Review Article

Diabetic foot infection

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ABSTRACT

Diabetic foot infection (DFI) is simply defined as suspected or documented infection of the tissues that comprise the foot of a diabetic patient. Diabetic foot infection is often caused by introduction of an infection into the otherwise sterile soft tissues of the foot through a minor skin break down. Diabetic foot infection may be mild usually restricted to the uppermost layers of the skin, moderate extending down to the soft tissues of the foot or severe infection associated with systemic toxicity or metabolic instability. The paper reviews the types of DFI, pathophysiology, microbiology of DFI, relevant anatomy of the foot, clinical evaluation, measures of severity of DFI, the role of radiological investigations, and the role of early surgical intervention in the prevention of progressive foot infection and limb salvage. It is concluded that the diagnosis of DFI should be suspected at an early stage based on the presence of local signs of inflammation with or without systemic signs of toxicity or metabolic instability. Optimal treatment of DFI requires a multimodality approach directed at controlling hyperglycemia, administration of systemic antibiotics, and local wound management to prevent the spread and dissemination of infection.

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Diabetic foot infections (DFI) are commonly encountered problems in the practice of clinical medicine today. They are among the most frequent and serious complications of diabetes mellitus and responsible for most of the non-traumatic lower limb amputations.[1,2] In the United States, diabetic foot infections are the most common diabetes related cause of hospitalization accounting for almost half of all hospital days.[3] The annual incidence of foot ulcers among patients with diabetes is approximately 2-5% with a prevalence of 4-10%.[3] It is also the most common cause of surgical admissions in Hajj pilgrims which is an important consideration to physicians in this region, this is due to physical exertion, exposure to injuries, and non adherence to treatment.[4] In general, the term DFI refers to constellation of signs and symptoms, which includes the presence of purulent discharge (pus), or 2 or more signs and symptoms of inflammation (redness, swelling, pain, tenderness, and warmth).[5] Diabetic foot infection should be suspected upon the first appearance of local problems such as the development of swelling, skin discoloration, pain, discharge, or ulceration. It should be suspected in diabetic patients presenting with systemic signs such as fever, malaise or poor glycemic control even if the local signs are less severe than might be expected.[5,6] Diabetic foot infections are usually associated with prolonged hospital stay, high financial costs and can cause long term morbidity and even mortality.[7,8] This article focuses on the pathophysiology, clinical forms, measures of severity, anatomical considerations, foot biomechanics, microbiology, laboratory and radiological diagnosis and management of DFI.

Pathophysiology of DFI. The underlying etiology of DFI has many components. Several studies have shown that peripheral sensory neuropathy, peripheral arterial disease and deformity are the major predisposing

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factors for foot ulceration and infections.[9,10] Other factors involved in the development of DFI are trauma, edema and hyperglycemia.[11] Following loss of skin integrity, underlying foot tissues become prone to infection. Direct extension of infection to the foot compartments or spreading of infection along tissue planes may lead to deep infections or bone involvement. This sequence of events can be progressing rapidly especially in ischemic limb and can lead to massive destruction of foot tissues with necrosis and gangrene.[12] The presence of underlying immunologic disturbances especially those affecting polymorphonuclear in some diabetic patients might be responsible for the rapid spread and the bad outcome of these infections.[13,14] A recent study showed that strong expression of adhesion molecules on endothelial cells in diabetic tissues was not associated with increased leukocyte migration into the dermis and formation of macrophage and lymphocyte infiltrates in comparison to what usually is seen in inflamed non-diabetic tissues.[15]

Diabetic neuropathy. Loss of protective sensation of the foot secondary to neuropathy is the major etiologic factor of most DFI. It is reported in more than 80% of diabetic patients with foot ulcers.[16] This may allow incidental trauma that goes unrecognized such as skin blistering or penetrating foreign body injury. Furthermore, the presence of dry and fissured skin resulting from autonomic neuropathy might act as possible ports of entry for microorganisms predisposing the skin to infection.[17] In addition, calluses formation which is common in the foot of diabetic patients, can turn into open sores and set the stage for ulcer formation.[17]

Peripheral arterial occlusive disease. Peripheral arterial disease (atherosclerosis) is an important risk factor for developing DFI. In patients with diabetes, the calf vessels are typically affected with relative sparing of proximal vessels and those in the foot.[18,19] It usually starts at an early age with equal gender distribution, and its prevalence increases with concomitant hyperlipidemia, hypertension and smoking.[18,19] Foot ischemia in diabetic patients may also result from microvascular disease both structural (thickened basement membrane, capillary wall fragility, and thrombosis) and functional (vasomotor neuropathy) which may lead to defective microcirculation and abnormal endothelial function.[19]

Trauma and foot deformity. Unrecognized steady or repetitive trauma to the foot often results from tight shoe which in the presence of underlying neuropathy, may lead to skin damage and inflammation. If the pressure was not relieved, skin rupture over pressure points will occur providing entry port for bacteria and subsequent DFI.[20] This is usually common over the ankle region, lateral or medial foot margins, and over the prominent metatarsal heads in the forefoot.[21,22] Inadvertent soft tissue injury during regular foot care such as nail trimming may also result in diabetic foot infection.[7] Foot deformities and joint stiffness in patients with diabetes are important risk factors for DFI because of their interference of foot biomechanics and the development of new pressure points which might cause foot infection.[3,22] Patients with deformed bones of the feet (Hallux valgus, claw toes, cock-up toes, hammer toes or toe nail pressing on the toe next to it) or patients with Charcot's foot deformity are also at risk of skin damage and infection.[23] The presence of lower limb edema especially around the ankle region can also predisposes diabetic patients to skin breakdown and heel ulceration.[24]

Metabolic hyperglycemia. Diabetic patients with persistent hyperglycemia are at a higher risk of developing foot ulcers.[25,26] Persistent hyperglycemia is a risk factor for surgical sepsis,[26,27] impaired wound healing,[28] and endothelial dysfunction.[29] In addition, glycation of proteins, including hemoglobin, albumin, collagen fibrin and lipoproteins associated with hyperglycemia contributes to both microvascular and macrovascular derangements. Furthermore, fasting hyperglycemia represents a catabolic state associated with negative nitrogen balance that might impair the synthesis of proteins such as collagen by the fibroblasts which is an important element in the healing of wounds and ulcers.[30]

Relevant anatomy and foot biomechanics. The feet are very complex structures, each composed of a network of bones, joints, ligaments, and many muscles that are working together to provide the body with support, mobility and balance. In the standing position, the body weight is transmitted from the femur and tibia through the heel bones (talus and calcaneus), and the heads of the metatarsals to the ground.[31,32] The development of septa from the deep aspect of the plantar aponeurosis divides the plantar aspect of the foot into 3 compartments; medial, central and lateral. The deep part of the central compartment can be considered as a separate interosseous compartment.[31,32] Increased intracompartmental pressure as a result of inflammation and infection, and inappropriate weight distribution may further interfere with the blood supply to the distal portions of the foot leading to poor healing and putting them at risk of gangrene.

Weight transmission is usually accomplished through the heel bone and the head of the metatarsal bones. The head of the first metatarsal bone plays an important role in this regard especially in the

last segment of walking.[33] The combined effects of muscles, tendons, ligaments, and bone function contribute to the normal mechanics of the foot and ankle. Walking mechanics are divided into 4 segments. Classically, "heel strike" is the first segment when the calcaneus makes direct contact with the ground and the muscles, tendons, and ligaments relax, providing for optimal energy absorption. The second segment is "midstance" when the foot is flat and is able to adapt to uneven surface, maintain equilibrium, and absorb the shock of touchdown. The calcaneus in these 2 segments plays an important role in keeping the front and back of the foot aligned for optimal weight bearing. The third is "heel rise" when the calcaneus lifts off the ground, the muscles, tendons, and ligaments tighten, and the foot regains its arch. This segment is followed by the fourth and the last segment "toe push-off".[33] The balance between the forces of the pushing down of the body weight and the pushing up of the ground reactive forces in addition to the shearing forces during dynamic walking create friction and compressive forces on the foot. If these forces are combined with intrinsic muscles wasting secondary to diabetes, they may cause an imbalance of the forces acting on the bony structures leading to toe deformities, prominent metatarsal heads, equinus deformity and varus position of the hind foot. Loss of sensation especially at pressure points may lead to persistent stress which may result in bunion and later skin breakdown and ulcer formation.[34] Several approaches are used to reduce abnormal foot pressures including callus debridement, wearing a special footwear, walking splints, ankle-foot orthosis, total contact cast, removable and irremovable cast walkers, and Achilles tendon lengthening. Off-loading of the diabetic ulcers is a key factor in successful wound healing, as it is associated with reduced inflammatory and accelerated repair processes.[34,35]

Microbiology of DFI. Knowledge of the microbial etiologies in DFI is crucial for the management; it is important in tailoring antibiotic therapy, and studying resistance in DFI. One can identify the microbiology of the DFI either from a swab culture of the ulcer, or more accurately from a deep tissue culture by curetting after debridement. In addition, obtaining blood cultures is helpful in patients with severe infection complicated by bacteremia.[36,37] All diabetic foot ulcers can be colonized with a variety of organisms. However, in these cases, antimicrobial therapy is not recommended unless there is a suspected or proved infection. In the early stages of superficial infections (minimal cellulites, superficial ulcerations) and no previous antimicrobial therapy together with good metabolic control, the aerobic gram-positive cocci are the predominant organisms; *S. aureus* and the *Streptococci* are the most commonly isolated microorganisms.[12] Patients with chronically infected ulcers, extensive necrosis, wet gangrene, and prolonged use of antibiotics have mixed microbial etiologies. Several microorganisms might be isolated from these patients such as *Enterococci*, *Enterobacteriaceae, Anaerobes,* and *Pseudomonas aeruginosa*. Occasionally, these infections might be monomicrobial; however, polymicrobial infection is far more common finding.[38-40] Currently, there is a gradual rise in antibiotic resistant organisms in DFI as a result of repeated hospitalizations, frequent exposure to antibiotic therapy, and low antibiotic concentration in infected tissues due to poor arterial supply. *Methicillin resistant S. aureus* (MRSA) and resistant gram-negative bacilli were reported in patients with DFI, and in some studies were associated with a worse outcome. Furthermore, the first 2 reported cases of vancomycin resistant *S. aureus* involved diabetic patients with foot infections.[41,42] Low virulence organisms such as coagulase negative *Staphylococci* and *Corynebacterium* "diphtheroids" can be isolated in mixed cultures; however, the interpretation of this should be taken with caution, as they may assume either a pathogenic or a colonizing role.[12]

A recent study showed a low incidence (4%) of Candida and mixed infections of diabetic foot ulcers, with a tendency to develop in chronic non-healing foot ulcers. The presentation of these infections in severe clinical situations suggests a possible role in secondary foot infection.[43]

Clinical forms of DFI. Diabetic foot infection can be classified into 3 clinical forms: superficial, soft tissue, and bone infection. Superficial DFI is usually restricted to the uppermost layers of the skin such as toe or limited foot cellulites (**Figure 1**), infected bleb or bullae or infected ingrowing toe nail.[44,45] Superficial DFI may occur in the absence of an apparent source of infection and is observed mostly in poorly controlled diabetics and in patients with lower limb swelling from concomitant renal or heart failure. It is usually related to foot contamination from skin flora which is translocated across the skin from an unrecognized minor skin laceration or from a web space maceration.[40]

Soft tissue infections in diabetic patients are usually deeper than superficial infections and are associated with local findings such as redness, pain, swelling, discharge and tissue loss (ulcer formation).[46] This infection often leads to discoloration of the skin around the involved structures resulting from

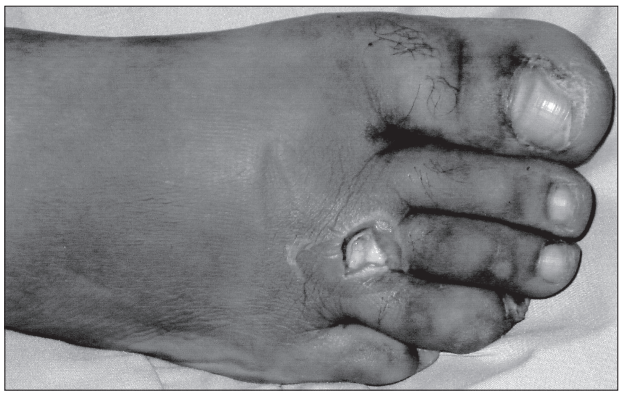

Figure 1 - Superficial diabetic foot infection is usually restricted to the uppermost layers of the skin such as toe or limited foot cellulites, infected bleb or bulle or infected ingrowing toe nail.

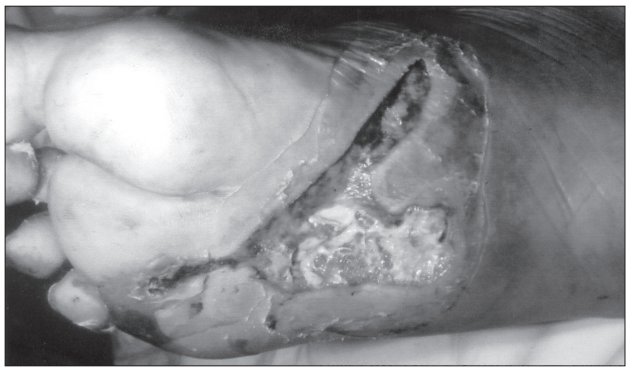

Figure 2 - Infected diabetic foot ulcer.

edema and congestion which might interfere with blood supply to distal structures causing toe or foot gangrene.[47] Infected diabetic foot ulcer (**Figure 2**), by far, is the most common form of soft tissue infection encountered in clinical practice today.[4, 17] It is caused by direct invasion of the ulcer and the underlying soft tissues by bacterial inoculum. Infection of diabetic ulcer is diagnosed if a foully smell or a purulent discharge were present with other local signs of infection (warmth, erythema, edema, pain). In spite of its innocent appearance, diabetic ulcers may be quite deep and tracking under the skin. It is recommended to probe the ulcer for a sinus or a track, and if bone can be probed at the base of the ulcer, bone infection must be suspected, and an x- ray of the foot is required.[17] Extension of soft tissue infection along the fascial planes may result in abscess formation inside foot compartments; the medial, lateral and the central compartment, but it may also extend to the ankle region or heel area, under the dorsal skin, or through the plantar fascia.[48-50]

Bone infection is the third clinical form of DFI and it is usually a complication of diabetic foot ulceration.[51] Associated contiguous bone infection may be present in up to two thirds of diabetic patients with moderate to severe foot infections.[37,51,52] It should be suspected in all cases of infected ulcers extending deep to the bones or in patients with radiological evidence of bone destruction. Bone infection should also be suspected in chronic non-healing ulcers that have not healed after 6 weeks of adequate treatment including offloading.[51] Crumbled red swollen toe or a so-called sausage toe, frequently indicates bone infection.[51-53] Risk factors for developing pedal bone infection are sensory neuropathy, vascular impairment and chronic infected foot ulcers. Diagnosing and eradicating bone infection is a major challenge in the management of DFI.[54-56] Any delay in the diagnosis and treatment of bone infection increases the risk for subsequent amputation.[17,51,57] In addition, the presence of an associated bone infection at the base of ulcers is the major contributing factor to the problem of non-healing of chronic foot ulcers. Radiological features of bone infection include patchy sclerosis, lucency, periosteal reaction, bone destruction and fracture.[58,59] However, these findings should be interpreted with caution in diabetic patients because neuro-osteoarthropathy can cause similar periosteal reaction and bone destruction.[37,60-62] The presence of elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) support the diagnosis of bone infection and can be used to monitor the response to antibiotic therapy.[51] Bone scanning is often falsely positive in bone infection because of hyperemia or Charcot's arthropathy. Indium-111- labeled leucocyte scanning has shown the best overall accuracy for the diagnosis of bone infection with an overall sensitivity of 89-100% and specificity of 78-96%.[60] Magnetic resonance imaging (MRI) however, is considered in many studies as the best imaging modality for bone infection in diabetic patients.[58,59] The presence of significant, neuro-osteoarthropathy; however, may interfere with the interpretation of the results.[61] Bone biopsy is the gold standard test in the diagnosis of bone infection. In addition to histopathological confirmation, bone biopsy can provide a useful culture and sensitivity results for the definitive antimicrobial therapy.[62]

Measures of severity of DFI. The severity of DFI can be estimated with both clinical and laboratory findings. Assessing the severity of DFI provides an idea about the magnitude of the problem, need for hospitalization, mode of drug administration

Table 1 - Severity of diabetic foot infection.

Mild infection
Superficial infection without systemic signs
Moderate infection (potential limb-threatening):
Ulceration to deep tissue
Cellulitis of foot or ankle >2 cm
All soft tissue infections and bone infections
No systemic signs or symptoms
Severe infection (potential life-threatening infection)
Spreading proximal cellulites
Spreading necrotizing fasciitis
Extensive wet gangrene
Any clinical form with 2 or more of the systemic inflammatory response syndrome, manifested by:
-Temperature <36°C, or >38°C
-Heart rate >90 beats/min
-Respiratory rate >20 beats/min
-$PaCO_2$ <32 mm Hg
-White blood cell count >12 000 or <4000 cells/mm^3, 10% immature (band) forms
-Uncontrolled hyperglycemia

and potential need for surgery. It is important to determine the existence of an associated underlying neuropathy, ischemia or bone deformity in all patients presenting with DFI because these factors influence the prognosis and the possible need for early vascular reconstruction or amputation.[3-5] In the absence of ulcers, most patients with superficial infections are considered to have "mild DFI" that can be treated on an outpatient bases. Infected ulcers, cellulitis of the foot or ankle >2cm, and all soft tissue and bone infections with no systemic signs of sepsis or metabolic instability are considered as "moderate DFI" (**Table 1**). Because of the serious nature of diabetic foot ulcers and their potential progress towards foot amputation, most of the known scoring system have focused on categorizing foot ulcers into several grades (Meggitt, Wagner, Pecoraro, University of Texas classification systems).[63-66] Our group has recently published a new scoring system for diabetic foot ulcers that utilizes the key elements of ulcers, depth, extent of bacterial invasion, phase of healing and associated etiology summarized by the acronym DEPA system.[67] Based on these different scoring systems, most infected ulcers can be either moderate or severe DFI.

Severe DFI results from the association between necrotizing foot infections and foot ischemia (wet gangrene). Usually patients with severe DFI present with systemic toxicity (leukocytosis, fever, and shock) or metabolic instability (hyperglycemia, metabolic acidosis).[5,68] These patients require early hospital admission for urgent management and close monitoring.[37,44] They also demonstrate significantly longer lengths of stay in the hospital, higher amputation rates, and higher mortality rates.[44]

Laboratory diagnosis of DFI. Once the diagnosis of DFI has been raised, laboratory data are required to estimate the severity of infection, the degree of metabolic control of diabetes, and assist in planning surgical therapy. However, patients with diabetes may have altered systemic response to infection because of impaired leukocyte function and often diabetic patients with severe foot sepsis do not respond to the infection with elevation of body temperature or white blood cell (WBC) count. In one study, approximately two thirds of the patients with limb-threatening infection, including abscesses and extensive soft tissue infection did not have temperature elevation, chills, or leukocytosis.[54] In another study, laboratory data in a large series of diabetic patients with serious pedal infection showed that in spite of a significantly elevated sedimentation rates, the mean WBC count was $9,700/10^2/mm^3$.[69] Moreover, Eneroth et al,[70] found that approximately 50% of patients with foot infection had temperatures under 37.8°C and WBC counts under $10,000/10^2/mm^3$. Based on these findings, the physician should not depend on elevated WBC counts and/or temperature elevation alone as indications of the severity of a DFI. Measurements of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in patients with DFI are useful, and the degree of elevation above normal provides an estimate of the severity of DFI and bone infection.[50] Blood sugar measurement provides an idea about the severity of infection and its control plays an important role in the management of DFI.[5] In addition, hyperglycemia is one of the signs of severe DFI and its return to normal levels generally follows the improving clinical course of foot infection. Plain radiography is useful to detect bone involvement or as baseline for future x-rays in DFI.

Management of DFI. Early surgical management and proper wound care are crucial to good outcome for most DFI. Appropriate antibiotic therapy and optimal metabolic control are also required.[67,68,71] The severity of infection and the most likely pathogen are the most important factors in determining the appropriate antibiotic therapy for a DFI. In addition, the adequacy of blood supply to the affected limb is another important factor in determining the control of infection.[72,73] Significant chronic vascular disease, or patients with the so-called "critical ischemia" have problems in the delivery of oxygen, leukocytes and other host defense factors as well as antibiotics.[74]

Thus, it is important to address the problem of vascular status of the limb as soon as possible. All patients with severe DFI, and most of the patients with moderate infection, should be hospitalized, at least initially. In addition, any patient who requires repeated surgical interventions (serial and deep debridement), complex local wound care, or patients with severe metabolic disturbances (diabetic keto-acidosis or hyperosmolar coma), or those who need intravenous antibiotics should be hospitalized.[44,66,75] Finally, elderly patients who are unable to care for themselves and lack household help to change dressings or stay off the infected foot, and take medications should also be hospitalized. Mild and superficial DFI can be treated on an outpatient basis. An oral antibiotic such as a first-generation cephalosporin, dicloxacillin, amoxicillin-clavulanate, or clindamycin can be given with the patient returning in one week for follow-up. If there is no improvement, hospitalization is recommended. The patient should then begin a regimen of parenteral antibiotics.[76,77]

Several antibiotics are currently used for parenteral treatment for coverage of limb-threatening and life-threatening infections (cefoxitin, cefotetan, ampicillin/sulbactam, imipenem/cilastatin, meropenem, ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin, clindamycin, and metronidazole). Many hospitals are using a monotherapy of third-generation cephalosporins (ceftriaxone and cefotaxime). In spite of their claimed potency and wide coverage, they should be combined with clindamycin, or metronidazole especially for deep seated infections. In patients with some degree of underlying nephropathy, aminoglycosides should be avoided if possible, the potential toxic effects of these agents are a serious concern. In addition, they also have minimal penetration into bone, making them a poor choice for patients with osteomyelitis. Patients with suspected or documented bone infection, should have a longer course of antibiotic therapy (at least 4-6 weeks) compared with 7-14 days for isolated soft-tissue infection. Oral clindamycin has a good bio-availability and bone penetration and maintains excellent activity against *Staphylococci, Streptococci,* and *Anaerobes*.[36,77]Antibiotics should not be stopped until the wound appears clean and surrounding cellulitis has disappeared. Patients with poor vascular perfusion, revascularization has priority if correctable ischemia is present. It should precede local surgical measures such as debridement or micro-amputation, because wound healing is delayed and infections tend to be more progressive in ischemic tissues. If vascular stenoses and occlusions are found, revascularization can be performed using either an endovascular or open surgical approach.[78-80] Local wound care is often needed for proper drainage and debridement of the infection allowing for thorough removal of all necrotic material and diminishing the bacterial load, thus promoting healing. This must be carried out early to decrease further tissue loss. All necrotic bone, soft tissue, and devascularized structures, should be removed. Curettage of any exposed or remaining cartilage is important to prevent this avascular structure from necrosis and becoming a nidus of infection. Once the infection is controlled, healing of diabetic ulcers can be expedited using moist dressings to promote the development of granulation tissue formation. These dressings not only provide protection against further bacterial contamination, but also maintains moisture balance, optimizes the wound pH, and reduces local pain. Large open ulcers are treated with a staged approach with frequent debridement and the establishment of a granulation base. Once these ulcers become clean they can be closed with a healthy tissue such as local or free-flap coverage or skin grafts especially on non-weight bearing areas.[81]

Diabetic foot infection is a common clinical problem and is associated with significant morbidity. Optimal management requires an early recognition of the problem, aggressive surgical debridement of infected tissues, proper local wound care, appropriate antimicrobial therapy, control of hyperglycemia, and improvement of concomitant arterial insufficiency.

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