

Diabetic Foot Infections.

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Abstract: Diabetes is known for its complications & Diabetic Foot infections are one of the most common problems in Diabetics. They are predisposed to foot infections because of a compromised vascular supply secondary to diabetes. Local trauma in association with lack of sensation because of neuropathy & microvascular disease, may result in various diabetic foot infections that run the spectrum from localised simple, superficial **Cellulitis to chronic osteomyelitis**.

Infections in patients with diabetes are difficult to treat because they have impaired microvascular circulation, which limits the access of phagocytic cells to the infected area along with poor concentration of antibiotics in the infected tissues. In addition, diabetic individuals can not only have a combined infection involving bone and soft tissue called fetid foot, a severe and extensive, chronic soft-tissue and bone infection that causes a foul exudate, but they may also have peripheral vascular disease involving large vessels, as well as microvascular and capillary disease that results in PVD with gangrene.

Normal Commensals of skin who are harmless in non diabetics can cause severe life threatening infections in Diabetic patients leading to loss of limb or life. Gas gangrene is conspicuous because of its low incidence in patients with diabetes, but deep-skin and soft-tissue infections, which are due to gas-producing organisms, frequently occur in patients with these infections.

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INTRODUCTION

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EPIDEMIOLOGY

Globally, diabetic foot infections are the most common skeletal and soft-tissue infections in patients with diabetes. The incidence of diabetic foot infections is similar to that of diabetes in various ethnic groups and elderly patients are more commonly affected. There are no significant differences between the sexes.

In USA incidence of Amputation was 40,000 per year (Lancet, 2005) & in India the Incidence rate is @ 80,000 to one lakh amputations per year (2010 data of Vasu.Society of India) which can be tip of the Iceberg because of poor registry in india and it is well established fact that more than 85% of amputations are preceded by trivial DFU which get infected.

The mortality risk is highest in patients with chronic osteomyelitis and in those with acute necrotizing soft-tissue infections.

PATHOPHYSIOLOGY

Patients with diabetes are particularly susceptible to foot infection primarily because of Neuropathy, Vasculopathy (vascular insufficiency), and Immunopathy (diminished neutrophil function).⁵ Peripheral neuropathy has a central role in the development of a foot infection and it occurs in about 50 to 70 percent of patients with diabetes. Patients with diabetes lose the protective sensations for temperature and pain, impairing awareness of trauma such as abrasions, blistering, or penetrating foreign body. Bare feet walking is very common in Indians particularly those of rural areas & with insensate foot diabetic patients donot come to know various local injuries made by small pebbles, thorn, Splinters, nails etc. Motor neuropathy can

result in foot deformities (e.g., Hammer & claw toe etc.) that contribute to increase local pressure from footwear, leading to corn or callus formation with s.c. haemorrhage making skin ulceration even more likely.

Once the skin is broken (typically on the plantar surface), the underlying tissues are exposed to colonization by pathogenic organisms. The resulting wound infection may begin superficially, but with delay in treatment and impaired body defence mechanisms, it can spread to the contiguous subcutaneous tissues and to even deeper structures (deep Plantar spaces)^{5,6}.



Plantar foot ulcers with a deep space infection.

Although most diabetic foot infections begin with an ulcer, localized cellulites and necrotizing fasciitis can develop in the absence of an ulcer or traumatic injury. Most diabetic foot infections occur in the setting of good dorsalis pedis pulses; this finding indicates that the primary problem in diabetic foot infections is micro vascular compromise.

If chronic osteomyelitis is left untreated for years, it may lead to complications such as amyloidosis or squamous cell carcinoma at the site of drainage through the skin.

MICROBIAL CHARACTERISTICS

The microbiologic features of diabetic foot infections vary according to the tissue infected. In patients with diabetes, superficial skin infections, such as cellulitis, are caused by the same organisms as those in healthy hosts, namely group A streptococci and *Staphylococcus aureus*. Group B streptococcal cellulitis is uncommon in healthy hosts but not uncommon in patients with diabetes. In diabetic individuals, group B streptococci may cause urinary tract infections and catheter-associated bacteriuria in addition to cellulitis, skin and/or soft-tissue infections, and chronic osteomyelitis. Such infections may be complicated by bacteremia.



Cellulitis of Leg

Furthermore, as previously mentioned, deep soft-tissue infections in diabetic persons can be associated with gas-producing, gram-negative bacilli. Clinically, these infections appear as necrotizing fasciitis, compartment syndrome, or myositis. Gas gangrene is uncommon in persons with diabetes.

Acute osteomyelitis usually occurs as a result of foot trauma in an individual with diabetes. The distribution of organisms is the same as that in an individual without diabetes who has acute osteomyelitis. In chronic osteomyelitis, however, the pathogens include group A and group B streptococci, aerobic gram-negative bacilli, and *Bacteroides fragilis*.

Other pathogens implicated in chronic osteomyelitis in patients with diabetes include *B fragilis*, *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.

Pseudomonas aeruginosa is generally not a pathogen in chronic osteomyelitis in these individuals. Although *P aeruginosa* is frequently cultured from samples obtained from a draining sinus tract or deep penetrating ulcers in patients with diabetes, these organisms are superficial colonizers and are generally not the cause of the bone infection.

Because *Pseudomonas* organisms are water-borne, superficial ulcers may be contaminated by bacteria in wet socks or dressings or walking bare feet in religious places (a common practice adopted by Indians washing their feet in common water trough while going inside Gurudwara / Temple or Mosque) or common bathing places or swimming pool.

Fetid foot usually represents a combined deep-skin and or soft-tissue infection caused by anaerobic micro-organisms. Anaerobic bacteria are usually part of mixed infections in patients with foot ischemia or gangrene.

The most common pathogens in acute, previously untreated, superficial infected foot wounds in patients with diabetes are aerobic gram-positive bacteria, particularly *Staphylococcus aureus* and beta-hemolytic streptococci (group A, B, and others).⁵ Infection in patients who have recently received antibiotics or who have deep limb-threatening infection or chronic wounds are usually caused by a mixture of aerobic gram-positive, aerobic gram-negative (e.g., *Escherichia coli*, *Proteus* species, *Klebsiella* species), and anaerobic organisms

(e.g., *Bacteroides* species, *Clostridium* species, *Peptococcus* and *Peptostreptococcus* species).⁸



Picture of MRSA bacteria greatly magnified.

Methicillin-resistant *S. aureus* (MRSA) is a more common pathogen in patients who have been previously hospitalized or who have recently received antibiotic therapy. MRSA infection can also occur in the absence of risk factors because of the increasing prevalence of MRSA in the community^{9,10}.

CONFIRMING THE DIAGNOSIS

Diabetic foot infection must be diagnosed clinically rather than bacteriologically because all skin ulcers harbour micro-organisms. The clinical diagnosis of foot infection is based on the presence of purulent discharge from an ulcer or the classic signs of inflammation (i.e., erythema, pain, tenderness, warmth, or induration). Other suggestive features of infection include foul odor, the presence of necrosis, and failure of wound healing despite optimal management¹¹. Local inflammatory findings may be less prominent or absent in some diabetic foot infections. For example, pain and tenderness may be reduced or absent in patients who have neuropathy, whereas erythema may be absent in those with vascular disease¹². Acute Charcot's foot is characterized by a progressive deterioration of weight-bearing joints, usually in the foot or ankle. It can clinically mimic cellulites and presents as erythema, edema, and elevated temperature of the foot. Most patients with diabetic foot infection do not have systemic features such as fever or chills. The presence of systemic signs or symptoms indicates a severe deep infection¹³.

OBTAINING CULTURES

Never take a superficial swab for Culture. Before an infected wound is cultured, any overlying necrotic debris should be removed by scrubbing the wound with saline-moistened sterile gauze to eliminate surface contamination^{5,14}.

For wound culture, tissue specimens should be obtained by scraping the base of the ulcer with a scalpel or curette, or by a biopsy of the wound or bone. The specimen should be processed for a Gram-stained smear and aerobic and anaerobic cultures.

ASSESSING VASCULAR STATUS

One should always palpate peripheral pulses (Dorsalis Pedis artery, Posterior Tibial artery, popliteal artery & Femoral artery) in case of diabetic Foot. Peripheral artery disease (PAD) can be diagnosed by absence of foot pulses, reduced ankle-brachial index (ABI) or ischemic flow pattern on Peripheral arterial Vascular Doppler followed by Angiography, if need arises. If a PAD diagnosis is confirmed and revascularization is planned, magnetic resonance angiography, computed tomography angiography, or contrast angiography can be performed for anatomic evaluation¹⁵.

Venous insufficiency can be diagnosed clinically by the presence of tortuous & engorged veins, edema and skin changes and confirmed by duplex ultrasonography.

ASSESSING NEUROPATHY

Touch, vibration, and pressure sensations should be checked routinely using cotton wool, tuning fork, and 10-g nylon monofilament, respectively.



Diagnostic Imaging

Diagnostic imaging is not necessary for every patient with diabetes

who has a foot infection. Plain radiography of the foot is indicated for detection of osteomyelitis, foreign bodies, or gas in soft tissue. Bony abnormalities associated with osteomyelitis may be indistinguishable from the destructive effects of Charcot's foot and are usually not evident on plain radiography until two to four weeks after initial infection¹⁷.

When plain radiography is negative but osteomyelitis is clinically suspected, radio-nuclide scan or magnetic resonance imaging should be performed. Combining Technetium Bone Scan with Gallium Scan or white blood cell scan may improve the diagnostic yield for osteomyelitis^{16,17}. Magnetic resonance imaging provides more accurate information regarding the extent of the infectious process¹⁸. Ultrasonography and computed tomography are also helpful in evaluating abnormalities in the soft tissue (e.g., abscess, sinus tract, cortical bone involvement) and may provide guidance for diagnostic and therapeutic aspiration, drainage, or tissue biopsy¹⁹.

ESTABLISHING SEVERITY OF INFECTION

The severity of the infection determines the appropriate antibiotic regimen and route of administration. It also is the primary consideration in determining the need for hospitalization and the indications and timing for any surgical intervention. A practical and simple approach to classifying diabetic foot infection is provided.

CLINICAL CLASSIFICATION OF DIABETIC FOOT INFECTION

IDSa (Infectious Diseases Society of America) Diabetic Foot Infection Classification²⁰.

- Uninfected: lacking purulence or signs of inflammation
- Mild: infection limited to superficial tissue, cellulites < 2 cm around ulcer, no systemic signs
- Moderate: Systemically well & metabolically stable, more than one of -Cellulites > 2 cm from ulcer, deep tissue involvement, abscess, gangrene, involvement of muscle, tendon, joint or bone
- Severe: foot infection and systemic toxicity and/or metabolic instability
- Fever or chills
- Confusion, vomiting
- Tachycardia, hypotension
- Leukocytosis
- Severe hyperglycemia, DKA or azotemia

ESTABLISHING EXTENT OF INFECTION



Small Abscess at base of III toe



Same case after Surgery

ICEBERG
Phenomenon of DFI

Diabetic Foot infections are like Iceberg, Most of the time only small part is visible.

Early recognition of the area of involved tissue can facilitate appropriate management and prevent progression of the infection. The wound should be cleansed and debrided carefully to remove foreign bodies or necrotic material and should be probed with a sterile metal instrument to identify any sinus tracts, abscesses, or involvement of bones or joints.

Osteomyelitis is a common and serious complication of diabetic foot infection that poses a diagnostic challenge. A delay in diagnosis increases the risk of amputation.²¹

Risk factors associated with osteomyelitis are summarized in *Table 1*. Visible bone and palpable bone by probing are suggestive of underlying osteomyelitis in patients with a diabetic foot infection.²² Laboratory studies, such as white blood cell count and the erythrocyte sedimentation rate (ESR), have limited sensitivity for the diagnosis of osteomyelitis. Osteomyelitis is unlikely with normal ESR values; however, an ESR of more than 70 mm per hour supports a clinical suspicion of osteomyelitis.²¹ Definitive diagnosis requires

Table: Risk Factors for Osteomyelitis in Patients with Diabetic Foot Infection

Appearance of a swollen, deformed red toe (also called sausage toe)
Bone visible or palpable on probing
Infected ulcer with an erythrocyte sedimentation rate of more than 70 mm per hour
Nonhealing ulcer after a few weeks of appropriate care and off-loading of pressure
Radiologically evident bone destruction beneath ulcer
Ulcer area greater than 2 cm ² or more than 3 mm deep
Ulceration presents over bony prominences for more than two weeks
Ulceration with unexplained leukocytosis

Information from references^{5,21-25}

percutaneous or open bone biopsy. Bone biopsy is recommended if the diagnosis of osteomyelitis remains in doubt after imaging²⁴.

CLINICAL EVALUATION

Treatment

Effective management of diabetic foot infection requires

- Appropriate antibiotic therapy,
- Surgical drainage, debridement and resection of dead tissue,
- Appropriate wound care and
- Correction of metabolic abnormalities.

ANTIBIOTIC THERAPY

The selection of antibiotic therapy for diabetic foot infection involves decisions about choice of empiric and definitive antibiotic agent, route of administration, and duration of treatment

Table 2: Principles of Antibiotic Therapy for Diabetic Foot Infection

- Empiric antibiotic regimen should include an agent active against *Staphylococcus aureus*, including methicillin-resistant *S. aureus* if necessary, and streptococci.
- Coverage for aerobic gram-negative pathogens is required for severe infection, chronic infection, or infection that fails to respond to recent antibiotic therapy.
- Necrotic, gangrenous, or foul-smelling wounds usually require anaerobic therapy.
- Initial empiric antibiotic therapy should be modified on the basis of the clinical response and culture or susceptibility testing.
- Virulent organisms, such as *S. aureus* and streptococci, should

always be covered in polymicrobial infection.

- Coverage for less virulent organisms, such as coagulase-negative staphylococci, may not be needed.
- Parenteral antibiotics are indicated for patients who are systemically ill, have severe infection, are unable to tolerate oral agents, or have infection caused by pathogens that are not susceptible to oral agents.
- Using oral antibiotics for mild to moderate infection and switching early from parenteral to oral antibiotics with appropriate spectrum coverage and good bioavailability and tolerability are strongly encouraged.
- Although topical antibiotics can be effective for the treatment of mildly infected ulcers, they should not be routinely used.
- Discontinuation of antibiotics should be considered when all signs and symptoms of infection have resolved, even if the wound has not completely healed.
- Cost should be considered when selecting antibiotic therapy.

Information from references^{5,25}

Initial empiric antibiotic therapy should be based on the severity of the infection, history of recent antibiotic treatment, previous infection with resistant organisms, recent culture results, current Gram stain findings, and patient factors (e.g., drug allergy). A Gram-stained smear of an appropriate wound specimen may help guide therapy. The overall sensitivity of a Gram-stained smear for identifying organisms that grow on culture is 70 percent.⁹ The empiric antibiotic regimen for diabetic foot infection should always include an agent active against *S. aureus*, including MRSA if necessary, and streptococci.^{5,26,27,28}

The patient should be reassessed 24 to 72 hours after initiating empiric antibiotic therapy to evaluate the response and to modify the antibiotic regimen, if indicated by early culture results. Several antibiotics have been shown to be effective, but no single regimen has shown superiority.^{1,2,3,5,29-32} Antibiotic therapy should not be used for foot ulcers without signs of infection because it does not enhance wound healing or prevent infection.

Clinical failure of appropriate antibiotic therapy might be because of patient nonadherence, antibiotic resistance, superinfection, undiagnosed deep abscess or osteomyelitis, or severe tissue ischemia.

SURGICAL TREATMENT

Surgery is the cornerstone of treatment for deep seated diabetic foot infection. Timely and aggressive surgical debridement or limited resection or amputation may reduce the need for more extensive amputation.³⁴ Procedures range from simple incision and drainage to extensive multiple surgical debridements and amputation. Indications for emergent surgery are severe infection in an ischemic limb, necrotizing fasciitis, gas gangrene, and an infection associated with compartment syndrome. Surgical excision of affected bone has historically been the standard of care in patients with osteomyelitis. Nevertheless, successful therapy with a long course of antibiotics alone has been achieved in two thirds of patients with osteomyelitis. Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up.³⁵ As infection is controlled and the wound starts to granulate, delayed primary closure may be successful. The wound may also be treated surgically with a flap or graft, left to heal by secondary intention, or managed with negative pressure dressings, NPWT or VAC (Vacuum Assisted Closure).³⁶ If the infected limb appears to be ischemic, the patient should be referred to a vascular surgeon. Although noncritical ischemia can usually be treated without a vascular procedure, early revascularization within a few days of the infection is required for

TABLE
Empiric Antibiotic Regimens for Treatment of Diabetic Foot Infection

Severity or extent of infection	Recommended therapy	Comments
Soft tissue infection		
Mild (duration of treatment is one to two weeks)	Dicloxacillin 500 mg orally four times per day	Oral agent of choice for MSSA
	Cephalexin (Keflex) 500 mg orally four times per day	For penicillin-allergic patients, except those with immediate hypersensitivity reactions
	Amoxicillin/clavulanate (Augmentin) 875/125 mg orally twice per day	Good option for polymicrobial infection
Moderate (duration of treatment is two to four weeks, depending on response; administer orally or parenterally followed by orally)	Clindamycin (Cleocin) 300 to 450 mg orally three times per day	Potential cross-resistance and emergence of resistance in erythromycin-resistant <i>Staphylococcus aureus</i> ; inducible resistance in MRSA
	Doxycycline (Vibramycin) 100 mg orally twice per day or Sulfamethoxazole/trimethoprim (Bactrim) 160/800 mg orally twice per day	Effective for MRSA
	Nafcillin 1 to 2 g IV every four hours	Parenteral drug of choice for MSSA
	Cefazolin 1 to 2 g IV every eight hours	For penicillin-allergic patients
Severe (duration of treatment is two to four weeks, depending on response; administer parenterally, then switch to orally)	Vancomycin 30 mg per kg IV twice per day	Parenteral drug of choice for MRSA
	Ampicillin/sulbactam (Unasyn) 3 g IV four times per day	—
	Ceftriaxone (Rocephin) 1 to 2 g IV once per day plus clindamycin 600 to 900 mg IV or orally three times per day or metronidazole (Flagyl) 500 mg IV or orally three times per day	—
	<i>Or</i>	
	Levofloxacin (Levaquin) 500 mg IV or orally once per day plus clindamycin 600 to 900 mg IV or orally three times per day	—
	Moxifloxacin (Avelox) 400 mg IV or orally once per day	—
	Ertapenem (Invanz) 1 g IV once per day	—
	Ciprofloxacin (Cipro) 400 mg IV twice per day plus clindamycin 600 to 900 mg IV three times per day	—
	Piperacillin/tazobactam (Zosyn) 3.375 to 4.500 g IV every six to eight hours	—
	Impipenem/cilastatin (Primaxin) 500 mg IV four times per day	—
Bone or joint infection	Vancomycin 30 mg per kg IV twice per day plus ciprofloxacin 400 mg IV twice per day plus metronidazole 500 mg IV or orally three times per day	Vancomycin is the parenteral drug of choice for MRSA; linezolid (Zyvox) 600 mg IV or orally twice per day or daptomycin (Cubicin) 4 mg per kg IV once per day can also be used for MRSA Use vancomycin for penicillin-allergic patients
	Tigecycline (Tygacil) 100 mg IV loading dose then 50 mg IV twice per day	Should be used when suspected polymicrobial infection, including MRSA
	No residual infected tissue	Use the above parenteral or oral antibiotic regimens for two to five days
Residual infected tissue only	Use the above parenteral or oral antibiotic regimens for two to four weeks	
Residual infected viable bone	Initially use the above parenteral antibiotics followed by oral antibiotics for four to six weeks	
Residual infected dead bone	Initially use the above parenteral antibiotics followed by oral antibiotics for eight to 12 weeks	

IV = intravenously; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*.

*— Risk factors for polymicrobial infection include chronic ulcers, recent antibiotic use, and foot ischemia or gangrene.

Information from references 1,2,3,5,29-32

successful treatment of an infected foot with critical limb ischemia.³⁷

WOUND MANAGEMENT

The wound should be dressed to allow for careful inspection for evidence of healing and early identification of new necrotic tissue. Necrotic or unhealthy tissue should be debrided, preferably surgically or with topical debriding agents. Removing pressure from the foot wound (i.e. Off-loading) is crucial for healing³⁸

Which can be achieved through total contact casting, removable cast walkers, and various ambulatory braces, splints, modified half-shoes, and sandals.³⁹ Edema of the legs can delay wound healing; controlling edema with leg elevation, compression stockings, or a pneumatic

pedal compression device enhances the healing process.⁴⁰

Evidence of resolution of infection includes formation of granulation tissue, absence of necrotic tissue, and closing of the wound. If osteomyelitis is present, signs of healing include a drop in ESR & CRP and loss of increased uptake on nuclear scan.

INDICATIONS OF HOSPITALIZATION

A clinician should remember certain indications of Hospitalization in Diabetic Foot Infections like-

- Serious Infection like Necrotising Fasciitis/Gas gangrene
- Patients who need Parenteral Therapy or fluid resuscitation
- Patients who require Surgical intervention

- To control metabolic derangements e.g. Diabetic Keto Acidosis
- Patient who is unable or unwilling to perform proper wound care
- Patient who can or will not be able to offload the Wound.

METABOLIC STABILITY

Good glycemic control may help eradicate the infection and promote wound healing.⁴¹ All patients should have blood glucose and A1C levels measured at initial presentation and then at regular intervals. Frequent home blood glucose monitoring is strongly encouraged. Other than Blood sugar control correction of fluid and electrolyte imbalances, acidosis, and azotemia is essential. Patient's nutrition should be taken care of particularly high protein diet (If no renal problem).

PROGNOSIS

The prognosis for cases of cellulitis, skin and/or soft-tissue infections, and acute osteomyelitis depends on the adequacy of antimicrobial therapy and surgical debridement. For cases of chronic osteomyelitis, the prognosis is directly related to the vascular supply in the affected limb and the adequacy of surgical debridement along with adequate off loading.

PREVENTION

Prevention of diabetic foot ulcers begins with identifying patients at risk. All patients with diabetes should have an annual foot examination that includes assessment for anatomic deformities, skin breaks, nail disorders, loss of protection sensation, diminished arterial supply, and inappropriate footwear. Patients at higher risk of foot ulceration should have examinations more often.⁴² Educating patients and caretakers about proper foot care and periodic self-foot examinations are effective interventions to prevent ulceration. Other effective clinical interventions include optimizing glycemic control, smoking cessation, debridement of calluses and certain types of prophylactic foot surgery.⁴³

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