8, 10, 12, 33). In 2002, the age-adjusted LEA rate among men was 7.0 per 1,000 persons with diabetes compared with to the rate among women reported at 3.3 per 1000 persons with diabetes (10).

Several ethnic differences occur in the frequency of diabetes-related amputations. Mexican (Hispanic) Americans, Native Americans, and African Americans each have at least a 1.5- to 2-fold greater risk for diabetes-related amputation than age-matched diabetic Caucasians (8, 10, 16, 17, 34, 35). When LEA risk is compared between diabetic and nondiabetic populations worldwide, it is apparent that both diabetes and ethnicity have profound implications on rates of lower limb amputation (1, 17).

Survival rates after amputation are generally lower for diabetic versus nondiabetic patients (16, 17, 29). The 3- and 5-year survival rates are about 50% and 40%, respectively, with cardiovascular disease being the major cause of death (8). Although mortality rates following major amputation are high among both diabetic and nondiabetic patients, a recent study reported no significant difference between these two populations. The mean survival was approximately 6.5 years, with a 68% mortality after 9 years regardless of diabetes status (36). An earlier study from Sweden reported a 5-year mortality rate of 68% after lower limb amputation, with survival rates lower among patients who underwent higher levels of amputation (29). Similar trends were found in a review of amputations within the Veterans Affairs system, but worse survival outcomes were observed for older patients, those with renal disease, and those with peripheral arterial disease (37). Researchers have reported a 50% incidence of serious contralateral foot lesion (ie, ulcer) following an LEA, and a 50% incidence of contralateral amputation within 2 to 5 years of an LEA (16, 29).

Total (direct and indirect) annual health care costs for persons with diabetes were estimated to be $132 billion in 2002. Direct medical expenditures, including hospitalization, medical care, and supplies, accounted for $91.8 billion (13). The estimated cost for foot ulcer care in the US ranges from $4,595 per ulcer episode to nearly $28,000 for the 2 years after diagnosis (19, 38). One report estimates 800,000 prevalent ulcer cases in the US, with costs averaging $5,457 per year per patient or total national annual costs of $5 billion (39). A study of Medicare claims data found that expenditures for patients with lower extremity ulcers averaged 3 times higher than expenditures for Medicare beneficiaries in general. With 24% of their total costs allocated to ulcer-related expenses, lower extremity ulcer patients cost the Medicare system $1.5 billion in 1995 (40). According to a large prospective study of diabetic patients with foot ulcers,

about 7% will subsequently require a lower extremity amputation (31). While hospital LOSs for diabetes-related LEA have progressively decreased in the US, the overall direct costs remain high (10, 16). Direct and indirect costs of LEA—which range from $20,000 to $40,000 per event—vary by year, payer, level of amputation, LOS, and attendant comorbidities (16). If the lower figure is applied to the 82,000 amputations performed in 2002, estimated total costs of LEA might exceed $1.6 billion annually. When outpatient costs for ulcer care preceding these amputations is added, the estimated total costs in the US for diabetic foot disease can easily approach or exceed $6 billion annually.

Risk for Ulceration

Foot ulceration is the most common single precursor to lower extremity amputations among persons with diabetes (28-30). Treatment of infected foot wounds comprises up to one quarter of all diabetic hospital admissions in the US and Britain, making this the most common reason for diabetes-related hospitalization in these countries (41-43). The multifactorial nature of diabetic foot ulceration has been elucidated by numerous observational studies (16, 22, 24, 26, 27, 44-48). Risk factors identified include peripheral neuropathy, vascular disease, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, a history of ulceration or amputation, and impaired visual acuity (25, 49, 50). These and other putative causative factors are shown in Figure 1.

Peripheral sensory neuropathy in the face of unperceived trauma is the primary factor leading to diabetic foot ulcerations (24, 27, 46, 49). Approximately 45% to 60% of all diabetic ulcerations are purely neuropathic, while up to 45% have neuropathic and ischemic components (24, 51). According to an important prospective multicenter study, sensory neuropathy was the most frequent component in the causal sequence to ulceration in diabetic patients (24).

Other forms of neuropathy may also play a role in foot ulceration. Motor neuropathy resulting in anterior crural muscle atrophy or intrinsic muscle wasting can lead to foot deformities such as foot drop, equinus, hammertoe, and prominent plantar metatarsal heads (25, 26, 52-54). Ankle equinus with restricted dorsiflexory range of motion is fairly common in patients with diabetic neuropathy and can be a consequence of anterior crural muscle atrophy (55-60). The decreased ankle motion, which confers higher-than-normal plantar pressures at the forefoot, has been implicated as a contributory cause of ulceration as well as recurrence or recalcitrance of existing ulcers (57, 58, 60, 61).

Autonomic neuropathy often results in dry skin with cracking and fissuring, creating a portal of entry for bacte-

Risk Factors for Ulceration

General or Systemic Contributions

- Uncontrolled hyperglycemia
- Duration of diabetes
- Peripheral vascular disease
- Blindness or visual loss
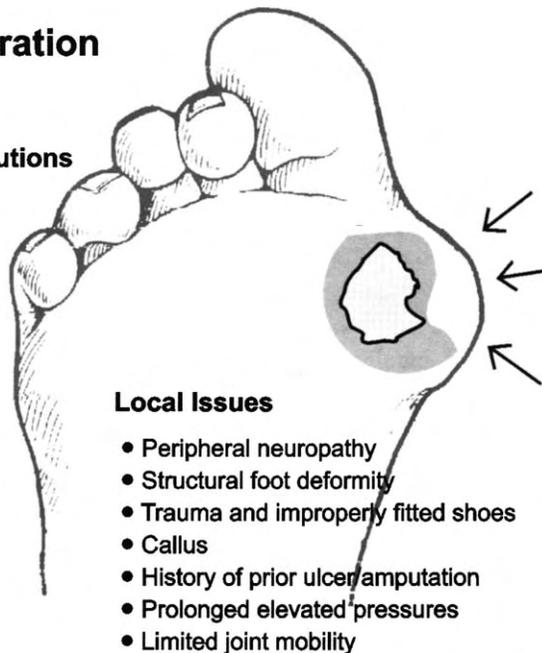- Chronic renal disease
- Older age

Local Issues

- Peripheral neuropathy
- Structural foot deformity
- Trauma and improperly fitted shoes
- Callus
- History of prior ulcer/amputation
- Prolonged elevated pressures
- Limited joint mobility

Figure 1 The risk factors for ulceration may be distinguished by general or systemic considerations versus those localized to the foot and its pathology.

ria (42, 63). Autosympathectomy with attendant sympathetic failure, arteriovenous shunting, and microvascular thermoregulatory dysfunction impairs normal tissue perfusion and microvascular responses to injury. These alterations can subsequently be implicated in the pathogenesis of ulceration (63-67).

Foot deformities resulting from neuropathy, abnormal biomechanics, congenital disorders, or prior surgical intervention may result in high focal foot pressures and increased risk of ulceration (24, 48, 50, 57, 68-71). The effects of motor neuropathy occur relatively early and lead to foot muscle atrophy with consequent development of hammertoes, fat pad displacement, and associated increases in plantar forefoot pressures (53, 72-75). Although most deformities cause high plantar pressures and plantar foot ulcerations, medial and dorsal ulcerations may develop as a result of footwear irritation. Common deformities might include prior partial foot amputations, prominent metatarsal heads, hammertoes, Charcot arthropathy, or hallux valgus (69, 76-79). A large prospective population-based study found that elevated plantar foot pressures are significantly associated with neuropathic ulceration and amputation (80). The study also revealed a trend for increased foot pressures as the number of pedal deformities increased.

Trauma to the foot in the presence of sensory neuropathy is an important component cause of ulceration (24). While trauma may include puncture wounds and blunt injury, a common injury leading to ulceration is moderate repetitive stress associated with walking or day-to-day activity (69, 76, 81). This is often manifested by callus formation under the metatarsal heads (48, 82, 83). A recent report suggests that even with moderate activity, ulceration may be precipitated by a higher degree of variability in activity or periodic "bursts" of activity (84). Shoe-related trauma has also been identified as a frequent precursor to foot ulceration (28, 51, 54, 85, 86).

Peripheral arterial disease (PAD) rarely leads to foot ulcerations directly. However, once ulceration develops, arterial insufficiency will result in prolonged healing, imparting an elevated risk of amputation (28, 87, 88). Additionally, attempts to resolve any infection will be impaired due to lack of oxygenation and difficulty in delivering antibiotics to the infection site. Therefore, early recognition and aggressive treatment of lower extremity ischemia are vital to lower limb salvage (30, 52, 89-91).

Limited joint mobility has also been described as a potential risk factor for ulceration (92-94). Glycosylation of collagen as a result of longstanding diabetes may lead to stiffening of capsular structures and ligaments (cheiroarthropathy) (95). The subsequent reduction in ankle, subtalar, and first metatarsophalangeal (MTP) joint mobility has been shown to result in high focal plantar pressures with increased ulceration risk in patients with neuropathy (92, 96, 97). Several reports also attribute glycosylation and altered arrangement of Achilles tendon collagen to the propensity for diabetic patients to develop ankle equinus (98, 99).

Other factors frequently associated with heightened ulceration risk include nephropathy, poor diabetes control, duration of diabetes, visual loss, and advanced age (48, 69,
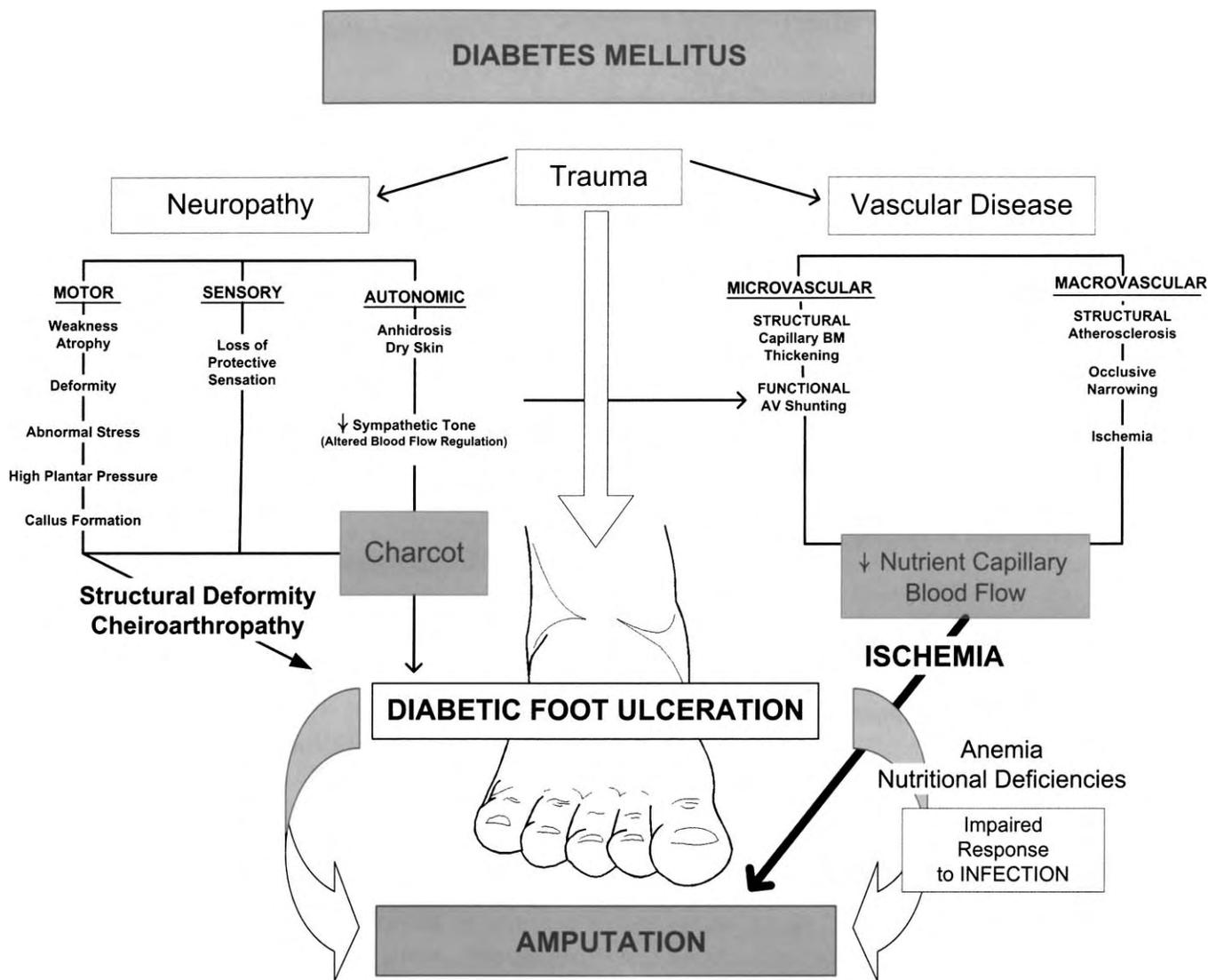
Figure 2 Diabetes mellitus is responsible for a variety of foot pathologies contributing to the complications of ulceration and amputation. Multiple pathologies may be implicated, from vascular disease to neuropathy to mechanical trauma.

93, 100). Soft tissue changes (other than cheiroarthropathy) in the feet of diabetic patients might also contribute to ulceration through the pathway of altered pressure distributions through the sole of the foot. Such alterations include a reported increased thickness of the plantar fascia with associated limitation of hallux dorsiflexion, decreased thickness of plantar soft tissue, accentuated hardness/stiffness of the skin, and a propensity to develop calluses (82, 96, 101-105). While these changes are presumably caused by glycosylation of collagen, their sum effect is to enhance plantar pressures in gait. In the presence of neuropathy, the accentuated plantar pressures can be implicated in the development of ulceration (70, 80, 92, 106).

Mechanisms of Injury

The multifactorial etiology of diabetic foot ulcers is evidenced by the numerous pathophysiologic pathways that can potentially lead to this disorder (24, 43, 54, 62, 90, 107). Among these are two common mechanisms by which foot deformity and neuropathy may induce skin breakdown in persons with diabetes (69, 108, 109).

The first mechanism of injury refers to prolonged low pressure over a bony prominence (ie, bunion or hammertoe deformity). This generally causes wounds over the medial, lateral, and dorsal aspects of the forefoot and is associated with tight or ill-fitting shoes. Shoe trauma, in concert with loss of protective sensation and concomitant foot deformity, is the leading event precipitating foot ulceration in persons with diabetes (24, 28, 57, 85).

Regions of high pedal pressure are frequently associated with foot deformity (68, 73, 76, 77, 106, 107). When an abnormal focus of pressure is coupled with lack of protective sensation, the result can be development of a callus, blister, and ulcer (110). The other common mechanism of ulceration involves prolonged repetitive moderate stress (108). This normally occurs on the sole of the foot and is related to prominent metatarsal heads, atrophied or anteriorly displaced fat pads, structural deformity of the lower extremity, and prolonged walking. Rigid deformities such as hallux valgus, hallux rigidus, hammertoe, Charcot arthropathy, and limited range of motion of the ankle (equinus), subtalar, and MTP joints have been linked to the development of diabetic foot ulcers (27, 57, 71, 80, 94, 96). Numerous studies support the significant association between high plantar pressures and foot ulceration (26, 70, 80, 92, 106, 111, 112). Other biomechanical perturbations, including partial foot amputations, have the same adverse effects (57, 68, 80, 113).

Figure 2 summarizes the various pathways and contributing factors leading to diabetic foot complications.

Risk for Infection

Infections are common in diabetic patients and are often more severe than infections found in nondiabetic patients. Persons with diabetes have an increased risk for developing an infection of any kind and a several-fold risk for developing osteomyelitis (114). With an incidence of 36.5 per 1,000 persons per year, foot infections are among the most common lower extremity complications in the diabetic population (excluding neuropathy), second only to foot ulcers in frequency (115).

It is well documented that diabetic foot infections are frequently polymicrobial in nature (30, 116-121). Hyperglycemia, impaired immunologic responses, neuropathy, and peripheral arterial disease are the major predisposing factors leading to limb-threatening diabetic foot infections (122-124). Uncontrolled diabetes results in impaired ability of host leukocytes to fight bacterial pathogens, and ischemia also affects the ability to fight infections because delivery of antibiotics to the site of infection is impaired. Consequently, infection can develop, spread rapidly, and produce significant and irreversible tissue damage (125). Even in the presence of adequate arterial perfusion, underlying peripheral sensory neuropathy will often allow the progression of infection through continued walking or delay in recognition (126, 127).

Risk for Charcot Joint Disease

It has been estimated that less than 1% of persons with diabetes will develop Charcot joint disease (128-130). Data on the true incidence of neuroarthropathy in diabetes are limited by the paucity of prospective or population-based studies in the literature. One large population-based prospective study found an incidence of about 8.5 per 1,000 persons with diabetes per year (115); this equates to 0.85% per year and is probably the most reliable figure currently available. Much of the data clinicians rely upon have been extracted from retrospective studies of small, single-center cohorts. The incidence of reported Charcot cases is likely to be underestimated because many cases go undetected, especially in the early stages (131-134).

Primary risk factors for this potentially limb-threatening deformity are the presence of dense peripheral sensory neuropathy, normal circulation, and history of preceding trauma (often minor in nature) (50, 135, 136). Trauma is not limited to injuries such as sprains or contusions. Foot deformities, prior amputations, joint infections, or surgical trauma may result in sufficient stress that can lead to Charcot joint disease (137-140).

Risk for Amputation

The reported risk of lower extremity amputations in diabetic patients ranges from 2% to 16%, depending on study design and the populations studied (19, 21, 32, 115, 141-144). LEA rates can be 15 to 40 times higher among the diabetic versus nondiabetic populations (8, 16, 34, 35). Although one author suggests that amputation may be a marker not only for disease severity but also for disease management, it is clear that amputation remains a global problem for all persons with diabetes (32, 143). The same risk factors that predispose to ulceration can also generally be considered contributing causes of amputation, albeit with several modifications (Fig 3).

While peripheral arterial disease may not always be an independent risk factor for ulceration when controlling for neuropathy, it can be a significant risk factor for amputation (24, 28, 88, 142, 145, 146). PAD affecting the feet and legs is present in 8% of adult diabetic patients at diagnosis and in 45 % after 20 years (147, 148). The incidence of amputation is 4 to 7 times greater for diabetic men and women than for their nondiabetic counterparts. Impairment of arterial perfusion may be an isolated cause for amputation and a predisposing factor for gangrene. Early diagnosis, control of risk factors, and medical management as well as timely revascularization may aid in avoiding limb loss (30, 52, 77, 88, 149).

Figure 3 The risk factors for amputation are multifactorial and similar to those for ulceration.
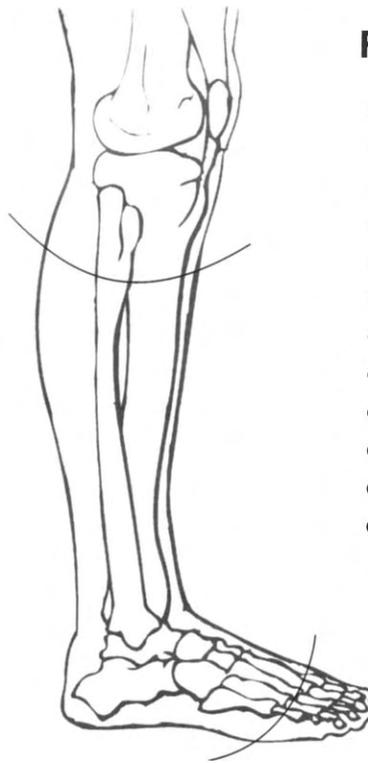
Risk Factors for Amputation

- Neuropathy LOPS
- Peripheral arterial disease (PAD)
- Infection
- History of prior foot ulcer or amputation
- Structural foot deformity
- Trauma
- Charcot foot
- Impaired vision
- Poor glycemic control
- Older age
- Male Sex
- Ethnicity (greatest rates in blacks & Hispanics)

While infection is not often implicated in the pathway leading to ulceration, it is a significant risk factor in the causal pathway to amputation (24, 28). Lack of wound healing, systemic sepsis, or unresolved infection can lead to extensive tissue necrosis and gangrene, requiring amputation to prevent more proximal limb loss. This includes soft tissue infection with severe tissue destruction, deep space abscess, or osteomyelitis. Adequate debridement may require amputation at some level as a means of removing all infected material (77, 123, 150, 151).
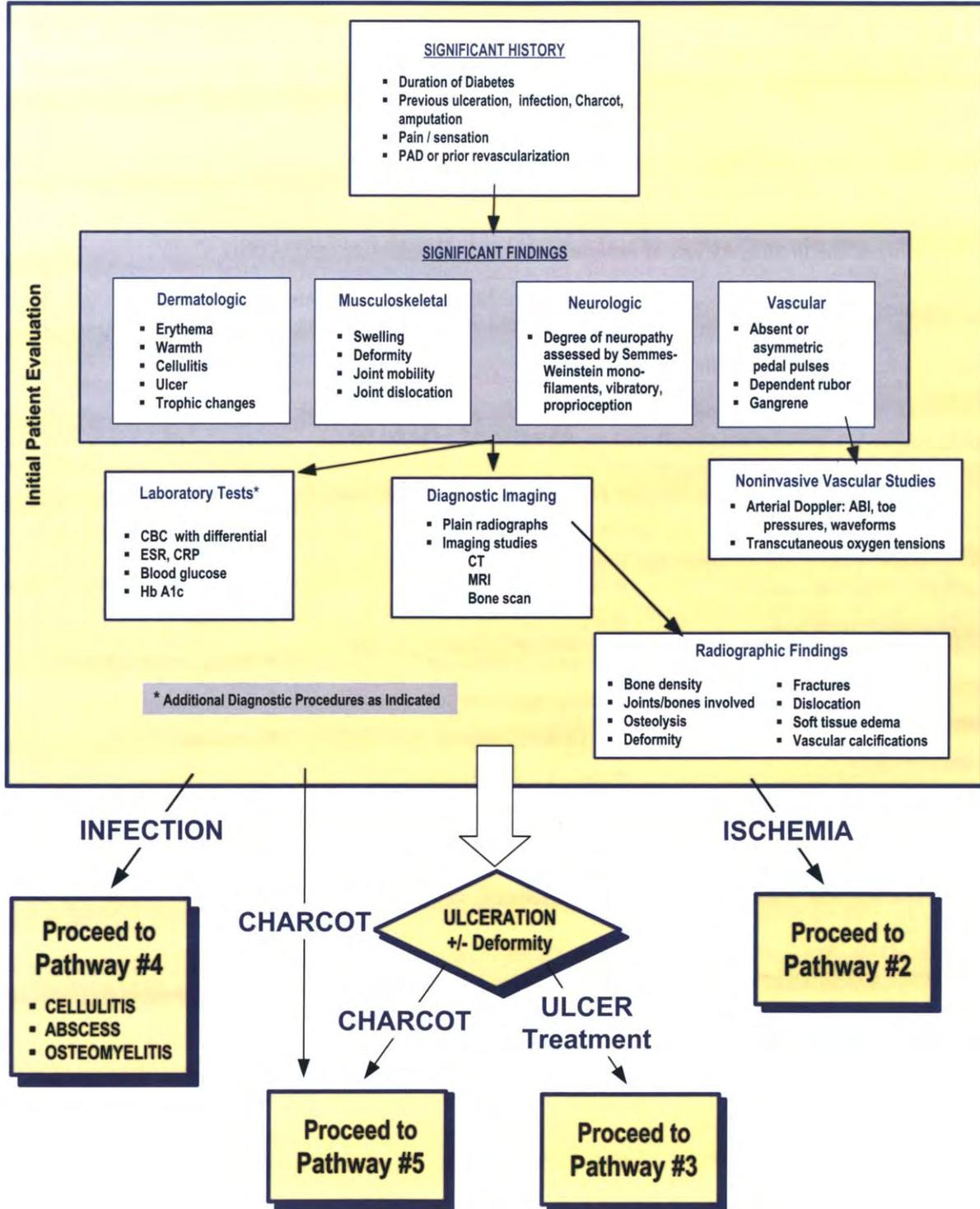
Another frequently described risk factor for amputation is chronic hyperglycemia. Results of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) support the long-held theory that chronic poor control of diabetes is associated with a host of systemic complications (152, 153). The link between degree of glucose control and incidence or progression of numerous diabetic complications has been well established by these and other studies (154, 155). Such complications include peripheral neuropathy, microangiopathy, microcirculatory disturbances, impaired leukocyte phagocytosis, and glycosylation of tissue proteins. Each has adverse effects on the diabetic foot: They can contribute to the etiology of foot ulceration, delay normal wound healing, and subsequently lead to amputation (25, 30, 48, 50, 72). Several studies have reported a significant correlation between elevated glucose and LEA (21, 141,

156-161). Amputation has also been associated with other diabetes-related comorbidities such as nephropathy, retinopathy, and cardiovascular disease (21, 48, 144). Aggressive glucose control, management of associated comorbidities, and appropriate lower extremity care coordinated in a team environment may indeed lower overall risk for amputation (30, 90, 162-166).

The best predictor of amputation is a history of previous amputation. A past history of a lower extremity ulceration or amputation increases the risk for further ulceration, infection, and subsequent amputation (29, 142, 157, 167). It may also be inferred that patients with previous ulceration possess all the risk factors for developing another ulceration, having demonstrated that they already have the component elements in the causal pathway (24, 27, 28, 57). Up to 34% of patients develop another ulcer within 1 year after healing an index wound, and the 5-year rate of developing a new ulcer is 70% (164, 168). The recurrence rate is higher for patients with a previous amputation because of abnormal distribution of plantar pressures and altered osseous architecture. The cumulative risks of neuropathy, deformity, high plantar pressure, poor glucose control, and male gender are all additive factors for pedal ulceration in these diabetic patients (26, 46, 50, 57, 111). Re-amputation can be attributed to disease progression, nonhealing wounds, and additional risk factors for limb loss that develop as a result of the first amputation. Tragically, the 5-year survival rate

PATHWAY #1

DIABETIC FOOT DISORDERS

Initial Patient Evaluation

SIGNIFICANT HISTORY

- Duration of Diabetes
- Previous ulceration, infection, Charcot, amputation
- Pain / sensation
- PAD or prior revascularization

SIGNIFICANT FINDINGS

Dermatologic
- Erythema
- Warmth
- Cellulitis
- Ulcer
- Trophic changes

Musculoskeletal
- Swelling
- Deformity
- Joint mobility
- Joint dislocation

Neurologic
- Degree of neuropathy assessed by Semmes-Weinstein monofilaments, vibratory, proprioception

Vascular
- Absent or asymmetric pedal pulses
- Dependent rubor
- Gangrene

Laboratory Tests*
- CBC with differential
- ESR, CRP
- Blood glucose
- Hb A1c

Diagnostic Imaging
- Plain radiographs
- Imaging studies
  CT
  MRI
  Bone scan

Noninvasive Vascular Studies
- Arterial Doppler: ABI, toe pressures, waveforms
- Transcutaneous oxygen tensions

* Additional Diagnostic Procedures as Indicated

Radiographic Findings
- Bone density
- Joints/bones involved
- Osteolysis
- Deformity
- Fractures
- Dislocation
- Soft tissue edema
- Vascular calcifications

INFECTION

Proceed to Pathway #4
- CELLULITIS
- ABSCESS
- OSTEOMYELITIS

CHARCOT

ULCERATION +/- Deformity

CHARCOT

Proceed to Pathway #5

ULCER Treatment

Proceed to Pathway #3

ISCHEMIA

Proceed to Pathway #2

after a diabetes-related LEA has been reported to be as low as 28% to 31% (169, 170). Persons with renal failure or more proximal levels of amputation have a poor prognosis and higher mortality rate. Those who undergo a diabetes-related amputation have a 40% to 50 % chance of undergoing a contralateral amputation within 2 years (36, 171, 172).

ASSESSMENT OF THE DIABETIC FOOT (Pathway 1)

The pedal manifestations of diabetes are well documented and potentially limb-threatening when left untreated. Recognition of risk factors and treatment of diabetic foot disorders require the skill of a specialized practitioner to diagnose, manage, treat, and counsel the patient. Integration of knowledge and experience through a multidisciplinary team approach promotes more effective treatment, thereby improving outcomes and limiting the risk of lower extremity amputation (30, 173).

The evaluation of the diabetic foot involves careful assimilation of the patient's history and physical findings with the results of necessary diagnostic procedures (Pathway 1). Screening tools may be valuable in evaluating the patient and determining risk level (Appendix 1). Early detection of foot pathology, especially in high-risk patients, can lead to earlier intervention and thereby reduce the potential for hospitalization and amputation (100). This is also facilitated by an understanding of the underlying pathophysiology of diabetic foot disorders and associated risk factors. Identification of abnormal historical and/or physical findings can therefore improve the prognosis for a favorable outcome through appropriate—and early—referral (91, 174).

History

A thorough medical and foot history must be obtained from the patient. The history should address several specific diabetic foot issues (Table 2).

Physical Examination

All patients with diabetes require a pedal inspection whenever they present to any health care practitioner, and

Table 2

Medical History

Global History	Foot Specific History	
	General	**Wound / Ulcer History**
● Diabetes - duration		● Location
● Glycemic management/control	● Daily activities, including work	● Duration
● Cardiovascular, renal and opthalmic evaluations	● Footwear	● Inciting event or trauma
● Other comorbidities	● Chemical exposures	● Recurrence
● Treating physicians	● Callus formation	● Infection
● Nutritional status	● Foot deformites	● Hospitalization
● Social habits: alcohol, tobacco, drugs	● Previous foot infections, surgery	● Wound care
● Current medications	● Neuropathic symptoms	● Off-loading techniques
● Allergies	● Claudication or rest pain	● Wound response
● Previous hospitalizations/surgery		● Patient compliance
		● Interference with wound care (Family or social problems for patient)
		● Previous foot trauma or surgery
		● Presence of edema - unilateral vs bilateral
		● Charcot foot - previous or active
		● Charcot treatment

they should receive a thorough lower extremity examination at least once annually (175). Patients with complaints relating to the diabetic foot require more frequent detailed evaluations. The examination should be performed systematically so that important aspects are not overlooked (62). It begins with a gross evaluation of the patient and extremities. Any obvious problem can then receive closer scrutiny.

Key components of the foot examination are presented in Table 3. Although not specifically mentioned in this section, it is assumed that a general medical assessment (including vital sign measurements) will be obtained.

Diagnostic Procedures

Diagnostic procedures may be indicated in the assessment and care of the diabetic foot. Consideration should be given to the following tests in concert with those suggested by members of the consulting team. It should be noted that many of the following tests lack the ability to impart a definitive diagnosis, necessitating clinical correlation.

Laboratory Tests

Clinical laboratory tests that may be needed in appropriate clinical situations include fasting or random blood glucose, glycohemoglobin (HbA1c), complete blood count (CBC) with or without differential, erythrocyte sedimentation rate (ESR), serum chemistries, C-reactive protein, alkaline phosphatase, wound and blood cultures, and urinalysis. Caution must be exercised in the interpretation of laboratory tests in these patients, because several reports have documented the absence of leukocytosis in the presence of severe foot infections (117, 122, 151, 176-178). A common sign of persistent infection is recalcitrant hyperglycemia despite usual antihyperglycemic regimens (150).

Imaging Studies

The diabetic foot may be predisposed to both common and unusual infectious or noninfectious processes, partially because of the complex nature of diabetes and its associated vascular and neuropathic complications. As a result, imaging presentations will vary due to lack of specificity in complex clinical circumstances (179-181). Such variability creates a challenge in the interpretation of imaging studies. Therefore, imaging studies should only be ordered to establish or confirm a suspected diagnosis and/or direct patient management. Distinguishing osteomyelitis from aseptic neuropathic arthropathy is not easy, and all imaging studies (Fig 4) must be interpreted in conjunction with the clinical findings (123, 151).

Plain radiographs should be the initial imaging study in diabetic patients with signs and symptoms of a diabetic foot disorder (180, 182). Radiographs can detect osteomyelitis, osteolysis, fractures, dislocations seen in neuropathic arthropathy, medial arterial calcification, soft tissue gas, and foreign bodies as well as structural foot deformities, presence of arthritis, and biomechanical alterations (183). Acute osteomyelitis might not demonstrate osseous changes for up to 14 days. Serial radiographs should be obtained in the face of an initial negative radiographic image and a high clinical suspicion of osseous disease (117, 123).

Technetium-99 methylene diphosphonate (Tc-99 MDP) bone scans are often used in diabetic foot infection to determine the presence of osteomyelitis. Although highly sensitive, this modality lacks specificity in the neuropathic foot (184, 185). Osteomyelitis, fractures, arthritis, and neuropathic arthropathy will all demonstrate increased radiotracer uptake. However, a negative bone scan is strong evidence against the presence of infection. To improve the specificity of nuclear imaging, white blood cells can be labeled with Tc-99 hexamethylpropyleneamineoxime (Tc-99 HMPAO), indium-111 oxime, or gallium-67 citrate (179, 186-189).

Indium-111 selectively labels polymorphonuclear leukocytes and is more specific for acute infections than Tc-99 MDP scanning. Chronic infections and inflammation are not well imaged with indium-111, because chronic inflammatory cells (ie, lymphocytes) predominate and are not well labeled with indium. Combining Tc-99 MDP and indium-111 increases the specificity of diagnosing osteomyelitis (190). This combined technique is useful, because the Tc-99 MDP scan localizes the anatomic site of inflammation and the indium-111 labels the infected bone (180, 191). The indium-111 scan is not typically positive in aseptic neuropathic arthropathy, although false-positive indium scans can occur (192-194). A 100% sensitivity and 89% specificity have been reported with the combined technique in evaluating diabetic infections (190, 191, 195).

In Tc-99 HMPAO scanning, white blood cells are labeled in a similar manner as in indium scanning. However, with Tc-99 MHPAO scans, imaging occurs 4 hours following administration versus 24 hours postadministration with indium scanning. Tc-99 HMPAO uses a smaller radiation dose, is less expensive, and offers improved resolution compared with indium scanning. The sensitivity and specificity of both techniques are comparable (186, 196). Tc-99 HMPAO scans cannot be combined with Tc-99 MDP scans because of similar labeling characteristics.

Tc-99 sulfur colloid is useful in distinguishing osteomyelitis from neuropathic arthropathy (183). This tracer is picked up by the bone marrow and any hemapoetically-active marrow will be positive. Infected bone replaces normal bone marrow, so it shows up as a relative

Table 3   **Lower Extremity Diabetic Foot Exam**

Vascular Examination

- Palpation of pulses
  Common femoral, popliteal
  Dorsalis pedis, posterior tibial

- Handheld Doppler examination

- Skin / limb color changes
  Cyanosis, erythema
  Elevation pallor, dependent rubor

- Presence of edema

- Temperature gradient
  (ipsilateral and contralateral extremity)

- Dermal thermometry

- Integementary changes
  Skin atrophy - thin, smooth, parchment-like skin
  Abnormal wrinkling
  Absence of hair growth
  Onychodystrophy

- Previous hospitalizations/surgery

Neurologic Examination

- Vibration perception
  Tuning fork 128 cps
  Measurement of vibration perception threshold
  (biothesiometer)

- Light pressure:
  Semmes-Weinstein 10 gram monofilament

- Light touch: cotton wool

- Two point discrimination

- Pain: pinprick (sterile needle)

- Temperature perception: hot and cold

- Deep tendon reflexes: patella, Achilles

- Clonus testing

- Babinski test

- Romberg test

Footwear Examination

- Type of shoe (athletic, oxford, comfort, etc.)
- Fit
- Depth of toe box
- Shoewear, patterns of wear
- Lining wear
- Foreign bodies
- Insoles, orthoses

Dermatologic Examination

- Skin appearance
  - Color, texture, turgor, quality
  - Dry skin

- Calluses
  - Discoloration / subcallus hemorrhage

- Fissures (especially posterior heels)

- Nail appearance
  - Onychomycosis, dystrophic, gryphotic
  - Atrophy or hypertrophy
  - Paronychia

- Hair growth

- Ulceration, gangrene, infection
  Note location, size, depth, infection status, etc.

- Interdigital lesions

- Tinea pedis

- Markers of diabetes
  - Shin spots - diabetic dermopathy
  - Necrobiosis lipoidica diabeticorum
  - Bullosum diabeticorum
  - Granuloma annulare
  - Acanthosis nigricans

Musculoskeletal Examination

- Biomechanical abnormalities

- Structural deformities
  - Hammertoe, bunion, tailor's bunion
  - Hallux limitus/rigidus
  - Flat or high-arched feet
  - Charcot deformities
  - Postsurgical deformities (amputations)

- Prior amputation

- Limited joint mobility

- Tendo-Achilles contractures / equinus

- Gait evaluation

- Muscle group strength testing
  - passive and active, non-weightbearing and weightbearing
  - Foot drop
  - Atrophy - intrinsic muscle atrophy

- Plantar pressure assessment
  - Computerized devices
  - Harris ink mat, pressure sensitive foot mat

Figure 4 Diagnostic imaging plays an important role in the evaluation of diabetic foot infections. *(A)* This patient presented with a deep foul-smelling necrotic ulcer of the heel that had been present for more than 1 month. *(B)* In the past, a technetium bone scan typically would be performed, but the imaging is nonspecific and many false positive results interpretative as osteomyelitis were seen. *(C)* White blood cell tagged imaging with indium or technetium is a more reliable technique for detecting the presence of infection.

"cold spot." This technique is best combined with indium scanning, and osteomyelitis would appear as a "hot" indium scan and a "cold" sulfur colloid scan (183, 193).

Computed tomography (CT) scans may be indicated in the assessment of suspected bone and joint pathology not evident on plain radiographs (180, 197). CT offers high anatomic detail and resolution of bone with osseous fragmentation and joint subluxation (198). Subluxation of the transverse tarsal or tarsometatarsal joints can be seen prior to being visualized on radiographs.

Magnetic resonance imaging (MRI) is usually preferred over CT for the investigation of osteomyelitis, because of its enhanced resolution and ability to visualize the extent of any infectious process (183, 199). MRI is often used in evaluating soft tissue and bone pathology. This scan may be indicated to aid in the diagnosis of osteomyelitis, deep abscess, septic joint, and tendon rupture. It is a readily available modality that has a very high sensitivity for bone infection and can also be used for surgical planning (123, 200-203). Despite its high cost, MRI has gained wide acceptance in the management of diabetic foot infections. When neuropathic arthropathy is present, the T1 and T2 bone images are hypointense (ie, decreased signal) and the soft tissues show edema. Increased signal on T-2 bone images is seen in osteomyelitis; however, tumors and avascular necrosis can also be hyperintense on T-2 (204). MRI is an excellent modality for assessing the presence of a soft tissue abscess, especially if gadolinium administration is utilized (205, 206). Postcontrast fat suppression images should be obtained, if available (207).

Positive emission tomography (PET) scanning is a promising new technique for distinguishing osteomyelitis from neuropathic arthropathy, but it currently is not widely available (109, 208, 209). A recent meta-analysis comparing the diagnostic accuracy of PET scanning with bone and leukocyte scanning found that PET scans were the most accurate modality for diagnosing osteomyelitis, providing a sensitivity of 96% and specificity of 91% (190). When PET scanning was unavailable, an indium-labeled leukocyte scan was found to be an acceptable alternative, offering a sensitivity of 84% and specificity of 80% in the peripheral skeleton (190).

The use of ultrasound for detecting chronic osteomyelitis has been shown to be superior to plain radiographs, providing sensitivity comparable to Tc-99 MDP bone scanning (210). Although ultrasound is a widely available, cost-effective imaging modality, MRI is more accurate and is the imaging study of choice if radiographs are normal and clinical suspicion is high for bone or soft tissue infection (211).

Vascular Evaluation

The lower extremity must be assessed for vascular and neuropathic risk factors. Although positive findings in the neurologic examination rarely require further evaluation, positive findings of vascular insufficiency may require further consultation. The indications for vascular consultation include an ankle brachial index of less than 0.7, toe blood pressures less than 40 mmHg, or transcutaneous oxygen tension (TcPO$_2$) levels less than 30 mmHg, since these measures of arterial perfusion are associated with impaired wound healing (27, 47, 87, 90, 212, 213).
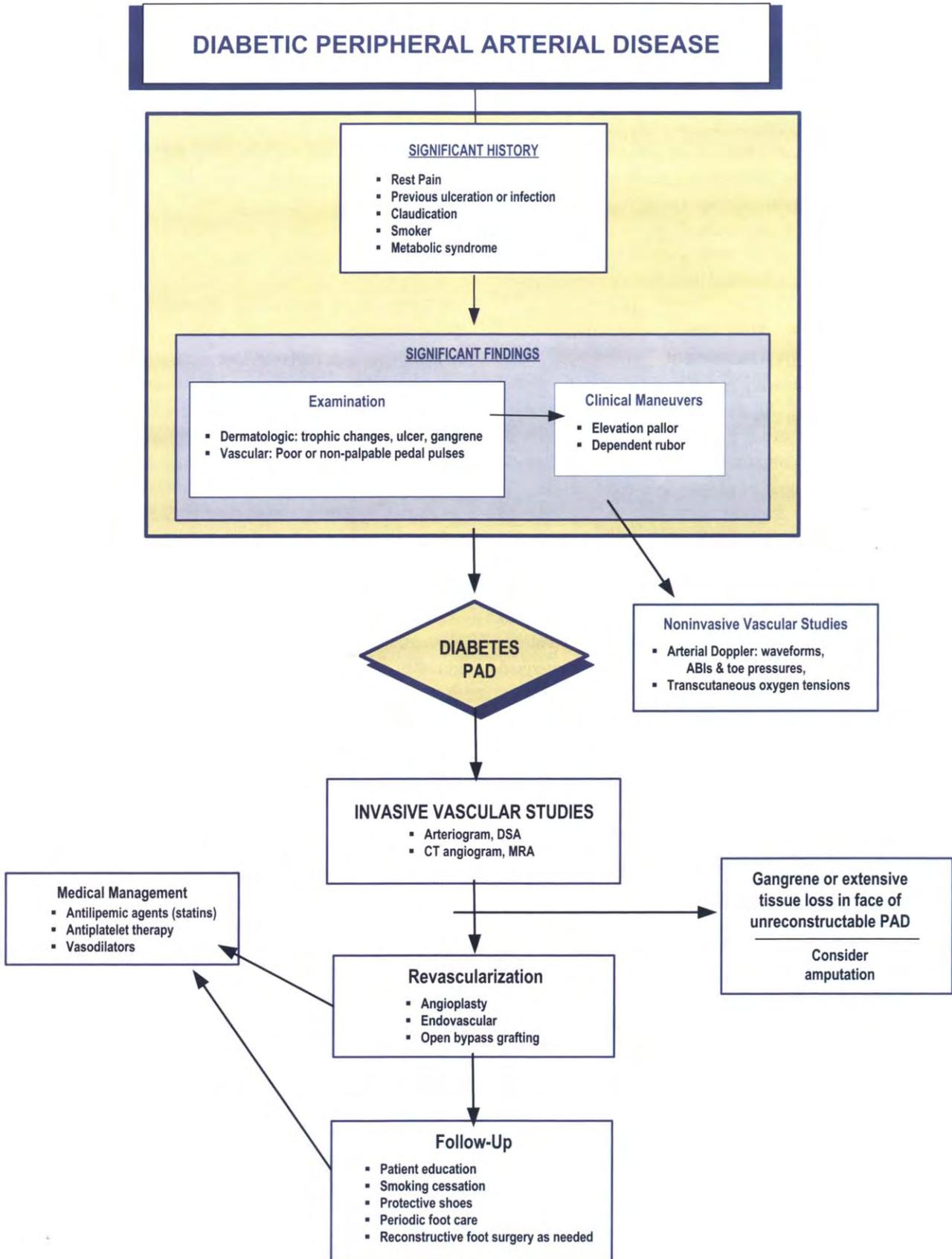
If the history and physical examination suggest ischemia (ie, absent pedal pulses) or if a nonhealing ulcer is present, further evaluation in the form of noninvasive testing is warranted (Pathway 2).

Noninvasive arterial studies should be performed to determine lower extremity perfusion. Such studies may include Doppler segmental arterial pressures and waveform analysis, ankle-brachial indices (ABI), toe blood pressures, and TcPO$_2$ (89, 214, 215). Ankle-brachial indices may be misleading, because ankle pressures can be falsely elevated due to medial arterial calcinosis and noncompressibility of affected arteries (52, 216, 217). A growing body evidence suggests that toe blood pressures in diabetic patients may have a role in predicting foot ulceration risk as well as predicting successful wound healing (213, 218, 219). TcPO$_2$ measurements have received similar support in the literature (47, 87, 212). Although not consistently predictive of wound healing outcomes, these physiologic measures of tissue oxygenation are highly predictive of wound healing failure at levels below 25 mmHg (87, 212, 220). Both tests can be performed distally on the foot regardless of arterial calcification in the major pedal arteries, and they are both favorable at pressures in the range of 40 mmHg (90, 212, 213).

Laser Doppler velocimetry and measurement of skin perfusion pressure (SPP) have primarily been used in research settings, but can accurately assess blood flow and oxygen tension in the superficial arterioles and capillaries of the skin (220-225). Several recent reports indicate that laser Doppler measurement of SPP can be highly predictive of critical limb ischemia and wound healing failure at levels less than 30 mmHg (223, 224).

Vascular consultation should be considered in the presence of abnormal noninvasive arterial studies or a nonhealing ulceration (30, 54, 173, 215, 226). Arteriography with clearly visualized distal runoff allows appropriate assessment for potential revascularization (227-229). Magnetic resonance angiography (230) or CT angiogram are alternatives for evaluation of distal arterial perfusion (229, 231).

PATHWAY #2

DIABETIC PERIPHERAL ARTERIAL DISEASE

SIGNIFICANT HISTORY

- Rest Pain
- Previous ulceration or infection
- Claudication
- Smoker
- Metabolic syndrome

SIGNIFICANT FINDINGS

Examination

- Dermatologic: trophic changes, ulcer, gangrene
- Vascular: Poor or non-palpable pedal pulses

Clinical Maneuvers

- Elevation pallor
- Dependent rubor

DIABETES PAD

Noninvasive Vascular Studies

- Arterial Doppler: waveforms, ABIs & toe pressures,
- Transcutaneous oxygen tensions

INVASIVE VASCULAR STUDIES

- Arteriogram, DSA
- CT angiogram, MRA

Medical Management

- Antilipemic agents (statins)
- Antiplatelet therapy
- Vasodilators

Gangrene or extensive tissue loss in face of unreconstructable PAD

Consider amputation

Revascularization

- Angioplasty
- Endovascular
- Open bypass grafting

Follow-Up

- Patient education
- Smoking cessation
- Protective shoes
- Periodic foot care
- Reconstructive foot surgery as needed

Neurologic Evaluation

Peripheral sensory neuropathy is the major risk factor for diabetic foot ulceration (24, 26, 27, 46, 50). The patient history and physical examination utilizing the 5.07 Semmes-Weinstein monofilament (10-g) wire are sufficient to identify individuals at risk for ulceration (26, 232-235).

Vibration perception threshold assessment with the biothesiometer is also useful in identifying patients at high risk for ulceration (44, 57, 236). More sophisticated studies such as nerve conduction studies are rarely necessary to diagnose peripheral sensory neuropathy. Patients with neuropathic ulcerations usually have such profound sensory neuropathy that these studies add little to their clinical management (49).

Plantar Foot Pressure Assessment

High plantar foot pressure is a significant risk factor for ulceration (26, 45, 59, 70, 76, 80, 237). Measurement of high plantar foot pressure is possible utilizing a variety of modalities. Several computerized systems can provide quantitative measurement of plantar foot pressure (76, 81, 238-241). While these measurements may be important in identifying areas of the foot at risk for ulceration and possibly in evaluating orthotic adjustments (57, 59), they are primarily used in diabetic foot research. The Harris mat, while not as sophisticated, can provide a qualitative measurement of plantar foot pressures and can identify potentially vulnerable areas for ulceration.(242). A newer noncomputerized device (PressureStat®, FootLogic, New York City, NY), which is similar to the Harris mat and uses pressure-sensitive contact sheets that provide a semi-quantitative estimation of pressure distribution under the foot, has been suggested as an inexpensive screening tool for identifying areas at high risk for ulceration (76, 243).

Risk Stratification

Following a thorough diabetic foot examination, the patient may be classified according to a cumulative risk category. This enables the physician to design a treatment plan and determine whether the patient is at risk for ulceration or amputation. Several risk stratification schemes have been proposed, assigning different weights to important risk factors for ulceration including peripheral neuropathy, arterial insufficiency, deformity, high plantar pressures, and prior history of ulceration or amputation (48, 57, 62, 90, 244-246). Although no one system has been universally adopted to predict complications, Table 4 presents a simplified risk stratification that has been endorsed by an international consensus group and others (90, 247).

THE HEALTHY DIABETIC FOOT: PREVENTION STRATEGIES

A healthy, intact diabetic foot is best maintained by a consistent and recurrent preventive treatment strategy (2, 30, 43, 48, 90, 163, 246, 248). This is best accomplished through a multidisciplinary approach involving a team of specialists and personnel who provide a coordinated process of care (Fig 5). Team members may include a podiatrist, internist, ophthalmologist, endocrinologist, infectious disease specialist, cardiologist, nephrologist, vascular surgeon, orthopedic surgeon, nurse (educator, wound care, and home care), and pedorthist/orthotist.

Patient and family education assumes a primary role in prevention. Such education encompasses instruction in glucose assessment, insulin administration, diet, daily foot inspection and care, proper footwear, and the necessity for prompt treatment of new lesions (163, 174, 249-251). Regularly scheduled podiatric visits, including debridement of calluses and toenails, are opportunities for frequent foot examination and patient education (163, 252). Such visits can provide early warning of impending problems and subsequent modification of activity and care (30, 253).

Diabetes is a lifelong problem, and the incidence of diabetic foot complications increases with age and dura-

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Table 4 — Risk Categorization System

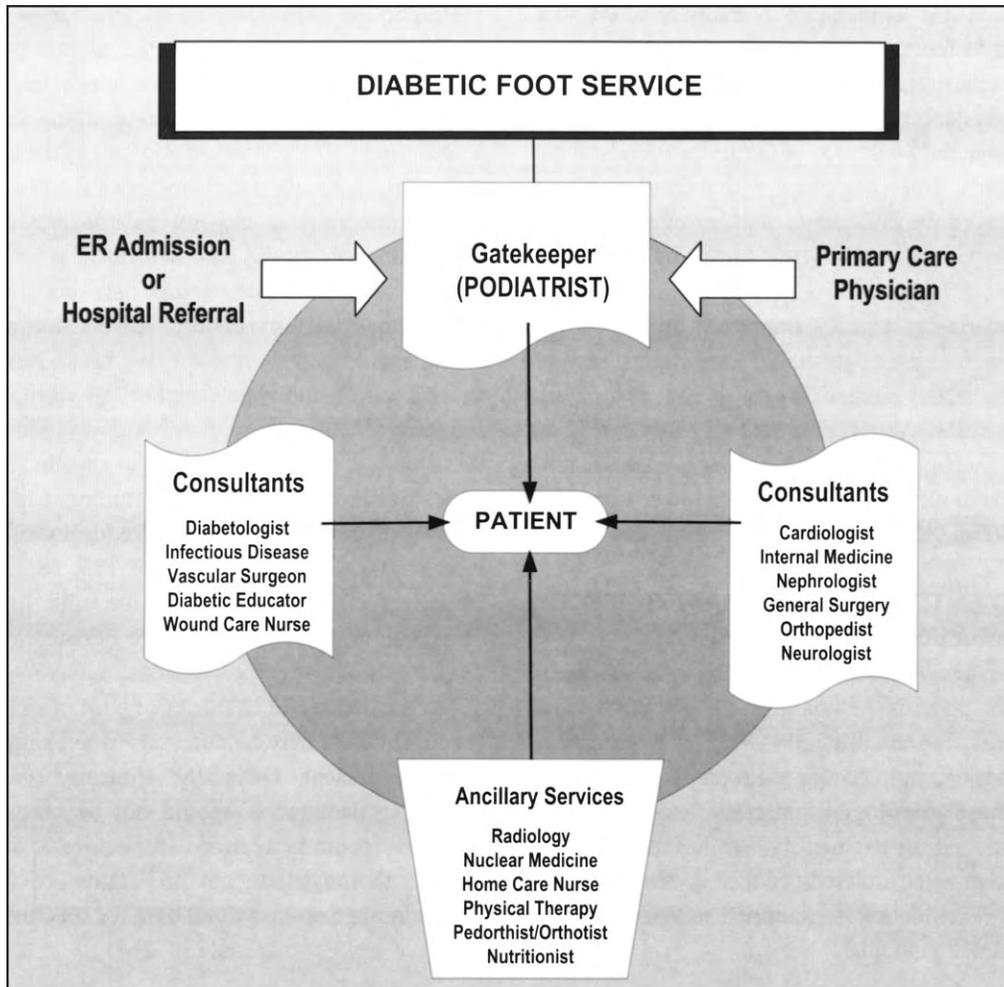| Category	Risk Profile	Evaluation Frequency
0	Normal	Annual
1	Peripheral neuropathy (LOPS)	Semi-annual
2	Neuropathy, deformity and/or PAD	Quarterly
3	Previous ulcer or amputation	Monthy to quarterly

Figure 5 A diabetic foot service is composed of a variety of specialists generally needed to evaluate and treat the pathology seen in the patient with diabetes. Effective management must include appropriate consultation for treatment of known comorbidities.

tion of the disease. A recent Markov analysis of the cost effectiveness of foot care according to published guidelines found that such preventive care can improve survival, reduce ulceration and amputation rates, is cost-effective, and can even save on long-term costs when compared with standard care (254).

Risk stratification based on the presence of predisposing causal risk factors, including prior history of ulceration, also serves as a guide to the frequency of foot care visits. By identifying high-risk patient and tailoring a total foot care prevention program accordingly, the incidences of ulceration and lower extremity amputations can be reduced (253, 255-258).

Therapeutic shoes with pressure-relieving insoles and high toe boxes are important adjunctive treatments that can reduce the occurrence of ulceration and resultant amputation in high-risk patients (51, 86, 259-262). While most studies support the efficacy of protective footwear in this regard, two reports suggest that shoes in the absence of a comprehensive prevention program might not be sufficient to prevent new lesions (263, 264). Nevertheless, patients with foot deformities that cannot be accommodated by standard therapeutic footwear should have custom shoes that provide appropriate fit, depth, and a rocker insole (260, 265-269). If structural deformities cannot be accommodated by therapeutic footwear, prophylactic surgical correction should be considered, but patients must be carefully selected (173, 255, 270-273).

Diabetic patients at risk for foot lesions must be educated about risk factors and the importance of foot care (48, 274-276), including the need for self-inspection and surveillance, monitoring foot temperatures, appropriate daily foot hygiene, use of proper footwear, good diabetes control, and prompt recognition and professional treatment of newly dis-

covered lesions. Home temperature assessment of the foot has been shown to reduce the incidence of foot ulcers 10-fold compared with standard preventive care (277). Patients with visual or physical impairments that preclude their own care should engage the assistance of family or friends to aid in this regard (275). When combined with a comprehensive approach to preventive foot care, patient education can reduce the frequency and morbidity of limb threatening diabetic foot lesions (274, 278, 279).

Provider education is equally important in prevention, since not all clinicians are cognizant of important signs and risk factors for pedal complications (163, 174, 276). Furthermore, provider education is effective in reinforcing proper diabetes management and foot care practices, resulting in reductions in ulceration and adverse lower extremity outcomes (48, 276, 280-282).

PATHOLOGIC ENTITIES OF THE DIABETIC FOOT (Foot Ulcer, Infection, Charcot Foot)

Effective management of diabetic foot disorders requires knowledge of the potential pathologies, the associated classification systems, and the principle tenets of intervention. Ulceration, infection, and Charcot arthropathy are the most significant of these pathologies and classification systems have been developed for each entity. While the conditions may be seen either as an isolated event or coexisting in the same extremity, each entity is examined independently in this clinical practice guideline.

DIABETIC FOOT ULCERS (Pathway 3)
Evaluation of Ulcers

The initial evaluation of the diabetic foot ulcer must be comprehensive and systematic to ascertain the parameters that might have led to its onset as well as determine the presence of factors that can impair wound healing (25, 52, 54). Critical in this regard are assessments for vascular perfusion (ischemia), infection/osteomyelitis, and neuropathy. As previously discussed, a thorough vascular evaluation must be performed; this includes palpation of pulses, clinical evaluation of capillary filling time, venous filling time, pallor on elevation, and dependent rubor (283). If pulses are not palpable or if clinical findings suggest ischemia, noninvasive arterial evaluation (eg, segmental Doppler pressures with waveforms, ankle brachial indices, toe pressures, $TcPO_2$ measurements) and vascular surgical consultation are warranted. When required, these physiologic and anatomic data can be supplemented with the use of magnetic resonance angiography (230) or CT angiography (CTA) and subsequent use of arteriography with digital subtraction angiography (DSA) as necessary (77, 89, 284).

Description of the ulcer characteristics on presentation is essential for the mapping of the ulcer's progress during treatment (30, 43). While some characteristics are more important than others, they all have prognostic value during management. The presumed etiology of the ulcer (ie, chemical vs mechanical) and character of the lesion (neuropathic, ischemic, or neuroischemic) should be determined (90). The evaluation should also describe the size and depth of the ulcer as well as the margins, base, and geographic location on the extremity or foot. All but the most superficial ulcers should be examined with a blunt, sterile probe. The description should note whether the sterile probe detects sinus tract formation, undermining of the ulcer margins, or dissection of the ulcer into tendon sheaths, bone, or joints. A positive probe to bone (PTB) finding is highly predictive of osteomyelitis, although the frequency of false-negative tests reduces its sensitivity (119, 123, 285). Perhaps most importantly, the positive predictive value for PTB falls off significantly when the prevalence of osteomyelitis decreases (286).

The existence and character of odor or exudate should be noted. Cultures may be necessary when signs of inflammation are present. Generally, clinically uninfected ulcers without inflammation should not be cultured (30, 123). Current recommendations for culture and sensitivity include thorough surgical preparation of the wound site with curettage of the wound base for specimen or with aspiration of abscess material (30, 287).

Classification of Ulcers

Appropriate classification of the foot wound is based on a thorough assessment. Classification should facilitate treatment and be generally predictive of expected outcomes. Several systems of ulcer classification are currently in use in the US and abroad to describe these lesions and communicate severity (62, 90, 288-292). Perhaps the easiest system is to classify lesions as neuropathic, ischemic, or neuroischemic, with descriptors of wound size, depth, and infection (90). Regardless of which system is used, the clinician must be able to easily categorize the wound and, once classified, the ensuing treatment should be directed by the underlying severity of pathology.

Although no single system has been universally adopted, the classification system most often used was described and popularized by Wagner (292). In the Wagner system (Table 5), foot lesions are divided into six grades based on the depth of the wound and extent of tissue necrosis. Since these grades fail to consider the important roles of infection, ischemia, and other comorbid factors, subsequent authors have modified the classification system by including
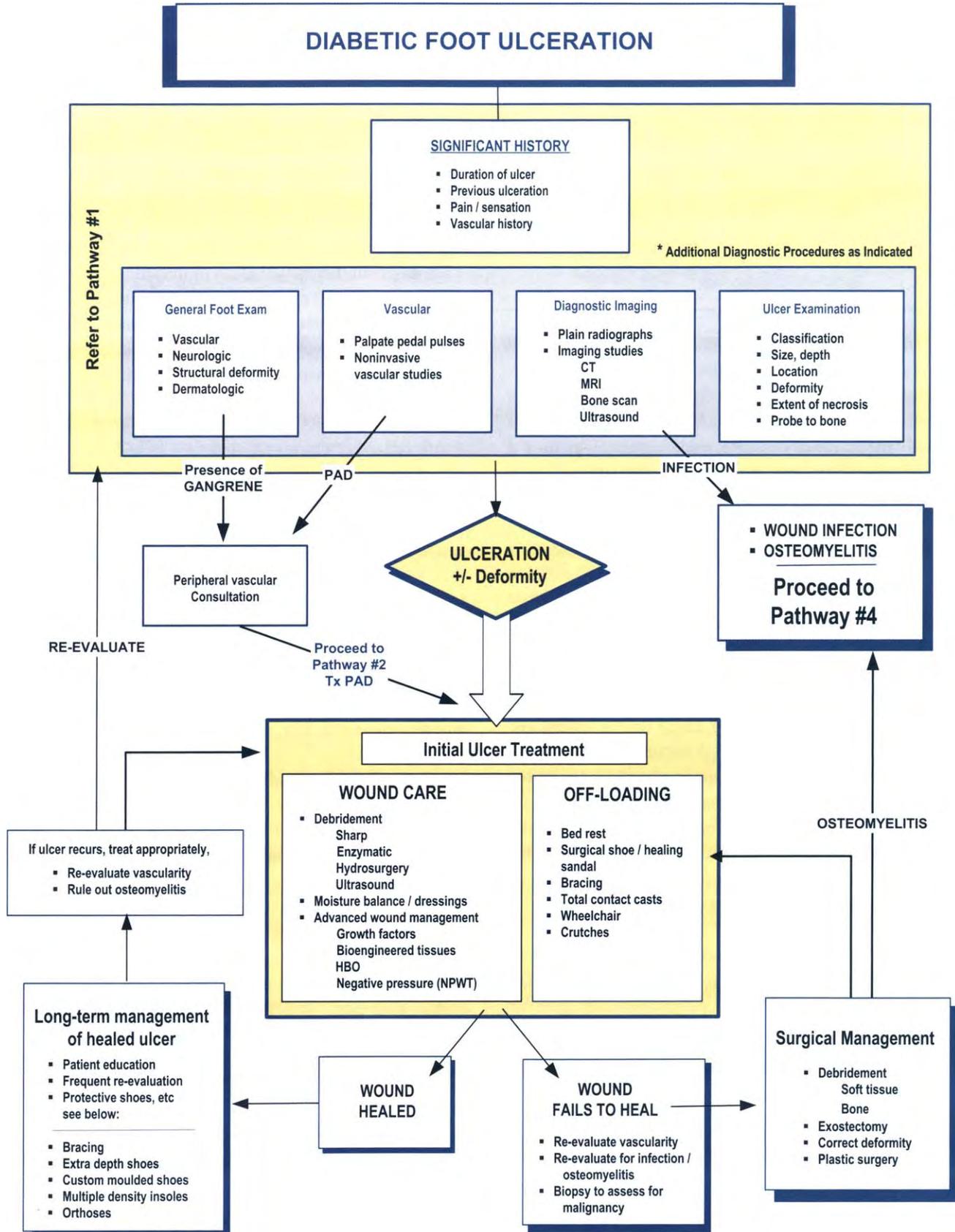
PATHWAY #3

DIABETIC FOOT ULCERATION

Refer to Pathway #1

SIGNIFICANT HISTORY
- Duration of ulcer
- Previous ulceration
- Pain / sensation
- Vascular history

* Additional Diagnostic Procedures as Indicated

General Foot Exam
- Vascular
- Neurologic
- Structural deformity
- Dermatologic

Vascular
- Palpate pedal pulses
- Noninvasive vascular studies

Diagnostic Imaging
- Plain radiographs
- Imaging studies
  CT
  MRI
  Bone scan
  Ultrasound

Ulcer Examination
- Classification
- Size, depth
- Location
- Deformity
- Extent of necrosis
- Probe to bone

Presence of **GANGRENE**

PAD

INFECTION

ULCERATION +/- Deformity

- **WOUND INFECTION**
- **OSTEOMYELITIS**

Proceed to Pathway #4

Peripheral vascular Consultation

RE-EVALUATE

Proceed to Pathway #2 Tx PAD

If ulcer recurs, treat appropriately,
- Re-evaluate vascularity
- Rule out osteomyelitis

Initial Ulcer Treatment

OSTEOMYELITIS

WOUND CARE
- Debridement
  Sharp
  Enzymatic
  Hydrosurgery
  Ultrasound
- Moisture balance / dressings
- Advanced wound management
  Growth factors
  Bioengineered tissues
  HBO
  Negative pressure (NPWT)

OFF-LOADING
- Bed rest
- Surgical shoe / healing sandal
- Bracing
- Total contact casts
- Wheelchair
- Crutches

Long-term management of healed ulcer
- Patient education
- Frequent re-evaluation
- Protective shoes, etc see below:

- Bracing
- Extra depth shoes
- Custom moulded shoes
- Multiple density insoles
- Orthoses

WOUND HEALED

WOUND FAILS TO HEAL
- Re-evaluate vascularity
- Re-evaluate for infection / osteomyelitis
- Biopsy to assess for malignancy

Surgical Management
- Debridement
  Soft tissue
  Bone
- Exostectomy
- Correct deformity
- Plastic surgery

Table 5   **Wagner Classification System**

Grade	Lesion
0	No open lesions: may have deformity or cellulitis
1	Superficial ulcer
2	Deep ulcer to tendon or joint capsule
3	Deep ulcer with abscess, osteomyelitis, or joint sepis
4	Local gangrene - forefoot or heel
5	Gangrene of entire foot

descriptors for these considerations (62, 290, 291). For example, the University of Texas San Antonio (UTSA) system (Table 6) associates lesion depth with both ischemia and infection (290). This system has been validated and is generally predictive of outcome, since increasing grade and stage of wounds are less likely to heal without revascularization or amputation (290, 293). The UTSA system is now widely used in many clinical trials and diabetic foot centers. Another hybrid system, the PEDIS system, evaluates five basic characteristics: perfusion, extent/size, depth/tissue loss, infection and sensation (294) (Table 7). While this system has yet to be validated, it provides the benefit of having been developed by a consensus body.

Imaging studies play an important role in the assessment and evaluation of the diabetic foot ulcer (179, 180, 183, 197). Plain x-rays are indicated based on the extent and nature of the ulcer. Clinical change in the appearance of the ulcer or failure to heal with appropriate treatment may dictate repeating the radiograph periodically to monitor for osseous involvement (30). Additional imaging modalities such as nuclear medicine scans, ultrasonography, MRI, and CT may be indicated, depending on the clinical picture. These modalities have been previously discussed in this document.

Figure 6 summarizes the important elements of the overall assessment of the patient with a diabetic foot ulcer. The assessment addresses underlying pathophysiology, possible causal factors, and significant predictors of outcome (25, 49, 54, 100, 272).

Treatment of Diabetic Ulcers: Guiding Principles

The primary treatment goal for diabetic foot ulcers is to obtain wound closure as expeditiously as possible. Resolving foot ulcers and decreasing the recurrence rate can lower the probability of lower extremity amputation in the diabetic patient (30, 43, 162, 168, 295-297). The Wound Healing Society defines a chronic wound as one that has failed to proceed through an orderly and timely repair process to produce anatomic and functional integrity (288). A chronic wound is further defined as one in which the healing cascade has been disrupted at some point, leading to prolonged inflammation and failure to re-epithelialize and allowing for further breakdown and infection. Early advanced or appropriate wound care practices may be more cost-effective than standard care practices for decreasing the incidence of lower extremity amputations (43, 298).

The essential therapeutic areas of diabetic ulcer management are as follows: management of comorbidities; evaluation of vascular status and appropriate treatment; assessment of lifestyle/psychosocial factors; ulcer assessment and evaluation; tissue management/wound bed preparation; and pressure relief.

Management of Comorbidities

Because diabetes is a multi-organ systemic disease, all comorbidities that affect wound healing must be assessed and managed by a multidisciplinary team for optimal outcomes in the diabetic foot ulcer (163-165, 173, 278, 299-301). Many systemic manifestations affect wound healing. Among the most common comorbidities are hyperglycemia and vascular diseases such as cerebral vascular accidents, transient ischemic attacks, myocardial infarctions, angina, valvular heart disease, atrial fibrillation, aneurysms, renal dysfunction, hypertension, hypercholesterolemia, and hyperlipidemia (48, 275, 302-304).

Evaluation of Vascular Status

Arterial perfusion is a vital component for healing and must be assessed in the ulcerated patient, since impaired circulation contributes significantly to nonhealing of ulcers and subsequent risk for amputation (52, 77, 89, 214, 305). Early evaluation and referral are important (91). Symptoms of vascular insufficiency may include edema, altered skin characteristics (lack of hair, diseased nails, altered moisture), slow healing, cool or cold extremities, and impaired arterial pulsation. Vascular reconstructive surgery of the occluded limb improves prognosis and may be required prior to debridement, foot sparing surgery, and partial amputation (88, 227, 306, 307).

Assessment of Lifestyle/Psychosocial Factors

Lifestyle and psychosocial factors may influence wound healing. For example, smoking has a profound effect on

Table 6

University of Texas Classification System

Stage	Grade			
	O	**I**	**II**	**III**
A	Pre- or post-ulcerative lesions completely epithelized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infected	Infected	Infected	Infected
C	Ischemic	Ischemic	Ischemic	Ischemic
D	Infected and ischemic	Infected and ischemic	Infected and ischemic	Infected and ischemic

wound healing due to its associated vasoconstriction and low oxygen-carrying capacity of blood (308, 309). Other factors (eg, alcohol and drug abuse, eating habits, obesity, malnutrition, and mobility and activity levels) should also be noted. In addition, depression and mental illness may impact the outcome of treatment, since these conditions can directly affect the patient's adherence to recommendations and attitude towards healing (310, 311).

Ulcer Assessment and Evaluation

The importance of a thorough and systematic evaluation of any ulceration cannot be overemphasized; indeed, the findings of an ulcer-specific examination will directly guide subsequent treatment (25, 100). Initial evaluation and detailed description of any ulcer should encompasses location, size, depth, shape, inflammation, edema, exudate (quality and quantity), past treatment, and duration (123, 272). The margins of the ulcer should be assessed for callus formation, maceration, and erythema. The presence of erythema along with other signs such as tenderness and warmth might suggest infection (312). The quality of the tissue (ie, moist, granular, desiccated, necrotic, undermining, slough, eschar, or liquefied) should be noted (313). Thorough evaluation is used to determine the presence of sinus track or deep abscess.

Table 7

PEDIS Ulcer Classification

	Grade			
	1	**2**	**3**	**4**
Perfusion	Normal	Non-critical PAD	Critical limb ischemia	
Extent/size (cm²)				
Depth tissue loss	Full thickness	Deep	Bone and / or joint	
Infection	None	Mild	Moderate / severe	SIRS*
Sensation	Intact	LOPS		

* Systemic inflammatory response syndrome

Skin / Ulcer
 - description, depth, location, classification

Infection
 - gram stain, cultures, radiographs, scans

Vascular
 - pulses, color, skin temperatures, Doppler, TcPO$_2$

Neuropathy
 - sensory disturbances, monofilament, VPT, DTRs

Deformity
 - deformity, joint mobility, contractures

Etiology
 - mechanical, thermal, chemical

Figure 6 Assessment of a diabetic foot ulcer includes not only a description of the skin lesion but also the findings necessary for accurate assessment of the contributing factors and etiology.

Frequent re-evaluation with response-directed treatment is essential. Once the ulcer is healed, management consists of decreasing the probability of recurrence.

Tissue Management / Wound Bed Preparation

Debridement. Debridement of necrotic tissue is an integral component in the treatment of chronic wounds since they will not heal in the presence of unviable tissue, debris, or critical colonization (314, 315). Undermined tissue or closed wound spaces will otherwise harbor bacterial growth (312, 316, 317). Debridement serves various functions: removal of necrotic tissue and callus; reduction of pressure; evaluation of the wound bed; evaluation of tracking and tunneling; and reduction of bacterial burden (318, 319). Debridement facilitates drainage and stimulates healing (320). However, debridement may be contraindicated in arterial ulcers (321). Additionally, except in avascular cases, adequate debridement must always precede the application of topical wound healing agents, dressings, or wound closure procedures (30, 288, 322, 323). Of the five types of debridement (surgical, enzymatic, autolytic, mechanical, biological), only surgical debridement has been proven to be efficacious in clinical trials (323).

Surgical debridement. Surgical debridement is the cornerstone of management of diabetic foot ulcers. Thorough sharp debridement of all nonviable soft tissue and bone from the open wound is accomplished primarily with a scalpel, tissue nippers, curettes, and curved scissors (324). Excision of necrotic tissue extends as deeply and proximal-

ly as necessary until healthy, bleeding soft tissue and bone are encountered. Any callus tissue surrounding the ulcer must also be removed. The main purpose of surgical debridement is to turn a chronic ulcer into an acute, healing wound (325). A diabetic ulcer associated with a deep abscess requires hospital admission and immediate incision and drainage (178). Joint resection or partial amputation of the foot is necessary if osteomyelitis, joint infection, or gangrene are present (41, 100, 123, 151, 180, 271). The principles guiding the surgical management of diabetic foot ulcers are discussed under "Surgical Management of the Diabetic Foot."

Necrotic tissue removed on a regular basis can expedite the rate at which a wound heals and has been shown to increase the probability of attaining full secondary closure (323, 326). Less frequent surgical debridement can reduce the rate of wound healing and secondarily increase the risk of infection. Surgical debridement is repeated as often as needed if new necrotic tissue continues to form (327). Frequent debridement, referred to as "maintenance debridement," is commonly required (328). While the terms surgical debridement and sharp debridement are often used synonymously, some clinicians refer to surgical debridement as that done in an operating room whereas sharp debridement is performed in a clinic setting (325).

Hydrosurgery (Versajet ®, Smith & Nephew, Inc., London, UK) is a novel system indicated for the surgical debridement of damaged and necrotic tissue in traumatic, ulcerated, and chronic wounds, surgical incisions, and burns

(329, 330). Among its properties are precision, selective cutting, and minimal thermal damage to the tissues (331).

When surgical or sharp debridement is not indicated, other types of debridement can be used. For example, vascular wounds may benefit from enzymatic debridement, while an extremely painful wound may benefit from autolytic debridement. Mechanical debridement is often used to cleanse wounds prior to surgical or sharp debridement. In areas where the medical staff is not trained in surgical or sharp debridement, these other forms of debridement may be useful (325).

Enzymatic debridement. A highly selective method, enzymatic debridement consists of the application of exogenous proteolytic enzymes manufactured specifically for wound debridement. Various enzymes have been developed, including bacterial collagenase, plant derived papain/urea, fibrinolysin/DNAse, trypsin, streptokinase-streptodornase combination; only the first three products are widely available commercially (319). Collagenases are enzymes that are isolated from *Clostridium histolyticum.* These display high specificity for the major collagen types (I and II), but they not active against keratin, fat, or fibrin (312, 332, 333). Papain, obtained from the papaya plant, is effective in the breakdown of fibrinous material and necrotic tissue. When combined with urea, it denatures nonviable protein matter (312). The enzymatic compounds are inactivated by hydrogen peroxide, alcohol, and heavy metals, including silver, lead, and mercury (334). One study found that wounds treated with papain-urea developed granulation tissue faster than those treated with collagenase, but no contrasts between rates of complete wound healing were made (335).

Autolytic debridement. Autolytic debridement occurs naturally in a healthy, moist wound environment when arterial perfusion and venous drainage are maintained.

Mechanical debridement. A nonselective, physical method of removing necrotic tissue, mechanical debridement may include wet-to-dry dressings and high-pressure irrigation or pulsed lavage and hydrotherapy (30, 62, 336, 337). Wet-to-dry is one of the most commonly prescribed and overused methods of debridement in acute care settings (312, 338). Hydrotherapy in the form of whirlpool may remove surface skin, bacteria, wound exudates, and debris. There may be justification in the early stages of a wound for the use of this technique, but it is detrimental to friable granulation tissue (312, 334).

Biological (larval) therapy. Larval therapy utilizes the sterile form of the *Lucilia sericata* blowfly for the debridement of necrotic and infected wounds. Maggots secrete a powerful proteolytic enzyme that liquefies necrotic tissue (339-342). It has been noted that wound odor and bacterial count, including methicillin-resistant *Staphylococcus aureus*, diminish significantly (343) with larval therapy. Larval therapy seems to be beneficial, but there is paucity of controlled studies to support its routine use in the diabetic foot wound.

Moisture Balance. One of the major breakthroughs in wound management over the past 50 years was the demonstration that moisture accelerates re-epithelialization in a wound (315, 344, 345). Tissue moisture balance is a term used to convey the importance of keeping wounds moist and free of excess fluids. A moist wound environment promotes granulation and autolytic processes (325). Effective management of chronic wound fluids is an essential part of wound bed preparation; it also helps in addressing the issues of cellular dysfunction and biochemical imbalance (328, 346-348).

Wound dressings can be categorized as passive, active, or interactive (349). Passive dressings primarily provide a protective function. Active and interactive dressings and therapies are capable of modifying a wound's physiology by stimulating cellular activity and growth factor release (350). An example is ORC/collagen (Promogran , Johnson & Johnson, Inc., New Brunswick, NJ). Composed of collagen and oxidized regenerated cellulose, this bioreabsorbable matrix decreases tissue destruction and prevents growth factor degradation (351, 352). Recently, silver has been added to this product (Prisma , Johnson & Johnson, Inc., New Brunswick, NJ) to also provide an effective antibacterial barrier. Although these products are commonly used in clinical practice, they have not yet been conclusively shown to expedite wound healing. A wide variety of wound care products is available; a brief listing of dressings and topical agents is presented in Table 8.

Inflammation and Infection. In chronic wounds, inflammation persists due to recurrent tissue trauma and the presence of contaminants. Nonhealing wounds can become "stuck" in the inflammatory phase of healing, increasing cytokine response with subsequent elevated protease levels and impaired growth factor activity (314, 347, 352-357). The presence of infection must be ascertained and identified as local (soft tissue or osseous), ascending, and/or systemic. In diabetes, where the host response is reduced and normal signs of infection (ie, fever, pain, leukocytosis) may be absent, other factors such as elevated glucose levels can be helpful as an indicator of infection (41, 358). It is important to obtain specimens for culture prior to antimicrobial therapy. Tissue specimens collected by curettage or biopsy are preferred, because they provide more accurate results than superficial swabs (287).

Table 8

Wound Care Products

Category	Indications	Contraindications
Dressings		
Gauze pads (312, 338, 352) - sterile gauze - sterile cotton	- Low to heavily draining wounds or surgical wounds - Wet to dry debridement	- Undefined
Transparent films (312, 352) - polyurethane film with drainage adhesive layer, semipermeable	- Dry to minimally draining wounds - Promote tissue hydration	- Infection - Significant drainage - Over prominence or friction
Hydrogels (312, 352) - gel, sheet, gauze (95% water or glycerin)	- Dry to minimally draining wounds	- Moderate or heavy drainage
Foam (312, 352) - polyurethane foam (open cell, absorbent)	- Moderate, large exudate - Clean wound surface - Super absorbent and conformable to topography	- Dry wounds
Hydrocolloids (312, 352) - wafer with adhesion, (carboxymethylcellulose,pectin, gelatin) impermeable to oxygen	- Low to moderate drainage * Prevents tissue hydration	- Heavy drainage - Sinus tract
Calcium alginates (312, 352) - fiber pad derived form seaweed (may be combined with silver or collagen)	- Heavy exudative wounds	- Minimal drainage or dry wounds
Collagen dressings (302, 312, 325, 352) - particles or composite pads with collagen component (derived from bovine collagen)	- Low to heavily draining wounds	- Dry wounds
Antimicrobial dressings (312, 334, 352) - contain silver, iodine in various forms preparations (eg, cadoxemer iodine)	- Infected or clean wounds to prevent infection	- Allergies to components
Topical Therapies / Agents		
Saline (302, 352) **Amorphous hydrogels** **Skin cleansers** - isotonic solutions for irrigation, hydrating dressings	- Clean or infected wounds	- Undefined
Detergents/Antiseptics (302, 352) - povidone-iodine, - chlorhexidine - chloroxylenol - hypochlorite - benzethonium chloride	- Contaminated or infected wounds	- Healthy granulating wounds
Topical Antibiotics (302, 320, 352) - bacitracin, neomycin - mupirocin, polymyxin B - silver sulfadiazine - mafenide (creams, ointments)	- Contaminated or infected wounds	- Healthy granulating wounds
Enzymes (302, 312, 319, 328, 332-335) - collagenase - papain-urea	- Necrotic tissue - Escharotic wounds	- Healthy or infected wounds

Advanced Wound Care Modalities. Wound bed preparation offers clinicians a comprehensive approach to removing barriers to healing and stimulating the healing process so that the benefits of advanced wound care can be maximized (314, 359). Advanced care may sometimes be the only means of rapidly and effectively attaining wound closure (360). The advent of therapeutic growth factors, gene therapy, tissue-engineered constructs, stem cell therapy, and other drugs and devices that act through cellular and molecular-based mechanisms is enabling the modern surgeon and wound-care provider to actively promote wound angiogenesis to accelerate healing (361-363).

Growth factor therapy. Chronic ulcers have demonstrated benefit from autologous platelet releasates or genetically-engineered products such as recombinant DNA platelet-derived growth factor becaplermin gel (Regranex™, Johnson & Johnson, Inc., New Brunswick, NJ) (361, 362, 364). This agent has been shown to stimulate chemotaxis and mitogenesis of neutrophils, fibroblasts, monocytes and other components that form the cellular basis of wound healing (326, 365-368). In one pivotal randomized placebo-controlled blinded trial involving patients with full thickness diabetic foot ulcers, recombinant human platelet-derived growth factor (becaplermin) demonstrated a 43% increase in complete closure versus placebo gel (50% vs 35%) (362).)Other growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and keratinocyte growth factor (KGF), have been under study but are not yet approved for use in the US.

Autologous platelet-rich plasma treatments (Fig. 7) utilize the patient's own blood to create a gel that is applied to the wound (364). Activation of the plasma after centrifugation stimulates the release of multiple growth factors from the platelet's alpha granules and the conversion of the plasma fibrinogen to a fibrin matrix scaffold. Both actions may assist with new tissue formation. A large retrospective study reviewing this treatment protocol in commercial wound healing centers suggested a benefit in healing larger, more severe neuropathic ulcerations (369).

Bioengineered tissues. Bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers (370-374). Currently, two bioengineered tissues have been approved to treat diabetic foot ulcers in the US: Apligraf™ (Organogenesis Inc., Canton, MA), and Dermagraft™ (Smith & Nephew, Inc., London, UK); both have demonstrated efficacy in randomized, controlled trials. Tissue-engineered skin substitutes can provide the cellular substrate and molecular components necessary to accelerate wound healing and angiogenesis. They function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements (370, 375).
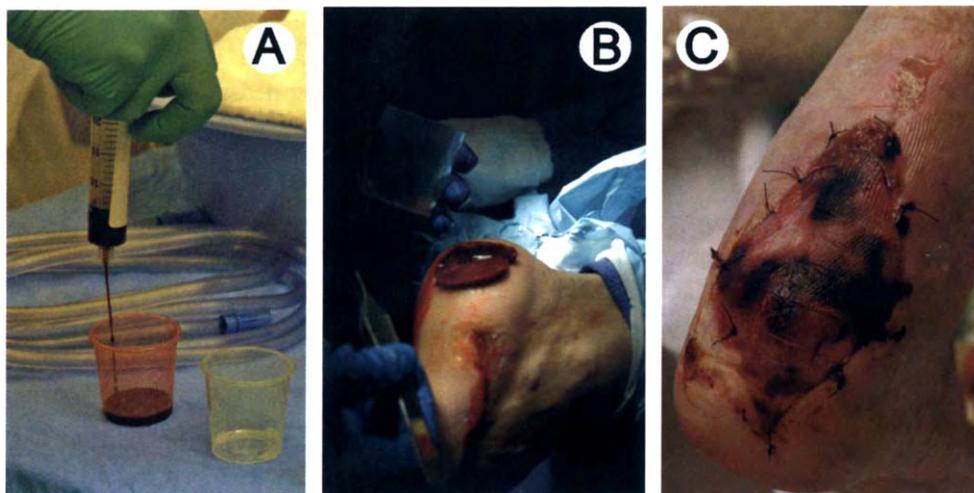

Figure 7   New technologies have been developed that have proved useful for management of diabetic ulcerations. *(A)*Platelet-rich plasma (PRP) involves use of the patient's blood, which is collected and then fractionated through centrifugation. A platelet-rich and platelet-poor supernatant remains. *(B)* This case involved use of autologous platelet-rich plasma gel activated with thrombin and placed onto a healthy wound bed. *(C)* The platelet gel or clot may also be covered with a synthetic skin graft substitute.

Bilayered skin substitutes (living cells) include bilayered skin equivalent (Apligraf™) and cultured composite skin (OrCel™ bilayered cellular matrix, Ortech International, Inc., New York City, NY). Apligraf™ has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers (371, 376). Dermagraft™ is no longer available in the US.

Extracellular matrices (nonliving) are generally derived from devitalized tissue to produce an immunologically inert acellular dermal matrix. These include dermal regeneration template (Integra™, Integra LifeSciences Holdings Corp., Plainsboro, NJ), allogenic dermal matrix (AlloDerm™, LifeCell, Branchburg, NJ), matrix of human dermal fibroblasts (TransCyte™, Smith & Nephew, Inc., London, UK), and porcine small intestine submucosa (Oasis™, Healthpoint, Fort Worth, TX). Oasis™, composed of structural cellular components and growth factors utilized to promote natural tissue remodeling (377, 378), recently completed a randomized trial that showed non-inferiority to becaplermin gel in the healing of diabetic foot ulcers (379). Integra™ dermal regeneration template, a collagen-chondroitin sponge overlaid with silicone originally developed for burns, has been shown to be ideally suited to chronic and pathologic wounds (380).

Adjunctive Modalities. Regenerative tissue matrix (GraftJacket™, Wright, Arlington, TN) is a new therapy used in diabetic foot ulcers, although it has not undergone any randomized clinical trials to date (381). This allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and vacularization.

Hyperbaric oxygen therapy (HBO) has shown promise in the treatment of diabetic foot wounds with hypoxia severe enough to interfere with healing (382-387). However, most of the HBO studies were hampered by methodological errors that preclude any definite role for this modality in the routine treatment of diabetic foot ulcers (382, 388, 389). Nevertheless, in 2003, Medicare and Medicaid coverage for HBO extended to ulcers classified as Wagner grade 3 or higher that failed standard wound care therapy. Clearly, a large multicenter randomized clinical trial is needed to properly test the efficacy of this expensive modality (388).

Several new ultrasound devices are being used to both debride the wound and provide ultrasonic therapy. The MIST Therapy™ system (Celleration™, Eden Prairie, MN) is an ultrasonic device approved by the Food and Drug Administration (FDA) for wound debridement and cleansing. MIST Therapy™ uses a fine saline spray that allows ultrasound to be administered directly to the wound bed without contact to the affected tissue, thus minimizing potential trauma to delicate capillary buds and emerging islands of epithelium (390-392).

Negative pressure wound therapy (NPWT) has become a common adjunctive treatment modality for diabetic foot ulcerations (393-397). Use of a vacuum-assisted closure® device (V.A.C.®, KCI, San Antonio, TX) promotes wound healing through the application of topical, subatmospheric, or "negative" pressure to the wound base (398, 399). This therapy removes edema and chronic exudate, reduces bacterial colonization, enhances formation of new blood vessels, increases cellular proliferation, and improves wound oxygenation as the result of applied mechanical force. These actions are synergistic (400, 401). Numerous applications of this modality have proven successful, including use over exposed bone, tendons, and hardware to generate granulation tissue (394, 395, 402-405). It is also frequently used to facilitate adherence of split thickness skin grafts, rotational flaps, or tissue substitutes to a wound bed (396, 406-409). A recent clinical trial of the V.A.C.® device for the treatment of open amputation wounds in the diabetic foot showed significantly faster healing and development of granulation tissue with NPWT compared with standard moist wound care (410).

The rationale for using electrical stimulation in wound healing stems from the fact that the human body has an endogenous bioelectric system that enhances healing of bone fractures and soft tissue wounds. Laboratory and clinical studies provide an abundance of support for the use of electrical stimulation in wound care (411, 412). In a randomized, controlled study evaluating wound healing using electrical stimulation in neuropathic ulcers, significant differences in healed ulcer areas and number of healed ulcers at 12 weeks were found in the group receiving electrical stimulation compared with the control group (413).

Pressure Relief/Off-loading

The reduction of pressure to the diabetic foot ulcer is essential to treatment (26, 76, 80, 107, 414-417). Proper off-loading and pressure reduction prevents further trauma and promotes healing. This is particularly important in the diabetic patient with decreased or absent sensation in the lower extremities (50, 418). Furthermore, recent studies provide evidence that minor trauma (eg, repetitive stress, shoe pressure) plays a major role in the causal pathway to ulceration (24). A list of off-loading modalities is presented in Figure 8.

The choice of off-loading modality should be determined by the patient's physical characteristics and ability to comply with treatment as well as by the location and severity of the ulcer. Various health care centers prefer specific initial modalities, but frequently clinicians must alternate treat-

- Total nonweightbearing: crutches, bed rest, wheelchair
- Total contact casting
- Foot casts or boot
- Removable walking brace with rocker bottom sole
- Total contact orthoses - custom walking braces
- Patella tendon-bearing braces
- Half shoes or wedge shoes
- Healing sandal - surgical shoe + molded plastazote foot bed
- Accommodative dressings: felt, foam, felted foam
- Shoe cutouts - toe box, medial, lateral, dorsal pressure points
- Assistive devices: crutches, walker, cane

Figure 8 Diabetic foot ulcers are most often located under weightbearing areas of the foot. Essentials of management include "off-loading" of the foot or area of ulceration. Healed ulcers may be managed with shoes and variations of molded or multiple density insoles, while the total contact cast remains the standard approach to off-loading areas of ulceration.

ments based on the clinical progress of the wound. Even as simple a method as a felted foam aperture pad has been found to be effective in removing pressure and promoting healing of foot ulcers (419-421). A study published in 2001 noted that use of a total contact cast (TCC) healed a higher portion of wounds in a shorter time than a half shoe or removable cast walker (RCW) (414). More recently, investigators compared TCC use with that of a removable cast walker that was rendered irremovable (iTCC) by circumferential wrapping of an RCW with a single strip of fiberglass casting material. They concluded that the latter may be equally efficacious, faster to place, easier to use, and less expensive than TCC in the treatment of diabetic neuropathic plantar foot ulcers (422). The findings of this study and another study also suggest that modification of the RCW into an irremovable device may improve patient compliance, thereby increasing the proportion of healed ulcers and

the rate of healing of diabetic neuropathic wounds (417).

Regardless of the modality selected, no patient should return to an unmodified shoe until complete healing of the ulcer has occurred (30, 77, 90, 255). Furthermore, any shoe that resulted in the formation of an ulcer should never again be worn by the patient.

Wounds That Fail to Heal

Wounds that do not respond to appropriate care, including debridement, off-loading, and topical wound therapies, must be reassessed. Infection and ischemia are especially important considerations and common reasons for failure to heal.

The presence of infection must be determined and identified as either soft tissue, osseous, or both. Excessive bioburden can be indicated by pale or friable granulation tissue, persistent drainage, or fibrinous surface layer (314).

Table 9   Factors Favoring Wound Chronicity (426)

- Nutritional deficiency
  - Protein calorie
  - Vitamins
  - Minerals

- Tissue hypoxia
  - Ischemia
  - Venous insufficiency
  - Edema

- Infection / bioburden

- Metabolic
  - Diabetes
  - Chronic renal insuffiency

- Malignancy

- Immune compromise
  - Immunosuppressive drugs
  - Steroids

- Mechanical
  - Pressure
  - Shear
  - Friction
  - Repetitive injury

- Miscellaneous
  - Inadequate debridement
  - Toxic wound care products
  - Radiation therapy
  - Aging / debility

Indicators for frank infection will also include pain (especially in the neuropathic patient), erythema, and induration. When bone or joint is visible or palpable at the depth of the ulcer, osseous infection becomes more likely (285, 423). A thorough discussion of the management of infected wounds is presented later in this document and summarized in Pathway 4.

Unrecognized ischemia will also impair wound healing and must be diagnosed prior to development of infection or ischemic necrosis of the ulcer. When no progress or enlargement of the wound has taken place, re-examination of the vascular status of the extremity is warranted (Pathway 2). This should include arterial Doppler segmental pressures with waveforms, digital arterial pressures, or measurement of transcutaneous oxygen partial pressures ($TcPO_2$) (52, 212). Vascular surgical consultation should also be considered for further evaluation and treatment.

Other parameters critical to wound healing should also be addressed, including the need for further debridement or a change in off-loading modality. Nonadherence to prescribed treatments or off-loading can be especially problematic in patients with peripheral neuropathy (424, 425). Additional concerns may include renal insufficiency, biochemical imbalances, chronic anemia, nutritional deficiencies, or ulceration due to nondiabetic etiologies (ie, radiation, malignancy, etc) (354, 426). Biopsy of chronic, nonhealing wounds should always be considered. Table 9 summarizes the range of possible impediments to wound healing.

DIABETIC FOOT INFECTIONS (Pathway 4)

Foot infection is a major reason for hospitalization among patients with diabetes and also an important causal factor for lower limb amputation (122, 151, 427). There are various presentations of diabetic foot infections as well as several ways to classify these entities. (428)

Classification of Diabetic Foot Infections

Foot infections may be described in terms of severity, extent of involvement, clinical appearance, location, and etiology. Any system for classifying these infections should also serve to facilitate management and predict outcomes. One well accepted method simply provides two categories: non-limb-threatening and limb-threatening infections (30, 41, 77, 151, 177, 429). This scheme implies severity of infection and, accordingly, directs subsequent management while also portending a general prognosis for outcome.

Clinically, non-limb-threatening infections are usually seen with ulceration that is superficial, without significant ischemia, and a wound that does not probe to bone or joint (41). Ulceration, however, does not need to be present, since non-limb-threatening infections can result from small puncture wounds, scratches, or simple fissures. Cellulitis in this category of infections is 2 cm or less from the ulceration or portal of entry. Patients with non-limb-threatening infections are medically stable and usually do not present with signs and symptoms of systemic involvement. This relatively mild to moderate infection can be managed on an outpatient basis, with close supervision from the clinician (30, 430).

Limb-threatening diabetic foot infections have cellulitis that extends beyond 2 cm (430). Additional clinical features may include fever, edema, lymphangitis, hyperglycemia, leukocytosis, and ischemia; however, the diabetic patient with a relatively severe infection may not necessarily present with these signs and symptoms (178). If an ulcer is present it may probe to bone or joint, which is highly predictive of osteomyelitis (285). Therefore, it is important to review the patient's entire clinical assessment (see Table 3) to guide the clinician to the proper course of treatment. Gangrene, abscesses, osteomyelitis, and necrotizing fasciitis may also
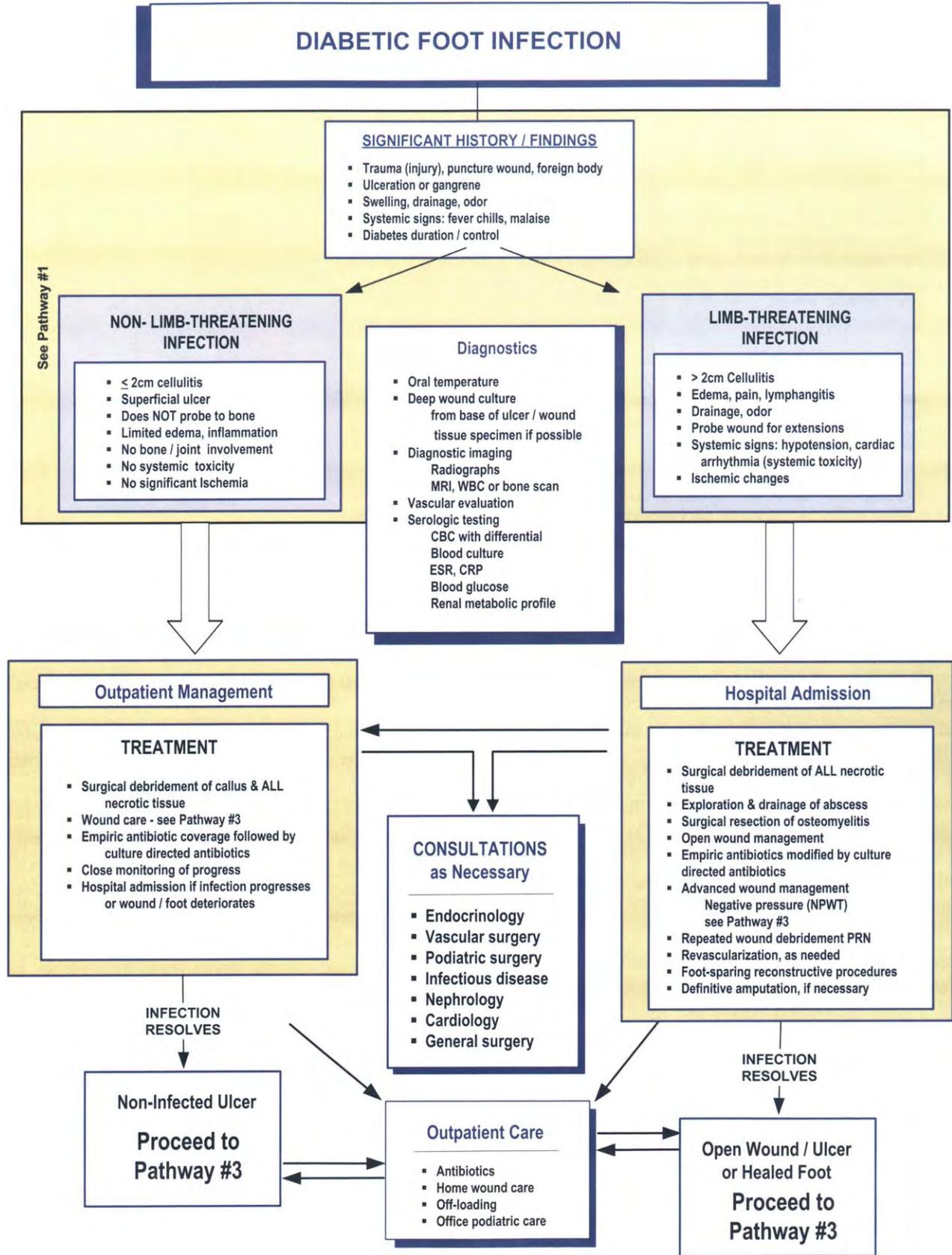
PATHWAY #4

DIABETIC FOOT INFECTION

See Pathway #1

SIGNIFICANT HISTORY / FINDINGS

- Trauma (injury), puncture wound, foreign body
- Ulceration or gangrene
- Swelling, drainage, odor
- Systemic signs: fever chills, malaise
- Diabetes duration / control

NON- LIMB-THREATENING INFECTION

- ≤ 2cm cellulitis
- Superficial ulcer
- Does NOT probe to bone
- Limited edema, inflammation
- No bone / joint involvement
- No systemic toxicity
- No significant Ischemia

Diagnostics

- Oral temperature
- Deep wound culture
  from base of ulcer / wound
  tissue specimen if possible
- Diagnostic imaging
  Radiographs
  MRI, WBC or bone scan
- Vascular evaluation
- Serologic testing
  CBC with differential
  Blood culture
  ESR, CRP
  Blood glucose
  Renal metabolic profile

LIMB-THREATENING INFECTION

- > 2cm Cellulitis
- Edema, pain, lymphangitis
- Drainage, odor
- Probe wound for extensions
- Systemic signs: hypotension, cardiac arrhythmia (systemic toxicity)
- Ischemic changes

Outpatient Management

TREATMENT

- Surgical debridement of callus & ALL necrotic tissue
- Wound care - see Pathway #3
- Empiric antibiotic coverage followed by culture directed antibiotics
- Close monitoring of progress
- Hospital admission if infection progresses or wound / foot deteriorates

CONSULTATIONS as Necessary

- Endocrinology
- Vascular surgery
- Podiatric surgery
- Infectious disease
- Nephrology
- Cardiology
- General surgery

Hospital Admission

TREATMENT

- Surgical debridement of ALL necrotic tissue
- Exploration & drainage of abscess
- Surgical resection of osteomyelitis
- Open wound management
- Empiric antibiotics modified by culture directed antibiotics
- Advanced wound management
  Negative pressure (NPWT)
  see Pathway #3
- Repeated wound debridement PRN
- Revascularization, as needed
- Foot-sparing reconstructive procedures
- Definitive amputation, if necessary

INFECTION RESOLVES

Non-Infected Ulcer

Proceed to Pathway #3

Outpatient Care

- Antibiotics
- Home wound care
- Off-loading
- Office podiatric care

INFECTION RESOLVES

Open Wound / Ulcer or Healed Foot

Proceed to Pathway #3

Table 10

IDSA Guidelines for the Clinical Classification of Diabetic Foot Infections

Clinical Evidence of Infection	Infection Severity	PEDIS Grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of ≥2 manifestations of inflammation (purulence, erythema, pain, tenderness, warmth, or induration), but cellulitis/erythema extends ≤2 cm from margins of ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but has 1 of the following characteristics: cellulitis extending >2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (eg, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe	4

be present. Hospitalization is required to treat the infection as well as systemic sequelae. Patients with poor vascular status and ischemia have an increased potential for amputation and require prompt consultation for potential revascularization (30, 77, 200).

In 2004, the Infectious Disease Society of America (IDSA) developed new guidelines for the diagnosis and treatment of diabetic foot infections (123). The guidelines incorporate the infection portion of the PEDIS system into IDSA's preferred clinical classification for infections in the diabetic foot (Table 10).

Assessment of Diabetic Foot Infections

When evaluating the patient with a diabetic foot infection, a problem-directed history and physical examination should be obtained. A systematic approach to the complete assessment of these patients is required, since there is evidence that they are often inadequately evaluated, even when hospitalized (431). The past medical history should assess the patient's neurologic, cardiovascular, renal, and dermatologic status. Use of current medications as well as previous antibiotics may interfere with planned treatments or indicate that standard treatments will likely be ineffective. Pain should be considered an unreliable symptom in ttindividuals with peripheral neuropathy. The patient should be questioned regarding previous ulcerations, infections, trauma, and surgeries at the present site or at any other past location of infection.

Constitutional symptoms (eg, nausea, malaise, fatigue, vomiting, fever, chills) are important clinical clues when presented with an infected diabetic foot. Severe infection or sepsis must be considered when these symptoms are present. However, in about 50% of diabetic patients presenting with significant infection, systemic signs (fever and leukocytosis) are absent (178). Frequently, the only indication of infection is unexplained or recalcitrant hyperglycemia. Laboratory testing might include a CBC with or without differential, blood cultures, glycosylated hemoglobin, fasting blood sugar, sedimentation rate, and urinalysis. Other tests should be performed as indicated by the patient's condition or comorbidities.

The history of the wound or infection should include the onset, duration, and appearance before infection of the area. Depth or size of the ulcer, amount of drainage, swelling, color, odor, and extent of infection should be evaluated. The infection or ulcer should be probed to determine the presence of bone or joint involvement, sinus tracts, or extension into tendon sheaths. The latter are common routes for the spread of infection both distally and proximally. Reliable aerobic and anaerobic cultures should be obtained from
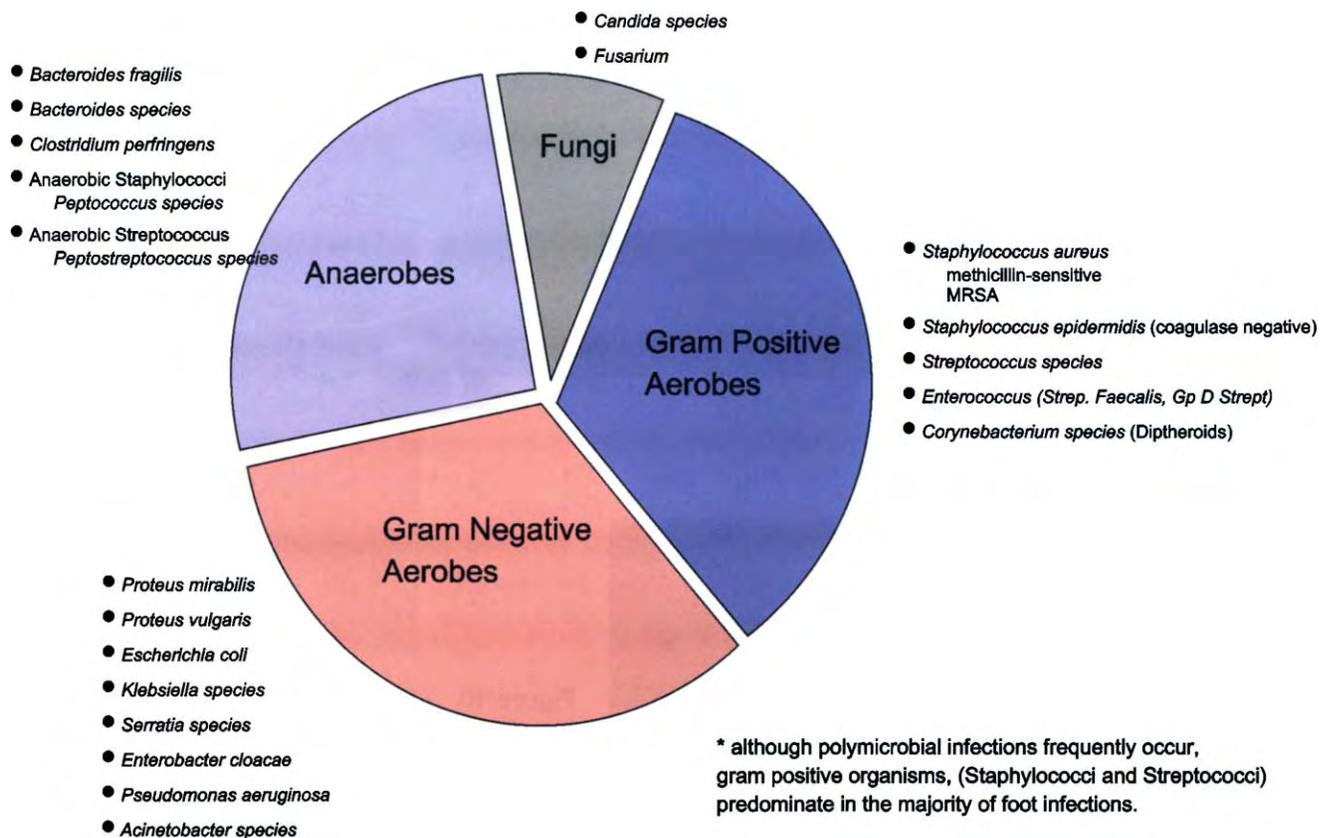
Candida species
Fusarium

Fungi

Bacteroides fragilis
Bacteroides species
Clostridium perfringens
Anaerobic Staphylococci
  Peptococcus species
Anaerobic Streptococcus
  Peptostreptococcus species

Anaerobes

Gram Positive
Aerobes

Staphylococcus aureus
  methicillin-sensitive
  MRSA
Staphylococcus epidermidis (coagulase negative)
Streptococcus species
Enterococcus (Strep. Faecalis, Gp D Strept)
Corynebacterium species (Diptheroids)

Gram Negative
Aerobes

Proteus mirabilis
Proteus vulgaris
Escherichia coli
Klebsiella species
Serratia species
Enterobacter cloacae
Pseudomonas aeruginosa
Acinetobacter species

* although polymicrobial infections frequently occur,
gram positive organisms, (Staphylococci and Streptococci)
predominate in the majority of foot infections.

Figure 9   Diabetic foot infections are generally considered polymicrobial, because multiple organisms are frequently found in a wound milieu. *Staphylococcus* and *Streptococcus* remain the most important organisms causing infection.

purulent drainage or curettage of the ulcer base, since studies have shown good concordance with the true pathogen (116, 428, 432). Simple swab cultures of an ulcer surface are generally not advisable because they tend to be unreliable, especially in the presence of osteomyelitis or sinus tracts (123, 433, 434).

For patients with clinically uninfected or noninflamed neuropathic ulcers, the role of antibiotic therapy is still in question (30). Therefore, in these instances, wound culture is probably unnecessary (123). If osteomyelitis is suspected, bone cultures are necessary to make the definitive diagnosis and isolate the true pathogen (180, 435, 436). However, this must be balanced against the potential for contaminating noninfected bone in the presence of an active soft tissue infection. Intraoperative frozen section is also useful in assessing for deep infection. The presence of more than 5 to 10 neutrophils per high power field is suggestive of acute infection (437).

The majority of wounds are caused by *Staphylococcus aureus*, beta-hemolytic streptococci, and other gram positive cocci (Fig 9) (151, 438, 439). Although community-acquired cases of resistant bacterial infections have been reported, patients who have been previously hospitalized with an open wound are more likely to develop an infection from resistant bacteria such as methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant enterococci (VRE) (440). Chronic wounds may develop a more complex assortment of bacteria, including gram negative rods, obligate anaerobes, *Pseudomonas aeruginosa*, and enterococci.

Imaging studies are also important in the overall assessment of diabetic foot infections, notwithstanding their shortcomings. Plain film x-rays may indicate the presence of bony erosions and/or gas in the soft tissues. It should be noted that the demonstration of osteomyelitis by plain radiographs lags the onset of bone involvement by 10 to 14 days (180, 197). Radionucleotide bone scans such as Tc-99 may demonstrate abnormal uptake of the radionucleotide before changes are visible on radiographs (179). This may be less specific in patients with peripheral neuropathy or with any preexisting osseous condition that causes increased bone turnover (eg, surgery, fracture, neuropathic arthropathy) (441). A combination of scans such as the Tc-99m and an indium-labeled leukocyte scan or the Tc-99m HMPAO-labeled leukocyte scan may aid the clinician in differentiat-
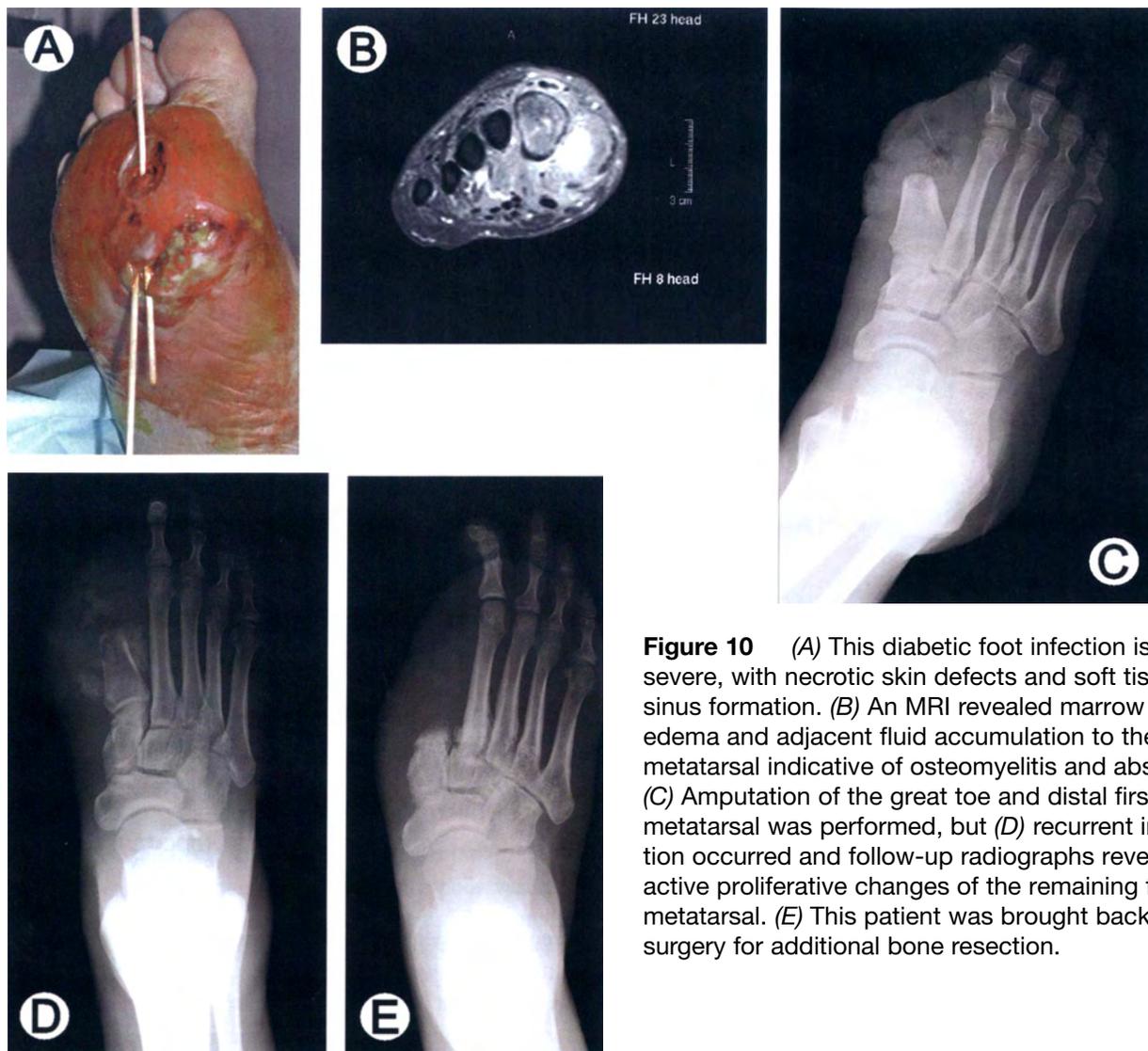
Figure 10 *(A)* This diabetic foot infection is quite severe, with necrotic skin defects and soft tissue sinus formation. *(B)* An MRI revealed marrow edema and adjacent fluid accumulation to the first metatarsal indicative of osteomyelitis and abscess. *(C)* Amputation of the great toe and distal first metatarsal was performed, but *(D)* recurrent infection occurred and follow-up radiographs revealed active proliferative changes of the remaining first metatarsal. *(E)* This patient was brought back to surgery for additional bone resection.

ing Charcot arthropathy and osteomyelitis with greater accuracy (185, 186, 203). MRI has generally supplanted the CT scan in the early diagnosis of osteomyelitis (Fig 10), due to its higher tissue contrast and ability to detect both soft tissue and marrow inflammation (183, 200, 202, 442). Additionally, MRI can be used to follow the resolution of infection or as an aid in surgical planning (201, 443). However, none of these imaging modalities are 100% sensitive and specific for diagnosing or ruling out bone infection. Furthermore, these tests are expensive and may not be readily available. Appropriate clinical assessment and diagnostic acumen should therefore remain the guiding principles to management.

Treatment of Diabetic Foot Infections

Diabetic foot infections should be managed through a multidisciplinary team approach utilizing appropriate con-

sultations (173, 178, 300). Hospitalization of patients with limb-threatening infections is mandatory. All diabetic foot infections must be monitored closely. Equally important for the best possible outcome are patient compliance and education, especially in outpatient management.

Treatment of Non-Limb-Threatening Infections

Treatment of diabetic foot infections is guided by the severity of the infection. As previously discussed, non-limb-threatening infections involve superficial ulcerations without significant ischemia and they do not involve bone or joint (430). Typically, cellulitis does not extend 2 cm beyond the ulcer margins and there is an absence of systemic symptoms (e.g. fever, chills, nausea, vomiting). These less severe infections that frequently complicate diabetic foot ulcers, may be initially treated in an outpatient setting (41, 438, 444). Many mild or moderate infections are

monomicrobial, with *S aureus, S epidermidis*, and strepto-cocci the most common pathogens (119, 121, 439). Reliable specimens for cultures may be obtained through curettage of the infected ulcer (120, 123, 445, 446). In addition to the standard treatment for ulcerations (ie, nonweightbearing and dressing changes), oral antibiotic therapy is usually sufficient as initial therapy (Table 11). Antimicrobial treatment should be started as soon as possible with an agent providing adequate gram positive coverage, recognizing that gram negative organisms might also be involved (287, 438, 439). Although the incidence of MRSA infections has increased dramatically in the past several years, methicillin-sensitive *S aureus* (MSSA) remains the most likely pathogen in community-acquired diabetic foot infections (123, 447). Therefore, initial antibiotic coverage must be tailored to cover MSSA, unless a reliable culture and sensitivity is available or there is a history of other pathogens (eg, MRSA, *Pseudomonas*, enterococcus) that require specific coverage. Antibiotics should be adjusted according to culture results and the patient's response to treatment.

While many useful oral antimicrobial agents (eg, cephalexin, clindamycin, amoxicillin/clavulanate, levofloxacin) are available for managing mild to moderate diabetic foot infections, relatively few have been studied or have demonstrated superiority in prospective randomized clinical trials (123). Therefore, IDSA guidelines contain no specific recommendations for antimicrobial regimens in the management of diabetic foot infections.

All antibiotic treatments should be monitored for development of resistance. Most cases of cellulitis respond within 3 to 5 days of initiation of appropriate antibiotics. If cellulitis is slow to respond, worsens, or recurs following several days of treatment, the ulceration should be reassessed and possibly recultured. Bacteria frequently develop resistance to an antimicrobial agent, especially with prolonged therapy. This is not uncommon with the quinolones.

Table 11   Empiric Antibiotic Therapy: Diabetic Foot Infections

Limb-Threatening

- Ampicillin / Sulbactam
- Ticarcillin / Clavulanate
- Piperacillin / Tazobactam
- Ceftazidime + Clindamycin
- Cefotaxime ± Clindamycin
- Fluoroquinolone + Clindamycin
- Vancomycin + Levofloxacin + Metronidazole
- Linezolid
- Imipenem / Cilastatin
- Ertapenem
- Tigecycline

Life-Threatening

- Ampicillin / Sulbactam + Aztreonam
- Piperacillin / Tazobactam + Vancomycin
- Vancomycin + Metronidazole + Ceftazidime
- Imipenem / Cilistatin
- Fluoroquinolone + Vancomycin + Metronidazole
- Ertapenem
- Tigecycline

Non-Limb-Threatening[*]

- Cephalosporin (Celphalexin, Cefadroxil, Cefdinir)
- Fluoroquinolones (Levofloxacin, Moxifloxacin, Gatifloxacin)
- Penicillins (Dicloxacillin, Amoxicillin/Clavulanate)
- Linezolid
- Trimethoprim / Sulfamethoxazole
- Doxycycline

[*] Generally oral agents are utilized for non-limb-threatening infections as most are treated outpatient.

Superinfection can also develop when antibiotics select out opportunistic organisms, as in the case of *Pseudomonas* or yeast (*Candida* sp). Because MRSA infections have become increasingly more common pathogens and are associated with prior antimicrobial exposure (447, 448), patients with clinical infection and a prior history of MRSA should be considered to have the same pathogen until proven otherwise and treated accordingly.

Antimicrobial therapy alone is not sufficient for treating infections associated with foot ulcers (272, 449, 450). The wound should be assessed and cleansed thoroughly, using proper debridement as indicated. While there are several topical antimicrobial agents that can be used on the infected wound, there is little data on topical treatment (287). Therefore, such therapy at present can only be considered adjunctive to systemic antimicrobial therapy.

The wound should be managed according to the principles discussed previously. Most importantly, the patient should be reassessed within 48 to 72 hours. If no improvement is noted, hospitalization with intravenous antibiotics should be considered. Management of this type of infection should also include close monitoring of the patient's hyperglycemia and general health status. Patient compliance as well as a reduction in the pressure of the infected limb must be considered early on in the treatment of any diabetic foot infection (77, 451).

Treatment of Limb-Threatening Infections

By definition, limb-threatening infections are much more serious and more often acute compared with the milder non-limb-threatening infections. In the PEDIS system (Table 10), limb-threatening infections are classified as grade 3 or 4, depending on severity and the presence of systemic manifestations (122, 123, 452). Neuropathy often predisposes such infections to progression to an emergent situation before the patient even becomes aware of the infection's presence. Limb-threatening infections may have life-threatening complications, especially when left untreated. Because of diabetes-associated immunosuppression, up to 50% of patients with limb-threatening infections may exhibit no systemic symptoms or leukocytosis (118, 178, 453). However, other patients present with evidence of systemic toxicity, including fever, chills, loss of appetite, and malaise. Such findings in diabetic patients should alert clinicians to the severity of infection. Most will note uncontrollable hyperglycemia despite usual therapy and loss of appetite (41, 454).

Limb-threatening infections are recognized as having one or more of the following findings: greater than 2 cm of cellulitis around an ulcer, lymphangiitis, soft tissue necrosis, fluctuance, odor, gangrene, osteomyelitis (30, 77, 430). When such an infection is recognized, the patient requires emergent hospital admission for appropriate intervention (116, 200, 272). Upon admission, a complete history and physical examination are undertaken. The patient's cardiovascular, renal, and neurologic risks should be evaluated to assess for secondary complications of diabetes and associated comorbidities. A thorough foot evaluation is undertaken to determine the clinical extent of the infectious process. Vascular status must be assessed to ensure that appropriate arterial inflow is present. If perfusion is inadequate, this should be addressed prior to definitive reconstruction to enhance healing at a more distal level.

Radiographs are necessary to evaluate for evidence of osteomyelitis or soft tissue gas. If gas is identified in the ankle or hindfoot, radiographs of the lower leg should be obtained to assess the extent of the gas formation. Blood cultures are required if clinical findings indicate septicemia. Other appropriate laboratory studies, including CBC with differential and sedimentation rate, are obtained as warranted. Glucose management must be initiated to optimize metabolic perturbations and improve leukocyte function (455). The patient's nutritional and metabolic status must be assessed and properly maintained, since relatively common nutritional and metabolic impairments in these patients can adversely affect wound healing and resolution of infection (314, 456, 457).

Consultations are typically required in the risk assessment and management of these complex cases. Medical, endocrinology, cardiology, nephrology, and diabetic teaching nurse consultations are often routinely needed to optimize patient care and fully assess surgical risks (181, 429). Infectious disease and vascular surgery consultations are also obtained when complex infections or significant ischemia are identified, respectively. A multidisciplinary approach to the management of these cases has been shown to significantly improve outcomes (163, 165, 173, 278, 300, 458-461).

Early surgical treatment of the affected site is typically necessary as an integral part of infection management (178, 451, 460, 462). This may include simple debridement of the soft tissues, wide incision and drainage of the pedal compartments, or open amputation to eliminate extensive areas of infection (124, 463, 464). At the time of debridement, aerobic, anaerobic, and fungal tissue cultures should be obtained from the depth of the wound to provide reliability (287, 432, 446). Although many initial drainage procedures can be performed at the bedside for neuropathic patients, most require thorough debridement in the operating room. Anesthesia for such interventions may include local, region-

al, or general anesthetics. However, spinal blocks are typically avoided in patients who may be septic.

Even the sickest of patients should be considered for emergent incision, drainage, and debridement procedures, because their illness in this regard is directly attributable to the infection severity. Such life-threatening infections necessitate immediate surgical attention, without delay in obtaining radiologic or medical work-up of other comorbid conditions (41, 77, 462, 463). Polymicrobial infection should be anticipated in these patients (Fig 9), with a variety of gram positive cocci, gram negative rods, and anaerobic organisms predominating (287, 465, 466). Accordingly, empirical antibiotic therapy typically includes broad-spectrum coverage for more common isolates from each of these three categories (Table 11). Fully comprehensive empiric coverage is usually unnecessary unless the infection is life-threatening (118, 123).

Hospital therapies are usually initiated with intravenous medications, although most oral fluoroquinolones and oral linezolid have the same bioavailability as parenteral therapy (119, 438, 467). Once wound culture results become available, the initial antimicrobial therapy may require adjustment to provide more specific coverage or provide therapy against resistant organisms causing persisting infection. Recent evidence also supports the efficacy of initial parenteral therapy followed by the appropriate oral agent in the management of these patients (438, 466, 468). If the patient develops evidence of recurrent infection while receiving antibiotic therapy, repeat cultures should be obtained to assess for superinfection. Methicillin-resistant staphylococci, which have emerged as important pathogens in chronically-treated diabetic foot ulcer patients (447, 448), must be detected early and treated appropriately to avoid further tissue loss or extension of infection.

The surgical wound may require repeated surgical debridement to completely eradicate infection and soft tissue necrosis (451, 460, 463). Wound care is initiated on day 1 or day 2 postsurgery and may initially involve saline gauze dressing changes. Other dressings may be used to aid in healing. Negative pressure wound therapy (V.A.C.®, KCI, San Antonio, TX) has been found particularly useful in this regard (393, 404, 410). If the wound fails to show signs of healing, the patient's vascularity, nutritional status, infection control, and wound off-loading must be re-evaluated.

Once soft tissue infection is under control and management of any osseous infection has been initiated, consideration may be given to wound closure or definitive amputation. Restoration and maintenance of function and independence is the ultimate goal for the patient (77, 463). The residual extremity requires close follow-up, regular diabetic foot exams, periodic foot care, and appropriate footwear therapy (25, 30, 151, 272).

Osteomyelitis and joint infection (Fig 11), when identified by clinical assessment or imaging studies, require a sampling of bone for microbiologic and histopathologic evaluation (200, 469). If the patient's soft tissue infection is controlled, consideration may be given to stopping antibiot-

Figure 11   This 60-year-old female with diabetes and a history of plantar callus presented with *(A)* ulceration sub 4th metatarsal head and *(B)* 4th left toe, and poor diabetic control. A severe foot infection was apparent and *(C)* radiographs showed erosive disorganization of the 4th MTP joint. The patient developed a foot infection secondary to the plantar callus that progressed to osteomyelitis of the 4th toe and 4th metatarsal. *(D)* She was treated with parenteral antibiotics and ray resection.

ic therapy 24 to 48 hours presurgery to improve culture accuracy. A diagnosis of osteomyelitis requires that both culture and biopsy studies reveal positive findings, including necrosis, chronic inflammatory infiltrates, and positive isolation of bacteria (180). Resection of infected bone with or without local amputation and concurrent antimicrobial therapy is the most optimal management for osteomyelitis (124, 470). However, the routine need for surgery in this condition has recently been questioned (435). In some cases, based on patient morbidity or preferences, medical therapy alone for osteomyelitis might be warranted (123). If the affected bone has been completely resected or amputated, the infection may be treated as a soft tissue infection. However, if residual bone is present in the wound, the patient will likely require 4 to 8 weeks of antibiotic therapy based on the culture results (119, 287).

Intravenous or oral agents may be used, depending on the microbial isolates and infection severity (123). Antibiotic impregnated bone cement has been advocated for treatment of osteomyelitis, but it should only be used if the bone has been thoroughly debrided and the soft tissue envelope is adequate for wound closure following antibiotic-impregnated bead placement (471, 472). Gentamicin, tobramycin, or vancomycin are typically used in the beads. It is generally recommended that antibiotic beads be removed 2 weeks or so after placement. An alternative to bone cement is absorbable bone graft substitutes mixed with antibiotic powder (473). The pellets are gradually resorbed as the antibiotic is eluted, thus offering the advantage of avoiding a second operation for removal. While widely used in this regard, studies are lacking as to the efficacy of either modality compared with systemic antimicrobial therapy alone. If the infection fails to respond to therapy, the patient should be fully reassessed as previously discussed.

DIABETIC CHARCOT FOOT (NEUROPATHIC OSTEOARTHROPATHY) (Pathway 5)

Charcot foot (neuropathic osteoarthropathy) is a progressive condition characterized by joint dislocation, pathologic fractures, and severe destruction of the pedal architecture. This condition can therefore result in debilitating deformity or even amputation (129, 131, 133-135, 474).

Etiology of Neuropathic Osteoarthropathy

The etiology of Charcot neuroarthropathy is most likely a combination of the effects involved in the neurovascular and neurotraumatic theories (79, 129, 130, 135, 138, 140, 475-477). Trauma superimposed on a severely neuropathic extremity is the most widely accepted theory regarding the development of an acute Charcot foot (478). As a result of associated autonomic neuropathy, blood flow to the foot increases, resulting in osteopenia and attendant weakness of the bone (130, 139, 476, 479, 480). Because of the loss of protective sensation that accompanies peripheral sensory neuropathy, the patient is unaware of the initiating trauma and the profound osseous destruction that often occurs during ambulation. A vicious cycle ensues in which the patient continues to walk on the injured foot, allowing further damage to occur (129, 134, 478, 481) (Fig 12).

There is good evidence suggesting that the effects of neuropathy combined with associated vascular response are involved in the development of Charcot arthropathy (479, 482). Additionally, recent findings suggest that type 1 diabetes may have a greater preponderance of decreased bone density than type 2 diabetes (130, 483). Furthermore, the age of onset for acute Charcot arthropathy appears to be lower for type 1 than type 2 diabetes. Large cohorts of patients or patients with type 2 diabetes alone tend to be in their sixth to seventh decades at presentation, while patients with type 1 diabetes generally develop neuroarthropathy in the fourth to fifth decades (478, 483, 484). Various metabolic factors have also been implicated as potentially etiologic. One recent theory receiving much interest is the role of proinflammatory cytokines and the RANK-L - N-FkB pathway (485, 486). RANK-L, a member of the TNF-a superfamily, causes upregulation of the nuclear transcription factor kB (NF-kB), leading to an increase in osteoclastogenesis and subsequent osteolysis. A decoy receptor for RANK-L, osteoprotegerin (OPG), modulates the activity of RANK-L and NF-kB expression. The excessive inflammation characteristic of the acute Charcot event likely disturbs the normal RANK-L/OPG balance and promotes the excessive osteolysis seen in this disorder. Vascular calcification, which is common in these patients, is also linked to this pathway (479, 487, 488).

Clinical Diagnosis of Acute Charcot Arthropathy

The initial diagnosis of acute Charcot arthropathy is often clinical, based on profound unilateral swelling, increased skin temperature, erythema, joint effusion, and bone resorption in an insensate foot (136, 478, 489, 490). These characteristics in the presence of intact skin are often pathognomonic of acute neuroarthropathy. In more than 75% of cases, the patient will present with some degree of pain in an otherwise insensate extremity (135). The diagnosis is complicated by the fact that in some cases, patients first present with a concomitant ulceration, raising questions of potential contiguous osteomyelitis (140, 491, 492).
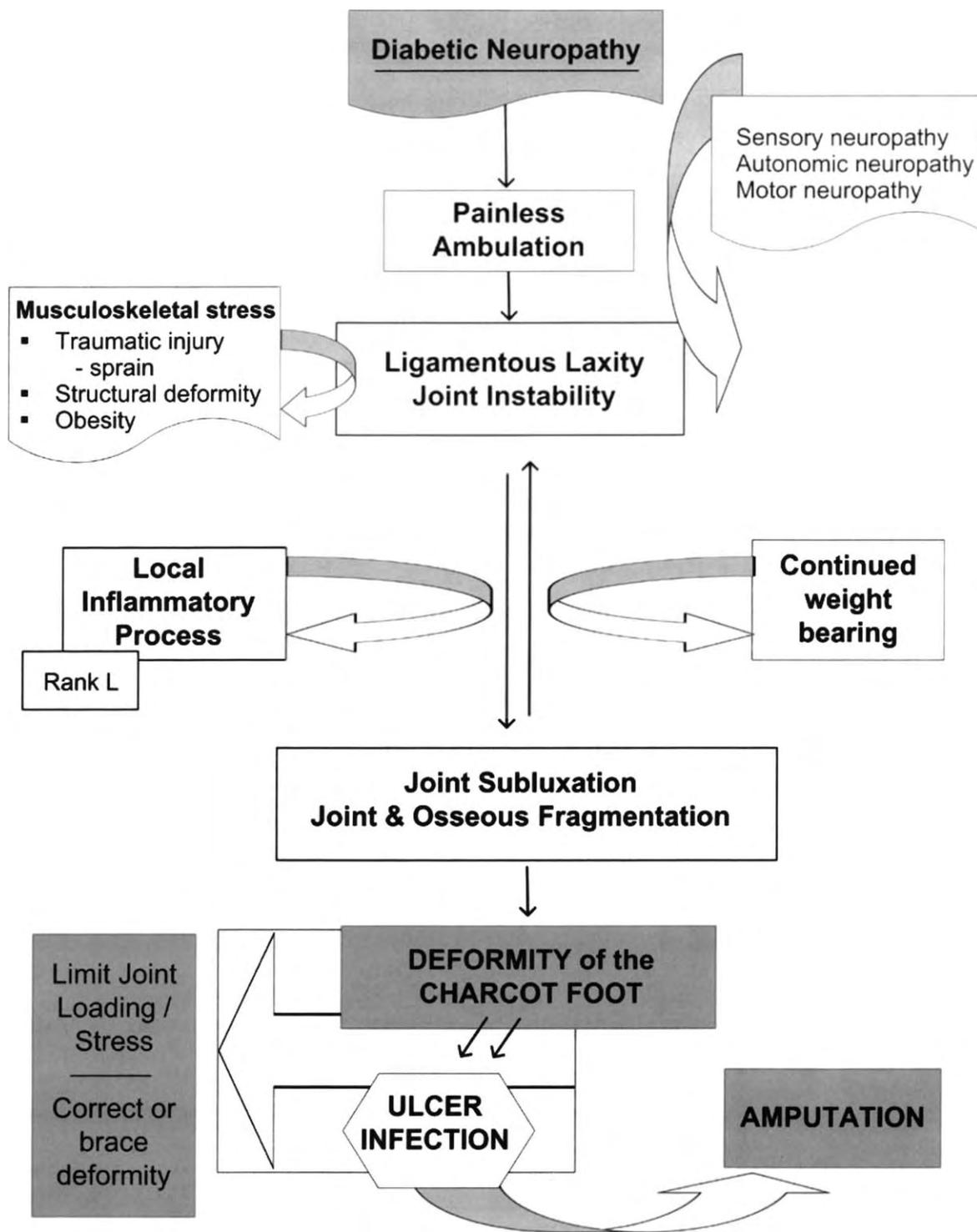
PATHWAY #5

CHARCOT FOOT

Refer to Pathway #1

SIGNIFICANT HISTORY

- Onset of morphologic changes
  - Progressive / static
  - Erythema
  - Swelling
- Trauma: type, when, repetitive
- LOPS +/- pain
- Previous ulcer &/or Charcot
- Long-standing diabetes

SIGNIFICANT FINDINGS

Dermatologic
- Erythema
- Warmth
- Cellulitis
- Xerosis
- +/- Ulcer

Musculoskeletal
- Swelling
- Deformity
- Joint dislocation
- Equinus

Neurologic
- LOPS
- Autonomic neuropathy
- Motor neuropathy
- Absent DTRs

Vascular
- Papable pedal pulses
- Swelling

- Laboratory tests
  - CBC differential
  - ESR, CRP
  - Blood glucose
  - Hb A1c
  - Alkaline phosphatase
- Bone biopsy
- Bone culture

Diagnostic Imaging
- Plain radiographs
- Imaging studies
  - CT
  - MRI
  - Bone scan
  - Bone density

Radiographic Findings
- Joints/bones involved
- Osteolysis
- Fractures
- Bone density
- Dislocation
- Soft tissue edema
- Vascular calcifications
- Deformity

* Additional Diagnostic Procedures as Indicated

DIAGNOSIS

ACUTE

Treatment of Acute Charcot

- Restriction of weight-bearing
  - Crutches
  - Wheelchair
- Immobilization with splint, cast or removable cast until hyperemia resolved
- Continue immobilization 4-6 months until quiescence (chronic Charcot)
- Pharmacologic
- Bone stimulation

CHRONIC

Treatment of Chronic Charcot

Foot Unstable
- Bracing
- Extra depth shoes
- Custom molded shoes
- Multiple density insoles
- Orthoses

Foot Stable
- Supportive measures
- Therapeutic footwear
- Patient education
- Periodic evaluation to prevent recurrence

Foot remains UNSTABLE not responsive to off-loading & immobilization

Consider surgical stabilization

Convert to Stable Foot

Once quiescent, treat as chronic

Remains unstable
Chronic ulceration
Chronic osteomyelitis

Consider amputation

If ulcer recurs, treat appropriately, see Pathway #3

Figure 12 Diabetic neuroarthropathy, or Charcot foot, is believed to be a neurologically-mediated complication of diabetes, with the development modified by musculoskeletal stress. The result is osseous fragmentation and joint subluxation with often significant morphologic changes in the architecture of the foot. Complications of the Charcot foot include ulceration under areas of bony prominence and potential amputation often related to infection/osteomyelitis that develops adjacent to the area of ulceration.

If the patient presents with a warm, edematous, erythematous, insensate foot, plain radiographs are invaluable in ascertaining presence of osteoarthropathy (493, 494). In most cases, no further imaging studies are required to make the correct diagnosis. With a concomitant wound, it may be difficult to differentiate acute Charcot arthropathy from osteomyelitis using plain radiographs alone (133, 183). Additional laboratory studies may prove useful in arriving at a correct diagnosis. The white blood cell count (WBC) with a left shift will often be elevated in acute osteomyelitis, although this can be blunted in diabetic patients (453). While the erythrocyte sedimentation rate and C-reactive protein level may also be elevated in acute infection, they often respond similarly to any inflammatory process and are therefore nonspecific. Bone biopsy, when indicated, is the most specific method for distinguishing osteomyelitis from osteoarthropathy in these circumstances. A biopsy consisting of multiple shards of bone and soft tissue embedded in the deep layers of synovium is pathognomonic for neuropathic osteoarthropathy (495).

Technetium bone scans are generally nonspecific in assisting in the differentiation between osteomyelitis and acute Charcot arthropathy (179, 185). Indium scanning, while more expensive, has been shown to be more specific (179, 193, 496). Additional studies to aid in differentiating osteoarthropathy from osteomyelitis include bone scans utilizing Tc HMPAO-labeled white blood cells, MRI, and PET scanning (183, 186, 190, 207).

Other serologic markers can be helpful for the diagnosis of acute Charcot osteoarthropathy. A marker for increased osteoclastic activity, 1CPT (carboxyterminal telopeptide of type 1 collagen), has been shown to be elevated but occurs without increased levels of procollagen carboxyterminal propeptide (P1CP), a marker for osteoblastic activity (497-499). Nonetheless, the most important diagnostic aid in this situation remains a high index of clinical suspicion when a neuropathic patient presents with a swollen or deformed foot (478, 493, 494).

Classification of Charcot Arthropathy

The most common classification system of Charcot arthropathy—the Eichenholtz classification system—is based on radiographic appearance as well as physiologic stages of the process. It divides the condition into three stages: developmental, coalescent, and reconstructive (495). The developmental stage is characterized by significant soft tissue swelling, osteochondral fragmentation, or joint dislocation of varying degrees. The coalescent stage is marked by a reduction in soft tissue swelling, bone callus proliferation, and consolidation of fractures. The reconstructive stage is denoted by bony ankylosis and hypertrophic proliferation.

Radiologically, the Eichenholtz system is very descriptive and useful, but its practical applicability has limitations. In clinical practice, the initial stage is considered active, while the coalescent and reconstructive stages are considered quiescent or reparative. More recently, several authors have proposed an earlier stage 0 that corresponds to the initial inflammatory period following injury but prior to the development of characteristic bony radiographic changes (500-503). This prodromal period might be considered a "Charcot *in situ*" stage. Diagnosis of the condition during this period, in which no deformity has yet developed, could ostensibly arrest further progression of the destructive inflammatory process (494).

Another popular classification system is based on five anatomic sites of involvement but does not describe disease activity (129, 136) (Fig 13). Several other classification schemes are described in the literature, but none has been found to be superior or predictive of outcome (500, 504-506).

Management of Acute Charcot Neuroarthropathy

Immobilization and stress reduction are the mainstays of treatment for acute Charcot arthropathy (129, 131, 135, 136, 478, 507, 508). Many clinicians advocate complete non-weightbearing through the use of crutches or other assistive modalities during the initial acute period. While this is an accepted form of treatment, three-point gait may in fact increase pressure to the contralateral limb, thereby predisposing it to repetitive stress and ulceration or neuropathic fracture (509). A short leg plaster or fiberglass non-weightbearing cast can additionally be used for acute Charcot events, even in patients with noninfected ulcerations (129, 135, 481). A soft compressive dressing in concert with a removable cast walker or pneumatic walking brace can also be used effectively in this regard (136, 139). Some centers prefer to initially apply a weightbearing total contact cast in the management of acute osteoarthropathy (135, 140, 493, 510-512). These ambulatory total contact casts should be changed at least every 1 to 2 weeks to adjust to limb volume changes as the edema decreases.

Following the initial period of off-loading, reductions in skin temperature and edema indicate the stage of quiescence, at which point the patient progresses into the postacute phase of treatment. Progression to protected weightbearing is permitted, usually with the aid of an assistive device. Through the use of appropriately applied total contact casts or other off-loading modalities (eg, fixed ankle walker, bivalved casts, total contact prosthetic walkers,
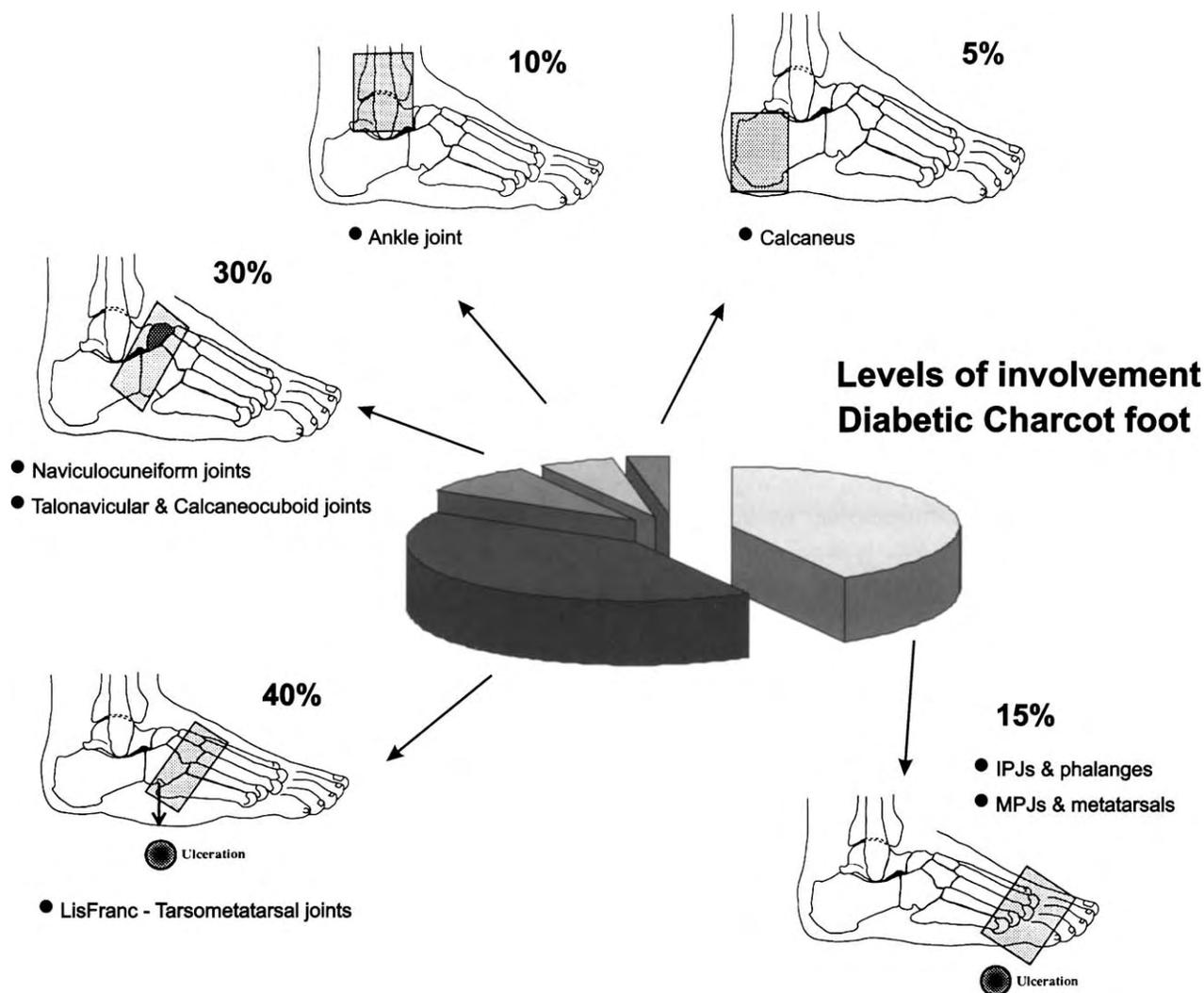
Figure 13 Diabetic neuroarthropathy may be classified according to the anatomic location of joint involvement. The relative percentage of frequency of involvement is given. (Adapted from Sanders LJ and Frykberg RG. *The High Risk Foot in Diabetes Mellitus*, p108, Churchill Livingstone, New York, 1991)

patellar tendon-bearing braces), most patients may safely ambulate while bony consolidation of fractures progresses (129, 135, 477, 478). Charcot restraint orthotic walkers (CROW) or other similar total contact prosthetic walkers have gained acceptance as useful protective modalities for the initial period of weightbearing (513-515). A more readily available option is a pneumatic walking brace or similar removable cast walker that might incorporate a cushioned foot bed or insole. These "instant total contact casts" are made nonremovable by simply applying tape or a fiberglass cast roll around the body of the walker to help encourage compliance (50, 516).

The mean time of rest and immobilization (casting followed by removable cast walker) prior to return to permanent footwear is approximately 4 to 6 months (133-135, 474, 478, 493). Custom full-length inserts and comfort or

extra-depth shoes should be worn when protective bracing is no longer required (136, 138, 513). Moderately unstable ankles will benefit from an ankle foot orthosis (AFO) and high-top therapeutic shoe, while a severely unstable or maligned rearfoot will require a patellar tendon-bearing (PTB) brace incorporated into a custom shoe (493, 517, 518). The PTB brace has reportedly decreased mean rearfoot peak forces by at least 32% (517).

There is recent interest in the adjunctive use of bisphosphonate therapy in acute Charcot arthropathy to help expedite conversion of the acute process to the quiescent, reparative stage (519-521). These pyrophosphate analogs are potent inhibitors of osteoclastic bone resorption and are widely used in the treatment of osteoporosis, Paget's disease, and reflex sympathetic dystrophy syndrome (50, 130). One randomized trial in the UK compared the use of a sin-

gle intravenous infusion of pamidronate with the use of saline infusion (498). The treatment group had significant declines in temperature and bone turnover markers (deoxypyridinoline crosslinks and bone specific alkaline phosphatase) in subsequent weeks compared with the control group, but no differences in clinical or radiographic outcomes were reported. A small trial comparing 6 months of oral alendronate plus off-loading with standard off-loading alone in acute Charcot patients found that the study group had significant reductions in 1CTP and hydroxyprolin, both of which are markers of bone resorption and increased foot bone density (499); no differences in clinical outcomes were noted.

Similarly, electrical bone growth stimulation has been applied to the management of acute neuroarthropathy to promote rapid consolidation of fractures (522-524). Low-intensity pulsed ultrasound (LIPUS) has also been suggested as a useful adjunct in promoting healing of Charcot fractures (525). Although promising in theory, none of these adjunctive treatments have yet been conclusively proven effective through large prospective multicenter, randomized trials.

Surgical Management of Charcot Osteoarthropathy

Reconstructive surgery in acute Charcot may be considered if a deformity or instability exists that cannot effectively be controlled or accommodated by immobilization and off-loading (136, 140, 478, 500, 510, 511, 526). If the neuroarthropathy is identified in its early stages and non-weightbearing is instituted, surgery is usually unnecessary. According to consensus opinion, surgery in the acute stage is generally nonadvisable due to the extreme hyperemia, osteopenia, and edema present (131, 132, 134, 135, 477, 511, 527, 528). However, surgical intervention during the acute phase may be considered in the presence of acute subluxation without osteochondral fragmentation (509, 529). One small series reported successful arthrodeses rates with preserved foot function in patients with acute arthropathy of the midfoot (530). Nevertheless, this aggressive surgical approach needs confirmation through larger comparative trials prior to its adoption in the routine management of the acute Charcot foot.

As few as 4% to as many as 51% of patients presenting to tertiary centers are reported to undergo surgical procedures for Charcot deformities (474, 527, 528). However, such centers often receive chronic cases from multiple referral
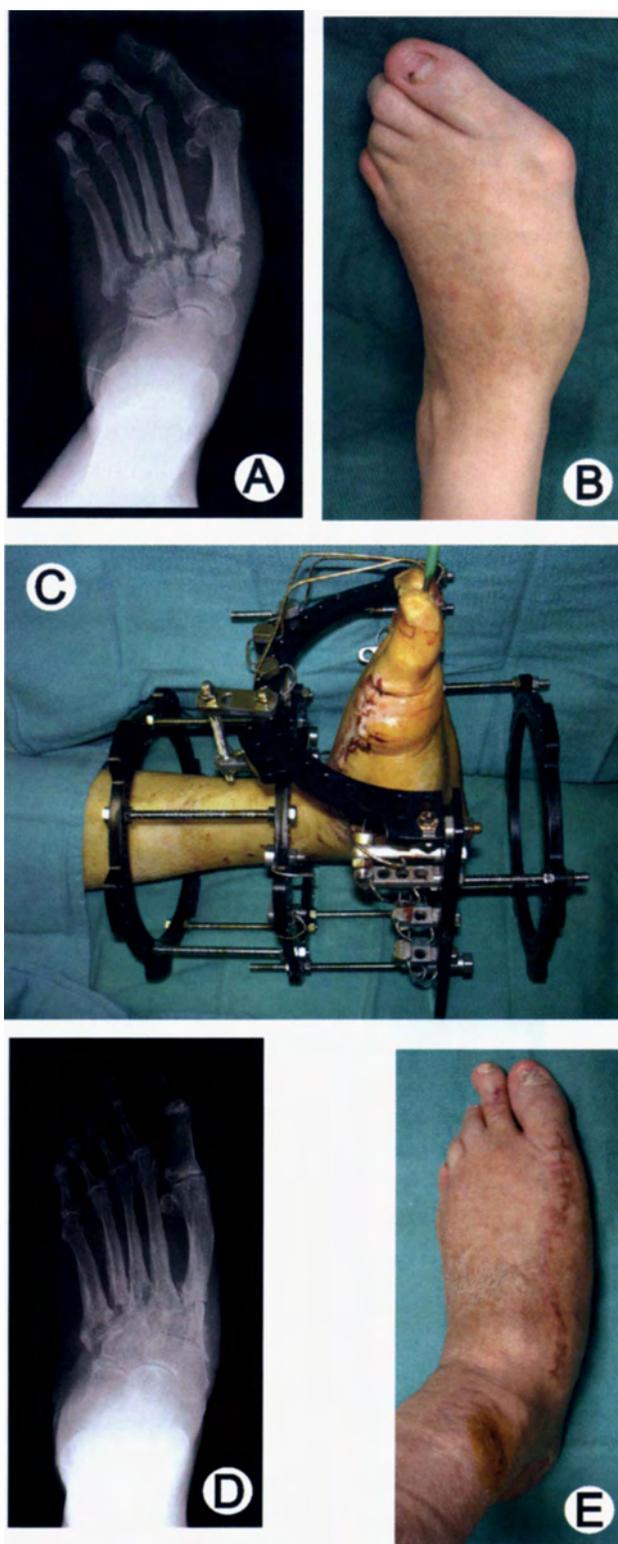
Figure 14 Severe midfoot collapse due to Charcot neuroarthropathy as shown *(A)* on radiograph and *(B)* in clinical presentation. *(C)* This patient was treated with tarsometatarsal arthrodesis using a multiplanar circular external fixator. *(D)* A postoperative radiograph and *(E)* clinical photograph at 4 months postoperative are shown here.

sources and with various degrees of deformity present; therefore, their rate of operation on these patients does not reflect the true incidence or need for such treatment in the community. A recent review of one center's experience with midfoot neuroarthropathy in 198 patients (201 feet) indicated that more than half of these patients could be successfully managed without surgery (510). Hence, large population-based studies are needed to assess the need for surgical intervention and compare the efficacy of various conservative therapies (474, 493, 520).

The goal of any surgery on the acute or chronic Charcot foot is to create a stable, plantigrade foot that may be appropriately accommodated (140, 478, 510, 530, 531). Most operations on chronic Charcot feet consist of exostectomies for prominent plantar ('rocker-bottom") deformities causing ulceration when the remainder of the foot is stable (135, 505, 511, 532) (Fig 14). However, more complex arthrodesis procedures are performed with increasing frequency and success, often using circular external fixation or intramedullary nails (140, 478, 526, 531, 533-537). These include isolated or multiple midfoot (Fig 15) or hindfoot fusions, triple arthrodeses, tibiocalcaneal fusions (Fig 16), and ankle fusions (538-542).

Following surgery, patients are immobilized until skin temperatures and postoperative edema normalize. As with patients treated nonsurgically, after prolonged cast immobi-

Figure 15 *(A)* This Charcot patient presented with a recalcitrant ulceration below an area of bony prominence, *(B)* as shown on radiograph. Surgical management consisted of excision of the ulcer, *(C)* exostectomy, and *(D)* primary wound closure.
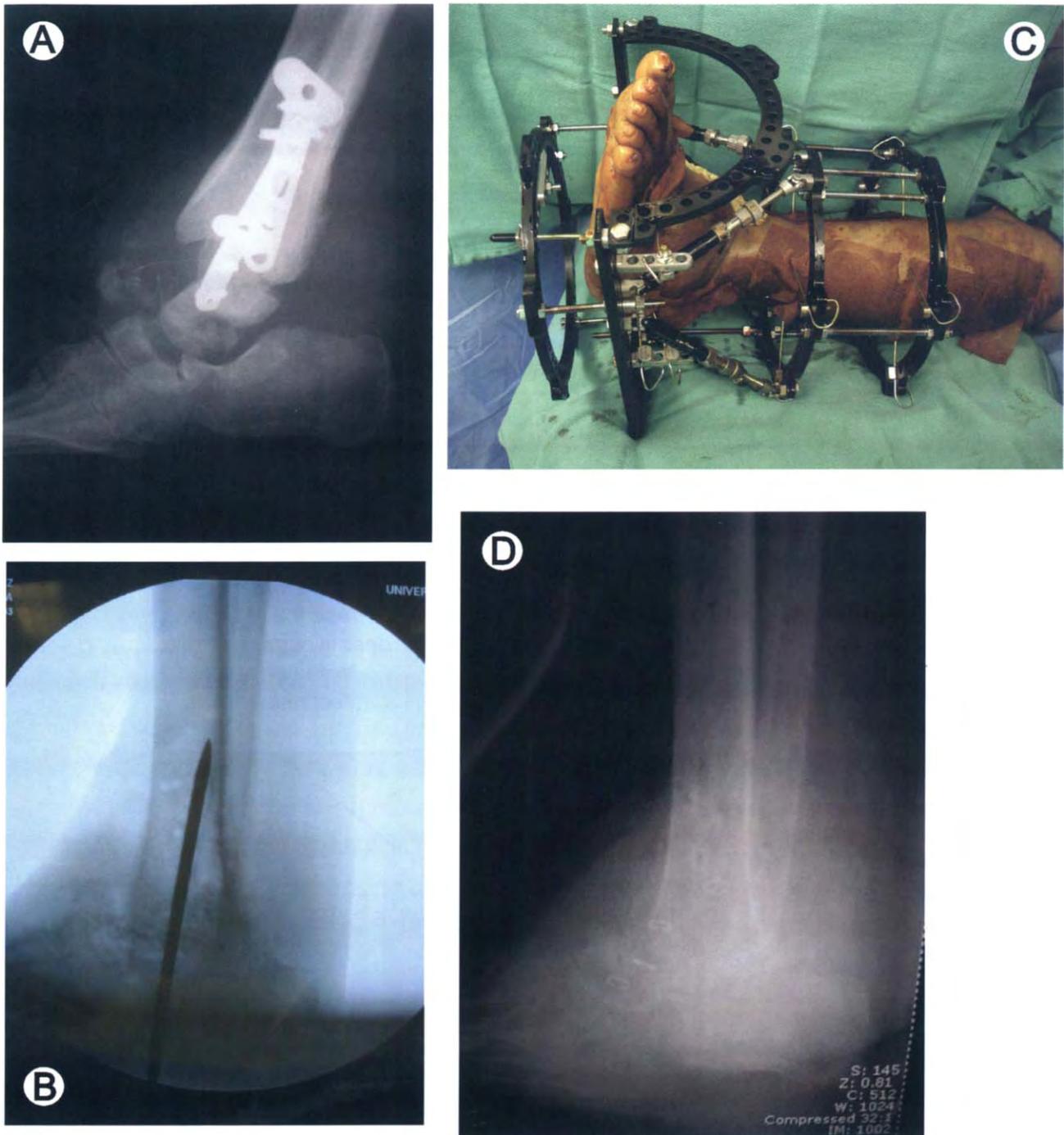
Figure 16 This neuropathic diabetic patient sustained an ankle fracture and underwent open reduction internal fixation. *(A)* At 3 months postoperatively, radiographs revealed Charcot disorganization and loss of reduction. *(B)* The patient was brought back to surgery for talectomy and tibiocalcaneal fusion, shown in this intraoperative image. *(C)* A multiplanar circular external fixator was applied to accomplish the arthrodesis procedure. *(D)* Radiograph shows union at the arthrodesis site at 5 months postoperative.

PATHWAY #6

SURGERY OF THE DIABETIC FOOT

Refer to previous Pathways

SIGNIFICANT HISTORY/FINDINGS

- Ulceration/open wound
  Progressive / static
- Infection
- Charcot +/- deformity
- Orthopedic deformity

* PAD if present, already addressed

Critical limb ischemia PAD → **Proceed to Pathway #2**

NO WOUND / **WOUND**

NO WOUND

Presence of foot deformity

Intact protective sensation

Presence of deformity combined with LOPS

ELECTIVE SURGERY

TO TREAT A PAINFUL FOOT DEFORMITY

- Structural correction of musculoskeletal deformity

PROPHYLACTIC SURGERY

TO REDUCE RISK OF ULCERATION OR AVOID REULCERATION

- Structural correction of musculoskeletal deformity

WOUND

Presence of ulcer, open wound, necrotic tissue or acute infection/abscess

CURATIVE SURGERY

TO ASSIST IN HEALING AN OPEN WOUND

- Repair deformity
- Resect infected bone or joint
- Plastic surgical reconstructive flaps or wound closure

Presence of acute infection

EMERGENT SURGERY

TO ARREST OR LIMIT PROGRESSION OF ACUTE INFECTION

- Ablative surgery aimed at elimination of infected and necrotic tissues

lization patients transition to a removable cast walker, followed by permanent prescription footwear or bracing (135, 543). Mean time from surgery to therapeutic shoes has been reported to be about 27 weeks (7 months) (135, 140, 530). Careful patient selection and management is the rule with these complex diabetic cases, since amputation can be a complication of failed surgical procedures (138, 474, 511, 527, 528, 533).

SURGICAL MANAGEMENT OF THE DIABETIC FOOT (Pathway 6)

Surgical management of the diabetic lower extremity can be a daunting task, but with appropriate patient and procedural selection, successful resolution of ulceration and correction of inciting pathology may be achieved (270). Diabetic foot surgery performed in the absence of critical limb ischemia is based on three fundamental variables: presence or absence of neuropathy (LOPS), presence or absence of an open wound, and presence or absence of acute limb-threatening infection (270).

Classifications of Surgery

Surgical intervention has previously been classified as curative, ablative, or elective (100, 271). More recently, a modification of this scheme has been proposed that encompasses more procedures and a broader spectrum of patients (270), as follows:

Class I: *Elective* foot surgery (performed to treat a painful deformity in a patient without loss of protective sensation)

Class II: *Prophylactic* foot surgery (performed to reduce risk of ulceration or re-ulceration in patients with loss of protective sensation but without open wound)

Class III : *Curative* foot surgery (performed to assist in healing an open wound)

Class IV: *Emergent* foot surgery (performed to arrest or limit progression of acute infection).

For any of these classes, the presence of critical ischemia should prompt a vascular surgical evaluation to consider the urgency of the procedure and possible revascularization prior to or subsequent to the procedure.

Elective Surgery. The goal of elective surgery is to relieve the pain associated with particular deformities such as hammertoes, bunions, and bone spurs in patients without peripheral sensory neuropathy and at low risk for ulceration. Essentially any type of reconstructive foot operation can fall into this category, including rearfoot and ankle arthrodeses as well as Achilles tendon lengthenings (544). However, amputations are generally not performed as elective procedures, except in cases of severe deformity or instability resulting from prior injury or neuromuscular diseases.

Prophylactic Surgery. Prophylactic procedures are indicated to prevent ulceration from occurring or recurring in patients with neuropathy, including those with a past history of ulceration (but without active ulceration). These pro-
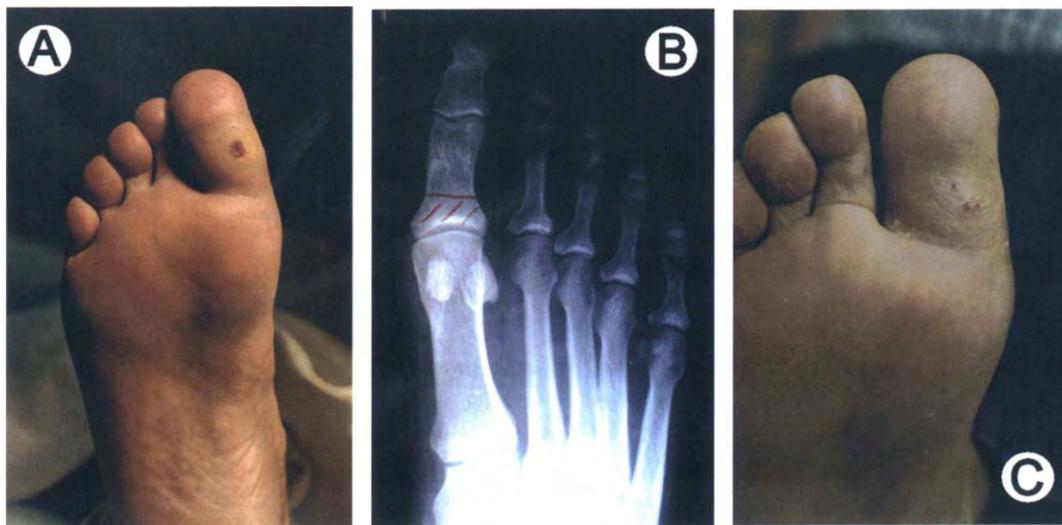
Figure 17 This patient has a *(A)* hallux ulceration related to the loss of normal joint mobility that is often seen in diabetes. During weightbearing, this clinical hallux limitus/rigidus places untoward pressure at the interphalangeal joint. *(B)* Radiograph illustrates planned resection arthroplasty of the 1st MTP joint. *(C)* The ulcer subsequently healed during the immediate postoperative period.
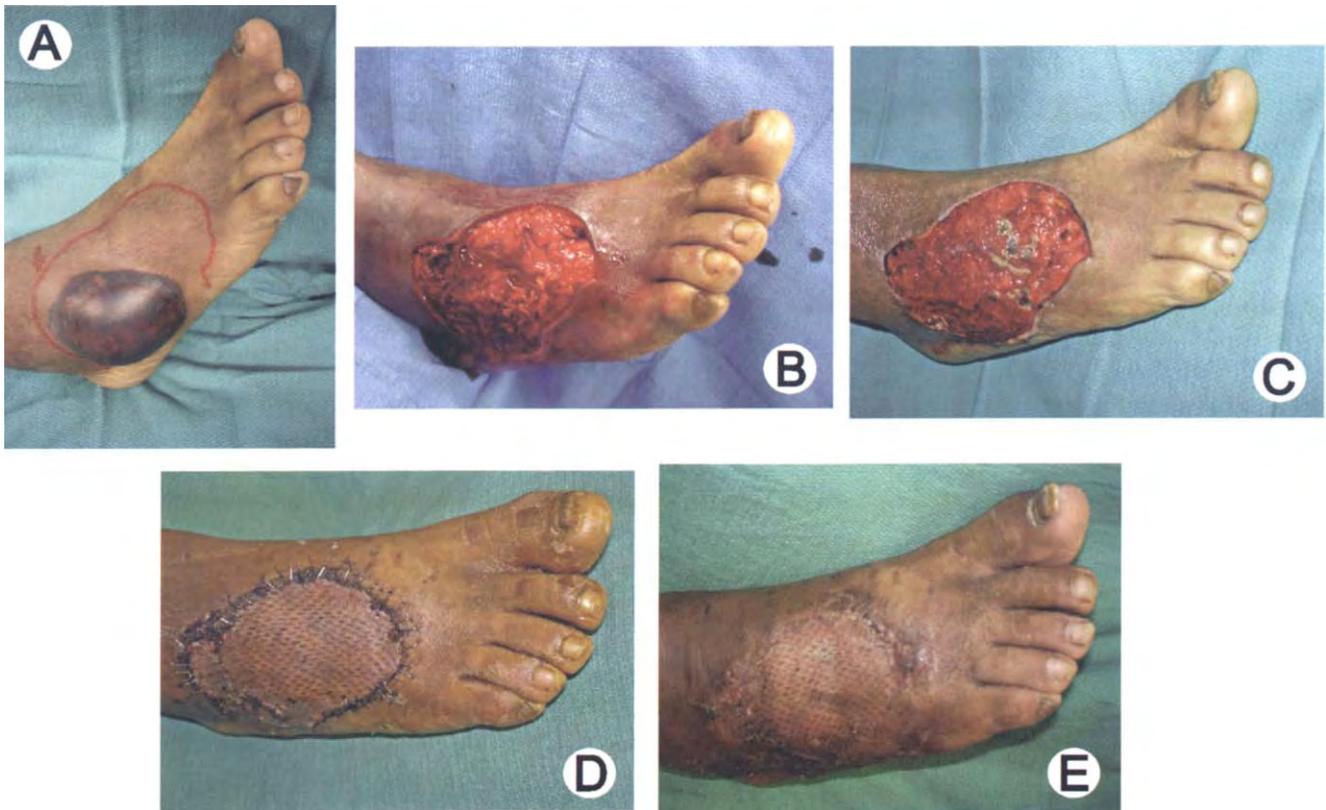
Figure 18 This diabetic patient presented with *(A)* a bullous abscess with peripheral cellulitis. Initial treatment included debridement, revealing *(B)* extensive necrosis. Local wound care allowed for *(C)* development of a healthy granulating wound base, followed by application of a split-thickness skin graft. *(D)* Foot at 3 weeks postoperative and *(E)* later at 7 weeks shows healing of this potential limb-threatening infection.

cedures involve correcting an underlying tendon, bone, or joint deformity. Many reconstructive procedures in this category would be considered elective if the patient did not have sensory neuropathy and a higher risk for ulceration (270).

Curative Surgery. Curative procedures are performed to effect healing of a nonhealing ulcer or a chronically recurring ulcer when off-loading and standard wound care techniques are not effective (100, 271). These include multiple surgical procedures aimed at removing areas of chronically increased peak pressure as well as procedures for resecting infected bone or joints as an alternative to partial foot amputation (30, 54, 77, 173). Operations frequently performed in this regard include exostectomy, digital arthroplasty, sesamoidectomy, single or multiple metatarsal head resection, joint resection (Fig 17), or partial calcanectomy (272, 273, 545-557). Some surgeons have proposed the advantages of combining plastic surgical flaps and skin grafts with these procedures to expedite wound healing and provide for more durable soft tissue coverage (54, 173, 558-563).

Emergent Surgery. Emergent procedures are performed to stop the progression of infection. Such ablative surgical intervention, most often involving amputation, requires removal of all infected and necrotic tissue to the level of viable soft tissue and bone (Fig 18). When possible, they are also performed in a manner to allow for the maximum function from the remaining portion of the limb (77, 272).

Wounds may be closed primarily if the surgeon is confident no infection or ischemic tissue remains and if enough soft tissue is available. Other wounds may initially be packed open, requiring well controlled and frequently assessed wound care, with delayed primary closure or closure by secondary intention. Another popular option is negative pressure wound therapy using a V.A.C.® device, which has been found to significantly expedite granulation tissue formation and healing of open partial-foot amputations (410). Mechanical assistance using a variety of skin-stretching devices are the surgeon's option and may help attain delayed primary closure for some wounds (564, 565). More often, V.A.C.® therapy is used to manage large or

deeper wounds until delayed primary closure can be achieved (393, 404, 566). Other approaches include plastic surgical techniques utilizing split and full-thickness skin grafts and a variety of flaps (173, 558, 559, 562, 563).

Each patient must be assessed for the selection of the surgical management that best meets his or her needs. Secondary wound healing with or without adjunctive wound therapies may still be the best choice for some patients. Pathway 6 lists the various types of surgical procedures commonly used for managing diabetic foot complications.

In the carefully selected patient, prophylactic or elective surgical correction of structural deformities that cannot be accommodated by therapeutic footwear can serve to reduce high pressure areas and ultimately prevent ulcer recurrence (255, 270, 271, 273, 545, 547, 548, 550, 567-569). Many of the procedures mentioned in the discussion on curative surgery would also be indicated in the elective/prophylactic reconstruction of the nonulcerated foot. Common operations performed in this regard include the correction of hammertoes, bunions, and various exostoses of the foot. Tendo-achilles lengthening procedures are often performed as ancillary procedures to reduce forefoot pressures that contribute to recurrent ulcerations (55, 58, 61, 568, 570).

Once healed, these surgical patients are at high risk for future ulceration and require appropriate ongoing care consistent with those prevention strategies already discussed (30, 163, 173, 253, 255, 256, 571).

Amputation Considerations

Amputation, a well recognized consequence in the management of the diabetic foot, is performed for a variety of reasons and can be characterized as curative or emergent. Indications for amputation include removal of gangrenous or infected tissue, often to control or arrest the spread of infection; removal of portions of the foot that frequently

Figure 19 *(A)* This 65-year-old male presented with a severe limb-threatening infection with deep necrosis of the forefoot. *(B)* He underwent incision and drainage with wound debridement including tendons on the dorsum of the foot and hallux amputation. *(C)* This was later converted to a transmetatarsal amputation with continuing dorsal wound care. *(D)* Good granular response allowed for later placement of a split-thickness skin graft.

Amputation Prevention Program
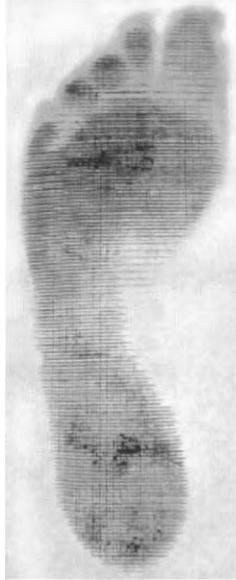
1. Podiatric Foot Care
   - Regular visits, examinations, and footcare
   - Risk assessment
   - Early detection and treatment of new lesions

2. Protective Shoes
   - Adequate room to protect from injury
   - Well cushioned walking sneakers
   - Extra depth or custom-molded shoes
   - Shoe modifications as needed

3. Pressure Reduction
   - Cushioned multiple density insoles
   - Custom orthotic devices or braces
   - Padded hosiery
   - Pressure measurements - computerized or pressure sensitive mat

4. Prophylactic Surgery
   - Correct structural deformity: hammertoes, bunion, exostoses
   - Prevent recurrent ulcers over deformities

5. Preventive Education
   - Patient education - need for daily inspection & necessity for early intervention
   - Physician education - significance of foot lesions, importance of regular foot examinations, & current concepts of diabetic foot management

Figure 20 An effective amputation prevention program includes regular podiatric foot care, protective shoes, and pressure reduction as well as prophylactic foot surgery combined with both patient and physician education programs.

ulcerate; and creation of a functional unit that can accommodate either normal or modified shoe gear.

In general, the amputation should be performed at a level that balances preservation of limb length and function with the capacity for the surgical site to heal primarily (572-575). Although this concept is intuitive, several factors may influence the selection of the level of amputation. It is well recognized that energy expenditure increases as the level of amputation becomes more proximal (576, 577). Simple tasks such as ambulating to the bathroom or other activities of daily living become increasingly more difficult for the patient commensurate with the level of amputation. In addition, patients with more proximal amputations are far more difficult to rehabilitate to a functional community or household ambulation level.

Recent advances in vascular surgery have enabled the level of amputation to become more distal or "limb sparing" (77, 166, 173). The capacity to re-establish distal perfusion with endovascular techniques or bypass surgery to the distal tibial, peroneal, and pedal arteries has greatly enhanced the potential for more distal amputation (306, 307). In most circumstances, patients should be given the opportunity for vascular surgical intervention prior to definitive amputation so that the most distal level of amputation can be successful.

Goals of Selection of Amputation Level

The selection of the level of amputation should incorporate the following goals:
Creation of a distal stump that can be easily accommodated by a shoe insert, orthotic device, modified shoe gear, or prosthesis
Creation of a distal stump that is durable and unlikely to break down from exogenous pressure

Creation of a distal stump that will not cause muscle or other dynamic imbalances. Examples include medial migration of the lesser digits after 1st MTP joint disarticulation; varus deformity and lateral overload after 5th ray resection; and equinus contracture after transmetatarsal or Chopart amputation.

Healing with primary intention. In most instances it is advisable to perform an amputation at the most distal level that would allow for primary healing.

Unfortunately, there are few objective tests or strategies that can consistently and reliably predict healing potential.

The cost of failure of an amputation at a given level is multifaceted. Increased costs associated with a more proximal level of amputation involve hospitalization, surgical procedures, prostheses, and psychological effects on the patient. It is difficult to stratify the importance of each of these parameters; each should be given consideration before any amputation.

Curative Versus Emergent Surgery

Although it is usually preferable to perform the amputation in an elective, controlled environment, this is not always possible or prudent. When infection, necrotizing fasciitis, or gas gangrene are present, an open amputation may need to be done on an emergent basis (150, 578) (Fig 19). Prior to the definitive amputation, residual infection and ischemia can be addressed. When performed under elective and stable conditions, the amputation should be fashioned so that it is curative. This generally means that the primary incision site can be closed primarily and that no further surgery is anticipated. With primary or even secondary wound healing, the patient can then be fitted for appropriate shoe gear or walking aids. When performed under emergent conditions, the procedure should usually be done proximal to the level of all necrotic tissue. It is anticipated that additional surgical procedures will be necessary to attain a closed wound and a stump that can accommodate shoes, custom inserts, or a prosthesis (575).

Amputation prevention strategies are identical to those employed for preventing ulceration and have previously been discussed (Fig 20). Prevention is best facilitated through a multidisciplinary approach that focuses not only on the aggressive management of diabetic foot lesions or infections, but also on periodic screening of all diabetic patients, regular surveillance of high-risk persons, education on risk factors and daily foot care, and provision of therapeutic footwear for patients with a history of ulceration, ischemia, or structural deformities (163, 251, 255, 301).

CONCLUSION

Ulceration, infection, gangrene, and lower extremity amputation are complications often encountered in patients with diabetes mellitus. These complications frequently result in extensive morbidity, repeated hospitalizations, and mortality. They take a tremendous toll on the patient's physical and mental well-being as well as impose a substantial economic burden, often removing the patient from the workforce and placing a financial drain on the health care system. According to a recent study, the mean annual cost of treating an uninfected ulcer was $9,306, while the cost of treating an ulcer with osteomyelitis exceeded $45,000 (579). Indeed, the estimated annual cost of treating diabetic peripheral neuropathy with its complications (including ulceration and amputation) ranges from $1.5 and $13 billion (40, 579).

Not all diabetic foot complications can be prevented, but it is possible to dramatically reduce their incidence through appropriate management and prevention programs. The multidisciplinary team approach to diabetic foot disorders has been demonstrated as the optimal method to achieve favorable rates of limb salvage in the high-risk diabetic patient (165, 166, 173, 253, 278, 300, 458, 459). Foot care programs emphasizing preventive management can reduce the incidence of foot ulceration through modification of self-care practices, appropriate evaluation of risk factors, and formulation of treatment protocols aimed at early intervention, limb preservation, and prevention of new lesions. The foot and ankle surgeon should play an integral role in this scheme, providing ongoing surveillance, education, and management of new or impending lesions (48, 255, 296). A significant reduction in both major and minor diabetic limb amputations is certainly attainable if clinicians embrace these principles and incorporate them into daily patient care.

Appendix 1 p1

Diabetic Foot Evaluation

Patient: _____

Chart # _____ Age: _____

Date: _____

Mark areas of callus, ulcer or pre-ulcer, erythema, swelling, tenderness or deformity

Medications:

Type 1
Type 2
Rx - Insulin
    - Incretin
    - Oral Hypoglycemic
    - Diet

Diabetes duration_____

Attending MD   ————————————

Height _____ Weight _____

BP _____ HbA1C _____

History of:

Foot Ulcer _____
Infection _____
Amputation _____
Revascularization _____
Renal Disease
CAD _____
Stroke _____
Tobacco _____
Alcohol _____

Paresthesia/Tingling   toes
Numbess   plantar
Burning   feet to above ankle
Sharp Pain   ... to below knee
Night Pain   night
Muscle Weakness   daily
Gait Difficulties   occasionally
Claudication

    wheelchair
    walker
    cane
    brace
Shoes _____ foot orthosis
    MDI

Skin:

Turgor _____
Color _____
Temperature _____
Texture _____

Lesions
Fissures _____
Corns _____
Calluses _____
Ulcers _____
Nails _____

Musculoskeletal

Joint Flexibility _____
Deformities _____
  or Sites of _____
    High Pressure _____
Gait assessment _____

Appendix 1 p2

Neurologic Exam

Sensory - Semmes-Weinstein Monofilament
Ability to detect 5.07 or 10 gm Monofilament: + or -

Deep Tendon Reflexes (+Present; - Absent)

	Right	Left
Patella	_____	_____
Achilles	_____	_____
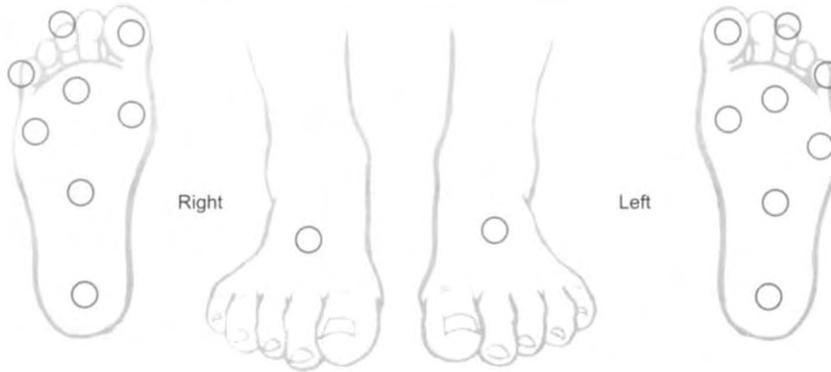
Right

Left

Vascular Exam

Pulses:	Right				Left			
Dorsalis Pedis	0	+1	+2	+3	0	+1	+2	+3
Posterior Tibial	0	+1	+2	+3	0	+1	+2	+3

Pulse Exam
0	absent
+1	diminished
+2	normal
+3	bounding

	Right		Left	
Elevation Pallor	Absent	Present	Absent	Present
Dependent Rubor	Absent	Present	Absent	Present
Capillary Filling Time	<1 1-3 >3		<1 1-3 >3	
Edema	Absent		_____	

Risk Status

0   No Sensory Neuropathy, No PAD,
     Negative Hx of Foot Ulcer
I   Neuropathy (LOPS), No PAD, No Deformity
II   Sensory Neuropathy + PAD &/or
     Foot Deformity
III   Previous Foot Ulcer or Amputation
    — Prior Ulceration &/or Amputation
    — Charcot Deformity - Location
    _____
    _____

Examiner: _____

Date: _____

Recommended Management:

Periodic Foot Care
Extra Depth Shoes
Multiple Density Insoles (MDI), Orthotics
Bracing
Vascular Testing: Doppler
Consultation:
Other: Diabetic Education

_____
_____
_____
_____
_____
_____
_____

Appendix 2: Definitions

Amputation: The complete or partial removal of a limb or body appendage by surgical or traumatic means. A minor amputation is defined as occurring distal or through the tarsometatarsal joint (Forefoot, Transmetatarsal, and Lisfranc). Major amputations are those that occur proximal to the tarsometatarsal joint (Chopart, Boyd, Syme, Below Knee, and Above Knee).

Charcot foot (arthropathy, osteoarthropathy, neuroarthropathy): Non-infectious destruction of bone and joint that is associated with neuropathy.

Diabetic foot: Describes the foot of a diabetic patient that has the potential risk of pathologic consequences, including infection, ulceration, and destruction of deep tissues associated with neurologic abnormalities, various degrees of peripheral arterial disease, and metabolic complications of diabetes in the lower limb. (Based on the World Health Organization definition)

Diabetes, type 1: Formerly called insulin-dependent diabetes mellitus (IDDM), describes an autoimmune disease of younger individuals with a lack of insulin production that causes hyperglycemia and a tendency toward ketosis.

Diabetes, type 2: Formerly called non-insulin-dependent diabetes mellitus (NIDDM), describes a metabolic disorder resulting from the body's inability to produce enough insulin or properly utilize insulin. Individuals with type 2 diabetes also have hyperglycemia but are ketosis-resistant.

Epidemiology: The study of frequency, determinants, and distribution of disease.

Gangrene: The death or necrosis of a part of the body secondary to injury, infection, and/or lack of blood supply. This indicates irreversible damage where healing cannot be anticipated without loss of some part of the extremity.

Incidence: The rate at which new cases of disease occur within a specified time period.

Infection: An invasion and multiplication within body tissues by organisms such as bacteria, fungi, or yeast, with or without the clinical manifestation of disease.

Intrinsic minus foot: Describes a neuropathic foot with intrinsic muscle wasting and associated claw toe deformities.

Ischemia: The impairment of blood flow secondary to an obstruction or constriction of arterial inflow.

LEAP: Acronymn for Lower Extremity Amputation Prevention program.

Limited joint mobility: Describes the stiffness or restricted range of motion of a joint (cheiroarthropathy) due to protein glycosylation.

LOPS: Acronym for loss of protective sensation. Describes the progression of neuropathy in the diabetic foot to the point that the foot is at risk for ulceration.

Neuropathy. A nerve dysfunction affecting sensory, motor, and/or autonomic fibers, with varying degrees of impairment, symptoms, and signs. **Diabetic peripheral neuropathy** is the presence of symptoms and/or signs of peripheral nerve dysfunction in individuals with diabetes after exclusion of other causes.

Prevalence: A measure of frequency describing the percent of persons in a given population with a stated disease or characteristic at a point in time.

Ulceration (ulcer): A partial- or full-thickness defect in the skin that may extend to subcuticular tissue, tendon, muscle, bone, or joint.

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