REVIEW ARTICLE

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Diabetic foot infections: current concept review

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The purpose of this manuscript is to provide a current concept review on the diagnosis and management of diabetic foot infections which are among the most serious and frequent complications encountered in patients with diabetes mellitus. A literature review on diabetic foot infections with emphasis on pathophysiology, identifiable risk factors, evaluation including physical examination, laboratory values, treatment strategies and assessing the severity of infection has been performed in detail. Diabetic foot infections are associated with high morbidity and risk factors for failure of treatment and classification systems are also described. Most diabetic foot infections begin with a wound and once an infection occurs, the risk of hospitalization and amputation increases dramatically. Early identification of infection and prompt treatment may optimize the patient's outcome and provide limb salvage.

Keywords: *diabetic foot infection*; *ulcer*; *guidelines*; *surgery*

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More than 25 million people in the United States are estimated to have diabetes mellitus (DM), and 15–25% will develop a diabetic foot ulceration (DFU) during their lifetime (1, 2). Over 50% of these ulcerations will become infected, resulting in high rates of hospitalization, increased morbidity and potential lower extremity amputation. Diabetic foot infections (DFI) are one of the most common diabetes related cause of hospitalization in the United States, accounting for 20% of all hospital admissions (3). Readmission rates for DFI patients are approximately 40% and nearly one in six patients die within 1 year of their infection (4). In a large prospective study of patients with DFU, the presence of infection increased the risk of a minor amputation by 50% compared to ulcer patients without infection (5).

The goal of this article is to review the pathophysiology, identifiable risk factors, classification systems and recommended evaluation of DFI.

Pathophysiology of diabetic foot infections

Several factors predispose diabetic patients to developing a DFI, including neuropathy, vasculopathy and immunopathy. Peripheral neuropathy occurs early in the pathogenesis of diabetic foot complications and is considered the most prominent risk factor for diabetic foot ulcers (6). Diabetic patients with impaired protective sensation and altered pain response are vulnerable to trauma and extrinsic forces from ill-fitting shoewear. Motor neuropathy causes muscle weakness and intrinsic muscle imbalance leading to digital deformities such as hammered or clawed toes. This results in elevated plantar pressure due to metatarsophalangeal joint instability. Autonomic dysfunction leads to changes in microvascular blood flow and arteriolar-venous shunting, diminishing the effectiveness of perfusion and elevating skin temperatures. With the loss of sweat and oil gland function, the diabetic foot becomes dry and keratinized which cracks and fissures more easily, leading to a portal for infection. The most commonly utilized clinical method of objectively diagnosing sensory neuropathy in the foot and ankle setting involves the use of a Semmes-Weinstein 10-g monofilament to assess for protective sensation and a 128 Hz tuning fork for loss of vibratory sensation (7).

Diabetic angiopathy is reported to be the most frequent cause of morbidity and mortality in diabetic patients (8). Macroangiopathy manifests as a diffuse multisegmental involvement typically involving the infrapopliteal vessels, and is also associated with compromised collateral circulation. This is considered an atherosclerotic obstructive disease of large vessels, which leads to peripheral arterial disease (PAD) of the lower extremities. In a case control study of 112 hospitalized diabetic

patients by Peters et al. (9), PAD was independently associated with a 5.5 fold increased risk for DFI. Microangiopathy results in capillary basement membrane thickening, altered nutrient exchange, tissue hypoxia and microcirculation ischemia. Non-invasive vascular studies such as the ankle brachial index (ABI) is a reproducible and quantitative test for vascular evaluation (10). An ABI value <0.90 or >1.30 is indicative of PAD; with the latter significant for falsely elevated values secondary to medial arterial calcification. An increasing body of evidence supports the role of toe pressures in the prediction of patients at risk for ulceration and potential for wound healing, with an absolute pressure >70 mmHg being normal. The toe brachial index (TBI) may be substituted in those patients with elevated ABIs secondary to lower extremity arterial calcification. A normal TBI of >0.7 has been shown to be superior to ABI for excluding the presence of PAD as calcification is not usually present in digital vessels. Another clinical test that can be performed, regardless of arterial calcification in major pedal arteries, includes transcutaneous oxygen (TcPO2) tension measurements. Although not highly prognostic of wound healing potential, TcPO2s are predictive of wound healing failure at levels below 25 mmHg (11). Segmental pressure volume recordings are also considered a secondary tier approach for patients with non-compressible vessels. The shape of the observed pulse waveform is analyzed to evaluate the presence, location, and severity of vascular disease. Lastly, skin perfusion pressure (SPP) utilizes a laser Doppler measurement to indicate the presence or absence of perfusion in the lower extremities through cutaneous capillary circulation. Though SPP requires specialized equipment, it has proven more sensitive than other vascular tests for evaluation and diagnosis of PAD.

Immunopathy has been implicated in the diabetic patient's inherent susceptibility to infection as well as the potential to mount a normal inflammatory response. Impaired host defenses secondary to hyperglycemia include defects in leukocyte function and morphologic changes to macrophages. Bagdade et al. (12) demonstrated that leukocyte phagocytosis was significantly reduced in patients with poorly controlled diabetes, and improvement of microbiocidal rates was directly correlated with correction of hyperglycemia. Decreased chemotaxis of growth factors and cytokines, coupled with excess of metalloproteinases, impede normal wound healing by creating a prolonged inflammatory state. Fasting hyperglycemia and the presence of an open wound create a catabolic state. Negative nitrogen balance ensues secondary to insulin deprivation, caused by gluconeogenesis from protein breakdown. This metabolic dysfunction impairs the synthesis of proteins, fibroblasts and collagen, and further systemic deficiencies are propagated which lead to nutritional compromise. Research indicates impairment of the immune system with serum glucose levels ≥ 150 ml/dl (13). Patients with diabetes tolerate infection poorly and infection adversely affects diabetic control. This repetitive cycle leads to uncontrolled hyperglycemia, further affecting the host's response to infection.

Risk factors for diabetic foot infections

Risk factors for DFU are clearly defined in current literature; however, the body of evidence is not as great for risk factors for DFI. In a large prospective study by Lavery et al. (14), significant independent risk factors for DFI included wounds that penetrated to bone, wounds with a duration >30 days, recurrent wounds, wounds with a traumatic etiology and the presence of PAD. Foot wounds preceded all but one infection in their 151 patients, and the risk of developing an infection was 2,193 times greater in those subjects with a current wound. Foot infection was a contributing factor for hospitalization in 71.7% of their patients, and the risk of hospitalization was 55.7 times greater for patients with a DFI. The risk of amputation was 154.5 times greater in patients with DFI compared to those without. Other published studies associate neuropathy and history of previous amputation as significant risk factors for infection. Socioeconomic, demographics, and other clinical characteristics such as elevated body mass index (BMI) and duration of diabetes have not been found to be significantly associated with DFI (9).

Evaluation of the diabetic foot infections

Diabetic foot infections are among the most serious and frequent complications encountered in patients with DM. Diagnosing a DFI begins with clinical suspicion through a comprehensive history and physical exam, validated with a complete laboratory evaluation, microbiology assessment and diagnostic imaging. The diagnosis of a DFI is made on the basis of clinical findings. According to the Infectious Disease Society of America (IDSA) guidelines, infection is present if there is obvious purulent drainage and/or the presence of two or more signs of inflammation (erythema, pain, tenderness, warmth, or induration) (15). Managing and treating DFI can be challenging and should engage a multidisciplinary team of experts including surgeons, infectious disease specialists, hospitalists, diabetologists and nursing.

Patients present with a variety of complaints ranging from local to systemic signs of infections. Local signs of infection may include pain/tenderness, erythema, edema, purulent drainage and new-onset malodor. Systemic signs of infection include anorexia, nausea, vomiting, fever, chills, night sweats, change in mental status and a recent worsening of glycemic control. A complete diabetic history should be obtained, including duration of disease, insulin dependence, previous

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complications or ulcerations and assessment of recent glycemic control. Past medical history should focus upon related complications or comorbidities such as renal, liver, cardiovascular disease, neuropathy and retinopathy. A current medication list should be obtained, including past or current antibiotic use. Social history must not be overlooked, including use of tobacco or alcohol, quantity of weight-bearing and ambulation level, diet and exercise and home support network. An extensive review of systems should be used to evaluate the severity of a potential infectious process.

Objective physical examination should begin by acquiring vital signs, BMI and assessment of patient's general well-being. Hypothermia ($<36^{\circ}$C) or fever (38°C), hypotension, tachycardia, and tachypnea are considered signs of severe infection and sepsis (15). However, patients with DM may have an impaired neuroinflammatory response and not manifest typical signs of infection. Armstrong et al. (16) has documented that 82% of patients admitted for osteomyelitis (OM) were afebrile on admission often failing to mount a physiological response to infection. Therefore, secondary signs of infection must be assessed such as exudate production, delayed wound healing and wound breakdown. Detailed wound descriptions such as length, width and depth of the wound, color and consistency of drainage, and character of wound base (granular, fibrous or necrotic) should be documented. The lower extremity can also be elevated for 5 min to assess for dependent rubor since erythema associated with infection typically does not resolve with elevation. Osteomyelitis should be considered if bone is visible or palpable in the base of an ulcer. In 1995, Grayson et al. (17) demonstrated that a positive probe to bone test had a sensitivity of 66% and specificity of 85% in diagnosing OM in a cohort of hospitalized patients. Lavery et al. (18) reported that a negative probe to bone test was a stronger predictor for the absence of bone infection with a negative predictive value of 98% compared to their positive predictive value of only 57%. Shone et al. (19) also found a lower positive predictive value of 53% and emphasized the importance of the prevalence of osteomyelitis in the population being studied. The major difference between the populations studied by Grayson, Lavery and Shone was the prevalence of OM. Grayson's patients were hospitalized with infection while Lavery and Shone studied patients in the outpatient setting. A thorough vascular assessment is critical in the evaluation of DFI. The extent and nature of edema should be documented, along with documentation of lower extremity pulses and capillary fill time. A hand-held Doppler should be used for patients with faint or non-palpable pedal pulses. Acquiring an ABI has proven to be a reliable and simple exam to evaluate PAD. Falsely elevated ABI values may warrant more vascular studies such as those discussed earlier. If there is a high degree of clinical suspicion of PAD, vascular consultation and angiography should be considered, as an intervention may be warranted in patients with ischemic infections. The neurological exam should include testing for sensory, motor and autonomic neuropathy including evaluation of the Achilles reflex. Foot deformity, osseous prominences, range of motion and gait abnormalities should be documented.

Plain film radiography is important for the initial assessment for evaluation of infection of soft tissue and osseous structures, deformity and foreign bodies. Soft tissue emphysema represents an emergent situation and must be treated immediately. Osteomyelitis appears as permeative radiolucencies, periosteal reaction and destructive changes on plain films following 30–50% loss of bone mineralization (20). Plain films are considered 67% specific and 60% sensitive for OM (21). Magnetic resonance imaging (MRI) is the most specific and sensitive non-invasive test to evaluate OM and is also useful for the evaluation of a probable abscess or sinus tract formation (22). Bone scans, such as the white blood cell labeled Indium-111, Technetium-99m HMPAO and Sulfur Colloid Marrow Scan, may prove beneficial between distinguishing acute and chronic infections, with the latter useful for identifying OM from Charcot neuroarthropathy by specifying bone marrow reactivation and neutrophil production (23).

Laboratory values are essential in DFI to establish a baseline and assess on the response to treatment. Armstrong et al. (16) found that fewer than 50% of DFI patients mounted an elevated white blood cell (WBC) in his study of 28 hospitalized DFI, with the mean WBC count being $11.9 \pm 5.4 \times 10^3$ cells/mm. A metabolic panel should also be ordered for the assessment of renal function, electrolytes, acidosis, and blood glucose level. Hemoglobin A1C levels provide a barometer of glycemic control averaged over the previous 2–3 months. Acute phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein level (CRP) are markers of inflammation that are elevated in response to inflammation, tissue injury and infections. Recent evidence supports the use of ESR and CRP for the evaluation of possible OM. Based on a study by Butalia et al. (24), an ESR >70 mm/hr significantly increases the probability of OM. Fleischer et al. (25) concluded a CRP >3.2 mg/dl was a useful marker for differentiating OM from cellulitis. Akinci et al. (26) studied acute phase reactants at admission and 1 week following treatment in hospitalized patients with DFIs. The authors found that baseline and post-treatment CRP, ESR and WBC were significantly elevated in patients who ultimately required amputation. These results suggest that a prominent acute phase response after beginning treatment, as demonstrated by post-treatment CRP levels, was a strong predictor of treatment failure and

increased amputation risk in DFI. Serum prealbumin and albumin, well known as determinants of nutritional status, are also acute-phase proteins which are down regulated during inflammatory states. Hypoalbuminemia can result from decreased albumin production secondary to protein malnutrition, defective synthesis due to hepatocyte damage, deficient intake of essential amino acids, increased loss through inadequate GI and renal function and commonly through acute and chronic inflammatory states (27). Akinci et al. (26) reported DFI patients who required amputation had significantly lower serum album compared to those patients who did not require amputation. Nearly 30 years ago, Dickhaut et al. (28) related protein-calorie malnutrition to increased morbidity and mortality of patients undergoing surgery. In his study of 23 diabetic patients, those with a serum albumin level of >3.5 g/dl, healed primarily following a Symes level amputation compared to those patients who fared below the normal range (28). To the best of our knowledge, no study has directly correlated albumin or prealbumin levels with severity of DFI although Lipsky et al. (29) demonstrated that lower serum albumin levels were predictive of treatment failure in the SIDESTEP study. The mean albumin in those who had a favorable response was 3.8 g/dl compared to 3.5 g/dl in those who failed treatment. More research is warranted to better assess the relationship of serum albumin and prealbumin levels with DFI.

Diabetic foot ulcerations are colonized by pathogenic bacteria that may predispose a susceptible patient to a lower extremity infection, defined as invasion and multiplication of microorganisms in body tissues associated with tissue destruction or host inflammatory response. Once a colonized wound progresses to an infected wound, microbiological analysis permits the appropriate selection of antimicrobial therapy. Deep tissue cultures have remained the standard for assessing infection, and the use of superficial swabs, especially in clinically uninfected wounds is discouraged. Causative organisms are more reliably detected in specimens that are obtained deep rather than superficial swabs, as the latter will include colonizing organisms that may cause false results (30). In a study of 84 randomly selected hospitalized patients with severe DFI, 83% of cultures demonstrated polymicrobial flora with an average of 2.8 species per specimen and aerobic to anaerobic bacteria ratio of 3:1 (31). The most frequent isolated organisms were *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus* species. Among anaerobes, *Peptostreptococcus magnus* and *Bacteroides fragilis* were noted. Calhoun et al. (32) found that aerobic gram-positive cocci were the most common organisms isolated from diabetic wounds in various studies, especially DFI that were categorized as mild to moderate. Cultures of limb-threatening infections identified *Staphylococcus aureus*, *group B streptococci, enterococcus*, and facultative gram-negative bacilli. *Pseudomonas aeruginosa* may be identified in macerated wounds and obligate anaerobes may be present in necrotic or gangrenous infections (15). Among hospitalized patients, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in DFI is 15–30% depending on the geography (33).

Assessing the severity of a DFI is important for selecting an antibiotic regimen and route of drug administration, need for hospitalization and evaluating the potential necessity of surgery with likelihood of amputation. A mild DFI may be treated with oral antibiotic therapy in an outpatient setting, whereas a moderate to severe infection can be limb- or life-threatening requiring inpatient antibiotic therapy, fluid resuscitation and control of metabolic derangements. Properly classifying DFI will serve as a clinical utility to appropriately identifying treatment strategies and patient outcome.

Classification of diabetic foot infections

Several classification systems have been proposed and utilized for the assessment of DFU and DFI. There is no one universally accepted classification system. Most systems employ a matrix of grades based upon depth and size of wound. Only a few classification systems have incorporated important parameters such as presence of ischemia, neuropathy and severity of infection.

Wagner's classification is one of the most widely used and universally accepted grading systems for DFU, consisting of six simplistic wound grades used to assess ulcer depth (grades 0–5) (34) (Table 1). This classification is limited by the inability to recognize ischemia and infection as independent risk factors in all classification grades (35). For example, this system only identifies the most severe findings of peripheral vascular disease in grades 4 and 5, not accounting for more subtle signs of ischemia. Similarly, only grade 3 acknowledges the presence of infection and OM, limited to only deep wounds.

A more recently proposed and popularized DFU classification is the University of Texas Health Science Center San Antonio (UT) classification system (Table 2) (35). This system incorporates a matrix structure of four grades of wound depth with subgroups to denote the

Table 1. Wagner classification system

0	Pre-ulcerative area without open lesion
1	Superficial ulcer (partial/full thickness)
2	Ulcer deep to tendon, capsule, bone
3	Stage 2 with abscess, osteomyelitis or joint sepsis
4	Localized gangrene
5	Global foot gangrene

Source: Adapted from Wagner (34).

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Table 2. University of Texas Health Science Center San Antonio classification system

	0	1	2	3
A	No open lesion	Superficial Wound	Tendon/Capsule	Bone/Joint
B	With infection	With infection	With infection	With infection
C	Ischemic	Ischemic	Ischemic	Ischemic
D	Infection/Ischemia	Infection/Ischemia	Infection/Ischemia	Infection/Ischemia

Source: Adapted from (45).

presence of infection, ischemia or both. Wounds with frank purulence and/or two or more local signs of inflammation such as warmth, erythema, lymphangitis, lymphadenopathy, edema, pain and loss of function may be classified as 'infected.' Lower extremity vascular insufficiency is made by a combination of one or more clinical signs or symptoms of claudication, rest-pain, absent pulses, dependent rubor, atrophic integument, absence of pedal hair or pallor on elevation coupled with one of more non-invasive values such as a TCPO2 $<$40 mmHg, ABI $<$0.8 or absolute toe systolic pressure $<$45 mmHg. A study by Oyibo et al. (35) evaluated 194 DFU, utilizing both Wagner and UT classifications to compare patient prognosis. Their results revealed that the UT grade had a slightly greater association with increased risk of amputation and prediction of ulcer healing, and they concluded that this system a greater predictor of clinical outcome than Wagner's classification.

The IDSA classification scheme includes four progressive levels of infection based upon severity correlated to clinical findings (15) (Table 3). This classification scale, developed in 2004 and now widely accepted in many academic and clinical circles, was later validated and shown to predict clinical outcomes in a prospective observational study by Lavery et al. (36). In their study of 1,666 patients with DFI, there was an observed trend toward a significant increase in hospitalization rates and lower extremity amputation as it corresponded to increased severity of infection. Mild infections are characterized by $<$2 cm of erythema while moderate infections have $>$2 cm of erythema. Severe infections are associated systemic toxicity and/or metabolic instability. One of the weaknesses of this classification is that it does not adequately describe the local wound environment. The IDSA classification system may further be supplemented with the UT classification system to incorporate depth of ulceration and presence of ischemia (e.g. 'the patient presents with a UT 3B wound with an IDSA category moderate infection').

Treatment of diabetic foot infections

The IDSA formulated guidelines and key recommendations for treatment of DFI stating that an empirical antibiotic regimen should be implemented primarily on the basis of infection severity and likely pathologic agents (15). Optimally, definitive therapy should be based upon culture and susceptibility analysis. The antibiotic regimen should always include an agent active against gram positive cocci with special attention for MRSA in high risk patients. Previously treated or severe DFI should include extended coverage for gram-negative bacilli and

Table 3. Diabetic foot infection classification schemes: Infectious Diseases Society of America (IDSA)

Clinical description	Infectious Diseases Society of America	International Working Group on the Diabetic Foot
Wound without purulence or any manifestations of inflammation	Uninfected	1
$\geq$2 Manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration); any cellulitis or erythema extends $\leq$2 cm around ulcer, and infection is limited to skin or superficial subcutaneous tissues; no local complications or systemic illness	Mild	2
Infection in a patient who is systemically well and metabolically stable but has $\geq$2 cm; lymphangitis; spread beneath fascia; deep tissue abscess; gangrene; muscle, tendon, joint, or bone involvement	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycemia, or azotemia)	Severe	4

Source: Adapted from Lavery et al. (36).

enteroccocus species. Gangrenous and foul smelling wounds may require anti-anaerobic therapy. Cost of therapy is also an important factor in selecting a treatment regimen as well as consideration of potential drug side effects, pharmacokinetics and bioavailability, and frequency and route of administration. McKinnon et al. (37) demonstrated that therapy with ampicillin/sulbactam was similarly efficacious but significantly less expensive than imipenem/cilastin for moderately severe DFI secondary to lower drug and hospitalization costs. The SIDESTEP study, a randomized, double-blinded, multicenter trial of 586 patients with a moderate or severe DFI, concluded the clinical and microbiological outcomes of those patients treated with ertapenem were equivalent to those treated with pipercillin/tazobactam (29). This study suggests that the once daily dosed ertapenem is advantageous in the DFI setting, despite the fact that ertapenem does not cover most *enterococci* or *Pseudomonas aeruginosa,* indicating these organisms may only be contaminants in polymicrobial DFIs. Optimal duration of antibiotic therapy has yet to be defined based upon clinical studies. In general, moderate and severe DFI are typically treated from 2 to 4 weeks of intravenous (IV) antibiotic therapy with 4–6 weeks of therapy for OM.

Surgical management of moderate to severe DFI is often required and includes aggressive incision, drainage and debridement of non-viable soft tissue and bone. Multiple debridements are often necessary to provide adequate drainage and control of infection. One study reported amputation rates of 2.8, 46.2 and 77.7% in mild, moderate and severe infections respectively (36). The need for both minor (removal of a portion of foot distal to the ankle joint) and major amputations (proximal to the ankle joint) increased as the severity of infection increased. Foot infections can extend proximally into the leg through the tarsal tunnel, resulting in rapidly ascending limb and life threatening infection. Early surgical treatment of DFI may reduce the need for major amputations. Tan et al. (38) retrospectively evaluated two groups of patients treated for DFI. Patients in group 1 were treated with only IV antibiotic therapy, while patients in Group 2 received IV antibiotic therapy in addition to surgical management within the first 3 days of hospital admission. Patients in Group 2 were found to have fewer above ankle amputations and a 6-day shorter hospital course than Group 1. With severe life threatening DFI, open amputation or guillotine procedures may take precedence to limb salvage regardless of vascular status (39). It is preferable to preserve as much distal viable soft tissue and bone as possible when performing an amputation, potentially allowing for delayed closure and functional weight bearing.

Adjunctive therapies include the use of antibiotic impregnated beads, application of negative pressure wound therapy and hyperbaric oxygen treatment (39–41). Developing research continues to be directed at therapies for improving the clinical outcome of patients with DFI (42).

Predictors of treatment failure in diabetic foot infections

Increased WBC and severe UT wound grades 2 and 3 were significant independent risk factors for clinical failure in patients treated for a DFI in the SIDESTEP study (43). Clinical failure was noted in 23% of the patients with UT wounds 2B,D and 3B,D at baseline compared with 11% with a wound stage of 0 or 1. The mean WBC was 9,777 cells/mm^3 for those patients who failed treatment compared to 7,933 cells/mm^3 for those with a favorable response. CRP and ESR values greater than 9.1 and 54.4 respectively were associated with treatment failure. A meta-analysis of data from randomized controlled trials on DFIs observed a treatment failure of 22.7% in 18 studies (44) Isolation of MRSA was found to be a significant factor associated with treatment failure, although the presence or absence of OM did not impact the outcome. In a retrospective cohort study of the outcome of DFIs treated conservatively, fever, increased serum creatinine, prior hospitalization for DFI and gangrenous lesions were independent factors associated with treatment failure (42).

Conclusion

In 2010, 1.9 million Americans were newly diagnosed with DM. (2). As this trend continues to rise, the plausible threat of DFI becomes even more substantial with dire financial consequences and severe limb and life threatening outcomes. Understanding the pathophysiology and promptly identifying risk factors for DFI is essential. A thorough evaluation of DFI utilizing a multidisciplinary team is recommended to achieve optimal outcomes. It is important to accurate classify DFI to guide treatment regimens, facilitate consistent communication between health care providers and predict patient outcomes. The IDSA and UT classifications provide a relatively simplistic and objective method of classifying DFI. Prompt recognition and treatment of DFI is mandatory to achieve a goal of maximal limb salvage.

Conflict of interest and funding

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