

Treatment of Diabetic Foot Infections and the Role of Hyperbaric Oxygen

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Abstract: This review focuses on evaluation and treatment of more severe diabetic foot infections. The author reviews rational antimicrobial management, adjunctive therapies, and hyperbaric oxygen.

MeSH Words: Diabetes, cellulitis, ulcer, antimicrobial, hyperbaric oxygen

Introduction

Foot infections now account for the largest number of hospital bed-days for diabetics (1) and are the most common cause of nontraumatic amputations (2). Optimal management of diabetic foot infections can reduce morbidity, hospitalization and amputation rates but these infections are frequently not managed appropriately; to help with optimal management, a multidisciplinary team approach is helpful.

The focus of this review is the management of the more severe types of diabetic foot infections. It should also be noted that many diabetic foot ulcers are probably not infected and these will generally not be discussed here, as these diabetic

ulcers may be managed with appropriate wound care and topical applications.

Lower extremity disease is much more common in diabetics than in non-diabetics. In adults over age 40, lower extremity disease (including arterial disease, neuropathy and ulcers) occurs in 17.6% of those without diabetes and 30.2% of those with diabetes (3).

Foot ulcers are frequent and dangerous in diabetics. About 2% of the general population have diabetes and 12-15% of them experience foot ulcerations which tend to relapse at a high rate (4,5) . Of those diabetics with foot ulcers,

Grade	Wagner Ulcer Characteristics
0	Pre-ulcerative lesion Healed ulcers Presence of bony deformity
1	Superficial ulcer without subcutaneous tissue involvement
2	Penetration through the subcutaneous tissue: may expose bone, tendon, ligament, joint capsule
3	Osteitis, abscess, or osteomyelitis
4	Gangrene of digit
5	Gangrene of foot requiring disarticulation

Table 1 – Wagner Ulcer Classification

12% progress to lower extremity amputation (6) . The amputation rate in diabetics is 15-70 times that in the general population (4,5). The rate of amputations in diabetics is 5.5 per 1000 persons and 60% of all lower extremity nontraumatic amputations occur in diabetics (7) . About 85% of these amputations are preceded by a foot ulcer (8).

It is clear that foot ulcers in diabetics are a warning sign for very serious disease. Diabetic foot ulcers occur more commonly in the following situations: longer duration of diabetes, insulin-requiring diabetes, smokers, obesity, and elderly. Diabetic foot infections occur predominantly in diabetics who have peripheral neuropathy which then can lead to ulceration due to trauma or excessive pressure on a deformed foot. The lesions are enhanced by poor arterial blood supply, infection and various immunologic disturbances predominantly involving polymorphonuclear leukocytes.

Classification

Diabetic foot infections are classified primarily based on the depth of infection and presence of gangrene (Wagner classification) (Table 1). Alternatively one can use the PEDIS grade which is an acronym for Perfusion, Extent/Size, Depth/Tissue Loss, Infection and Sensation (See Table 2) (9, 10). The milder infections can be treated as outpatients whereas the more severe infections usually require hospitalization. The moderate infections can be treated using varied approaches and urgency depending on the patient’s general status and the nature of the local foot infection (10).

Microbiology

Aerobic Gram positive cocci: Staphylococci and streptococci are the most commonly isolated bacteria from diabetic wound infections. Any choice of antibiotics for diabetic foot infections should include coverage for these organisms.

Aerobic Gram negative bacilli: these bacteria, which include enteric organisms and pseudomonas, tend to infect more complex wounds, primarily those that are chronic or have already been treated with prior antibiotic therapy.

Anaerobic bacteria: Mixed infections with anerobic bacteria are virtually always present in advanced diabetic foot infections with necrosis, gangrene and a foul smell.

The presence of resistant organisms such as MRSA (methicillin-resistant Staph. Aureus) or VRE (vancomycin-resistant enterococci) Should be considered in patients with multiple prior surgical procedures, prolonged hospitalization or a stay in the Intensive Care Unit

The chronic forms of diabetic foot infections are always polymicrobial, with three to five bacterial isolates. An early uncomplicated cellulitis in the foot of a diabetic is similar to cellulitis in non-diabetics: empiric therapy would be adequate without attempting to get culture confirmation as long as the therapy is appropriate to cover staphylococci and streptococci - the usual pathogens. Blood cultures are not necessary unless the patient has a severe infection and is systemically ill. Appropriate cultures from ulcers should only be taken from the base of the ulcer after debridement has been done; this would help to ensure that the colonizing bacteria have been removed and the deeper causative organisms are present. One should similarly avoid taking cultures just from the wound drainage because of surface contamination with colonizing bacteria. Optimal cultures are taken by needle aspirate from deep purulent collections or from subcutaneous tissue in the presence of a cellulitis. In the presence of ulcers, needle aspirates are best done by inserting the needle through intact skin and not through the open ulcer; this method will again avoid contaminating surface bacteria.

Clinical manifestations of infection	Infection severity	PEDIS grade
Wound lacking purulence or any inflammation	Uninfected	1
Presence of ≥ 2 manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤ 2 cm around the 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 which has ≥ 1 of the following: cellulitis > 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	Severe	4

Table 2: Clinical Classification of Diabetic Foot Infection Modified from Lipsky et al. (10)

Antimicrobial Therapy

Diabetic foot ulcers are considered to be clinically infected if there is purulent discharge or if there are either local signs of inflammation or systemic signs of infection in the absence of other causes. Uninfected ulcers need not be treated with systemic antibiotics.

Mild – Moderate Infections

These patients usually only require therapy for Gram-positive cocci, and can be treated with oral cephalexin or clindamycin. If necessary, intravenous cefazolin or vancomycin can be arranged for outpatient use; such patients generally only require 10-14 days treatment.

Patients who have mild-moderate infections but are at higher or proven risk of Gram negative infection can be treated with amoxicillin/clavulinate or ciprofloxacin plus clindamycin.

Severe Infections:

More severe infections are often characterized by systemic signs of toxicity, large areas of inflammation or foul-smelling discharge. Hospitalization is common, and intravenous therapy should be directed against polymicrobial infections. Piperacillin-tazobactam or a carbapenem (e.g. imipenem) are appropriate choices. Vancomycin might be added in the sickest patients or if there is suspicion of MRSA. Some of the newer quinolones such as moxifloxacin have good activity against anaerobic bacteria, streptococci, Gram-negative

bacilli and some of the more sensitive staphylococci. These quinolones can be used in some of the less ill patients. The quinolones are very well absorbed, so intravenous therapy may not be required.

The duration of therapy is not definite but is generally at least 4 weeks for severe infections and at least 6 weeks in the presence of osteomyelitis. Patients could be stepped down to oral therapy when improvement has occurred if a well-absorbed antibiotic can be used based on the microbiology results.

Clinical trials do not suggest that one antimicrobial combination is superior to another for treating the infected diabetic foot. The important aspect is anticipate the probable infecting bacteria, and then follow the appropriate guiding principles.

Adjunctive Therapies

Surgery – Surgical debridement is indicated if there is deep purulent infection or necrotic tissue, or if the infection is spreading rapidly. Vascular assessment is useful to determine which patients would benefit from revascularization. It is most useful to do this in early days in a course of treatment.

Wound Care – Debridement to remove dead or unhealthy tissue can usually be done at the bedside. Pressure should be removed from the foot wound with bedrest; various devices have also been employed to relieve pressure on the

affected foot. There is little evidence to support one form of wound dressing over another. Various adjunctive measures have been used such as a vacuum-drainage system, recombinant growth factors, skin substitutes and sterile larvae which are applied to the wound(10). Granulocyte colony-stimulating factors may be helpful; they do not accelerate resolution of the infection but may significantly reduce the need for operation.

Hyperbaric Oxygen

Hyperbaric oxygen therapy (HBOT) refers to the use of a mono- or multiplace compression chamber in which the environmental pressure is increased to 2.0 to 2.5 atmospheres absolute together with the administration of 100% oxygen for respiration (11,12). Although HBOT has been used for many conditions, there are only a few infectious diseases for which there is some scientific support demonstrating therapeutic benefit of HBOT. These conditions include gas gangrene, necrotizing fasciitis and treatment of diabetic foot ulcers.

Selection of appropriate patients for HBOT is often done using transcutaneous oximetry with the patient first breathing air, and then hyperbaric oxygen (13). Measured transcutaneous oxygen during HBOT that is greater than 200 mm is predictive of success. HBOT has multiple effects on the tissues including hyper-oxygenation of the tissue, angiogenesis, fibroblast activation, new collagen formation and downregulation of inflammatory cytokines. Enhanced killing by macrophages and potentiation of antibiotics is observed. Osteoclast stimulation to remove dead bone results in enhanced osteogenesis. In a rabbit model of facial irradiation, hyperbaric oxygen led to a marked increase in vascular density in tissue compared to appropriate controls. Thus, angiogenesis should increase oxygen delivery and enhance healing (14).

The main adverse effects of HBOT in humans relate to middle ear baro-trauma. This occurs in about 2%, but can be reduced by decongestant therapy such as pseudoephedrine. Additional adverse effects include sinus squeeze, claustrophobia, progressive myopia, cataracts and pulmonary baro-trauma, especially in those who have COPD.

HBOT has also been used in patients who have gas gangrene, and beneficial effects have been documented in many case series and cohort studies. It must be used early in the course, and is associated with a reduced mortality and reduced amputation rate. There is also a clarification of the demarcation between dead and living tissue, that facilitates a reduction in tissue loss from surgical debridement.

The evidence with respect to HBOT and diabetic foot ulcers is based on five clinical trials involving 175 patients (92 had HBOT and 83 were controls) (15-19). In these trials HBOT had the following benefits (11,12): significant wound reduction size by 20% immediately after HBOT; significant improvement in the chance of healing one year after therapy; a significant increase in tissue oxygen concentration; and most importantly, a reduction in the incidence of major amputation. There was no difference in the minor amputation rate. The pooled data from three trials with 118 patients showed reduction in the risk of major amputation, so that the relative risk was 0.31. One would have to treat four patients with HBOT to prevent one amputation in the short-term.

Some of the limitations of these studies include a modest sample size and methodological shortcomings. Mixed endpoints make it difficult to pool the data for conclusions. The guidelines from the Infectious Diseases Society of America (IDSA)(10) suggest that systemic hyperbaric oxygen therapy may help to prevent amputations, but the level of the evidence is noted to be B-I. HBOT was considered by the IDSA to be possibly useful for severe infections or for those that have not adequately responded to therapy despite correcting for all amenable local and systemic adverse factors.

Overall, if improvement is not occurring in diabetic foot ulcers despite optimizing other therapy, one should consider using hyperbaric oxygen therapy.

Conclusion: Diabetic foot infections remain a challenge, and outcomes are often poor. The best outcomes, and possible avoidance of amputation, are achieved using a multidisciplinary approach. This includes determining the microbial etiology and using appropriate antibiotics, attentive wound care, and consideration of adjunctive measures such as HBOT.

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