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REVIEW ARTICLE

Assessment and treatment of diabetic foot ulcer

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SUMMARY

Background and objectives: Foot ulcers are one of the main complications in diabetes mellitus, with a 15% lifetime risk in all diabetic patients. The rate of lower extremity amputation among diabetic patients is 17–40 times higher than in non-diabetics. A critical triad of neuropathy, minor foot trauma and foot deformity was found in > 63% of diabetic foot ulcers (DFU). Peripheral vascular disease (PVD) has been identified in 30% of foot ulcers. We present a comprehensive assessment and the treatment of DFUs. We also want to notify physicians not to ignore foot assessment and examinations in patients with diabetes. **Methods:** We conducted this study on DFU on the basis of: pathogenesis and risk factors, assessment and physical examination, paraclinic assessment, treatment, cost and mortality and prevention. **Results and findings:** Approximately 20% of hospital admissions among diabetic patients are the result of foot problems. Diabetic foot assessment should include dermatological, vascular, neurological and musculoskeletal systems. There are three basic treatments for management of DFU: (i) debridement; (ii) antibiotics and (iii) revascularization. The cost to treat one simple ulcer is $5000 to $8000. **Conclusion:** Awareness of physicians about foot problems in diabetic patients, clinical examination and paraclinical assessment, regular foot examination, patient education, simple hygienic practices and provision of appropriate footwear combined with prompt treatment of minor injuries can decrease ulcer occurrence by 50%.

Review Criteria

- By a search in the MEDLINE.
- By reviewing the related articles in recent years.
- By selecting the most important subject and materials and writing them in a valid and logical manner and order.

Message for the Clinic

- Reduction in lower extremity complications when prevention and treatment programmes are instituted.
- Primary care physicians, internists and surgeons should inspect patients' feet and perform tests for neuropathy, vascular disease or foot deformity.
- Decrease in ulcer occurrence can decrease the need for amputation.

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Introduction

Diabetes mellitus (DM) is one of the most important and common metabolic disorders affecting 2–5% of the population in Europe (1), approximately 5–10% of the population in the United States (2) and 20% of the population in various other parts of the world (1).

Foot ulcers are one of the main complications in DM, with a 15% lifetime risk in all diabetic patients (3). Incidence of diabetic foot ulcers (DFU) is 1.0–4.0% and prevalence is between 5.3% and 10.5% (4). DFU is responsible for more days of hospital stay than any other complication (5,6). Approximately 20% of hospital admissions among diabetic patients are the result of foot problems (7). Diabetes is the leading cause of lower extremity amputation (8). The rate of lower extremity amputation among diabetic patients is 17–40 times higher than that in non-diabetics (9).

Foot complications occur in both forms of diabetes (type I and II) and are related more to the period of time that the illness has been present, than to the age of onset (10).

Pathogenesis and risk factors

High levels of glucose cause cell membranes to lose pliability and function abnormally. Physiological changes induced by 'tissue hyperglycaemia' of the lower extremities include potential decrease in oxygen exchange by limiting the actual exchange process or through induction of damage to the autonomic nervous system causing shunting of oxygenated blood away from the skin surface. Nerves are damaged by hyperglycaemia in a number of ways, the smaller the nerve diameter and the less myelinated the nerve, the more readily it is injured. At least three mechanisms of nerve injury result from chronic hyperglycaemia: (a) metabolic effect, (b) mechanical conduction defect and (c) compartment compression effect.

Decreases in tissue oxygen, combined with impaired sensory and motor nerve function during a prolong period of time, create an environment in which traumatic events occur and can produce what is commonly known as a DFU. Oxygen deficiency caused by macrovascular and microvascular pathology is of primary importance (11).

Nerve damage in diabetes affects the motor, sensory and autonomic fibres. Kumar et al. (12) found that over 40% of type 2 DM patients have significant neuropathy. The EURODIAB IDDM complications study showed that the prevalence of diabetic neuropathy in type 1 DM patients across Europe was 28% (13).

Motor neuropathy causes muscle weakness, atrophy and paresis. Sensory neuropathy leads to loss of protective sensation of pain, pressure and heat. Autonomic dysfunction neuropathy causes vasodilation and decreased sweating (14) also results in loss of skin integrity, which provides an ideal site for microbial invasion (15).

A critical triad of neuropathy, minor foot trauma and foot deformity was found in > 63% of foot ulcers in one study (16).

Patients with DM have a high risk of atherosclerotic peripheral vascular disease (PVD). PVD has been identified in 30% of foot ulcers (16).

Functional changes are responsible for the observed impaired vascular response. These functional changes are due to three factors: (i) endothelial dysfunction, (ii) smooth muscle cell dysfunction and (iii) impairment of the nerve axon reflex (17). Atherosclerosis occurs commonly in the femoral, popliteal and tibialis arteries (14).

Restriction of joint mobility is well documented in diabetes and it is related mainly to collagen glycosylation that results in thickening of the periarticular structures, such as tendons, ligaments and joint capsules (18,19). Loss of sensation to a joint may result in a chronic, progressive and destructive arthropathy. The prototype of this disorder was described by Charcot in relation to tabes dorsalis.

At the foot level, the subtalar and metatarsalphalangeal joints are most commonly involved. Collagen glycosylation is also implicated in decreasing the resiliency of the Achilles tendon in diabetic patients. Decreased motion of the Achilles tendon creates an equines deformity. There is strong evidence that high foot pressure is associated with ulceration in diabetic patients (3).

Risk factors for diabetic foot ulceration can be categorized into three distinct groups: (i) pathophysiological changes, (ii) anatomical deformities and (iii) environmental influences (20). It is important to note that a combination of these risk factors triggers a pathway leading to ulceration. Table 1 shows the risk factors for DFU.

Several studies have conclusively shown that foot ulceration is more common in patients with a previous history of ulceration or amputation. Apelqvist et al. (21) found a recurrence rate of 34% after 1 year and 70% after 5 years.

Table 1 Risk factors for diabetic foot ulceration

1. Diabetic neuropathy
2. Peripheral vascular disease
3. Biomechanical factors
4. Previous foot ulceration
5. Poor glycaemic control
6. Long duration of DM
7. Race
8. Smoking
9. Retinopathy
10. Nephropathy
11. Age
12. Male sex
13. Insulin use and poor vision
14. Other factors

Asian patients with DM are less prone to foot ulcers than Caucasians (22). This may be related to joint hypermobility and cultural differences in self care (23). A number of studies have shown that smoking and Retinopathy do not appear to be a direct risk factor for DFU (12,24,25).

An increased risk of DFU with diabetic nephropathy was also detected by the American Diabetes Association consensus group (26). Male sex was identified as a risk factor in a cross-sectional study (3). The highest percentage of hospital discharges for foot ulcers was in patients aged 45–64 years and the lowest in patients younger than 45 years (4).

Evidence from a number of studies shows an association between greater body weight and higher risk for foot ulceration (24,27). Table 1 shows several risk factors for diabetic foot.

Assessment and physical examination

Physical examination of diabetic foot is based on assessment of the dermatological, vascular, neurological and musculoskeletal systems.

The dermatological examination should include visual inspection of the skin on the legs and feet, particularly the dorsal, plantar, medial, lateral, posterior surfaces and closely examine each of the toenails. The physician should compare the skin on the feet with the skin on the arms and hands (28).

Other important observation includes the presence of peeling skin and maceration or fissuring of the interdigital skin. Common skin disorders seen in patients with diabetes are diabetic dermopathy, necrobiosis lipoidica diabeticorum and bullous diabeticorum that must be noted (28).

Patients with diabetes should be considered at risk for PVD. The practitioner should palpate for pulses bilaterally in the dorsalis pedis, posterior

tibial, popliteal and superficial femoral arteries. The practitioner should assess skin temperature using the back of the hand. Normal skin temperature ranges from warm at the tibia to cool at the distal toes (28).

Subpapillary venous plexus filling time should be assessed by pressing the distal pulp of a toe until it blanches. Normal reperfusion takes from 0 to 3 s. Noninvasive tests for arterial insufficiency can be performed in the office setting including calculation of the ankle–brachial index (ABI) and toe–brachial index (TBI) (29).

The use of duplex ultrasonography has increased because its sensitivity and specificity rate is > 90% (30).

Although noninvasive vascular studies are useful as general screening tools, they are not as reliable as invasive studies to determine the location and extent of occlusive disease. Coordinated care with an interventional radiologist and a vascular specialist is an integral component of caring for the patient with diabetes (31).

There are some screening tests for peripheral neuropathy: deep tendon reflex, vibration sensation, monofilament test, pressure sensation, superficial pain and two-point discrimination. The absence of protective sensation is the single most important risk factor in the development of a foot ulcer (32).

A quantitative score can be calculated on physical examination (33)

•The Achilles tendon reflex is absent (two points for each foot)

• The Achilles tendon reflex is present with reinforcement (one point for each foot)

• The vibration sense is absent or reduced (one point for each foot)

• The pin prick sensation is absent or reduced (one point for each foot)

• The temperature sensation is reduced (one point for each foot)

Then the neurological signs score can be determined: 0–2, normal; 3–5, mild; 6–8, moderate and 9–10, severe.

Presence of erythema, warmth, tenderness or swelling and pus coming out of an ulcer site and/or a nearby sinus tract are signs of infection in diabetes ulcers.

Diabetic foot ulcers can be graded according to a scheme proposed by Wagner:

• Grade 0: no ulcer in high-risk foot

• Grade 1: superficial ulcer involving the full skin thickness but not underling tissues

• Grade 2: deep ulcer, penetrating down to ligaments and muscle but no bone involvement or abscess formation

• Grade 3: deep ulcer with cellulites or abscess formation often with osteomyelitis

• Grade 4: localized gangrene

• Grade 5: extensive gangrene involving the whole foot

Paraclinic assessment

Culture of the infected site should provide a guide for therapy; culture of the wound by swabbing a superficial ulcer is unreliable (34) but needle or open biopsy of the infected site is more reliable (35).

Haemoglobin A1c is used to measure blood glucose control during an extended period (e.g. several weeks). Mean HbA1c was higher in major amputation group than in the minor or non-amputation group ($p = 0.035$) (36).

Eckman et al. have recommended plain X-ray of the foot as the most cost-effective method of imaging (37) but it lacks sensitivity in detecting early osteomyelitis (38,39).

Several imaging techniques aid in determination of osteomyelitis in patient with diabetes. These include imageguided of bone biopsy (40), magnetic resonance imaging (41), three-phase bonescans (40,42), leucocyte scans (41,43,44) and computed tomography (CT) (41,44,45).

Treatment

Numerous investigators have emphasised that the team approach to the treatment of diabetic foot infection may be most cost-effective in reducing limb loss (46). Figure 1 suggests an approach to the care of a diabetic patient suspected of having a foot infection (47). There have been three basic treatments for the management of DFU: (i) debridement, (ii) antibiotics and (iii) revascularization (if it is necessary). Debridement is the first and most important step in healing a diabetic ulcer (48). The wound margins should be extended approximately 2–3 mm into healthy, bleeding, soft non-hyperkeratonic skin.

Infections in patient with DFU are commonly polymicrobial and contain both aerobic and anaerobic bacteria (49). Use of specific topical antibiotic agents is not recommended. Broad-spectrum antimicrobial agents, such as silver sulphadiazine, may have a role in suppression of colonisation. Systemic antibiotics are essential in infected wounds. Choices of agents depend on identification of systemic pathogens.

Table 2 lists the recommended antimicrobial agents for empirical therapy (50). In patients with superficial bacterial infection, antimicrobial therapy with agents effective against staphylococcus and streptococcus will suffice.

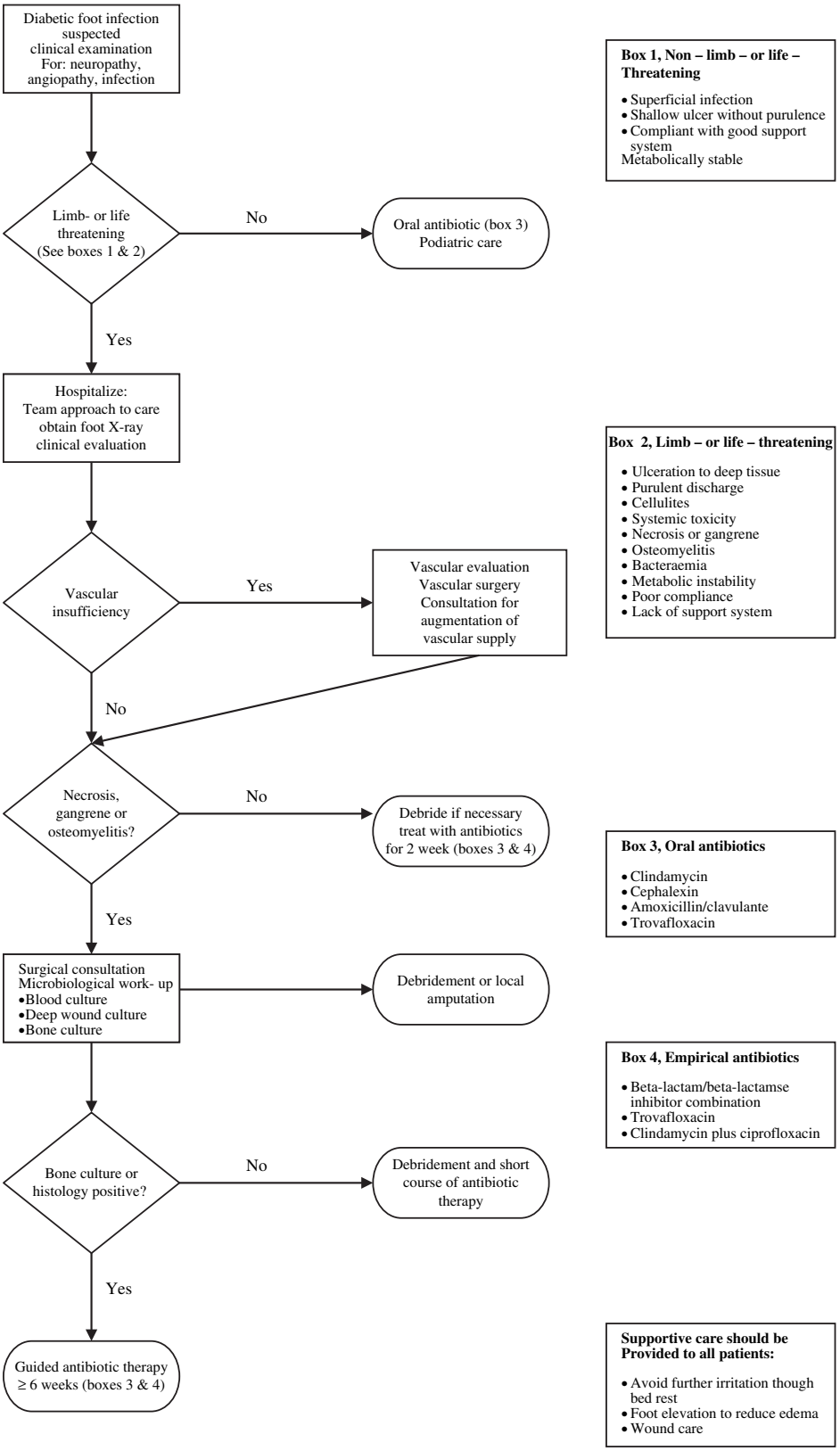

Figure 1 Flow chart for the care of the patient with suspected diabetic foot infection. Reprinted from *Journal of Best Practice & Research Clinical Rheumatology*, Vol. 13(1), James S. Tan et al., Diagnosis and treatment of diabetic foot infections, 149–161, Copyright (1999), with permission from Elsevier

Table 2 Suggested empirical antibiotic regimens, based on clinical severity, for diabetic foot infections

Route and agent(s)	Mild	Moderate	Severe
Advised route	Oral for most	Oral or parenteral, based on clinical situation and agent(s) selected	Intravenous, at least initially
Dicloxacillin	Yes	–	–
Clindamycin	Yes	–	–
Cephalexin	Yes	–	–
Trimethoprim-sulfamethoxazole	Yes	Yes	–
Amoxicillin/clavulanate	Yes	Yes	–
Levofloxacin	Yes	Yes	–
Cefoxitin	–	Yes	–
Ceftriaxone	–	Yes	–
Ampicillin/sulbactam	–	Yes	–
Linezolida (with or without aztreonam)	–	Yes	–
Daptomycina (with or without aztreonam)	–	Yes	–
Ertapenem	–	Yes	–
Cefuroxime with or without metronidazole	–	Yes	–
Ticarcillin/clavulanate	–	Yes	–
Piperacillin/tazobactam	–	Yes	Yes
Levofloxacin or ciprofloxacin with clindamycin	–	Yes	Yes
Imipenem-cilastatin	–	–	Yes
Vancomycin and ceftazidime (with or without metronidazole)	–	–	Yes

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In many studies *S. aureus* was the most common organism cultured and was found in diabetic patients (51–54). The most common location for a diabetic ulcer was the first metatarsal head and this too has been found in many studies (6,51,55).

If infection is superficial, the patient should be treated with oral antibiotics for 1–2 weeks. If dermatophyte infection is also present, an anti-fungal agent may also be started (47).

If vascular insufficiency is suspected, non-invasive vascular evaluation as well as a vascular surgery consultation should be considered. If necrosis, gangrene and osteomyelitis are not present, the lesion should be debrided, if necessary and treated as deep bacterial infection, starting with intravenous antibiotics. If necrosis, gangrene and osteomyelitis are suspected, immediate surgical consultation should be requested for debridement or local amputation and revascularization or angioplasty if possible (47).

In arthropathy (Charcot joints) of acute onset, avoidance of weight-bearing on the affected joint should be recommended until resolution of oedema and erythema occurs. Patients with the swollen uncomfortable hot foot of active Charcot arthropathy showed a marked improvement after pamidronate infusion (56). Symptomatic improvement was significantly greater in the pamidronate group over 12 months of observation (57). Oral bisphosphonates may also be useful, patients received alendronate (70 mg once weekly) had decrease in pain and it is a marker of bone turnover (urine C-terminal telopeptide of type I collagen) and increase bone mineralization in the foot (58).

Surgical management is the mainstay of treatment. Abundant data show that extensive debridement of wounds and removal of devitalised tissue is the single most important therapeutic step leading to wound closure and limb salvage (59).

Early diagnosis and treatment, including surgical intervention for non-gangrenous limb infections reduce the need for amputation (60). Every year, 82,000 limb amputations are performed in patients with DM. The majority of these amputations are performed in the elderly population (61). The risk of lower-limb amputation is 30–40 times higher in the diabetic, as apposed to the non-diabetic population (62).

Surgical revision of initial amputations and multiple amputations for contralateral or ipsilateral limbs are common in patients with diabetic foot (63).

Duloxetine and pregabalin are the only drugs formally approved by the European Medicines Agency and US Food and Drug Administration (FDA) for the treatment of diabetic polyneuropathy. Both drugs were effective for the treatment of diabetic neuropathy (64,65). Smaller clinical trials confirm the efficacy of several other drugs or classes of drugs, including

tricyclic agents, gabapentin, capsaicin, mexiletine, opioids and antioxidants (66–73).

The most effective offloading technique for treatment of neuropathic wounds is total contact casting (TCC). TCC is minimally padded and molded carefully to the shape of the foot. These special casts redistribute weight off the ulcer site and allow patients to walk while the ulcer heals. The goal of tissue-load management is to create an environment that enhances soft-tissue viability and promotes wound healing (59).

The silver cation has been shown to be effective in killing antibiotic-resistant strain of bacteria. Different types of topical long-acting silver applications that are effective include Acticoat, Aquacel Ag and Actisorb Silver 220 (74). Appropriate dressing types are determined by causes of DFU, wound location, depth, amount of eschar or slough, exudates, condition of wound margins, presence of infection, need for adhesiveness and conformability of the dressing (75).

In the past decade, dressing technology has improved significantly, and several new products have been developed for management of various types of chronic ulcers. For example, many dressing types today can kill bacteria and facilitate repair, some of these dressing types have been shown to provide a barrier against environmental contamination, bacteria and some viruses (76).

Cell therapy, also called biological therapy, presents an appropriate treatment option in some cases. The FDA approved two cell therapies to accelerate the closure of non-healing ulcers. These two commercially available products are Dermograft and Apligraf, also known as human skin equivalent, which contains both fibroblasts and keratinocytes (77,78). Individual synthetic growth factors can be generated by recombinant DNA technology. PDGF-BB was the first, and to date the only recombinant growth factor to be approved for treatment of a chronic wound (79).

Cost and mortality

It is estimated that, in 2002 alone, the costs associated with diabetes in the United States were $132 billion; $92 billion of this total was related to direct medical expenditures for these patients, the remaining $40 billion was related to lost productivity (80). The cost to treat one simple ulcer was $5000 to $8000. An admission for an infected ulcer costs approximately $15,000 and an amputation cost between $50,000 to $150,000 in direct expenses (81,82).

Diabetic foot ulcer is associated with increased morbidity and higher mortality rates (83,84). Studies in some underdeveloped countries indicate that patients with severe DFU who do not undergo surgery have mortality rate of up to 54% within 2 years (85). The most frequent causes of death were cardiovascular events. Mortality of the patients reported by Larsson et al. was 50% at maximum follow-up of 6 years (86).

Prevention

Several studies in Europe and the United States have reported reduction in lower extremity complications when prevention and treatment programmes were instituted (87).

Most diabetic patients will tell you that their primary care physician does not inspect their feet let alone test for neuropathy, vascular disease or foot deformity. Several authors have reported the relative infrequency of foot evaluation by primary care physicians and surgeons (88). In the primary care setting only 23–49% of persons with diabetes have their feet evaluated on a yearly basis (88).

There are a number of reasons why the diabetic foot is often ignored in general medical practice. The process leading to ulceration and amputation is still not well understood by many healthcare professionals (89). Regular foot examination, patient education, simple hygienic practices and provision of appropriate footwear combined with prompt treatment of minor injuries can decrease ulcer occurrence by 50% and can decrease the need for major amputation in non-ischaemic limbs to near zero (90).

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