REVIEW ARTICLE

Richard P. Cambria, MD, Section Editor

Management of diabetic foot problems

Jeffrey Kalish, MD, and **Allen Hamdan, MD,** *Boston, Mass*

Background: **Diabetic foot problems and their complications are a medical and economic challenge to the health care system and require an aggressive multidisciplinary approach to achieve limb salvage. The goals of this review article are to delve into this comprehensive topic and summarize key points regarding diabetic foot problems from the perspective of the vascular specialist treating these patients.**

Methods: **The MEDLINE database was searched to identify articles on this topic.**

Results: **We found 112 relevant articles. These were used to provide current data on (1) the pathogenesis leading to diabetic foot lesions (ie, the etiologic triad of ischemia, neuropathy, and infection), (2) the clinical presentation of these foot lesions and their systemic manifestations, (3) the optimal methods of diagnostic evaluation, including noninvasive testing and arteriography, (4) treatment selection guidelines to help delineate which patients require revascularization, and (5) medical and interventional treatments, including prevention strategies, wound healing strategies, use of antibiotics, and endovascular and open surgical options for revascularization.**

Conclusions: **The data presented in this review article allow vascular clinicians to optimize patient care and achieve effective limb salvage for this growing segment of the population. (J Vasc Surg 2010;51:476-86.)**

Despite refinements in medical and surgical care during the past decade, foot problems in diabetic patients remain a major public health issue and are the most common reason for hospitalization of a diabetic patient. A foot complication severe enough to require hospitalization will develop in approximately 15% of the nearly 24 million diabetic patients in the United States (U.S.) during their lifetime.[1] Because this small group of people with diabetes—only 7.8% of the U.S. population—accounts for >60% of all nontraumatic lower extremity amputations,[2] public health initiatives have focused on aggressive treatment of diabetic foot infections to halt the escalating number of amputations. Despite these widespread efforts, the annual financial costs relating to infection, ulceration, and amputation have increased to >$10 billion nationwide.[3] This increase has occurred even while many institutions have successfully adopted the recommended multidisciplinary approach to care for diabetic patients.[4,5]

EPIDEMIOLOGY

The lifetime risk that a diabetic patient will acquire foot lesions (ulcers/gangrene) has been estimated at 15% to 25%, with an annual incidence of 1.0% to 4.1%.[6] The incidence of these lesions appears similar in type 1 vs type 2 diabetic patients, although type 2 diabetic patients comprise approximately 90% of the total diabetic population. In >15% of these patients, ulcers will ultimately lead to amputation.[7]

The risk for an initial foot ulcer is increased in patients who have had diabetes for >10 years, are male, have poor glycemic control, and already have other cardiovascular, renal, or retinal comorbidities.[8] Foot ulcers occur in different rates in different parts of the world and rates of amputations differ as well, with the highest in Native Americans and lowest in Madrid, Spain.[9] Specifically in North America, foot ulcers and amputations are more common in ethnic minority groups, especially Hispanics and African Americans, as well as in other groups of patients who lack health insurance.[9]

PATHOGENESIS

Ischemia, neuropathy, and infection are the three pathologic components that lead to diabetic foot complications, and they frequently occur together as an etiologic triad. The most important principle in treating foot ischemia in patients with diabetes is recognition that the etiology of this ischemia is macrovascular occlusion of the leg arteries due to atherosclerosis.

For many decades, clinicians mistakenly ascribed to the theory of "small vessel disease," or microvascular occlusion of arterioles, as the cause of ischemic complications. This theory directly caused the widespread erroneous opinion that patients with diabetes and ulcers would absolutely need amputations because revascularization was not possible. The idea originated from a single histologic study of amputated limbs from diabetic patients, whereby a material positive for periodic acid-Schiff occluded the arterioles.[10] A subsequent prospective study[11] of amputation specimens,

From the Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center.

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Reprint requests: Jeffrey Kalish, MD, Fellow in Vascular & Endovascular Surgery, Beth Israel Deaconess Medical Center, 110 Francis St, LMOB 5B, Boston, MA 02215 (e-mail: jeffrey.kalish@bmc.org).

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however, refuted the notion of an arteriolar occlusive lesion associated with diabetes. It is now well-recognized that diabetic patients typically have tibial and peroneal arterial occlusive disease with relative sparing of the foot arteries, and ischemia results from atherosclerotic macrovascular disease as well as from microcirculatory dysfunction.[12]

Diabetic neuropathy has multiple manifestations in the foot because it encompasses sensory, motor, and autonomic fibers. The pathogenesis of diabetic neuropathy is not fully understood. Possible explanations are based on theories of alterations in the vasa nervorum or abnormalities in metabolism. The vascular theory relates to thickening of the nutrient vessels that may occlude with progression, resulting in ischemic injury to the nerve. A more popular theory is the increased activity of the polyol (sorbitol) pathway.[13] Accumulation of sorbitol has been shown in aortic intima and media. Excess sorbitol may produce toxic effects, resulting in demyelination and impaired velocity of peripheral nerve conduction. These pathologic findings have been reported in human diabetic neuropathy.[14]

Sensory neuropathy affects the small-diameter pain and temperature fibers first, and susceptibility to injury is increased because these patients are less sensitive to pressure-related trauma or other minor skin injuries. Motor neuropathy affects the longer fibers that innervate the foot, affecting both the intrinsic foot muscles and leg muscles. Autonomic neuropathy causes dry skin through the loss of sweat and oil gland function. Dry skin carries an increased susceptibility to breakdown and fissures, thus creating a portal of entry for bacteria. Overall, neuropathy results in a series of predictable structural changes in the foot that predispose to ulceration.

Although there are generally no fixed occlusive lesions of the small foot vessels, this does not imply that microcirculatory dysfunction does not exist. Neuropathy leads to a shunting away of the blood through arteriovenous connections in the microcirculation.[15] This results in decreased tissue perfusion, even in the presence of normal arterial supply. Oxygen saturation is reduced in the skin of diabetic patients, and this impairment is accentuated in the presence of neuropathy.[16,17]

Diabetes causes structural and functional changes within the arteriolar and capillary systems as well, notably, thickening of the basement membrane.[18] This thickened membrane impairs the migration of leukocytes and hampers the normal hyperemic or vasodilatory response to injury, thus simultaneously increasing the susceptibility to injury while also blunting the typical manifestations of such an injury.[19] Because of this blunted neuroinflammatory response, diabetic patients lack a crucial component of the body's natural first-line of defense against pathogens and thus are more susceptible to an ensuing foot infection.[20]

CLINICAL PRESENTATION

The clinical presentation of peripheral arterial disease (PAD) encompasses intermittent claudication, rest pain, and ulcers, with or without gangrene. Diabetic patients may exhibit these typical symptoms but more often, they present with a wound that fails to heal or with pain at the site of a callus, pressure point, or other bony prominence. Although diabetes alone increases the prevalence of symptomatic PAD by 3.5-fold in men and 8.6-fold in women,[21] the largest risk attributed to diabetic patients is for nontraumatic amputation, which increases 8-fold in all patients aged >45,[22] 12-fold in all patients aged >65, and 23-fold for those aged 65-74 years.[23] A thorough clinical examination of foot ulcers is necessary to evaluate the depth and extent of involvement, anatomic location, etiology, and presence of ischemia or infection.

On inspection, the neuropathic foot often has a characteristic appearance. The atrophy of the intrinsic foot muscles allows the strong flexor muscles to draw up the toes in a "clawed" position, and new pressure points emerge at the tips of the toes and the prominent metatarsal heads. The skin is usually dry or cracked due to the loss of sweating and oil secretion. Heavy, thick callus, which may ulcerate over time, is often abundant at points of increased pressure and weight bearing. Atrophy of small muscles of the foot may or may not be apparent.

Color and temperature changes can range from hyperemic and warm in a patient with an acute Charcot fracture, to pale and cool in a patient with concomitant ischemia and neuropathy. In the presence of arteriovenous shunting, an ischemic foot may appear pink and relatively warm even with a significant loss of arterial perfusion. In individuals with a Charcot foot, which is a progressive and degenerative arthropathy of single or multiple joints that ultimately leads to destruction of normal foot architecture, collapse of the arch, a "rocker bottom" deformity, or other abnormalities may be seen.

The neuropathic pain syndrome is not completely understood but may also be a clinical presenting symptom.[24] This manifestation of neuropathy is a component of impaired glucose tolerance and the metabolic syndrome, and as such, new symptomatic treatments with medications other than gabapentin have recently been approved (duloxetine hydrochloride and pregabalin).[25] A summary of the larger randomized, controlled trials is presented in Table I.[26-31] Although each of these trials points to the superiority of the tested drug vs placebo, the absolute clinical effectiveness of this pharmacotherapy is still unknown.

The typical inflammatory signs of infection, including erythema, rubor, cellulitis, or tenderness, may be absent or diminished. Also frequently absent are the usual systemic manifestations of infection, including fever, tachycardia, or elevated white blood cell count.[32,33] Unexplained hyperglycemia should prompt an aggressive search for a source of infection because the patient's elevated glucose level may be the only sign of impending problems.

Careful palpation of the foot for areas of tenderness or fluctuance is important to detect undrained abscesses in deeper tissue planes. All ulcers must be carefully inspected and probed, and superficial eschar unroofed, to look for potential deep space abscesses.

Ulcers and infections have been characterized by numerous classification systems that attempt to predict treatment failure or resulting amputations.[34] These classification schemes divide infections into mild (superficial and

Table I. Summary of randomized, controlled clinical trials evaluating pharmacotherapy for painful diabetic neuropathy

First author	*Medications (vs placebo)*	*Patients (total)*	*Treatment duration*	*Reported results of drug vs placebo*
Backonja,[26] 1998	Gabapentin (900-3600 mg/d)	165	8 wks	↓ Mean daily pain score ($P < .001$) ↑ Quality of life ($P = .01$) ↑ Adverse events: dizziness (24% vs 5%, $P < .001$); somnolence (23% vs 6%, $P = .04$); confusion (8% vs 1.2%, $P = .06$)
Serpell,[27] 2002	Gabapentin (up to 2400 mg/d)	305	8 wks	↓ Daily pain score from 21% to 14% ($P = .048$) ↑ Quality-of-life questionnaire scores
Lesser,[28] 2004	Pregabalin (75-600 mg/d)	338	5 wks	↓ Mean pain score with 300-mg + 600-mg dose ($P = .0001$) Responders (>50% ↓ pain score) in 46% vs 18% Improved pain and sleep scores as early as 1 week
Tolle,[29] 2008	Pregabalin (150-600 mg/d)	395	12 wks	Responders (>50% ↓ pain score) in 46% vs 30% ($P = .036$) at 600 mg Improved scores at 600 mg for sleep interference, quality-of-life models, and global impression of change
Wernicke,[30] 2006	Duloxetine (60-120 mg/d)	334	12 wks	Rapid onset of action; pain improvements starting at 1 week No difference in 60- vs 120-mg dosing
Raskin,[31] 2005	Duloxetine (60-120 mg/d)	348	12 wks	Significant improvement of 24-hour pain score ($P = .001$) Discontinuation due to adverse events: 12.1% for 120 mg/d vs 2.6% placebo

limited), moderate (deeper tissues), or severe (systemic signs or symptoms of infection, or metabolic derangements). The only relevance for the clinician is to determine if a patient's infection is limb- or life-threatening and then determine the appropriate course of treatment (outpatient management, hospitalization, débridement, or amputation). Although only 10% to 15% of diabetic patients will develop a foot infection during their lifetime, those infections range from mild (47%) to moderate (34%) to severe (18%).[35] Hospitalization, minor amputation, and major amputation rates vary significantly by the extent of infection (mild, 4.2%, 2.8%, 0%; moderate, 52%, 23%, 23%; and severe, 89%, 48%, 30%).[35]

DIAGNOSTIC EVALUATION

The presence of neuropathy can usually be determined by taking a careful patient history and physical examination. Loss of pin-prick sensation can be determined by the use of a Semms-Weinstein monofilament, a nylon monofilament attached to a plastic handle, which is applied under pressure to a patient's foot and assesses the level of sensation at 10 different dermatome points. In multiple prospective studies, this instrument has identified patients at risk for foot ulceration with a sensitivity ranging from 66% to 91% and a specificity ranging from 34% to 86%.[6] Vibratory sensation is tested with a tuning fork, although this is less predictive of ulceration than the Semms-Weinstein monofilament. Nerve conduction or electromyelography studies are not essential.

Osteomyelitis occurs after the spread of superficial infection of the soft tissue to the adjacent bone or marrow.[36] Although numerous expensive radiologic techniques are available to diagnose osteomyelitis, a simple sterile metallic probe will usually suffice.[37] Probing the ulcer determines the ulcer depth and extent and thus determines the involvement of bony structures.[38] Grayson et al[39] revealed that if this sterile probe hits bone, then osteomyelitis can be diagnosed with a sensitivity of 66%, a specificity of 85%, and a positive predictive value of 89%.

Plain radiographs of the foot should be obtained in every patient with suspected foot infection. X-ray images can reveal the presence of a foreign body, gas, osteolysis, or joint effusion, as well as delineate anatomy for surgical planning. A bone scan or tagged white blood cell scan should be reserved for cases in which the metal probe test is equivocal, when an abscess or multifocal disease is suspected, or in patients with Charcot foot because the associated bony changes and inflammatory response can be misinterpreted as osteomyelitis. Magnetic resonance imaging is a highly sensitive diagnostic tool (up to 100%) but is only about 80% specific because osteomyelitis and fracture may have similar appearances.[40] The conclusive diagnosis of osteomyelitis can be obtained by bone biopsy, but this is rarely necessary.[41]

A complete vascular examination is imperative in any patient reporting symptoms consistent with claudication or rest pain, although many diabetic patients who require revascularization will present with limb-threatening ischemia and have no antecedent vascular symptoms. These patients will present with a nonhealing ulcer with or without associated gangrene or infection. Some patients are referred after a minor surgical procedure when the foot fails to heal due to ischemia.

When the etiology of the patient's foot pain is unclear, noninvasive vascular laboratory studies are particularly useful. Patients with severe ischemia usually have ankle-brachial indices (ABI) of <0.4. The resting ABI may be normal in certain patients with claudication, and exercise testing may reveal that up to 31% of these patients then manifest a change in the ABI.[42] Many diabetic patients, however, will have artificially elevated ankle pressures due to calcification of the arterial wall,[43] the so-called noncompressible vessel. In this scenario, >250 mm of pressure is required, and the resultant ABI will underestimate the prevalence of arterial disease in this population.[44] Pulse volume recordings are then required. Some centers have found toe pressures[43] and transcutaneous oxygen measurements[45] to be useful in diabetic patients.

Intra-arterial digital subtraction arteriography is the most accurate method to evaluate the lower extremity arterial circulation. Although magnetic resonance arteriography had been used more frequently during the past decade in patients with marginal renal function,[46] recent reports detailing nephrogenic systemic fibrosis[47] have shifted clinical practice back to conventional arteriography. A carefully performed arteriogram must show the appropriate inflow source and outflow target artery and must incorporate the complete infrapopliteal circulation, including foot vessels.

Diabetic patients are at higher risk of contrast-induced nephropathy (CIN) after arteriography, regardless of their baseline creatinine level (although the combination of diabetes and chronic kidney disease carries an even higher risk of CIN).[48,49] However, the risk of CIN can be minimized by prehydration with sodium bicarbonate solution[50] and by using an isosmolar contrast such as Visipaque (GE Healthcare, Princeton, NJ).[49,51,52] The addition of N-acetylcysteine has not been definitively proven.[53] Selective catheterizations of the superficial femoral or popliteal artery allow excellent imaging of the foot vessels with a much reduced contrast load.

TREATMENT SELECTION

The most important principle driving all of this testing is to answer the difficult question of whether revascularization is needed for a certain lesion, for a certain patient. Some patients with very minimal and very distal gangrene and who have adequate pulse volume recordings or toe pressures may be candidates for a partial toe amputation without revascularization. Unfortunately, the limitations of noninvasive testing in these circumstances mainly center on the poor predictive value of adequate healing: pulse volume recording can predict failure in up to 50% of patients whose minor amputation would eventually heal, and vice versa.[54]

In the absence of deep infection or necrosis, minor infections or ulcers may be managed conservatively with local wound care, antibiotics, or both. On the other hand, noninvasive testing adds little information to the evaluation of a patient with more advanced foot ischemia and the absence of a palpable foot pulse. In these patients, contrast arteriography should be performed as the first diagnostic, and potentially therapeutic, test.

For patients who require revascularization of lower extremity occlusive disease, critical decisions need to be made about traditional surgical reconstruction vs less invasive endovascular interventions. Although the choice between these two treatment modalities is outside the scope of this review, various reasons exist in favor of and against both methods. Certain patients may not be appropriate candidates for arterial reconstruction because of their overall health status. Elderly patients with severe dementia who are nonambulatory or bedridden, or who have severe flexion contractures of the knee or hip, have no prospect of rehabilitation and are inappropriate candidates for traditional vascular procedures. Age alone, however, is not a contraindication for arterial reconstruction.[55,56] Patients with terminal cancer with a very short life expectancy or similar lethal comorbidities do poorly with open revascularization and are probably better served by endovascular intervention or primary amputation. Patients with an unsalvageable foot due to extensive necrosis from ischemia or infection also require primary amputation.

In patients with salvageable ischemic foot lesions and concomitant active infection, the infection needs to be controlled before vascular surgical intervention. In addition to instituting broad-spectrum antibiotics, options include open débridement and drainage or partial foot amputation. A short delay (usually <5 days) before revascularization to control active infection is justified; however, longer waits to "sterilize wounds" is inappropriate and may result in further necrosis and a lost opportunity to save the foot.[57] During this intervening period, contrast arteriography and other preoperative evaluations can be performed as necessary. Once cellulitis, lymphangitis, and edema have improved or resolved, especially in any areas of expected incisions for bypass, bypass can be undertaken without further delay.

On the other hand, in the absence of active infection, eschars may function as the body's natural "biologic dressing," and débridement of these noninfected areas of superficial gangrene may worsen the chances of limb salvage by creating larger open wounds in the setting of ischemia. This is especially true in cases of heel ulcers because of poor circulation in the heel fat pad as well as the danger of debriding into the calcaneus and thus fostering wound contraction instead of healthy granulation tissue. Although authors report complete healing rates of heel gangrene in 70% to 85% of patients ≤6 months with aggressive débridement and revascularization,[58,59] other studies point to the significant morbidity and poor healing rates once a calcanectomy is required for adequate débridement.[60] Overall, careful patient selection is extremely important to determine which patients should have revascularization vs primary amputation.

MEDICAL TREATMENTS

Primary prevention should be the first tenet of managing the diabetic foot, but secondary prevention with metic-

Table II. Summary of randomized trials comparing hyperbaric oxygen therapy to standard wound care

Author	*Patients*	*Treatment sessions*	*Reported results*	P
Faglia,[64] 1996	5 HBOT + standard wound care	38.8 ± 8	8.6% major amputation (RR, 0.26; 95% CI, 0.08-0.84)	.016
	33 standard wound care		33.3% major amputation	
Abidia,[65] 2003	8 HBOT	30	62.5% ulcer healing	
			100% median ↓ wound area 6 wks	.027
			100% median ↓ wound area 6 mo	NS
	8 control (air)	30	12.5% ulcer healing	
			52% median ↓ wound area 6 wks	
			95% median ↓ wound area 6 mo	
Kessler,[66] 2003	14 HBOT + standard wound care	20	Ulcer size decrease	
			42% ± 25% (day 15)	.037
			48% ± 30% (day 30)	NS
	14 standard wound care		22 ± 17% (day 15)	
			42 ± 27% (day 30)	
Duzgun,[67] 2008	50 HBOT + standard wound care	60-90	66% healing without surgery	<.05
			8% distal amputation	<.05
			0% major amputation	<.05
	50 standard wound care		0% healing with surgery	<.05
			48% distal amputation	<.05
			34% major amputation	<.05

CI, Confidence interval; *HBOT,* hyperbaric oxygen therapy, *RR,* relative risk.

ulous ulcer care may be a more realistic goal.[61] Primary prevention involves aggressive glycemic control (goal hemoglobin A_{1C} <6.5% to 7.0%); management of associated risk factors such as smoking, hypertension, hyperlipidemia, and obesity; periodic physical examinations, including a vascular examination; and probably most important, proper foot care and hygiene strategies.[6] Although the absolute success rate of preventing ulcers and amputations has never been fully quantified using these measures, most authorities agree on the usefulness of these strategies.[6] Furthermore, foot care behaviors are improved significantly at 12 months with aggressive education strategies in high-risk groups of diabetic patients.[62]

The first step in the treatment of any neuropathic ulcer is restriction of weight bearing of the involved extremity. Patients with limb-threatening foot infections and noncompliant patients will require hospitalization and bedrest, followed by evaluation and management of arterial ischemia. Uncomplicated neuropathic ulcers will often heal with topical therapy and nonweight bearing, and a trial of outpatient care is warranted. Topical dressings should be aimed at maintaining a moist environment with saline-impregnated gauze, topical antibiotic ointments, or other similar agents. The ulcer should be protected from excessive pressure by placing of an accommodative pad around the lesion to distribute pressure to surrounding tissues. Heavy callus around the edges of the lesion should be trimmed away to reduce peak plantar pressure, and shoes should be replaced with a stiff-soled "healing sandal." Custom-molded orthotics and extra-depth shoes, running shoes, or custom-molded shoes in the case of severe foot deformity, are also prescribed to prevent future recurrence.[63]

Hyperbaric oxygen therapy has received much attention in recent years as an adjunct to facilitate wound healing for diabetic foot ulcers and thus lower amputation rates. Proponents contend that hyperbaric oxygen therapy promotes wound healing through antiedema, antibacterial, and neovascularization effects. Multiple small, nonrandomized studies have pointed toward its effectiveness, but very few randomized studies compare hyperbaric oxygen therapy plus standard therapy with daily wound care including dressing changes, local débridements, and amputations vs standard therapy alone (Table II).[64-67] Although differentiation was typically not made between ischemic ulcers and pressure-related ulcers, the authors showed statistically significant improvements in amputation rates and wound healing when hyperbaric oxygen was used.

The management goals of Charcot foot are to offload the affected extremity, prevent further collapse and deformity, and protect the opposite foot. The first step of treatment is an extended period of nonweight bearing and cast- or splint immobilization to promote eventual healing of the joint. The use of accommodative footwear is essential to long-term management. Surgery is rarely indicated, and a stabilizing procedure is done most safely after the disease has reached a quiescent stage. Amputation is reserved for those rare patients with severe uncorrectable deformities, those with chronic ulcers plagued by such extensive osteomyelitis that the foot is unsalvageable, or after failed open reconstructions.

Patients with limb-threatening infections require immediate hospitalization, immobilization, and intravenous antibiotics. Cultures from the depths of the ulcer should be sent; wound swabs are unreliable and should not be performed. Empiric broad-spectrum antibiotic therapy should be initiated to cover the polymicrobial infections usually seen in diabetic patients.[1,68] Empiric antibiotic regimens are dictated by institutional preferences, local resistance patterns, availability, and cost. Numerous trials of antibiotic

Table III. Summary of antibiotic trials for diabetic foot infections

Author	*Antibiotic regimens*	*Design*	*Patients, No.*	*Treatment duration (days)*	*Reported results*	*95% CI*	P
Grayson,[68] 1994	Ampicillin/sulbactam	Randomized, double-blind, single-center	48	13 ± 6.5	81% cure; 67% eradication		NS
	Imipenem/cilastatin		48	14.8 ± 8.6	85% cure; 75% eradication		
Lipsky,[69] 2004	Linezolid IV or PO; ± aztreonam	Randomized, open-label, multicenter	241 (5% aztreonam)	17.2 ± 7.9	81% overall cure	−0.1 to 20.1	NS
	Ampicillin/sulbactam, or amoxicillin/clavulanate ± vancomycin or aztreonam		120 (9.6% vancomycin, 2.5% aztreonam)	16.5 ± 7.9	71% overall cure		
Clay,[70] 2004	Ceftriaxone + metronidazole	Randomized, open-label, single-center	36	44	72% treatment success		NS
	Ticarcillin/clavulanate		34	4	76% treatment success		
Harkless,[71] 2005	Piperacillin/tazobactam ± vancomycin	Randomized open-label, multicenter	155	9 median	81% cure or improvement	12.9 to 9.1	.124
	Ampicillin/sulbactam ± vancomycin		159	10 median	83.1% cure or improvement		
Lipsky,[72] 2005	Daptomycin ± aztreonam or metronidazole	Randomized, open-label, multicenter	47 (38% aztreonam)	7-14	66% cure	−14.4 to 21.8	NS
	Comparator (vancomycin or vancomycin or semi-synthetic PCN) ± aztreonam or metronidazole		56 (29) (27) (41% aztreonam)	7-14	70% cure		
Lipsky,[73] 2005	Ertapenem ± vancomycin	Randomized, double-blind, multicenter	295 (2.3% vancomycin)	11.1	87% favorable clinical response	−6.3 to 9.1	NS
	Piperacillin/tazobactam ± vancomycin		291 (1.7% vancomycin)	11.3	83% favorable clinical response		

CI, Confidence interval; *IV,* intravenous; *PCN,* penicillin; *PO,* oral administration.

therapy have been conducted to evaluate different regimens (Table III).[68-73]

The Study of Infections in Diabetic Feet Comparing Efficacy, Safety, and Tolerability of Ertapenem Versus Piperacillin/Tazobactam (SIDESTEP) is the largest and most recent randomized, multicenter study. It evaluated one-time-daily ertapenem vs four-times-daily piperacillin/tazobactam in moderate and severe diabetic foot infections. Investigators were permitted to add vancomycin as needed for methicillin-resistant *Staphylococcus aureus* (MRSA) enterococcus.[73] This trial found no difference in eradication rates, clinical outcomes, and adverse events between the two regimens. Although all of these trials adequately compared the various antibiotic regimens, they failed to focus on an inherent weakness of simply using antibiotics alone; that is, the reported "failure rates" in these trials of 11% to 12% for moderate infections and 19% to 30% for severe infections.[73] Furthermore, the presence of PAD predicts a higher failure rate for healing any diabetic foot lesion >1 year (31% failure vs 16% failure).[74]

Numerous antibiotic regimens are appropriate as initial therapy for limb-threatening infections. Given the increasing prevalence of MRSA in hospital-acquired infections, as well as in community isolates, empiric therapy with vancomycin is warranted.[75] Major advantages of fluoroquinolones are their potent activity against both gram-positive and gram-negative organisms, the high tissue concentrations obtained with oral administration, and the safety in penicillin-allergic patients. Metronidazole can be added to cover anaerobic bacteria against which fluoroquinolones have no activity.[76] Once culture results become available, antibiotics should be appropriately tailored to prevent development of resistance as well as to prevent unnecessary overuse and even abuse of antibiotics. Mild infections usually require only 7 to 10 days of antibiotic therapy, whereas moderate and severe infections may require up to 3 weeks of treatment.[77]

Traditional therapy for osteomyelitis was accepted as 4 to 6 weeks of intravenous antibiotics,[78] but recent studies have documented a >30% recurrence rate using this mo-

dality alone.[79,80] Predictors of failure include fever, elevated creatinine, prior hospitalization for foot lesion, and gangrene.[79] In fact, even though proponents point to their 70% success in avoiding surgery, the treatment with antibiotics can take up to 1 or 2 years to achieve this success.[81-83] On the other hand, aggressive surgical débridement of infected bone shortens healing times, decreases the need for long-term antibiotic therapy, limits the emergence of resistant bacteria, and reduces inpatient and outpatient economic costs.[84,85] Unfortunately, the data to support this surgical dogma are limited to single-center retrospective studies, and no randomized trials exist to adequately settle this debate.

SURGICAL AND ENDOVASCULAR TREATMENT

Patients with abscess formation or necrotizing fasciitis must undergo prompt incision, drainage, and débridement, including partial open toe, ray, or forefoot amputation.[86] Tendon sheaths should be probed as proximally as possible and excised if infected. Despite fears to the contrary, long and extensive drainage incisions will heal when infection is controlled and foot circulation is adequate. Limb salvage is 89.8% at 1 year and 82.3% at 5 years after an initial minor amputation.[87] It is imperative to make any necessary incision initially but at the same time to contemplate the implications of those incisions on the potential completion amputation. Wounds should be packed open with saline-moistened gauze, and dressings should be changed two to three times a day. Wounds should be examined daily, and additional bedside or operative débridement should be repeated as needed. Adequate dependent drainage is crucial, and limited incisions with closed-suction or Penrose drains should be avoided.

Numerous adjunctive modalities exist for wound care, such as topical growth factors, synthetic skin grafts, electrical stimulation, hyperbaric oxygen chambers, and negative-pressure wound therapy. Each has its own merits, but economic constraints and patient compliance should be kept in mind when comparing these with the well-established modality of simple gauze dressings. Multiple small trials have indicated that negative-pressure wound therapy is at least as good as or better than current local treatment options.[88]

A recent randomized trial involving 162 diabetic patients revealed the efficacy of the vacuum-assisted closure negative-pressure wound therapy system (V.A.C.; KCI Medical, San Antonio, Tex) compared with standard moist gauze dressings. In diabetic patients with partial foot amputations and adequate perfusion, V.A.C. therapy resulted in a higher proportion of healed wounds (56% vs 39%, $P = .04$), faster healing rates (median time to closure, 56 vs 77 days; $P = .005$), and potentially fewer reamputations than standard care (3% vs 11%, $P = .06$).[89] The average total cost to achieve healing was $25,954 in the V.A.C. group compared with $38,806 in the control group, mainly due to fewer surgical procedures performed, fewer dressing changes, and fewer outpatient treatment visits in the V.A.C. group.[90] Another recent multicenter randomized trial of 335 diabetic patients similarly confirmed the superiority of the V.A.C. system compared with standard moist dressings for complete ulcer closure (43% vs 29%, $P = .007$), median time to closure (96 days vs not determinable, $P = .001$), and subsequent amputation rate (4.1% vs 10.2%, $P = .035$).[91]

From a revascularization perspective, the most important difference in lower extremity atherosclerosis in the diabetic patient is the anatomic location or distribution of the arterial lesions.[12] Although diabetic patients who abuse nicotine may manifest iliac or femoral occlusive disease, they typically have significant occlusive disease in the infrapopliteal arteries, but arteries of the foot are spared.[92] This "tibial artery disease" requires a different approach to arterial reconstruction and presents special challenges for the surgeon.

Each operation must be individualized according to the patient's available venous conduit and arterial anatomy. In 10% of patients, a foot artery, usually the dorsalis pedis artery, is the only suitable outflow vessel; in an additional 15%, the dorsalis pedis artery will appear to be the best target vessel compared with other patent but diseased tibial vessels.[93] In one of the most comprehensive studies to date on dorsalis pedis revascularization in diabetic patients, Pomposelli et al[94] reported results from >1000 bypasses spanning a decade, with diabetic patients comprising 92% of the cohort. Primary patency, secondary patency, and limb salvage rates were 56.8%, 62.7%, and 78.2% at 5 years and 37.7%, 41.7%, and 57.7% at 10 years. Patient survival was 48.6% at 5 years and 23.8% at 10 years, and perioperative mortality was only 0.9%. The popliteal artery was the source of inflow in 53.2% of patients.

Even in the presence of foot infection, pedal bypass can be performed safely as long as invasive sepsis is controlled before surgery.[57] Although pedal bypass represents the most "extreme" type of distal arterial reconstruction, it is almost always possible, particularly when the surgeon is flexible in terms of venous conduit and location of proximal anastomosis.

Initially designed to study the effects of an E2F decoy on vein graft failure, the Edifoligide for the Prevention of Infrainguinal Vein Graft Failure (PREVENT III) trial constitutes the largest prospective, randomized study of vein bypass grafts for critical limb ischemia performed to date, and the overall surgical results serve as a benchmark for current practice.[95] For these 1404 patients, of which 64% were diabetic, 75% had tissue loss, 65% had infrapopliteal targets, and 24% had high-risk conduit. Early graft failure occurred in 5.2%. After 1 year, primary patency was 61%, secondary patency was 80%, limb salvage was 88%, and overall survival was 84%. The factors negatively affecting patency were high-risk conduit (nonsingle segment of great saphenous vein or diameter <3 mm) and African American race.

Although these results[94,95] justify surgical reconstruction as the current gold standard for diabetic foot revascularization, endovascular intervention has become a useful

Table IV. Summary of the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial

Procedure	*Demographics*	*Morbidity*	*Mortality*	*Amputation-free survival*	*Hospital data (cost first 12 months)*
PTA	224 pts (42% diabetic) 92% rest pain 75% tissue loss	41% overall[a] 2.5% MI 7.6% wound infection 20% immediate technical failure[a] 28% reintervention[a]	5% 30-day 39% at end of follow-up	71% 1-year 52% 3-year	£17,419 Total days in hospital = 36[a]
Bypass	228 pts (42% diabetic) 90% rest pain 73% tissue loss	57% overall[a] 6.6% MI 22.9% wound infection 3% immediate technical failure[a] 17% reintervention[a]	3% 30-day 35% at end of follow-up	68% 1-year 57% 3-year	£23,322 Total days in hospital = 46[a]

MI, Myocardial infarction; *PTA*, percutaneous transluminal angioplasty.
[a]Statistically significant difference.

alternative. With the potential pitfalls accompanying traditional surgical approaches to limb salvage, as well as the overall poor health and life expectancy of patients with PAD, less invasive endovascular therapy can represent an attractive option. Balloon angioplasty and stenting are well suited to focal, short-segment iliac stenoses or occlusions, which exist in 10% to 20% of diabetic patients.[96]

The morbidity of open surgery for outflow procedures can be quite significant and not simply limited to local wound complications or myocardial infarctions. Readmissions to the hospital, reoperations, slow time to healing, and time spent in rehabilitation must be factored into the risk-benefit analysis.[97] In fact, the ideal outcome—patent graft, healed wound, and no additional operations in a fully ambulatory patient who can sustain independent living—may only be obtainable 14% to 22% of the time at a mean follow-up of 42 months.[98] Although patency rates of bypass grafts have been shown to be equivalent in diabetic and nondiabetic patients,[94] endovascular interventions may be associated with worse patency rates in diabetic patients (53% vs 71% at 12 months, 49% vs 58% at 18 months; $P = .05$) due to their higher prevalence of limb-threatening ischemia as the presenting symptom.[99]

The TransAtlantic Inter-Society Consensus Working Group (TASC) initially stratified femoropopliteal and tibial lesions in 2000 and made recommendations for therapy based on lesion type (stenosis vs occlusion), location, and length.[96] The best scientific attempt to compare primary open and endovascular interventions was the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial (Table IV).[100] Although only 42% of the patients had diabetes, the level of ischemia in these 452 randomized patients was comparable with the typical disease patterns seen in a diabetic patient population. Perioperative (30-day) morbidity was higher with surgery, and all-cause mortality trended higher with surgery for the first 6 months but then trended lower for the next 6 months. Amputation-free survival was similar in both groups. Two-year post hoc analysis revealed that surgery was associated with a reduced risk of future amputation, or death, or both.

The trialists concluded that although the strategies are roughly equivalent for mortality and amputation-free survival at medium-term follow-up, angioplasty should be used first for patients with significant comorbidities and with a life expectancy of <1 to 2 years. Moreover, longer-term results favor surgery over angioplasty if there is a "good" vein and a medically fit patient.[101] More recent reviews have shown that after 2 years, tibial angioplasty requires repeat endovascular intervention in 28% of patients (72% of studied patients were diabetic), and another 15% of patients go on to have a surgical bypass, with TASC D lesions predicting the highest failure rate.[102]

The presence of renal failure presents special challenges. If acute renal failure occurs, which most commonly happens after contrast arteriography, surgery is delayed until renal function has stabilized or returned to baseline. Patients with end-stage renal disease who require dialysis can safely undergo arterial reconstruction with reasonable graft patency rates (primary patency, 60%; secondary patency, 86%) and with limb salvage rates up to 80%.[103,104] Gangrene and tissue loss are frequent, however, and the healing response is poor, even with restoration of arterial blood flow. Graft patency and limb salvage in these patients are lower compared with patients without renal failure, and 30% to 50% may come to amputation with a patent bypass graft.[105,106] Long-term survival is poor for this group, with 3-year survival of 18% and 5-year survival of only 5%.[104] As a result of this poor survival, many institutions prefer a complete endovascular approach to patients with renal failure, despite the lower limb salvage rates.[107,108]

A final aspect of managing diabetic foot ulcers is offloading to decrease pressure on the extremity. Offloading strategies involve combinations of bed rest, crutches or wheelchairs, casting, foams or padding, and healing shoes or walking boots. Only after wound healing has been achieved should weight bearing be reinstituted back to baseline levels, and consultation with a physical therapist should be obtained when necessary.

The last alternative remains amputation. Closed minor toe or transmetatarsal amputations are practical after infec-

tion control and revascularization and typically leave the patient with a functional foot for walking. In situations involving extensive tissue loss precluding a functional foot, when there are nonhealing wounds in the setting of patent grafts and for control of sepsis, amputation below the knee is necessary.[109] Surgeons should strive to preserve the knee joint because of its functional significance for rehabilitation, with 34% to 62% of below-knee amputees ambulating postoperatively vs 9% to 23% of above-knee amputees.[110,111] Above-knee amputations are reserved for debilitated patients with severe tissue loss or with no capacity to ambulate.[109] Because of modern advances in prostheses coupled with aggressive approaches to rehabilitation, amputation should be viewed as an acceptable modality to treat diabetic foot complications and not as a treatment failure.

AUTHOR CONTRIBUTIONS

Conception and design: JK, AH
Analysis and interpretation: JK, AH
Data collection: JK, AH
Writing the article: JK, AH
Critical revision of the article: JK, AH
Final approval of the article: JK, AH
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