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Diabetic Foot Infections: Treatment and Cure

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Abstract

Diabetic foot complications are common, costly, and difficult to treat. Peripheral neuropathy, repetitive trauma, and peripheral vascular disease are common reasons that lead to ulcers, infection, and hospitalization. Individuals with diabetes presenting with foot infection require optimal medical and surgical management to accomplish limb salvage and prevent amputation; aggressive short-term and meticulous long-term care plans are required. Multiple classification systems have been recommended to ease the understanding and the management of these infections. Multi-disciplinary approach is the mainstay for a successful management. Such teams typically include multiple medical, surgical, and nursing specialties across a variety of public and private health care systems. This review is an overview in how to approach to the diabetic foot infection with emphasis is soft tissue infection with medical and surgical approach.

Keywords: Diabetic foot complications; Diabetics mellitus; Foot care; Limb salvage; Amputation

Introduction

In the United States alone, there are 23.6 million (7.8% of the population) people affected by diabetes and its attendant increased mortality [1]. Plantar ulceration has been reported as the most frequently common diabetic foot complication with 20-25% of all hospital admissions owing to foot problems [2]. Approximately 56% of foot wounds become infected and foot complications are associated with approximately one quarter of all hospital days for people with diabetes [3]. Approximately 15% of people with diabetes will develop foot ulceration that will become complicated by osteomyelitis in two-thirds of the cases [4]. Early diagnosis is the key to adequate treatment and appropriate precautions to prevent the spread of infection, especially with resistant bacterial strains and immunocompromised individuals. Although, *Staphylococcus aureus* is the most common infecting organism in diabetic foot infections (DFI), as many as 46% of *Staphylococcus aureus* isolates are Methicillin resistant *Staphylococcus aureus* (MRSA) [5]. This review is an overview in how to approach to the diabetic foot infection with emphasis is soft tissue infection with medical and surgical approach.

Risk Factors

Neuropathy and immunopathy are the major contributing factors that attribute to patients acquiring an infection [6]. More often than not peripheral vascular disease coexists with neuropathy playing a major role in the healing potential. Neuropathy predisposes the foot to infections while vasculopathy and immunopathy determine the outcomes [7]. About 50% of all patients with diabetes experience lack of sensation which combined with repetitive stress leads to tissue break down and then eventually infection [8]. Patients with diabetic neuropathy alone are 1.7 times more likely to develop pedal ulcerations [9]. The etiology of diabetic neuropathy is not clearly understood, but one major theory has been described as angiopathy of the vasa nervosum causing ischemia of the nerve. Evidence of the metabolic disturbance has been found, including the accumulation of intraneural sorbitol and glycosylation of the nerve protein and reduction of axonal transport. Loss of protective sensation, combined with recurrent trauma, is the primary mechanism of tissue breakdown in the foot [10]. Poor glycemic control has been associated with the predisposition of diabetic patients to infections. The presences of high levels of glucose in the bloodstream decrease the ability of leukocyte chemotaxis, and phagocytosis [11]. In general, blood glucose of 250 or more places the patients in a compromised situation to develop an infection.

Evaluation

Infection is defined as the pathologic presence of bacteria in a site or wound which is supported by the body's response to inflammation and white blood cells [12]. Knowing that all skin wounds contain microorganisms, infections must be diagnosed clinically rather than microbiologically. Therefore patients with an infected foot ulcer may have diminished signs of inflammatory reaction possibly due to peripheral neuropathy or ischemia. Systemic signs of toxicity are uncommon in diabetic foot infections. Most patients are afebrile without elevated white blood cell count, or elevated sedimentation rate, or C-reactive protein and report no pain. If any these symptoms are present, then a severe infection most likely is present [13]. Once there is a suspicion of clinical infection, then microbiology is a useful tool to determine the causative agent once a clinical diagnosis of infection is made. At this time a treatment plan should be implemented. Generally, the treatment option will be dependent upon if the infection is mild, moderate or severe. Assessing the severity of the infection helps to determine the need for hospitalization, the potential necessity and timing of surgery, and the likelihood of amputation. As a general rule, mild diseases can be treated with oral antibiotics in the outpatient setting, whereas moderate and severe disease will usually require intravenous antibiotic therapy and hospitalization [14].

Commonly, patients with a DFI present with laboratory results such as white blood cell count within normal limits. More often than

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not, it does not exclude the fact that a diabetic person is infected. It has been suggested that patient with longstanding diabetes may not mount an effective immunological response to invading pathogens [13]. According to Kaleta in 2002, he performed a retrospective chart review that revealed patients with a sedimentation rate of 70 or higher were noted to have osteomyelitis and Armstrong found that 82% of the patients with osteomyelitis had normal oral temperatures [15,16].

Initial imaging should include weight-bearing plain radiographs to assess for fractures or dislocations, foreign bodies, subcutaneous emphysema, and associated degenerative changes. CT can be used to further evaluate the bony architecture. Suspicion of osteomyelitis may warrant additional evaluation with MRI. With either of these advanced imaging techniques, consideration must be given to the patient's renal function before administration of contrast material. Nuclear medicine studies, including technetium T c-99m and indium-In111-labeled leukocyte scans can be used in the setting of equivocal findings or relative contraindications to other imaging techniques. However, in DFI involving the soft tissues most of ancillary studies are not helpful [17,18].

In addition, a thorough and careful vascular examination must be performed. At minimum, this should include documentation of dorsalis pedis and tibialis artery pulses, with Doppler ultrasound and ABI assessment as needed. Further imaging, including CT angiography and magnetic resonance angiography, may be of benefit in terms of preoperative planning and does not have the risks inherent in invasive angiography.

Classifications of Diabetic Foot Infections

Most of the classification systems previously reported in medical literature have primarily focused on the depth of the ulceration and failing to comment on a patient's infection and arterial supply. The University of Texas Classification has the capability of not only staging the wound, but also risk stratifying the patient including infection (Table 1) [19]. Once the diagnosis of diabetic foot infections has been made, it is helpful to classify the infection by its severity to delineate a proper treatment plan. The Infectious Diseases Society of America and the International Working Group for the Diabetic Foot have suggested and validated a classification and grading system whereby such infections may be labeled mild, moderate, or severe based on clinical findings and the patient's systemic health status (Table 2). This scale has been validated in a prospective observational study [2,14].When applied to 1666 patients with a foot ulceration, there was a significant increase in rates of hospitalization and lower extremity amputation with increased severity of the infection. These classification systems have now been widely accepted. Gibbons et al. described a classification system to distinguish between the clinical presentations of mild, moderate, and severe infections and recommending treatment for each situation (Table 3) [20].

Medical Therapy

Based on the results of the available studies, no single drug or combination of agents appears to be superior to any others [21,22]. Since publication of the 2004 DFI guidelines, the FDA has approved 3 antibiotics (ertapenem, linezolid, and piperacillin-tazobactam) specifically for the treatment of "complicated skin and skin structure infections including DFI," but not for any accompanying osteomyelitis. Table 4 describes the suggested antibiotics for DFI depending upon the severity of the infection.

Whenever possible, clean biopsy and culture should be obtained to determine the appropriate organism-specific therapy. For ulcers with gross evidence of infection, the initial empiric regimen must take into account the severity of infection and likely etiologic agents. Empiric broad-spectrum antibiotic therapy should be reserved for severe infections and should be narrowed based on culture results and antibiotic susceptibility data. In a systematic review by *Peters* et al. 12 studies comparing different antibiotic regimens in the management of skin and soft-tissue infection, none reported a better response with any particular regimen. Of seven studies that compared antibiotic regimens in patients with infection involving both soft tissue and bone, one reported a better clinical outcome in those treated with cefoxitin compared with ampicillin/sulbactam. The author concluded that no published data support the superiority of any particular route of delivery of systemic antibiotics or clarify the optimal duration of antibiotic therapy in either soft-tissue infection or osteomyelitis. Therefore, further studies are necessary in answering the questions above [23].

Surgical Intervention

Once the decision that surgical intervention is necessary for infection control, the surgeon should follow a systematic approach. This approach includes: incision, inspection, debridement, culture, irrigation, hemostasis and post-operative care. The 4 D's approach for deep abscess is helpful to plan an appropriate treatment: decompression, drainage, debridement and drugs. Decompression could be done at the bedside or in the operating room. It is important to perform this initial procedure to avoid increase pressure within the foot compartment, thus gangrenous extension occur. The edema caused by the infection can precipitate thrombosis occlusion by compromising the blood flow to the distal arteries. The surgical approach to the infection will depend of the portal of entry of it. Most commonly than not, the incisional approach will follow the extensor or flexor tendon of the foot. Acute DFI will follow the path of least resistance which in the foot is the tendons. In 1980 Loeffler and Ballard describes the anatomical spaces of the foot and their interconnections within them (Figure 1) [24]. For instance, an infections originating from an ulcer on the hallux or under the 1st metatarsal head will most likely spread through the medial compartment via the flexor hallucis longus tendon (Figure 2). An infection present in the central digits or metatarsal heads will be confined to the central spaces. Infected lesions on the 5th toe or 5th metatarsal head will lead to lateral compartment infections. Dorsal compartment infections are caused mainly by web space origin. These compartments communicate between each other in various ways. Not much amount of compartmental pressure is required for the infection to spread from space to space. This is the reason why rapid incision and drainage is required in these scenarios. Often, these patients repeatedly

	0	1	2	3
A	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating tendon or capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and ischemia	With infection and ischemia	With infection and ischemia	With infection and ischemia

Table 1: University of Texas wound classification system.

Clinical manifestations of infection	Infection severity	PEDIS grade
Wound lacking purulence or any manifestations of 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 characteristics: cellulitis extending 12 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 (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe	4

Adapted from IDSA guidelines: Lipsky et al.: Diagnosis and treatment of diabetic foot infections, CID 2004: 39.

Table 2: Classification of diabetic foot infection.

Clinical severity	Characteristics	Therapy
Mild	Superficial ulceration Purulent discharge Minimal cellulitis	Oral antibiotics
Moderate potentially limb threatening	Ulceration to deep tissues Purulent discharge cellulitis Systemic toxicity Mild/moderate necrosis Osteomyelitis may be present	IV Antibiotics Surgical drainage/debridement Assess Need for Revascularization
Sever potentially life threatening	Ulcerations to deep tissues Purulent discharge cellulitis Systemic toxicity, including septic shock Marked necrosis/gangrene Osteomyelitis may be present Bacteremia	Urgent surgical drainage, debridement or amputation IV antibiotics Control hyperglycemia and ketoacidosis Assess need for revascularization

Table 3: Recommendation for management of diabetic foot infection.

Severity	Recommended	Alternate
Mild/Mod (oral)	Cephalexin (500 qid)	Levofloxacin (500 qd)
	Dicloxacillin (500 qid)	Clindamycin (300 tid)
	Amox/clav (875/125 bid)	Linezolid (600 bid)
Mod/Severe (iv → po)	Amp/sulb (2 g qid)	Pip/tazo (3.375 qid)
	Clindamycin (450 qid)+	Ceftazidime (2 g tid)+
	Ciprofloxacin (750 qid)	Clindamycin (600 tid)
Life-threat	Imipenem/cilast (500 qid)	Vancomycin (1 g bid)+(long iv)
	Clinda+Tobra (0.4 g qd)+	Aztreonam (2 g tid)+
	Ampicillin (0.5 g qid)	Metronidazole (0.5 g qid)

Table 4: Suggested antibiotics according to severity of infection. Adapted from IDSA guidelines: Lipsky et al.: Diagnosis and treatment of diabetic foot infections, CID 2004:39.

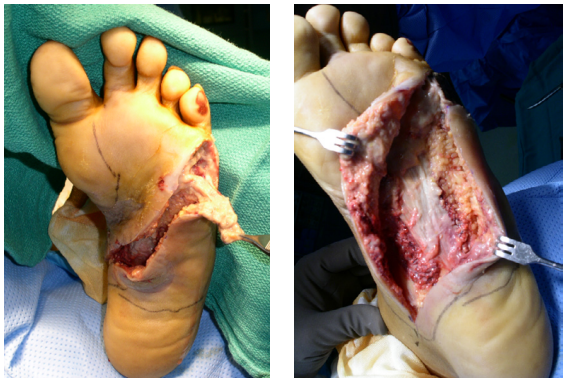

Figure 1: Loeffler and Ballard incision beginning at the 5th MPJ and following the flexor tendon.

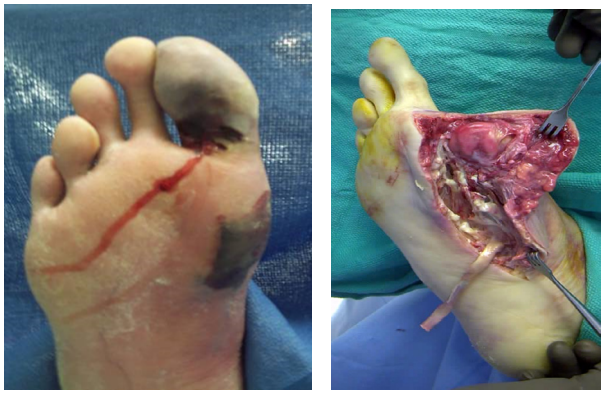

Figure 2: Infection involving the medial compartment of the foot.

visit the operation room because of continue debridement until the wound is clean. Negative pressure wound therapy (NPWT) has revolutionized the management of chronic specially, the post-operative wounds, by faster time to closure and decreasing amputation rate [25]. The wound, then, is ready for secondary closure by means of coverage, or delayed primary closure.

Conclusion

Diabetic foot infections are a common source of morbidity, disability, and potential limb loss. Diabetic foot infections are difficult to treat because the etiology is multifactorial. A systematic and multidisciplinary approach is essential for prevention and to guide therapy. Systemic signs of infection are often misleading. In patients with peripheral neuropathy, a large proportion of foot infections and associated morbidity can be prevented through careful surveillance, and preventive strategies. Surgical management is the mainstay for moderate and severe infections, and early recognition is the key for success.

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