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Diabetic foot infections: a comprehensive overview

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Abstract. – Diabetic foot ulcers (DFUs), a micro-vascular complication, are associated with a substantial increase in morbidity and mortality. DFUs are a complicated mixture of neuropathy, peripheral arterial diseases, foot deformities, and infections. Foot infections are frequent and potentially devastating complications. Infection prospers in more than half of all foot ulcers and is the factor that most often leads to lower extremity amputation. The complications of microbial flora span the spectrum from superficial cellulitis to chronic osteomyelitis and gangrenous extremity lower limb amputations. Wounds without confirmed soft tissue or bone infections do not require antibiotic therapy. Mild and moderate infections need empiric therapy covering Gram-positive cocci, while severe infections caused by drug-resistant organisms require broad-spectrum anti-microbials targeting aggressive Gram-negative aerobes and obligate anaerobes.

Key Words:
Diabetes mellitus, Diabetic foot ulcer, Infection, Amputation, Antibiotics, Mmicrobiology.

Introduction

Infections in ulcerated feet in patients with diabetes are a primary cause of morbidity, including discomfort, and reduced physical and mental quality of life, and they give rise to a need for visits by health-care providers, wound care, antimicrobial therapy, and often surgical procedures/debridements. As such, these infections comprise the most frequent grounds for both diabetes-associated hospitalization and lower extremity losses. In an acute presentation with diabetic foot infection (DFI), there is frequently a delay in the recognition of the causative organism, which may compel the use of empirical antibiotics,. According to Peters, the incidence of foot infections in people with diabetes ranges from an overall lifetime risk of 4% to a yearly risk of 7%. If infection advances to deeper structures, including the underlying bone, diabetic foot osteomyelitis (DFO) develops. DFIs are the most frequent diabetes-related complication requiring hospitalization, and DFO is present in 44-68% of patients with DFIs admitted to the hospital.

Infections in foot lesions should be clinically defined by the presence of inflammation or purulence, and then classified by severity. This approach helps clinicians make decisions about which patients to hospitalize, send for imaging procedures or recommend for surgical interventions. Many organisms, alone or in combination, can cause DFIs, but Gram-positive cocci (GPC), especially staphylococci, are the most common.

To achieve more successful outcomes and ultimately avoid amputations, a systematic approach to the management of DFIs must be adopted. If

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not treated promptly and appropriately, DFI can become incurable or even lead to septic gangrene. At least 60% of non-traumatic lower limb amputations occur among people with diabetes.

The existence of osteomyelitis further raises the costs of hospitalization because of the need for additional diagnostic studies, prolonged medical treatment and surgeries. Notably, the use of antibiotics in such cases is at least doubled. When amputation is needed, a high-level (i.e., transtibial) procedure is often indicated, more because of irreversible ischaemia than because of uncontrolled infection. However, most amputations reflect the multimodal foot problems related to diabetes, which highlights the need for a multidisciplinary approach (Figure 1). All clinicians regularly seeing persons with diabetes should have an understanding of how to prevent, diagnose

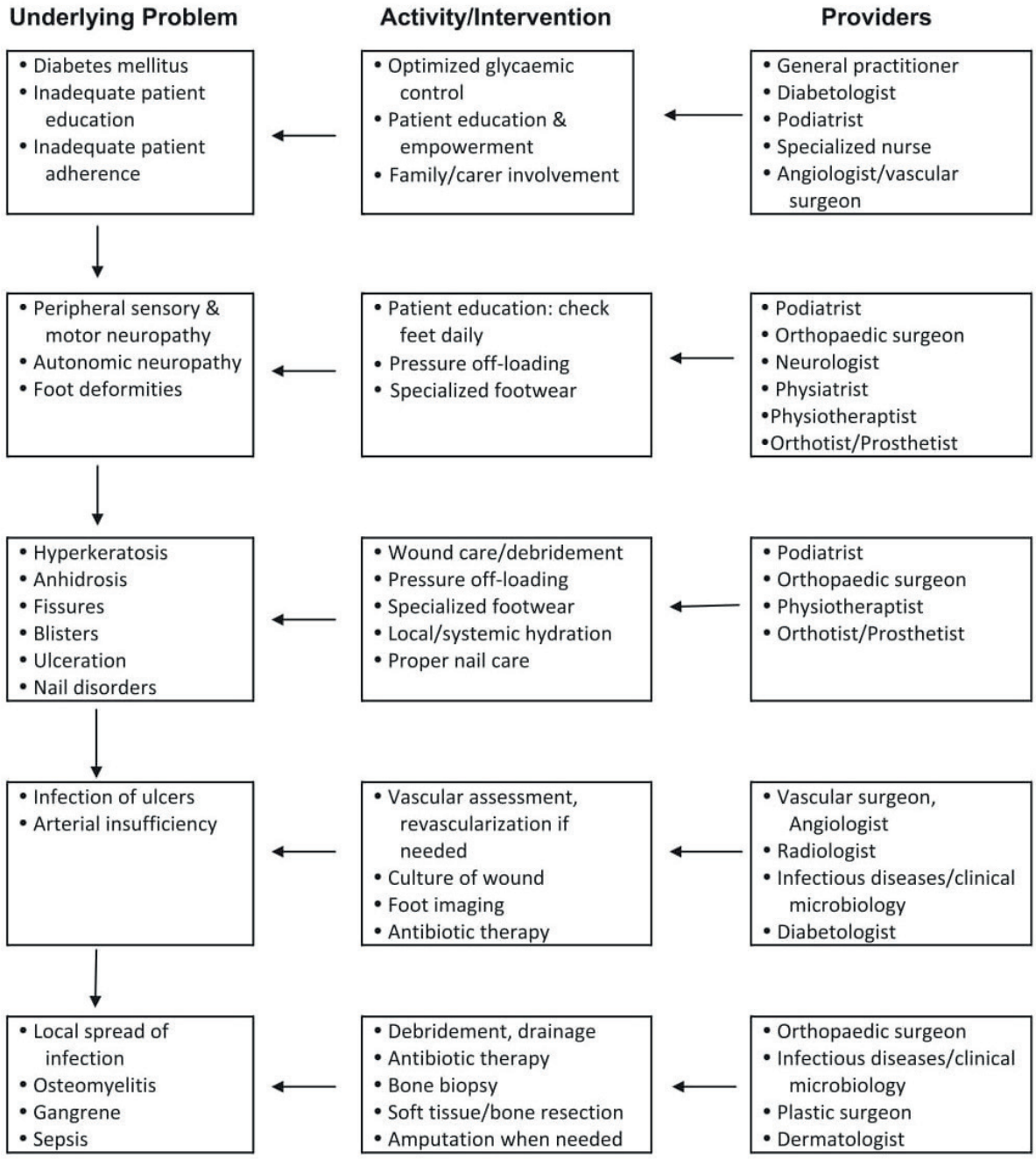


Figure 1. Multimodal foot problems related to diabetes and the need for a multidisciplinary approach.

and treat DFIs. Given the increasing amount of research in this area, this review aims to make clinicians aware of recent developments in this field.

Pathogenesis of Diabetic Foot Infection

The foot is the crossroad for many pathological processes in diabetics and it is an area in which almost all gears of the lower limb are involved: skin, subcutaneous tissue, muscles, bones, joints, nerves, and blood vessels. DFI is more often the consequence than the cause of diabetic foot ulcers. These infections usually begin with a split in the cutaneous envelope, typically in a site of trauma (mechanical/ thermal) or ulceration. Infection is best defined as an invasion by micro-organisms and their multiplication in host tissues induces inflammatory responses. This is followed by tissue destruction. DFI is defined by infection in soft tissue or bone anywhere below the malleoli in a diabetic person. Several factors predispose diabetic patients to developing a DFI, including neuropathy, vasculopathy, immunopathy, and foot biomechanics.

Sensory loss due to peripheral neuropathy in the diabetic foot is always considered to be the earliest developed and most prominent threat, and features in the development of ulcers. About 60% of diabetic patients with foot ulcers have neuropathy. Nerve dysfunction in diabetic patients may be described as sensory, motor, or autonomic. The lack of balances in the musculature of the foot due to motor neuropathy result in atrophy with muscle wastage, dislocation of fat pads and associated foot deformities, such as foot drop, clawed and hammerhead toes, and equinus deformities, creating areas susceptible to trauma. As a consequence of the reduced sensation, insults to lower extremities often go unnoticed, which progressively worsens the state, as the affected lesion is subjected to repetitive plantar pressure and shear forces from ambulation and weight bearing that damage the sensory nerves of extremities. With the loss of sweat and oil gland functions, the diabetic foot becomes dry and keratinized. Autonomic neuropathy leads to sudomotor function and abnormal blood flow to the soles of the feet. With displacement in functions of the foot's sweat and sebaceous glands, the skin becomes dry and keratinizes, so that it more easily cracks, generating a portal for infection,.

Diabetic angiopathy is the most frequent cause of morbidity and mortality in diabetic patients. Macroangiopathy reveals as diffuse multi-segmental involvement of the lower limb vessels. It is also connected to a damage of collateral circulation. This is considered to be an atherosclerotic obstructive disease of large vessels, which leads to peripheral arterial disease of the lower extremities. Little is known about the biology of peripheral arterial disease (PAD) in individuals with diabetes, but it is believed that the vascular changes observed with other manifestations of atherosclerotic disease are also applicable to patients with both peripheral arterial disease and diabetes. Peters et al suggest that previous amputation, peripheral vascular disease, and neuropathy are significant risk factors for DFI. Microangiopathy results in capillary basal membrane thickening, altered nutrient exchange, tissue hypoxia and microcirculation ischemia. There is evidence of diabetic foot from as early as ancient Egyptian times, as mummies with prosthetic toes have been discovered. Pryce reported a case of a foot ulcer associated with diabetes in 1887.

A lack of attention to foot hygiene and the use of poorly fitting footwear are the major factors that are preventable in the development of infection. Diabetic foot infection may range from fungal infections of the nail to severe necrotising limb- or life-threatening infections. Early diagnosis and prompt definitive treatment may be delayed due to a lack of foot sensation, the patient's poor eyesight, and poor judgement by the physician. Abrasions, rashes and loss of skin integrity can be the initiating factors in the development of diabetic foot infection. Approximately 60% of foot infections start in webbed spaces and 30% in nails, while 10% are secondary to punctures. In a diabetic, the clinical presentation ranges from acute cellulitis to life threatening necrotising fasciitis.

Debridement must be meticulous and repeated debridement is often necessary. Treatment priorities are: 1) aggressive treatment of infections, 2) diagnosis of ischemia and evaluation for possible revascularization, 3) relief of pressure on the wound and 4) improvement of the wound environment with debridement dressing and advanced care treatments. Treatment of a complicated diabetic foot ulcer can involve numerous pathways. After a complete ulcer evaluation, including measurements, x-rays and fundoscopy, an arterial Doppler ultrasound can be utilized.

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 defences secondary to hyperglycaemia include defects in leukocyte function and morphologic changes to

macrophages. Bagdade et al demonstrated that leukocyte phagocytosis was significantly reduced in patients with poorly controlled diabetes, and that an improvement in microbiocidal rates was directly correlated with the correction of hyperglycaemia. Decreased chemotaxis of growth factors and cytokines, coupled with an excess of metalloproteinases, impede normal wound healing by creating a prolonged inflammatory state. Fasting hyperglycaemia and the presence of an open wound create a catabolic state. A 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. A research indicates impairment of the immune system at serum glucose levels ≥150 ml/dl. Patients with diabetes tolerate infections poorly and infections adversely affect diabetic control. This repetitive cycle leads to uncontrolled hyperglycaemia, which further affects the host's response to infection.

Foot Architecture

The distinctive framework of the foot, which has several interconnected bony compartments, favours the spread of infection via proximal calcaneal convergence or direct perforation of septae. In addition, the soft tissues of the foot, like plantar tendons, aponeurosis, muscles sheaths, and fascia, cannot resist infections. Infection of the bone is an outcome of the contiguous spreading of infection to cortex (osteis) or bone marrow (osteomyelitis). A sterile metal probe is inserted into the ulcer. If it penetrates to the bone, it nearly always indicates the presence of infected bone. Ulcers >60 mm^2 in size, chronic discharge from the sinus tract, an erythrocyte sedimentation rate >70 mm/hour, or the presence of sausage toe, suggest the presence of underlying osteomyelitis. Plain radiographs are a cost-effective method for confirming osteomyelitis. Other sensitive techniques include CT scans, MRI, and radioisotope scans providing high-resolution images of bone and soft tissues,. Some independent risk factors for DFI include wounds that penetrate bones, recurrent lesions, and a history of amputations, neuropathy, wounds with traumatic etiologies, and the presence of PAD.

Assessment of Infection

Clinical assessment requires appropriate debridement to remove necrotic sections and calluses to fully visualize the wound. The diagnosis of infection is based on the presence of purulence, or at least two classic symptoms or signs of inflammation (e.g., erythema, edema, warmth, tenderness, pain or induration). However, in some cases, patients with diabetes may have a dull neuro-inflammatory response, such that they do not manifest typical signs of infection. Secondary signs in cases of neuropathic foot include friable or discoloured granulation tissue, a foul odour, non-purulent discharges, and delayed wound healing. A proper emphasis should be placed on evaluating the risk factors of DFI, including positive probe-to-bone (PTB), the presence of an ulceration for more than 30 days, a history of recurrent foot ulcers, a traumatic etiology, the presence of peripheral arterial disease in the involved limb, a history of lower extremity amputation, a lack of protective sensations, renal insufficiency or a history of walking barefoot. An adequate description of ulcer characteristics, such as size, depth, base, margins, appearance, and location, is necessary for mapping progress during treatment. A thorough assessment of the presence of granulation tissue or slough should be made in the floor of the ulcer to determine subsequent management. Patients with a diabetic foot infection should also be properly evaluated for arterial insufficiency and neuropathic conditions on a structured schedule based on defined risk factors. The presence of fever, tachycardia or tachypnea may indicate an infected wound. The vascular status should be documented by palpating all peripheral pulses, or by using a hand-held Doppler for non-palpable or faint pedal pulses. ABI is a common non-invasive tool used in diagnosing PAD, but false elevations due to calcified arteries warrant more vascular studies. Neurological examinations are also needed to clinically manage diabetic foot ulcers and healing.

Microbiology of Diabetic Foot Ulcers

The management of diabetic foot disease primarily focuses on avoiding amputation of the lower extremities. The basic principles of wound healing apply equally to DFU patients and patients with wounds at any other site. The healing of DFUs will occur in the presence of three conditions: adequate arterial inflow, appropriate control of infection, and the offloading of the wound site and the immediate surrounding area infection is defined as invasion and colonization by pathogenic microbes in a foot wound, which causes local tissue damage favoured by hyper-

glycaemia-mediated deranged host defences. Infections begin as minor problems and later progress to involve deep tissues, joints, or bones, especially if unmanaged.

Exploring the microbial etiology is an important aspect of DFI management. Foot wounds in diabetics lack many of the protective barriers and mechanisms associated with intact skin, thereby providing a portal for invasive microorganisms. The presence of non-replicating pathogens is termed "contamination", while wounds with fast-dividing microbes are "colonized". Critical colonization or a state of transition between colonization and invasion delays wound healing, and altered microbial-host interactions increase virulence. Diffused immune responses accelerate the process. When a colonized wound progresses to an infected wound, a microbiological analysis should be undertaken to evaluate the underlying pathogen(s). Management of a clinically overt diabetic foot infection requires apposite systemic antibiotic therapy, which is best guided by identifying the causative pathogens. Proper specimen collection, such as deep-tissue samples, can reveal the true flora and are preferred over wound swabs, as the latter may reveal colonizing agents and provide false results. A curettage or tissue scraping from the base of the ulcer provides a more accurate result if promptly sent for aerobic and anaerobic analysis. Swab or tissue specimens should be evaluated for phenotypic testing in line with CLSI guidelines. This can be attained through a culture of a specimen using selective or standard growth media along with antimicrobial sensitivity testing. Traditional microscopy and staining techniques, such as the Gram-stained smear, can provide additional organism characterization. Disadvantages of these techniques include the fact that they take at least a couple of days to process, they miss some facultative organisms, and they are less useful in patients undergoing antibiotic therapy.

Longstanding DFUs with severe infections are usually polymicrobial. In a clinico-microbiological study of 80 diabetic foot patients by Gadepalli et al[32], 82.5% demonstrated polymicrobial flora with an average of 2.3 species per patient and an aerobic to anaerobic ratio of 5.5. The most commonly isolated pathogens were *Staphylococcus aureus, Proteus spp,* and *Escherichia coli*. Among anaerobes, *Peptostreptococcus spp, Veilonella* species, and *Bacteroides* species were predominant. In another study, Zubair et al reported polymicrobial etiology in 65% cases of DFI with a predominance of *Escherichia coli* and *Staphylococcus aureus* among the aerobes and *Peptostreptococcus spp* among the anaerobes.

Infection in previously untreated DFUs is caused by Gram-positive cocci, mostly in a mono-microbial state, whereas chronic or severely infected lesions harbour polymicrobial strata with a mix of Gram-negative aerobes and anaerobes. Breen et al demonstrated that *Staphylococcus aureus* is the most important pathogen in DFIs and a component of polymicrobial etiology. Among the Gram-negative group, *Escherichia coli, Klebsiella pneumoniae,* and *Proteus* species are the most common pathogens, followed by *Pseudomonas aeruginosa*. Chronic or previously treated wounds harbour Gram-negative bacilli, especially from the Enterobacteriace family. Wounds involving deep tissues or ischemic necrosis are invaded by obligate anaerobes. *Pseudomonas* infections are common in wounds soaked in wet dressings and frequently seen in warmer regions. In foot ulcers, the methicillin-resistant *staphylococcus aureus* (MRSA) was high but MSRA was eradicated by regular debridement and topical treatments.

Our preliminary study showed that the Gram-positive cocci are the most common pathogens, and we observed that the percentage of MRSA was extremely high at 59.4% (Table I). We found that the six most common microbial species constitute almost 70% of diabetic foot infections registered at our clinic (Figures 2 and 3). These microbial species showed the following rates of resistance. For *S. aureus*, we detected a rate of resistance to oxacillin of 59.4% (MRSA), 65.9% to amoxicillin/clavulanic, 64.1% to ciprofloxacin, 0.6% to teicoplanin (n=2) and 0.4% to vancomycin (n=1). We found no resistance to linezolid. For

Table I. A total 765 episodes of DFI in 482 adult patients were identified.

Expected pathogens	Frequency	Percentage
S. aureus	335	26.8
Ent. faecalis D	166	13.3
P. aeruginosa	164	13.1
E. coli	85	6.8
P. mirabilis	65	5.2
B. fragilis	49	3.9
A. baumannii	44	3.5
K. pneumoniae	41	3.3
Ent. faecium D	34	2.7
S. agalactiae B	25	2.0
E. cloacae	21	1.7
S. haemolyticus	21	1.7
Morganella morganii	19	1.5
S. maltophilia	12	1.0

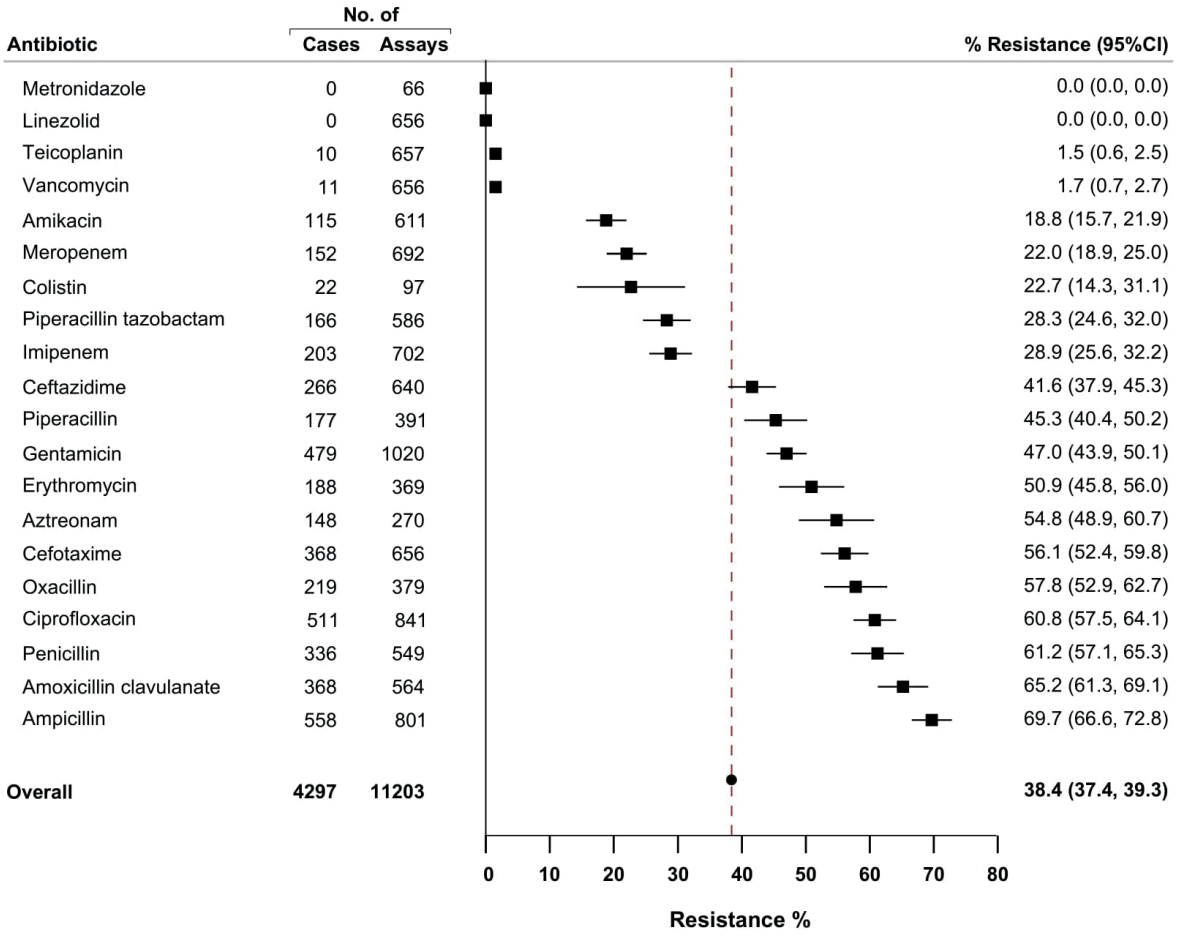
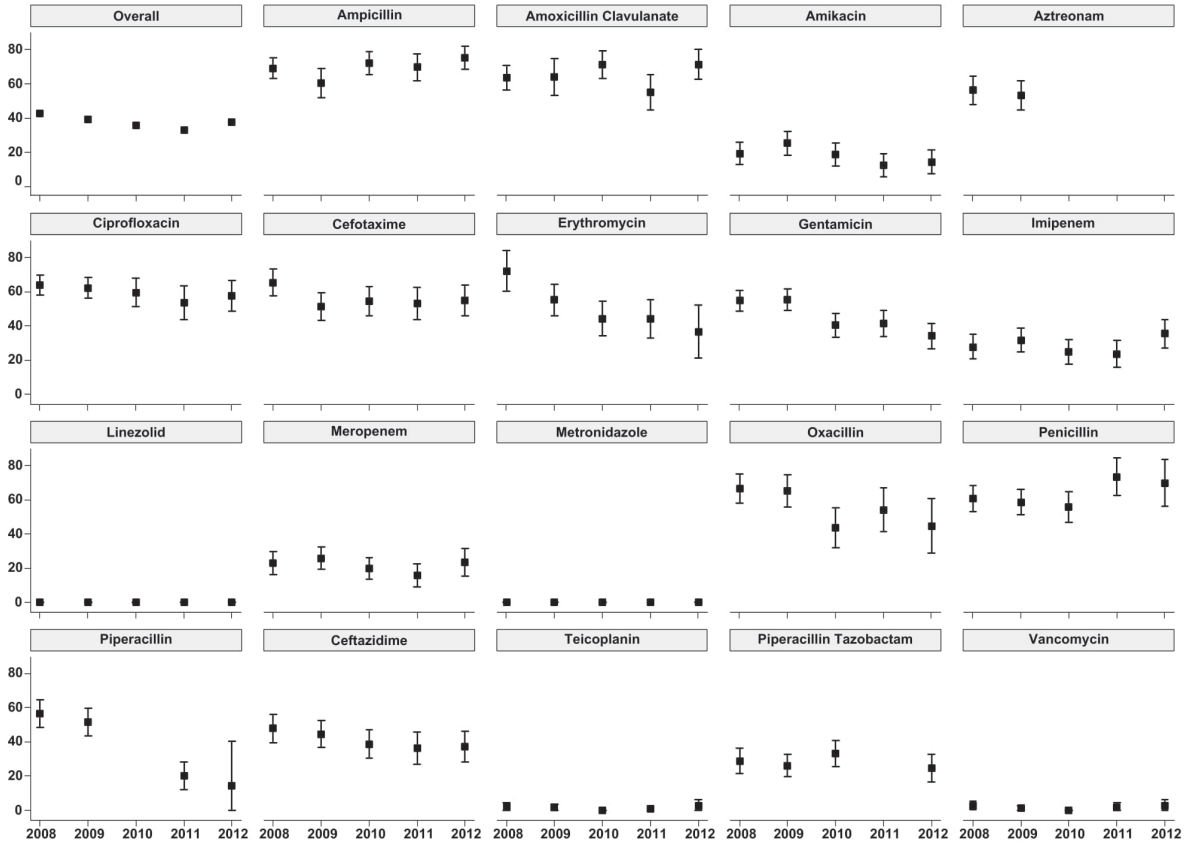


Figure 2. Overall antibiotic resistance.

P. aeruginosa, no antibiotics with a sensitivity of 100% were observed. We found the following rates of resistance to other antibiotics: 58.5% to ciprofloxacin, 44.5% to gentamicin, 34.1% to cefotazidime, 39.1% to imipenem, 28.2% to meropenem, and 18.3% to amikacin. For *P. mirabilis*, no resistance to meropenem was observed, while we detected the following rates of resistance to other antibiotics: 79.7% to ampicillin, 60.9% to ciprofloxacin, 45.2% to cefotaxime, 42.6% to amoxicillin/clavulanate, 37.5% to cefotazidime, and 14.1% to amikacin. For *E. faecalis D*, no resistance to linezolid was observed. We detected the following rates of resistance to other antibiotics: 4.3% to vancomycin, 4.2% to teicoplanin, and 3% to ampicillin. For *E. coli*, no resistance to imipenem and meropenem was observed, but we detected the following rates of resistance to other antibiotics: 80% to ampicillin, 69.4% to ciprofloxacin, 25% to amoxicillin/clavulanate, 37.6% to cefotaxime, 35.3% to gentamicin, 31.8% to cefotazidime, and 1.2% to amikacin. For *B. fragilis*, we observed resistance of 21.4% to piperacillin, but no resistance to amoxicillin/clavulanate, imipenem or meropenem.

The prevention of ulcers infected by multidrug resistant organisms (MDRO) should be in focus and resistance patterns should be carefully monitored. A mild or moderate DFI can be treated with oral antimicrobials, while chronic infection requires inpatient antimicrobial therapy or surgical treatment, as well as controlled metabolic derangements. Patients with DFI should initially be treated with an empirical regime covering Gram-positive cocci. The spectrum can be broadened to cover Gram-negative aerobes in chronic infections. Wounds that are necrotic, foul smelling or gangrenous require anti-anaerobic microbials. A definite diagnosis of bone infection usually requires histological findings consistent with bone infection along with microbiological examinations of an aseptically obtained bone



Significant (p<0.05) negative trends for Erythromycin (4-year reduction: -32.4%; 95%CI: -49.2, -15.5), Gentamicin (-22.2%; -31.0, -13.5), Oxacillin (-23.2%; -38.1, -8.3), Piperacillin (-49.0%; -65.3, -32.6), and Ceftazidime (-11.8%; -22.7, -0.9) [Supplementary Table 2]. Colistin data available only for one year.

Figure 3. Prevalence (%) of antibiotic resistance, by year.

sample. However, this is typically only necessary when the diagnosis is in doubt or determining the causative pathogen's antibiotic susceptibility is crucial. The primary treatment for bone infection should be parenteral and can be prolonged up to six weeks. Chronic osteomyelitis requires surgical intervention (i.e., removal of bone).

Classification of Diabetic Foot Infections

An adequate description of ulcer characteristics, such as size, depth, appearance, and location, allows for mapping of progress during treatment. The evaluation should determine the etiology of the ulcer and ascertain whether the lesion is neuropathic, ischemic or neuro-ischemic. Various classification systems have been used to evaluate the severity of diabetic foot lesions. These systems attempt to encompass different characteristics of the ulcer, including size, depth, ischemia, infection, and neuropathy.

One of the most commonly used classification systems is the Wagner-Meggit system. Although it was devised for dysvascular foot, it has been used for lesion classification for the past 25 years. This six-grade classification system takes into consideration the depth of the ulcer, the presence of gangrene, and the extent of tissue necrosis. Even though Wagner-Meggit's grading is one of the most widely used classification systems, it does not take into account important clinical parameters, such as ischemia, infection, or other co-morbid factors (Table II).

The University of Texas system primarily grades ulcers based on depth, and then, it stages which divide patients who have clean ulcers and those who are infected. More specifically, grade 0 in the Texas System classification (Table III) represents a pre- or postulcerative site. Grade 1 ulcers are superficial wounds through either the epidermis or the epidermis and dermis, but that do not penetrate to tendon, capsule, or bone. Grade 2 wounds penetrate to tendon or capsule, but the bone and joints are not complicated. Grade 3 wounds infiltrate bone or into a joint. Each wound grade consisted of 4 stages:

Table II. Wagner classification system.

0 Pre-ulcerative, with no open lesion or cellulitis
1 Superficial ulcer
2 Deep ulcer upto tendons and joint tissue
3 Deep ulcer with abscess, osteomyelitis, and joint sepsis
4 Localized gangrene of forefoot or heel
5 Gangrene of entire foot/global gangrene

clean wounds (A), nonischemic infected wounds (B), ischemic wounds (C), and infected ischemic wounds (D). The S(AD) SAD classification (Table IV) grades 5 ulcer features (size, depth, sepsis, arteriopathy, and denervation) on a 4-point scale (0-3). Similarly, the International Working Group on the Diabetic Foot has suggested the PEDIS classification (Perfusion (ischaemia), Extent (area), Depth, Infection, Sensation (neuropathy)), which grades the wound on a 5-feature basis: perfusion (arterial supply), extent (area), depth, infection, and sensation. Finally, according to the Infectious Diseases Society of America guidelines, the infected diabetic foot is subclassified into the categories of uninfected, mild (restricted involvement of only skin and subcutaneous tissues), moderate (more extensive or affecting deeper tissues), and severe (accompanied by systemic signs of infection or metabolic instability).

In an uncomplited clinical classification approach, diabetic foot ulcers can be described as neuropathic, ischemic, or neuroischemic, determined by how complications such as peripheral neuropathy and arterial disease affect the ulcer's etiology.

Choosing an Appropriate Antibiotic

As soon as a diagnosis of DFI is established, antibiotic treatment should be initiated. NICE (2016) guidelines state that all primary care settings should have care pathways in place for managing DFIs with specific antibiotic regimens that take local resistance issues into account. The antibiotic choice should be based on the likely proven causative pathogens, the severity of the infection and evidence of efficacy for DFIs while being cognisant of cost. The NICE guidelines also recommend that the choice of antibiotic treatment should be influenced by the care setting, patient preferences, the clinical situation, and the patient's medical history.

The IWGDF and NICE make specific recommendations concerning antimicrobial therapy for DFIs depending on the severity:

- For mild infections, initially offer oral antibiotics effective against Gram-positive organisms.
- A one- to two-week course of antibiotic therapy is usually sufficient for mild infections.
- For moderate and severe infections, administer antibiotics effective against Gram-positive and Gram-negative organisms, including anaerobic bacteria.

Table III. University of Texas Classification System.

	0	1	2	3
A	No open lesion	Superficial wound	Affected tendons/capsules	Affected 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

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

Clinical description	IDSA	IWGDF
Wound without purulence or any manifestations of inflammation	Uninfected	1
≥ 2 Manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration); any cellulitis or erythema extends 52 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 ≥ 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

- For moderate infections, offer oral or initial parental administration depending on the clinical situation and choice of antibiotic.
- For severe infections, administer parental therapy with a switch to oral therapy based on the clinical situation and the response to treatment.
- For DFO, offer six weeks of antibiotic therapy according to local protocols for patients who do not undergo surgical resection of the infected bone.
- For those who have undergone surgical intervention and all infected bone are resected, offer no more than one week of antibiotic therapy[37]. Lipsky et al[43] do not recommend prophylactic treatment of clinically uninfected wounds with antimicrobial therapy, and they advise against the use of any specific type of dressing for DFI with the aim of preventing an infection or improving its outcome.

Treatment of Diabetic Foot Infections

Founded on the results of the available studies, no single drug or combination of agents seems to be superior to any others. We have several antibiotic agents for treating DFIs, both by the oral and parenteral routes. It is important to bear in mind that while antibiotics are necessary for treating a DFI, they are not usually sufficient. All patients will need appropriate wound care (debridement, dressings, and pressure off-loading) and most will need some surgical interventions. An international survey found that developing a stewardship programme was associated with reductions in 96% of hospitals for inappropriate prescribing, 86% for broad-spectrum antibiotic use, 80% for antibiotic expenditure, 71% for healthcare-acquired infections, 65% for length of stay or mortality, and 58% for bacterial resistance. MRSA infections protract wound healing times and hospitalization stays, increase the need for surgical procedures, and result in treatment failure. The antibiotic regimen should take account of an agent active against Gram-positive cocci having a care for MRSA in high-risk patients. Treatment for previously treated or severe DFI should include extended coverage for Gram-negative bacilli and *enterococcus* species. Gangrenous and foul-smelling wounds may necessitate anti-anaerobic therapy. In a randomized study of ampicillin/sulbactam versus imipenem/cilastatin for the treatment of moderately severe DFI in 90 patients, there were no significant differences between the treatments in terms of clinical success rate, adverse-event frequency, duration of study antibiotic treatment, or length of hospitalization. In another randomized study, double-blinded, multicentre trial in diabetic adults (n=586) with a foot infection classified as moderate-to-severe it was found that ertapenem were equivalent to those for patients treated with piperacillin/tazobactam. The once-daily ertapenem is advantageous in the DFI setting, in spite of the fact that ertapenem does not cover most *enterococci* or *Pseudomonas aeruginosa*. Usually, moderate and severe DFI are typically treated with intravenous antibiotic therapy for two to four weeks, with four to six weeks of therapy for osteomyelitis.

Operating intervention of moderate to severe DFI is often essential, and includes aggressive incision, drainage and debridement of non-viable soft tissue and bone. With an increasing infection severity, there was a statistically significant trend toward an increased risk for amputation, an increased anatomic level of amputation. An increasing infection severity was associated to a significant trend toward increasing risk for experiencing other diabetic foot-related complications, such as neuropathy, vascular disease, and history of amputation. Foot infections can extend proximally into the leg through the tarsal tunnel, resulting in rapidly ascending limb- and life-threatening infections. Early surgical treatment of DFI may reduce the need for major amputations. An aggressive surgical approach against foot infection in diabetic patients may reduce the need for above-ankle amputation. Treatment of diabetic foot infection requires the combination of early surgical treatment and antimicrobial therapy. Many surgeons still advocate a transtibial amputation (TTA) as the primary surgical option for non-healing foot ulcerations. A bioabsorbable calcium sulphate antibiotic beads into the surgical wound can increase the effects of TMA for diabetic ulcerations of the forefoot. This method could have a significant impact on the management of diabetic forefoot ulcerations by preventing additional hospital stays for operative revisions, and thereby improving the patient's quality of life.

Adjunctive therapies include the use of antibiotic-impregnated beads, the application of negative-pressure wound therapy. Adjunctive HBOT has a positive effect on wound healing in diabetic foot with infection. Conservative treatment, including prolonged, culture-guided parenteral and oral antibiotics, is efficacious without amputation in a large percentage of diabetic patients admitted for a foot skin ulcer or suspected osteomyelitis[55].

Predictors of Treatment Failure in Diabetic Foot Infections

Clinical failure rates were 46% for patients with risk factors (elevated white blood cell count, C-reactive protein or erythrocyte sedimentation rate; high wound severity score; inpatient treatment; low serum albumin; male sex; and skin temperature of affected foot >10°C above that of unaffected foot) compared with 10% for patients with no risk factors and 16-17% for patients with one risk factor[56]. Increased WBC and severe UT wounds (grades 2 and 3) were significant independent risk factors for clinical failure in patients treated for DFI in the SIDESTEP study[46]. Clinical failure was noted in 23% of the patients with UT wounds 2B,D and 3B,D at baseline, which can be compared to 11% for 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 favourable response. CRP and ESR values greater than 9.1 and 54.4, respectively, were associated with treatment failure. A meta-analysis of data[57] from randomized controlled trials on DFIs showed a treatment failure rate of 22.7% in 18 studies. The isolation of MRSA was found to be a significant factor associated with treatment failure, although the presence or absence of OM did not affect the outcome. In a retrospective cohort study[46] of the outcomes of conservatively treated DFIs, fever, increased serum creatinine, prior hospitalization for DFI and gangrenous lesions were independent factors associated with treatment failure.

Conclusions

The prevalence of MRSA is high and the incorrect use of antibacterials, hospital environment, osteomyelitis, and nasal carriage of MRSA give to infection with MRSA. Understanding the pathophysiology and promptly identifying risk factors for DFI are essential. A thorough evaluation of DFI that utilises a multidisciplinary team is recommended to achieve optimal outcomes. It is important to classify accurately DFI in order to guide treatment regimens, facilitate consistent communication among health-care providers, and predict patient outcomes. The IDSA and UT classifications provide relatively simplistic and objective methods for classifying DFI. Prompt recognition and treatment of DFI are mandatory for ensuring maximal limb salvage.

Conflict of Interest
The authors have not received any funding or benefits from the industry to conduct this study.

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