

A Review of Diabetic Foot Osteomyelitis: Focus on Diagnosis, Clinical Presentation, Management and Outcomes

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ABSTRACT

Diabetic foot osteomyelitis (DFO) affects around 38.5 lakh patients in India. It is diagnosed using clinical and radiological approaches. Polymicrobial etiology, peripheral artery disease (PAD) and peripheral neuropathy are commonly observed. A high degree of clinical vigil is required to avoid underestimation of the extent of damage due to speed and spread of infection and prevent chances of lower extremity amputation. 'Time is Tissue' (time taken to access multidisciplinary care) aptly represents one of the critical factors affecting outcomes, along with anatomical location and presence of gangrenous tissues. Traditionally, DFO treatment is the most complex and controversial aspect of managing diabetic foot infections (DFIs). The therapeutic paradigm has evolved from high-level surgical resection of all necrotic and infected bone to the more refined and individualized surgical interventions along with appropriate antibiotics and topical antimicrobials. It is necessary to have a surgeon available with diabetic foot expertise. The surgical outcome is facilitated with strict off-loading, wound management, agitation (freshening and scrapping of wound edges), biofilm disruption and negative pressure wound therapy (NPWT) to accelerate healing. Formal protocol-driven treatment can be provided by a multidisciplinary team involving surgical, medical and podiatric specialties to reduce hospital stay and the need for repeat debridement. This review aims to present a complete overview of the diagnosis, clinical presentation, management and outcomes of DFO according to scientific recommendations and our experience, along with few illustrative case reports.

Keywords: Diabetic foot, osteomyelitis, foot ulcer, surgery, biofilms, anti-infective agents, local

Diabetic foot osteomyelitis (DFO) occurs when infection and inflammation in a diabetic foot ulcer (DFU) spread to the underlying bone(s) (cortex and bone marrow). In India, the burden of DFO is more than 3.85 million patients (point prevalence; Diabetic foot osteomyelitis occurs in 20% of patients with diabetic foot ulcers. The diabetic patients in India was 77 million in 2019; of these, 20-25% will develop diabetic foot ulcer.).^{1,2}

These patients often have comorbid peripheral artery disease (PAD) and diabetic neuropathy, and impaired

glycemia. The diagnosis is primarily clinical, along with imaging techniques.

As feet are farthest away from the heart and central nervous system and more prone to trauma due to their role in mobility and weight-bearing, there is a need for additional sensory protection. In a diabetic patient, these factors collectively lead to complications of feet, e.g., DFU, diabetic foot infection (DFI), DFO, etc.

Surgical debridement and medical approaches (systemic and topical antimicrobial drugs) are widely used to accelerate healing and reduce the chances of ¹ Lower Extremity Amputation (LEA) and associated mortality. Patient outcomes are influenced by the time taken to access multidisciplinary care, anatomical locations (risk of ankle amputation, hindfoot [50%], midfoot [18.5%] and forefoot [0.33%]), and presence of necrotic/gangrenous tissues.³

DIAGNOSIS

In a DFU patient with a suspected infection, DFO is diagnosed with a "Probe-to-bone test" using a sterile

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Anatomic type

Stage 1: Medullary osteomyelitis

Medullary osteomyelitis denotes infection confined to the intramedullary surfaces of the bone. Hematogenous osteomyelitis and infected intramedullary rods are examples of this anatomic type.

Stage 2: Superficial osteomyelitis

Superficial osteomyelitis is a true contiguous focus infection of bone; it occurs when an exposed infected necrotic surface of bone lies at the base of a soft-tissue wound.

Stage 3: Localized osteomyelitis

Localized osteomyelitis is usually characterized by a full thickness, cortical sequestration, which can be removed surgically without compromising bony stability.

Stage 4: Diffuse osteomyelitis

Diffuse osteomyelitis is a through-and-through process that usually requires an intercalary resection of the bone to arrest the disease process.

Diffuse osteomyelitis includes those infections with a loss of bony stability either before or after debridement surgery.

instrument (to check for bone at the base). The clinical findings include chronic or recurrent foot ulcers, purulent secretions, foul odor, the presence of necrosis and unhealthy borders of the ulcer. Foot X-rays are used to corroborate the severity of DFO.

DFIs impact soft tissues (cellulitis, abscesses and necrotizing infections), bones (osteomyelitis) or both. Osteomyelitis can be classified based on clinical presentation as – Osteomyelitis without ischemia and without soft tissue involvement, osteomyelitis with ischemia without soft tissue involvement, osteomyelitis with soft tissue involvement and osteomyelitis with ischemia and soft tissue involvement.⁴

The clinical diagnosis of deep soft tissue infections (STIs) associated with osteomyelitis may often be difficult to achieve before surgery. The division into the aforementioned four clinical types is essential as it shows a statistically significant trend toward increased severity, amputation rate and mortality.

HISTORY AND CLINICAL EXAMINATION

A detailed history to know all risk factors, including previous episodes of DFU, DFI and DFO and hospitalizations, are essential. The clinical examination should include local foot, limb and systematic assessment as described in Figure 1.⁵

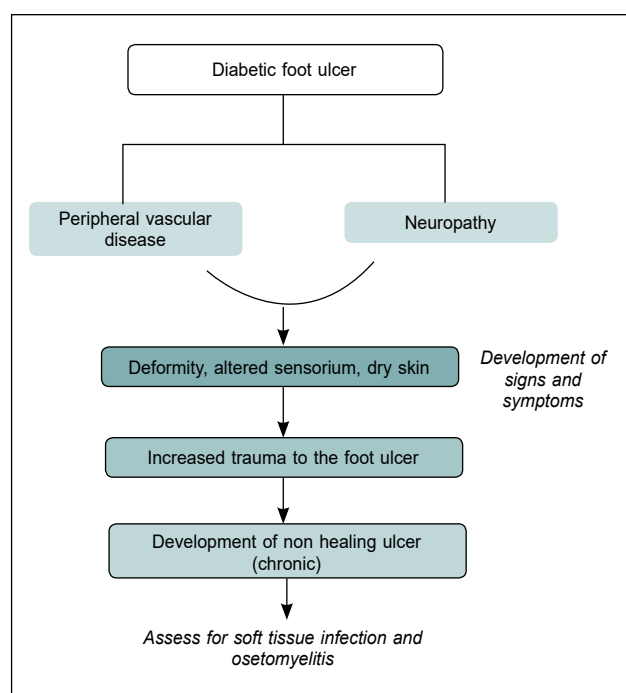


Figure 1. Flow diagram depicting steps in the assessment of a patient with DFU.

Local Foot Assessment

The foot needs to be examined for any pre-existing ulcer, its location (plantar/dorsal/medial/ lateral or interdigital) and associated tendinous infections. Attempts should be made to identify the point of bacterial entry, which leads to ulcer, infection and osteomyelitis.

The location of an ulcer close to the tendon should alert the clinician to the possibility of spreading tendon sheath infection. This spread occurs along tendons and their sheaths and via the interosseous compartment (from plantar-to-dorsal aspect).

Deeper infections often trigger neutrophilic vasculitis, thrombosis and necrosis of toes. Osteomyelitis of the metatarsal head damages the joint capsule and pus exudates from the dorsum aspect of the foot. DFO patients must be monitored using serial clinical photographs to assess their progress.

Necrotizing fasciitis is diagnosed when there is erythema, purpuric rash, swelling, pus, neuropathy, ischemia and deformity. A more severe, potentially limb-threatening (or even life-threatening) infection is suspected in DFI patients in the presence of systemic symptoms (e.g., fever and chills), marked leukocytosis or significant metabolic disturbances. Occasional patients may have a subtle presentation, which results in misdiagnosis.

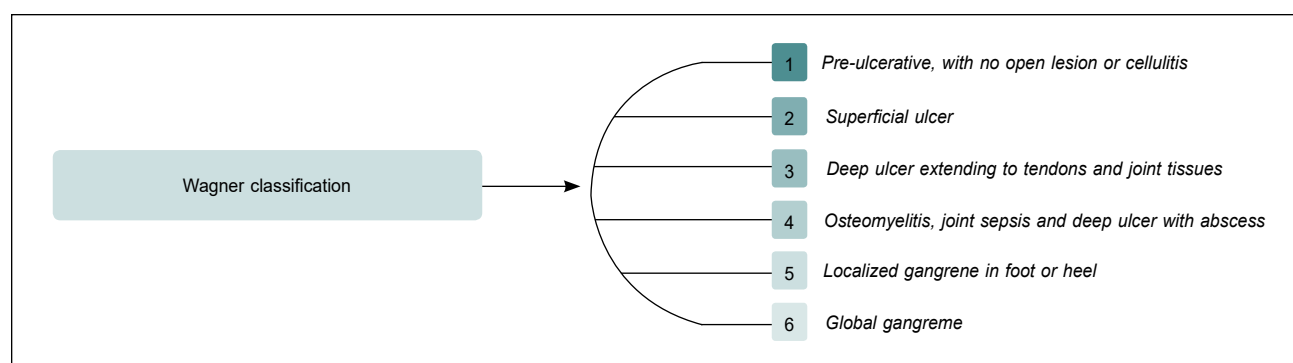


Figure 2. Wagner classification system.

To reduce the risk of LEA in patients with comorbid PAD, higher Wagner grade,⁶ wound infection and proteinuria, a specialist referral is required (Fig. 2).⁷

Many patients have associated retinopathy, nephropathy and cardiac-related complications, which require appropriate assessment and management in parallel to treating DFO. Etiology is primarily polymicrobial. It is important not to underestimate the extent of damage caused by the speed and spread of infection. The infection may often give a false impression to patients and non-specialists of being local but might have already spread along tendon sheaths and dermal plains. Delays in seeking appropriate multidisciplinary care increase the chances of higher morbidity and mortality.

In patients with comorbid PAD and peripheral neuropathy, these local signs may be absent due to marked reduction in sensation. DFO may thus go unnoticed, leading to delay in accessing treatment and a higher risk of LEA. “Time is tissue” represents the influence of time in accessing multidisciplinary care and treatment outcomes.⁸

PEDIS scale

The evaluation and management of DFU require a quantitative assessment of the local pathology, the extent of tissue damage and systemic factors, which may help to predict the chances of complications and outcomes. To facilitate this Perfusion, Extent, Depth, Infection and Sensation (PEDIS) tool was proposed by the International Working Group on the Diabetic Foot (IWGDF).

PEDIS scale evaluates diabetic foot according to five categories, i.e., risk factors: Perfusion status, the Extent of ulcer, Depth of ulcer, Infection status and Sensation (Table 1).⁹ Each risk factor is assessed, scored and a final sum is generated. A higher overall score correlates with a higher amputation risk.

In case of a diagnostic dilemma with X-ray tests, magnetic resonance imaging (MRI) is the preferred investigation. MRI findings also help in planning the incision and debridement procedure. Tests for serum inflammatory markers (erythrocyte sedimentation rate, leukocyte or antigranulocyte antibody test) and bone scans are less preferred diagnostic options. The clinical and radiological tests help to identify necrotic, damaged and healthy tissues.¹¹

X-rays help detect gas in soft tissues, while MRI shows abnormal fluid and cortical bone destruction. These approaches help in individualized and effective planning and a well-defined and precise surgical debridement.

Histological and microbiological examinations of an aseptically obtained bone are mandatory to obtain a definite diagnosis of bone infection (Table 2).¹⁰ These tests help in pathogen identification, diagnosis and selecting an appropriate drug. Soft tissue or sinus tract specimens are not recommended due to the higher possibility of contamination.

Staphylococcus aureus is the most common pathogen in DFO (bone cell penetration time of <30 min), followed by other Gram-positive organisms such as *Enterococcus* spp. and *Streptococcus* spp.

MANAGEMENT

DFO is primarily treated with surgical intervention (debridement of the infected bone) followed by 2 to 8 weeks of antibiotics (based on bone culture results). If the infected bone is removed, the antibiotic course may range from 1 to 2 weeks. However, if residual infected bone is left, 6 to 8 weeks of antibiotic treatment may be required.⁸

Treatment outcomes are influenced by the extent of infected tissues (determined by imaging), mapping of tissue planes (through which infection spreads), and

Table 1. PEDIS Scale

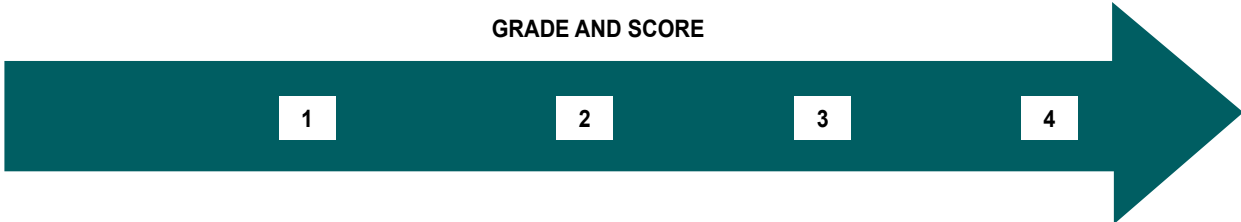
GRADE AND SCORE				
				
Perfusion	No peripheral arterial disease (PAD)	No critical limb ischaemia (CLI), PAD	CLI	
Extent & depth	< 1 cm ² Superficial	1-5 cm ² Fascia, muscle and tendon	5 cm ² Bone and joint	
Infection	NIL	In skin and subcutaneous tissue	Erythema > 2 cm plus one of swelling, Tenderness, warmth, discharge; or infection involving structures deeper than skin and subcutaneous tissues	Systemic Inflammatory response Syndrome (SIRS)
Sensation	No loss of protective sensation	Loss of protective sensation		

Table 2. Diagnostic Criteria to Guide the Management of Osteomyelitis in Patients with Diabetic Foot Disease

Definite	Probable	Possible
• Positive bone culture and histology • Appearance of pus in bone during surgery • Atraumatically detach bone fragment from Ulcer • MRI shows introsseous abscess	• Visible cancellous bone in ulcer • Bone sample with positive culture/ histology but absent or negative culture/ histology • MRI shows bone edema with signs of osteomyelitis	• Plain X-ray show cortical destruction • MRI shows bone edema or cloaca • Visible cortical bone • ESR greater than 70 mm/hr with no specific explanation • Non healing wound, perfusion for greater than 6 weeks, or ulcer greater than 2 weeks coupled with infection.

Score	Probability	Management
1 definite	>90%	Treat
2 probable or 1 probable + 2 possible or 4 possible	50-90%	Consider treating but may need further investigation
2 possible	10-50%	Further investigation advised before treatment

surgical intervention to reduce infected and necrotic/gangrenous tissues. Patients aged >60 years, or those with comorbid PAD and high C-reactive protein (CRP) levels

are more likely to have a poorer outcome. Traditional surgical approaches involve the removal of the infected bone with frequent amputation resulting in loss of the foot. It also predisposes the patient to contralateral amputation¹¹ (50% higher risk than nonamputated patients) and higher 3-year cumulative mortality rates² (50% due to cardiovascular reasons). With advances in the field of DFO management, it is possible to use targeted resection, tissue culture, specific antibiotics and topical antimicrobial beads, reducing amputation procedures and associated complications.^{12,13}

Debridement Procedures

Elliptical incisions facilitate surgical site closure and healing using negative pressure wound therapy (NPWT). Extensive tissue debridement should be

followed by assessment of relevant tendons, muscle bellies and lavage. Copious amounts of warm normal saline, ionic silver or polyhexamethylene biguanides (PHMB) are used for lavage. A re-inspection of the wound is carried out before leaving the operating room. Serial debridement is often done to activate senescent cells, stimulate the release of growth factors, remove inflammatory factors and reduce bioburden.

Strict off-loading, wound management, agitation (freshening and scrapping of wound edges), and biofilm disruption to accelerate healing are complementary to the debridement process. NPWT improves local blood supply, promotes angiogenesis and reduces debridement frequency. Post-debridement, there is no significant clinical data to substantiate the use of one dressing or wound healing approach over another, except for some preliminary data on the use of sucrose-octasulfate dressing for patients with critical limb ischemia. Due to limited evidence, various molecular growth factors and supplementary therapies for wound healing are not recommended by different CPGs.

Post-debridement assessment and management

During follow-up, if the healing process is impaired, the clinician should consider a re-evaluation at 48 hours with a particular focus on vascularity. PAD impairs wound granulation and healing, reduces antibiotic tissue concentration and increases the proliferation of multidrug-resistant microbes, resulting in higher odds of LEA. In contrast, diabetic polyneuropathy does not significantly impair wound healing in an off-loaded foot and has minimal influence on the risk of LEA.

Lower limb revascularization leads to better outcomes in some DFO patients with PAD. Formal protocol-driven treatment can be provided by a multidisciplinary team involving surgical, medical and podiatric specialties as it helps to reduce hospital stays and the need for repeat debridement. If surgical resection leads to instability of the foot and ankle, the surgeon should consider temporary stabilization with a windowed/bivalve total contact cast using a K-wire or an external fixator. This stability creates a conducive environment for the healing process.

Local Therapy

Local antimicrobials/antibiotics improve outcomes to complement surgery and systemic drugs. Local antibiotic eluting calcium sulfate formulations or similar products are used to fill the dead space in the bone or tissue defects created due to the debridement surgery. Currently, clinical evidence on the effectiveness

of local antibiotic formulations is limited. As local formulations in infected and inflamed tissue result in very high concentrations of antibiotics, they are commonly used for tissues with poor vascularity or in 'hard-to-reach' locations. Silo Technique leverages these principles and involves surgical debridement (based on MRI findings) and injection of antibiotic-loaded bio-ceramic in the bone tunnels for infection control. Though some clinical trials have been done with nonabsorbable polymethylmethacrylate-impregnated cement, the current focus is on biodegradable vehicles (e.g., gentamicin-collagen sponge, etc.).

Off-loading

There is emerging positive data on using off-loading techniques with local antibiotic formulations post-debridement. Off-loading is achieved using a total contact cast, knee-high air cast boot or ankle-high heel weight-bearing shoes or plaster booties.¹⁴

The IWGDF recommends nonremovable knee-high off-loading devices for patients with diabetes and neuropathic foot ulcers in the midfoot or forefoot.¹⁵ Alternate, less preferred options include removable knee-high or ankle off-loading devices or footwear with cushioning (felt foam).

Surgical off-loading is required for patients with metatarsal head and digital ulcers who fail to respond to nonsurgical off-loading. Achilles tendon lengthening, metatarsal head resection(s) or joint arthroplasty are preferred off-loading techniques in a surgical setting. To achieve infection control, the surgeon may remove functional structures such as tendons in some debridement cases. The resulting muscular imbalance (e.g., excision of the peroneal tendons) and loss of foot shape require monitoring and occasional prophylactic surgery, e.g., exostectomy and staged surgical reconstruction (osseous instability and recurrent ulceration).

Adjunctive Therapies

Skin grafting or other need-based plastic surgical procedures, may be required for the wound as part of the reconstructive ladder. Adjunctive therapies are often used, such as NPWT, appropriate footwear and bracing, hyperbaric oxygen, granulocyte-colony stimulating factor or larvae.

Factors Influencing the Choice of Intervention and Outcomes

Surgical or medical interventions are selected on the basis of the type of osteomyelitis acute/chronic (symptoms >2 weeks). The medical intervention involves using

Table 3. Brief Table on Basics of Approaching the Diagnosis and Treatment of Suspected Diabetic Foot Osteomyelitis

Basic approach and Treatment			
Dignostic parameters to be assessed • Clinical: Wound size/depth; visible/palpable; soft tissue infection; PAD • Laboratory: WBC count; erythrocyte sedimentation rate; C-reactive protein; procalcitonin • Imaging: Plain X-rays; advanced imaging if needed • Cultures: Deep tissue specimens; bone specimens, if possible	Surgery • Urgent if needed for soft tissue debridement, or pus drainage • Elective in most cases if mainly for bone debridement, resection, or amputation. • Preferred primary approach for patients with exposed bone or joints; necrotic soft tissue; fluid collection or abscess; advanced bone destruction; need for other surgical repairs; lack of response to antibiotics; high risk for antibiotic resistant pathogens or antibiotic related toxicity.	Antibiotics • Empirical: Broad spectrum, or targeted if available culture results, while awaiting results of culture and antibiotic sensitivity test. • Definitive: Based on culture and antibiotic sensitivity results; clinical response to empiric therapy; and antibiotic stewardship principles • Preferred primary therapy for patients with infection confined to the forefoot; adequate limb perfusion; no tissue necrosis; contraindication to high risk form, or patient preference to avoid surgery	Adjunctives • No treatment of proven benefit

a drug that can diffuse into the bone and maintain antibacterial activity. The lipophilic/hydrophilic nature of the medicine, whether it is bactericidal/bacteriostatic, is able to penetrate biofilms and is active against latent intracellular bacteria (Tables 3 and 4).^{12, 16} DFO response to treatment is best defined as 'remission' rather than 'cure'.

Due to resistant bacteria, ertapenem and daptomycin are the new agents effective in osteomyelitis.¹⁷

Impact of Osteomyelitis on DFI Treatment and Outcomes

Mutluoglu et al¹⁸ evaluated the impact of osteomyelitis in patients with DFI in 73 patients (37 with DFO group and 36 patients with soft tissue infections group).

In comparison to the STI group, the DFO group had a significantly longer length of stay (LOS) in the hospital, longer duration of antibiotic therapy and longer time to wound healing. During hospitalization, 22 patients in the DFO group and 5 in the STI group underwent minor amputation (59.4% vs. 13.8%, $p < 0.001$). Thus, the presence of osteomyelitis negatively affects both the treatment and outcome of DFIs.

ROLE OF SURGERY IN DFO

DFO patients with either a bone protruding through the ulcer or extensive and progressive tissue damage

Table 4. Criteria for Selecting Primarily Antibiotic or Surgical Approaches for Diabetic Foot Osteomyelitis¹⁶

Medical	Surgical
• Patient too unstable for surgery • Poor postoperative mechanics of foot likely (e.g., with midfoot or hindfoot infection) • No other surgical procedures on foot are needed • Infection is confined to small forefoot lesions • No adequately skilled surgeon is available • Surgery costs are prohibitive for the patient • The patient has a strong preference to avoid surgery • No hospitalization • There are no contraindications to prolonged antibiotic therapy	• Foot infection is associated with substantial bone necrosis or exposed joints • Persistent sepsis • Foot appears to be functionally unsalvageable • The patient is already nonambulatory • Major risks of antibiotic problems • Infecting pathogen is resistant to available antibiotics • Uncorrectable foot ischemia, patient has a strong preference for surgical treatment • Hospitalization

despite antibiotic treatment or damaged soft tissue envelope or gangrenous tissue respond better with surgical intervention.¹⁹

Several factors should be considered when considering surgery for DFO. It is necessary to have a surgeon available with diabetic foot expertise. Concerning the location of DFO, it is essential to consider whether isolated bone or a joint is involved. Surgery should be able to correct any bone deformity accompanying osteomyelitis. Attempts should be made to avoid or minimize destabilization of the foot due to extensive/radical surgery (case report 1).

Case Report 1

A male patient, 56 years old, a caterer by profession with depressive symptoms, presented to a surgical clinic in 2009 with bilateral diabetic foot disease. The right foot had a large planter ulcer on the heel, not healing for 2 years. He was operated on twice, and the surgeon gave him total contact casts (TCC) 2 to 3 times. The great toe of the left foot was amputated. The remaining toes had osteomyelitis with fungal infection (Fig. 3). The ABI (ankle-brachial index): right - 0.7, left - 0.7; hand-held arterial - biphasic both feet; random blood sugar was 360 mg/dL and creatinine level was 1.5 mg/dL.

The forefoot is the most frequent location of DFO and has a better prognosis than midfoot and hindfoot osteomyelitis. A wide range of surgical procedures can be done in diabetes patients with forefoot osteomyelitis while avoiding amputations.

Performing conservative surgery without amputation of any foot part is not always possible, especially in



Figure 3. Baseline presentation, surgical intervention and post treatment images (bilateral foot disease).

patients where the infection has destroyed the soft tissue envelope. Attempting conventional surgery in such scenarios risks infected tissues persisting in the wound bed leading to failure.

Forefoot Osteomyelitis

The forefoot (toes and metatarsals) is the most impacted part of osteomyelitis in diabetic patients (case report 3). Soft tissues surrounding the toes are leaner than those covering the metatarsal heads. In addition, the metatarsal-phalangeal joint of the great toe, including sesamoid bones, is quite complex compared to the lesser metatarsal-phalangeal joints, which impacts the outcomes.²⁰

Case Report 2

A 51-year-old female, a known diabetic for 10 years, presented to a surgical clinic with a dorsal forefoot ulcer. Despite treatment over 3 months, the ulcer was not healing. Random blood sugar was 210 mg/dL; X-ray showed osteomyelitis of the 4th metatarsal bone with a positive probe to bone test; surgical debridement and NPWT led to healing over 2 months (Fig. 4).

Case Report 3

A young male rickshaw driver had a nonhealing wound of the 4th phalanx and entire 4th metatarsal. His random blood sugar was 436 mg/dL; X-ray and MRI showed osteomyelitis; Wound healing occurred in 3 months following surgery (Fig. 5).





Figure 4. Serial photos depicting outcomes with surgical debridement and NPWT.



Figure 5. Serial photos depicting outcomes with surgery in a patient with DFO impacting the 4th phalanx and entire 4th metatarsal.

Sausage toe, hammer, mallet and claw toes **Sausage toe**

Diabetic patients with a local neuropathic ulcer are suspected of having pedal osteomyelitis when there is a 'sausage' deformity of the toe (swollen and erythematous with nonpitting edema).²¹ The 'sausage toe' should alert the physician of osteomyelitis so prompt treatment can be commenced.

Case Report 4

A 62-year-old male patient presented with DFU. A provisional diagnosis of DFO was made as a yellowish-white scab recurred 24 hours after debridement. DFO diagnosis was confirmed based on the tissue culture report, which showed the polymicrobial nature of the infection. Incision, drainage, amputation, flexor tenotomy and protective pads led to desired healing (Fig. 6).

Hammer, mallet and claw toes

Diabetic patients with deformities such as hammer, mallet and claw toes are more likely to have DFU. These deformities develop due to neuropathy-driven atrophy of the intrinsic muscles leading to an imbalance between intrinsic and extrinsic musculature. Flexor tenotomies are often the preferred treatment option for these patients, and it is recommended that all toes on one or both feet are tenotomized in one procedure.²²

Achilles Tendon Lengthening and Transmetatarsal Amputations

Achilles tendon lengthening (ATL) is the preferred surgical intervention to heal chronic forefoot neuropathic ulcers.²³ A more proximal level amputation, such as transmetatarsal, is the recommended surgical option to provide a more functional and reliable residual weight-bearing foot (case report 5). Trans-metatarsal amputations are more definitive than other lesser ray resections.^{12,24}

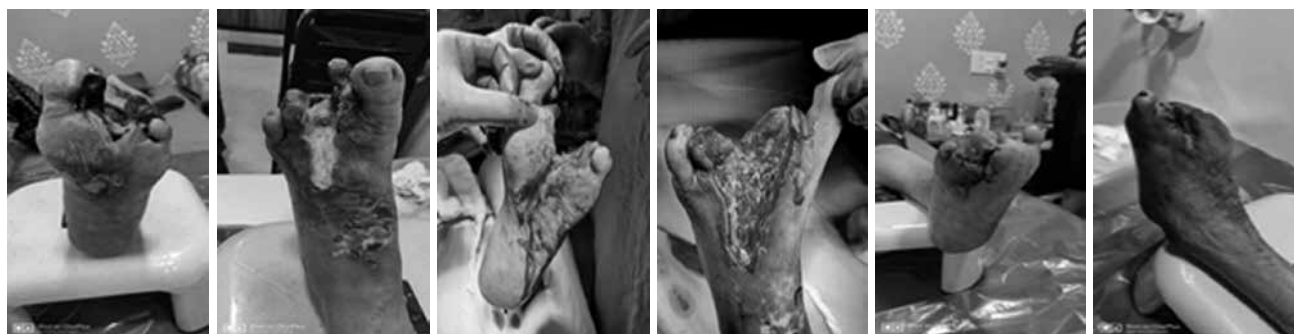


Figure 6. Serial photo depicting Transmetatarsal Amputations



Figure 7. Baseline presentation, surgical intervention and outcome images.

Case Report 5

A 56-year-old male patient, a meat seller by profession, presented to the family physician with an acute DFI. Despite antibiotic treatment, the foot swelling increased and he was referred to a general surgeon who admitted the patient. During treatment, the affected foot area changed color to bluish-black (Fig. 7). At presentation, his pulse rate was 114/min, blood pressure 90/60 mmHg, creatinine 3.4 mg/dL and total white blood cell (WBC) count 14,000/ μ L. Frank gangrene was found with severe pain extending to the leg. There was breathlessness and random blood sugar 505 mg/dL. The ABI was 1.2 and MRI showed osteomyelitis.

BIOFILMS

Biofilms are composed of a complex protective glycocalyx generated by bacterial communities, which shields them from host defenses and topical and

systemic antimicrobial therapy. It is present in ulcers that have a pale and edematous wound bed, yellowish exudate, fragile granulation tissue, wound pain, necrotic and rotting tissues, and a pungent smell.²⁵ The yellow exudate reappears within 24 hours after debridement.²⁶ Tissue culture helps to confirm the diagnosis when there is polymicrobial infection.

Biofilms are commonly seen in chronic wounds, particularly delayed healing. The characteristics of biofilm infections include persisting inflammation and destruction despite systemic antimicrobial therapy; requirement for an extended duration (usually ≥ 6 weeks) of antimicrobial treatment; recurrence of infection-related findings following successful treatment; and need for surgical intervention to remove infected tissue.

In the biofilms, bacteria communicate through 'quorum sensing' while being sustained and protected in the slimy matrix through channels that allow an exchange for nutrient, gas and chemical signal molecule

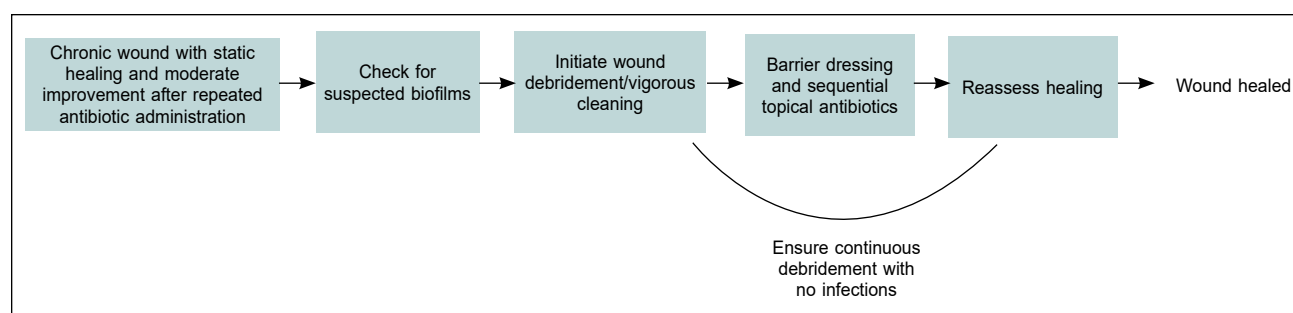


Figure 8. Treatment Options to Manage Wound Biofilm.

(‘autoinducers’).²⁷ In this state, bacteria are sessile and labeled as persister cells. They are relatively metabolically inert and protected.

More than 90% of chronic wounds have bacteria within a biofilm construct. Understanding microorganisms’ phenotypic state helps select targeted therapies and agents active against sessile organisms. Antibiotics (such as β -lactams) effectively work against planktonic microbial cells and multiplying bacteria. Sessile and metabolically inactive states augment the biofilm’s ability to help bacteria develop tolerance against antibiotics. These biofilm, and occasional small-colony variants, are why DFO cases often treated without surgical intervention either fail to resolve or recur.²⁸

Historically, managing DFO is widely considered to be the most complex and controversial aspect of dealing with DFIs. In the pre-antibiotic era, the only option for treating osteomyelitis was high-level surgical resection of all necrotic and infected bone. Still, the advent of antibiotic therapy has facilitated better outcomes with the appropriate use of both surgical and antibiotic approaches.

To manage biofilms effectively, it is essential to repeatedly remove and suppress their growth. Excisional debridement helps to establish a clean well-vascularized wound base.²⁹ Repeated debridement disintegrates biofilms, enhancing susceptibility to antibiotics and host defenses (Fig. 8)³⁰. Regular debridement decreases the time to healing and makes wound bioburden more susceptible to antibiotics and host defenses.^{13,31}

The use of topical biocides along with systemic antibiotics is critical to limiting regrowth. Debriding the wound every 7 days favors wound healing for 43% of the week while adding appropriate topical biocides and systemic antibiotics increases that time to 86%.

Based on current outcomes data, the most effective therapeutic options are topical (TPL) antibiofilm agents (ABF) combined with TPL antibiotics (ABX). In specific

patients, systemic ABX and selective biocides are also appropriate but not exclusive of ABF combined with TPL ABX.³² Thus, antibiofilm, medical approaches and surgical debridement (standard of care) result in better treatment outcomes. The most common debridement method is autolytic debridement. It is based on the body’s capacity to break down necrotic tissues and is facilitated by dressings that provide a moist environment. Isotonic solutions such as normal saline (NS) 0.9% NaCl are used for wound cleansing.³³

Some wound management products facilitate the removal of bacteria and debris and disturb biofilm, e.g., formulation of antimicrobial polyhexanide + surfactant betaine (propylbetaine/polyhexanide [PP]). PP is an excellent candidate compared to NS for accelerating autolytic debridement in the wound. When applied and kept in place for 10 minutes with packing, PP promotes a quicker reduction of wound size and inflammatory signs than NS.³⁴

NPWT has been used for decades as an adjunctive treatment of acute and chronic wounds. NPWT with instillation provides added advantage of a solution to the wound bed in a preprogrammed manner along with localized sub-atmospheric pressure.³⁵

NPWT has evolved from an in-patient therapy to a portable therapeutic modality as it is safe, effective, and reduces operative interventions for complicated wounds in diabetic patients. The interval, duration of negative pressure, solution dwell time and type of solution can be individualized to every patient. NPWT facilitates wound healing and wound bed preparation and occasionally may inhibit bacterial growth.³⁶

Antibiofilm agents (such as silver, polyhexamethylene biguanide (PHMB), iodine and honey dressings) are preferred for managing wounds containing biofilm or suspected biofilm.

Antiseptic dressings are recommended for the early treatment of locally infected tissues (cellulitis,

lymphangitis or erythema) or in wounds at high risk of infection. It is used preferably for 14 days (the 2-week rule), and the clinician should reassess the need for different topical antimicrobial therapy.³⁷ It should be discontinued if there is no further spread or resolution of infection. Concurrent topical antiseptic dressings and debridement reduce the local wound bioburden.

Silver dressings – Silver salt solutions such as silver nitrate for wound cleansing and creams or ointments such as silver sulfadiazine (SSD) are used as a topical antimicrobial in wound care. Silver is used as a coating within the dressing, part of the dressing or a combination of these approaches.

Iodine-based preparations (povidone-iodine and cadexomer iodine forms) have a long history in surgery and wound care. Evidence from a Cochrane review suggests that wound healing rates are higher with cadexomer iodine than with standard care. While its antimicrobial properties are well known, several studies have indicated that cadexomer iodine may potentially be effective against biofilms. A further study has demonstrated that cadexomer iodine penetrated biofilms more effectively than silver or PHMB.

Cadexomer iodine is composed of beads of dextrin and epichlorohydrin that carry iodine. Both releases sustained low concentrations of free iodine, which influences cellular function by binding to proteins, nucleotides and fatty acids. These beads effectively manage exudates as they absorb fluid up to 7 times their weight. It also results in a desloughing action, thereby removing debris, purulence and bacteria from the wound. The physical swelling of the beads allows the sustained release of iodine, which kills bacteria and biofilm for up to 72 hours, unlike 8 hours with povidone-iodine.³⁸

PHMB dressings

The antiseptic PHMB (*polyhexamethylene biguanide* hydrochloride) has been in general use for more than 50 years but has now been introduced for the management of bioburden in wounds as PHMB-impregnated dressings or gels and solutions for wound irrigation. The active compound effectively decreases bacterial load and prevents bacterial penetration of the dressing, reducing infection and preventing further progression.

Honey

Medical-grade honey dressings are nontoxic, 'natural' and easy to use. They are available as hydrocolloid,

alginate, synthetic tulle or gel-based dressings. It promotes autolytic debridement by osmosis while maintaining a moist wound environment. The application of honey also reduces or removes wound malodor. Hygroscopic characteristics of honey dehydrate bacteria, while its high sugar content causes inhibition of bacterial growth. It improves wound healing through anti-inflammatory effects and reduction in edema and wound exudate.

Surfactants

Surfactants facilitate the separation of loose, nonviable material on the wound surface and can potentially prevent and manage biofilm. They are thus widely used for skin disinfection. PHMB, undecylenamidopropyl betaine, octenidinedihydrochloride, phenoxyethanol, octenidine and ethylhexylglycerin are typical surfactants.

Hydrogel dressings – Improved healing has been shown in a pooled analysis of three trials following the use of hydrogel dressings compared with gauze as standard care in DFUs.

CONCLUSION

Osteomyelitis is a severe complication of DFI. It is commonly associated with delayed healing, increased length of hospital stay, amputation, and a high economic burden to patients and healthcare systems. An evidence-based approach is thus required for limb salvation in patients with DFO.

To better manage diabetic foot, health care settings need to provide patient education; have systems in place for identifying high-risk patients; provide guidance on ways and means to reduce the risk of DFU; provide easy and fast access to medical care; use standardized management protocols and provision for long-term follow-up and medical care.³⁸

Treatment outcomes are influenced by anatomical location, the extent of functioning tissues, the presence of gangrenous tissues, and the time taken to access multidisciplinary care involving a surgeon and podiatrist with diabetic foot expertise. In developing countries like India, affordability, and access to tertiary care often influences optimal use of NPWT, high-end antibiotics, in-patient care in hospitals and off-loading devices.

Institutional protocol-driven treatment for DFO comprising, conservative surgical resection of affected bone and medical interventions (antibiotics and topical antimicrobials) and affordable off-loading devices for long-term use should be provided by a team involving surgical, medical and podiatric specialties to reduce

hospital stay and the need for repeat debridement. This understanding will help in salvaging diabetic foot with osteomyelitis and biofilm.

REFERENCES

1. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA*. 2005;293(2):217-28.
2. Geraghty T, LaPorta G. Current health and economic burden of chronic diabetic osteomyelitis. *Expert Rev Pharmacoecon Outcomes Res*. 2019;19(3):279-86.
3. Aragón-Sánchez J, Lázaro-Martínez JL, Hernández-Herrero C, Campillo-Viloria N, Quintana-Marrero Y, García-Morales E, et al. Does osteomyelitis in the feet of patients with diabetes really recur after surgical treatment? Natural history of a surgical series. *Diabet Med*. 2012;29(6):813-8.
4. Aragón-Sánchez J. Clinical-pathological characterization of diabetic foot infections: grading the severity of osteomyelitis. *Int J Low Extrem Wounds*. 2012;11(2):107-12.
5. Basu S, Zhuang H, Alavi A. FDG PET and PET/CT imaging in complicated diabetic foot. *PET Clin*. 2012;7(2):151-60.
6. Pitocco D, Spanu T, Di Leo M, Vitiello R, Rizzi A, Tartaglione L, et al. Diabetic foot infections: a comprehensive overview. *Eur Rev Med Pharmacol Sci*. 2019;23(2 Suppl):26-37.
7. Ugwu E, Adeleye O, Gezawa I, Okpe I, Enamino M, Ezeani I. Predictors of lower extremity amputation in patients with diabetic foot ulcer: findings from MEDFUN, a multi-center observational study. *J Foot Ankle Res*. 2019;12(1):34.
8. Sun Y, Gao Y, Chen J, Sun H, Cai YT, Ge L, et al. Evidence mapping of recommendations on diagnosis and therapeutic strategies for diabetes foot: an international review of 22 guidelines. *Metabolism*. 2019;100:153956.
9. Hüsers J, Hafer G, Heggemann J, Wiemeyer S, John SM, Hübner U. Predicting the amputation risk for patients with diabetic foot ulceration - A Bayesian decision support tool. *BMC Med Inform Decis Mak*. 2020;20(1):200.
10. Powlson AS, Coll AP. The treatment of diabetic foot infections. *J Antimicrob Chemother*. 2010;65 Suppl 3:iii3-9.
11. Huseynova K, Sutradhar R, Booth GL, Huang A, Ray JG. Risk of contralateral lower limb amputation and death after initial lower limb amputation - a population-based study. *Heliyon*. 2018;4(10):e00836.
11. Lipsky BA, Uçkay İ. Treating diabetic foot osteomyelitis: a practical state-of-the-art update. *Medicina (Kaunas)*. 2021;57(4):339.
12. Ruke MG, Savai J. Diabetic foot infection, biofilm & new management strategy. *Diab Res Open Access*. 2019;1(1):7-22.
13. Ahluwalia RS, Reichert ILH. Surgical management of the acute severely infected diabetic foot - The 'infected diabetic foot attack'. An instructional review. *J Clin Orthop Trauma*. 2021;18:114-20.
14. Bus SA, Armstrong DG, Gooday C, Jarl G, Caravaggi C, Viswanathan V, et al. International Working Group on the Diabetic Foot (IWGDF). Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36 Suppl 1:e3274.
15. Lázaro Martínez JL, García Álvarez Y, Tardáguila-García A, García Morales E. Optimal management of diabetic foot osteomyelitis: challenges and solutions. *Diabetes Metab Syndr Obes*. 2019 Jun 21;12:947-959.
16. Senneville E, Nguyen S. Current pharmacotherapy options for osteomyelitis: convergences, divergences and lessons to be drawn. *Expert Opin Pharmacother*. 2013;14(6):723-34.
17. Mutluoglu M, Sivrioglu AK, Eroglu M, Uzun G, Turhan V, Ay H, et al. The implications of the presence of osteomyelitis on outcomes of infected diabetic foot wounds. *Scand J Infect Dis*. 2013;45(7):497-503.
18. Aragón-Sánchez J, Lázaro-Martínez JL, Alvaro-Afonso FJ, Molinés-Barroso R. Conservative surgery of diabetic forefoot osteomyelitis: how can I operate on this patient without amputation? *Int J Low Extrem Wounds*. 2015;14(2):108-31.
19. Cecilia-Matilla A, Lázaro-Martínez JL, Aragón-Sánchez J, García-Álvarez Y, Chana-Valero P, Beneit-Montesinos JV. Influence of the location of nonischemic diabetic forefoot osteomyelitis on time to healing after undergoing surgery. *Int J Low Extrem Wounds*. 2013;12(3):184-8.
20. Rajbhandari SM, Sutton M, Davies C, Tesfaye S, Ward JD. "Sausage toe": a reliable sign of underlying osteomyelitis. *Diabet Med*. 2000;17(1):74-7.
21. Hedegaard Andersen J, Rasmussen A, Frimodt-Møller M, Rossing P, Kirketerp-Møller K, Engberg S. The effect of needle tenotomy on hammer, mallet and claw toe deformities in patients with diabetes, a retrospective study. *J Clin Transl Endocrinol*. 2019;18:100208.
22. Holstein P, Lohmann M, Bitch M, Jørgensen B. Achilles tendon lengthening, the panacea for plantar forefoot ulceration? *Diabetes Metab Res Rev*. 2004;20 Suppl 1:S37-40.
23. Thorud JC, Jupiter DC, Lorenzana J, Nguyen TT, Shibuya N. Reoperation and reamputation after transmetatarsal amputation: a systematic review and meta-analysis. *J Foot Ankle Surg*. 2016;55(5):1007-12.
24. Hall-Stoodley L, Stoodley P, Kathju S, Høiby N, Moser C, Costerton JW, et al. Towards diagnostic guidelines for biofilm-associated infections. *FEMS Immunol Med Microbiol*. 2012;65(2):127-45.
25. Wolcott RD, Rumbaugh KP, James G, Schultz G, Phillips P, Yang Q, et al. Biofilm maturity studies indicate sharp debridement opens a time-dependent therapeutic window. *J Wound Care*. 2010;19(8):320-8.
26. Johani K, Fritz BG, Bjarnsholt T, Lipsky BA, Jensen SO, Yang M, et al. Understanding the microbiome of diabetic foot osteomyelitis: insights from molecular and microscopic approaches. *Clin Microbiol Infect*. 2019;25(3):332-9.
27. Leaper D, Assadian O, Edmiston CE. Approach to chronic wound infections. *Br J Dermatol*. 2015;173(2):351-8.

28. Attinger C, Wolcott R. Clinically addressing biofilm in chronic wounds. *Adv Wound Care* (New Rochelle). 2012;1(3):127-32.
29. Phillips PL, Wolcott RD, Fletcher J, Schultz GS. Biofilm made easy. *Wounds Int*. 2010;1(3).
30. Jones CE, Kennedy JP. Treatment options to manage wound biofilm. *Adv Wound Care* (New Rochelle). 2012;1(3):120-6.
31. Bellingeri A, Falciani F, Trapedini P, Moscatelli A, Russo A, Tino G, et al. Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds: a single-blind RCT. *J Wound Care*. 2016;25(3):160, 162-6, 168.
32. Kaehn K, Eberlein T. In-vitro test for comparing the efficacy of wound rinsing solutions. *Br J Nurs*. 2009;18(11):S4, S6-8, S10.
33. Kim PJ, Attinger CE, Steinberg JS, Evans KK, Powers KA, Hung RW, et al. The impact of negative-pressure wound therapy with instillation compared with standard negative-pressure wound therapy: a retrospective, historical, cohort, controlled study. *Plast Reconstr Surg*. 2014;133(3):709-16.
34. Anghel EL, Kim PJ. Negative-pressure wound therapy: a comprehensive review of the evidence. *Plast Reconstr Surg*. 2016;138(3 Suppl):129S-137S.
35. Leaper DJ, Schultz G, Carville K, Fletcher J, Swanson T, Drake R. Extending the TIME concept: what have we learned in the past 10 years? *Int Wound J*. 2012;9(Suppl 2):1-19.
36. Gupta S Jr, Shinde S, Shinde RK. Topical management of wound: a narrative review of cadexomer iodine ointment versus povidone iodine ointment. *Cureus*. 2022;14(4):e24598.
37. Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA; IWGDF Editorial Board. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36 Suppl 1:e3266.

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