Rev. Fac. Med. Hum. 2024; 24(2):139-155.
DOI: 10.25176/RFMH.v24i2.6518
REVIEW ARTICLES

ISSN Versión Online: 2308-0531
Facultad de Medicina Humana URP
RFMH

GLOBAL APPROACH TO THE PATIENT WITH DIABETIC FOOT: A REVIEW

ABORDAJE GLOBAL DEL PACIENTE CON PIE DIABÉTICO: UNA REVISIÓN

Jordi Viadé-Julià [1], John Longa-López [1,2], María Nicolás-Piera [3], Miquel Sabriá-Leal [1], Melcior Lladó-Vidal [1,5], Fernando José Muñoz-De La Calle [6], Xavier Madirolas-Alonso [1,4], Marc Sirvent-González [1,7], Clàudia Riera-Hernández [1,8], Cristian Carrasco-López [1,8], Ricard Pérez-Andrés [1,8], Alfonso Rodríguez-Baeza [1]

ABSTRACT

Introduction: The review article highlights the importance of the sole of the foot in ambulation and its adaptation to human needs. It focuses on diabetic foot (DF), defined by signs, symptoms, or ulcers on the foot due to chronic complications of diabetes. DF affects approximately 25 % of patients with diabetes mellitus (DM), with ulcers that can lead to severe infections and risk of amputation. Managing DF is complex and requires a multidisciplinary approach. This article proposes a "Diabetic Foot Evaluation and Treatment System," applicable in various clinical settings, which classifies ulcers according to their depth and infection and provides clear treatment guidelines. The epidemiology of diabetic neuropathy (DN) is also discussed, highlighting its high prevalence and morbidity, and the need for adequate diagnosis and treatment. The article provides a detailed analysis of Charcot neuropathy, a severe complication of DF, including its causes and diagnostic methods. Furthermore, the importance of a multidisciplinary approach in the treatment of DF ulcers is emphasized to reduce amputations and improve patients' quality of life. DF infections and antibiotic therapy are also addressed, recommending the use of appropriate antibiotics according to the severity of the infection and the performance of precise microbiological cultures. Finally, a comprehensive view of DF management is presented, highlighting the importance of a multidisciplinary approach and proposing an effective evaluation and treatment system that can be implemented in various clinical contexts.

Keywords: Diabetic Foot; Diabetes Mellitus; Infections. (Source: MeSH- NLM).

RESUMEN

Introducción: El artículo de revisión destaca la importancia de la planta del pie en la deambulación y su adaptación a las necesidades humanas. Se enfoca en el pie diabético (PD), definido por signos, síntomas o úlceras en el pie debido a complicaciones crónicas de la diabetes. El PD afecta a alrededor del 25% de los pacientes con diabetes mellitus (DM), con úlceras que pueden derivar en infecciones graves y riesgo de amputación. El manejo del PD es complejo y requiere un enfoque multidisciplinar. Este artículo propone un "Sistema de Evaluación y Tratamiento del Pie Diabético", aplicable en diversos entornos clínicos, que clasifica las úlceras según su profundidad e infección y ofrece guías claras para su tratamiento. Se discuten también la epidemiología de la neuropatía diabética (ND), destacando su alta prevalencia y morbilidad, y la necesidad de un diagnóstico y tratamiento adecuados. Se analiza en detalle la neuropatía de Charcot, una complicación severa del PD, incluyendo sus causas y métodos diagnósticos. Además, se enfatiza la importancia del enfoque multidisciplinar en el tratamiento de las úlceras del PD para reducir amputaciones y mejorar la calidad de vida de los pacientes. También se abordan las infecciones del PD y la antibioticoterapia, recomendando el uso de antibióticos adecuados según la gravedad de la infección y la realización de cultivos microbiológicos precisos. Finalmente, se presenta una visión global del manejo del PD, destacando la importancia de un enfoque multidisciplinar y proponiendo un sistema de evaluación y tratamiento eficaz que puede ser implementado en diversos contextos clínicos.

Palabras clave: Pie Diabético; Diabetes Mellitus; Infecciones. (Fuente: DeCS-BIREME)

[1] Universidad Autónoma de Barcelona. Barcelona, Spain.
[2] Instituto de Investigación en Ciencias Biomédicas, Universidad Ricardo Palma. Lima, Peru.
[3] Hospital Universitario Mútua de Terrassa. Barcelona, Spain.
[4] Parc Hospitalari Martí Julià. Girona, Spain.
[5] Hospital Universitario Son Espases. Palma de Mallorca, Spain.
[6] Hospital General de Medellín. Medellín, Colombia.
[7] Hospital General de Granollers. Barcelona, Spain.
[8] Hospital Universitario Germans Trias i Pujol. Badalona, Spain.

Cite as: Viadé-Julià J, Longa-López J, Nicolás-Piera M, Sabriá-Leal M, Lladó-Vidal M, Muñoz-De La Calle FJ, Madirolas-Alonso X, Sirvent-González M, Riera-Hernández C, Carrasco-LópezC, Pérez-Andrés R, Rodríguez-Baeza A. Global approach to the patient with diabetic foot: A review. Rev Fac Med Hum. 2024;24(2):139-155. doi 10.25176/RFMH.v24i2.6518

Journal home page: http://revistas.urp.edu.pe/index.php/RFMH

REVIEW ARTICLE

INTRODUCTION

The foot, specifically the sole, is the body region that contacts the ground in both standing and walking due to our bipedal posture. A significant aspect of ambulation is largely the cultural evolution of our species. This important function allows us different modes of movement such as walking, running, and practicing sports, among others. For this, we have a series of proprioceptive and nociceptive receptors. These receptors allow us to interact with the ground and maintain balance in various modes of ambulation through what is known as Hilton's Law[1].

There are evident homologies in the embryonic development [2] of the autopod observed around the sixth post-fertilization week of the hand and foot (hand and foot plates) and in the general anatomical organization of both structures (similarities between skeletal elements, intrinsic and extrinsic muscles, vessels, and nerves). However, the different functions determine the morphological adaptations observed in each.

Diabetic foot

Diabetic Foot (DF) is understood as the "presence of signs, symptoms, or ulcers on the foot as a consequence of chronic diabetes complications" [3]. DF is one of the most prevalent complications in patients with diabetes mellitus (DM) [4]. In patients with DM, the risk of developing a foot ulcer can reach up to 25% [5]. When a patient with DM develops an ulcer, several factors converge, such as changes in pressure points, deformities, or the use of inappropriate footwear, in addition to the total or partial loss of protective capacity (sensitivity), combined with underlying vegetative and vascular disorders. Consequently, the epidermal layer breaks down, and a lesion appears that can progress to deeper parts and reach the bone [3,5], endangering the limb and even the patient's life.

Managing foot lesions is usually complex and requires coordinated participation from different professionals. Studies have shown that a multidisciplinary approach is the most effective way to treat these patients and reduce the number of amputations [6-8]. Therefore, we propose our "Diabetic Foot Evaluation and Treatment System" to facilitate this approach[9].

This review aims to provide a comprehensive overview of DF management, highlighting the importance of a multidisciplinary approach and presenting an easy-to-use evaluation and treatment system applicable in any work setting, from primary care to hospitals or emergency services. Additionally, limitations and possible biases in the reviewed studies are discussed to provide a more balanced and critical view of the literature.

Epidemiology of diabetic neuropathy

The prevalence of diabetic neuropathy (DN) varies according to the series consulted, depending on the diagnostic methodology, criteria used, and disease duration in the studied population, making it difficult to compare prevalence rates across different regions. In this context, Pirart J. evaluated 4,400 patients with diabetes mellitus (DM) over 25 years of follow-up[10-13]. In this study, neuropathy was defined as a decrease in foot sensitivity and a decrease or absence of the Achilles reflex. The onset of neuropathy positively correlated with the duration of DM, and at 25 years, 50% of patients had developed neuropathy.

In Spain, Mundet et al. evaluated the prevalence and incidence of macro and microvascular complications over ten years of follow-up in a prospective population-based study that included 317 patients with type 2 DM, finding a DN prevalence of 26.8% [19.3-30.2] at the end of the study[14]. In Latin America and the Caribbean, a systematic review and meta-analysis of 29 studies from eight countries in the region reported an estimated DN prevalence of 46.5% (95% CI: 38.0-55.0) with significant heterogeneity (I^2 = 98.2%; $p < 0.01$), finding an increasing trend in cumulative DN prevalence over time. In this same study, four investigations in Peru with a sample size of 874 patients reported a DN prevalence of 52%[15].

However, it is important to note that up to 50% of patients with DN may be asymptomatic, increasing the gap of underdiagnosis of this complication. According to Longa J. in his study "Attitudes of Physicians Towards

the Management of Diabetic Neuropathy in Public and Private Health Facilities, 2023", of 143 physicians surveyed, 80.5% reported relying only on symptoms and signs referred by the patient to diagnose DN[16].

The high rate of DN produces substantial morbidity, including disability generated by painful neuropathic symptoms and the underlying neurological deficit, which have a significant impact on these patients' quality of life and result in manifestations such as ataxia, weakness, falls, fractures, lacerations, cranial trauma, recurrent lower limb infections, ulcerations, and subsequent amputations. Patients diagnosed with diabetic foot (DF) occupy more hospital beds than those with other diabetic complications[17]. The cumulative risk of lower limb amputation in one study was 11% 25 years after the DM diagnosis[18].

Risk factors for DN studied vary according to the strength of association. Those with a very strong association include diabetes duration, hyperglycemia, and age. Those with a strong association include prediabetes, height, hypertension, obesity, metabolic syndrome, oxidative stress, vitamin D deficiency, genetic factors, subclinical inflammation, and low physical activity. Those with a moderate association include glycemic variability, dyslipidemia, smoking, insulin resistance, alcohol consumption, hypoinsulinemia, platelet activation, and growth factor depletion [19].

Diagnosis of diabetic neuropathy

Screening for diabetic neuropathy (DN) should be performed in patients with type 2 diabetes mellitus (DM2) at the time of diagnosis. In patients with type 1 diabetes mellitus (DM1), screening should be performed five years after diagnosis. Additionally, prediabetic patients should be included in this screening if they present neuropathic symptoms. If the initial examination is negative, it should be repeated annually[20]. The diagnosis of DN is based on three fundamental pillars: evaluation of symptoms, signs, and, in some cases, the performance of neurophysiological and/or morphometric tests. Symptoms can be classified as positive or negative, depending on whether there is a gain or loss of function, resulting from the maladaptive response to somatosensory nervous system damage or pathology. The first group of symptoms (positive) includes paresthesias, spontaneous pain (burning, searing, stabbing, etc.), or evoked pain (hyperalgesia or allodynia). The second group (negative) can include sensory deficits such as hypoesthesia, anesthesia, hypoalgesia, or analgesia. These clinical manifestations can coexist or alternate throughout the natural history of DN.

Systematic evaluation of symptoms can be conducted through validated questionnaires, such as the Michigan Neuropathy Screening Instrument (MNSI), the Utah Early Neuropathy Scale (UENS), the United Kingdom Screening Test, and the Total Symptom Score (TSS). From a pathophysiological perspective, the involvement of thin nerve fibers (C or Aδ), characterized by being unmyelinated or finely myelinated, clinically manifests as burning pain, electric shocks, or stabbing pain. Autonomic symptoms can also occur since these fibers are responsible for thermoalgesic sensitivity and autonomic function.

As for the thick fibers (Aα or Aα/β), their involvement can cause numbness-type pain, a feeling of walking on cotton, difficulty performing fine tasks like turning book pages or buttoning a shirt, and balance or musculoskeletal trophism alterations, occasionally leading to an inability to stand on the tip of the toes or heels. These myelinated fibers control muscle function and tactile, vibratory, and proprioceptive sensitivity. In physical examination, signs such as dry skin, fissures, plantar hyperkeratosis, ulcers, overlapping or rigid toes, hammer or claw toes, deformities, bony prominences, Charcot neuroarthropathy, and atrophy of the interosseous muscles may be found. Clinical evaluation of the different types of nerve fibers depends on the availability of instrumental resources, and for this purpose, the Semmes-Weinstein 10 g monofilament, the 128 Hz tuning fork, and the reflex hammer can be used to assess thick fibers, while the thermal bar and pinprick are used to assess thin fibers. It is important to note that none of these tests alone achieve the

sensitivity and specificity needed for DN diagnosis, so combining two or more of them is necessary to confirm the diagnosis. Additionally, there is no standardization of the evaluation methodology, which can hinder early neuropathy detection [21].

Neurophysiological and/or morphometric tests are important tools but are limited in use due to their complexity and limited availability in routine medical practice. For thick fiber evaluation, nerve conduction velocity (NCV) studies for Aβ fibers and the DPNCheck, which evaluates Aβ fibers of the sural nerve with good sensitivity (92-95%) compared to NCV, are used. For thin fiber evaluation, skin biopsy can be used to assess C fibers by quantifying intraepidermal nerve fiber density (IENFD), considered the gold standard for this evaluation and capable of detecting early changes. Corneal confocal microscopy (CCM) also allows for evaluating Aδ and C fibers, being a non-invasive, reproducible, fast, and objective method.

Autonomic tests like the Neuropad, Sudoscan, and QSART are useful for assessing C fibers responsible for autonomic functions, including sudomotor functions. While these tools have different sensitivities and specificities, they are useful for this purpose. Quantitative sensory testing (QST) methods allow for the evaluation of both thin (Aδ and C) and thick (Aβ) fibers with good reproducibility [21].

Charcot neuropathy

Charcot neuroarthropathy has a multifactorial etiology, with two main theories proposed to explain its development: the neurotraumatic and neurovascular theories. The neurotraumatic theory suggests that poor pain perception in diabetic patients causes repetitive traumas to go undetected, resulting in multiple fractures and collapse of the foot's bone structure. On the other hand, the neurovascular theory postulates that bone destruction is due to a hypervascular state caused by sympathetic nerve alteration, leading to loss of vasomotor control. This condition causes bone mineral leaching, resulting in osteopenia or osteoporosis, making the tissue more susceptible to low-magnitude fractures. The inflammatory process is localized and persistent, without systemic repercussions, characterized by increased vascular flow and elevated levels of pro-inflammatory cytokines. This disrupts the RANKL (receptor activator of nuclear factor kappa B ligand) system, increasing the number and activity of osteoclasts, thus enhancing bone resorption. Molecules like calcitonin gene-related peptide, which normally stabilize the capsuloligamentous extracellular matrix, are released less in the context of diabetic foot, promoting an environment of biomechanical instability and generating pressure zones [22]. Additionally, healing is compromised due to reduced macrophage activity and angiogenesis, increasing infection risk due to a diminished immune response[23].

The diagnosis of Charcot neuroarthropathy is primarily clinical. Semiological signs include inflammation (phlogosis) and edema. It is crucial to investigate neuropathic changes in the anamnesis and objectively assess temperature differences greater than 2°C compared to the contralateral limb. In advanced stages, inflammatory signs become less noticeable, with bone prominences and foot deformities predominating, especially in the hindfoot, which may include claw toes and dry skin (xerotic) due to loss of moisture [24,25].

Laboratory tests such as bone-specific alkaline phosphatase and type 1 collagen carboxy-terminal telopeptide levels are useful for quantifying bone resorption in acute phases and decrease as chronicity sets in. Acute phase reactants, such as erythrocyte sedimentation rates below 70 mm/h, indicate a more neuroarthropathic than infectious process. Load-bearing radiographs (posteroanterior and lateral) with oblique views allow for observing deformities and classifying the disease according to the Eichenholtz classification[26]. It is important to evaluate deformities in the sagittal plane, considering inclinations at the Chopart level and the pitch of the calcaneal and fifth metatarsal angles.

Table 1. Eichenholtz Classification.

Stage	Description
Stage 0	Absence of osteoarticular injury. We find signs of phlogosis (inflammation, erythema, edema and temperature changes.
Stage 1	Acute phase: inflammation. Subtle dislocations, changes in calcaneal inclination with concomitant alteration of the talus-first metatarsal angle. Bone fragmentation and significant soft tissue edema are observed.
Stage 2	Coalescence phase (subacute): Reduction in inflammation, especially in temperature. Remodeling and reparative processes can be observed.
Stage 3	Consolidation phase (chronic): Complete resolution of inflammation, consolidation of fractures, and ossification, in many cases heterotopic.

Taken from Hastings et al.[26]

In the acute phase, magnetic resonance imaging (MRI) can reveal subchondral bone marrow edema and microfractures, facilitating the monitoring of the clinical process. Positron emission tomography/computed tomography (PET/CT) shows increased metabolism in the affected regions, allowing for a more sensitive evaluation. Differentiating Charcot arthropathy from an infectious or inflammatory process can be challenging, as they may coexist. Therefore, we propose an algorithm that is part of the diagnosis, evaluation, and treatment system (Figure 1).

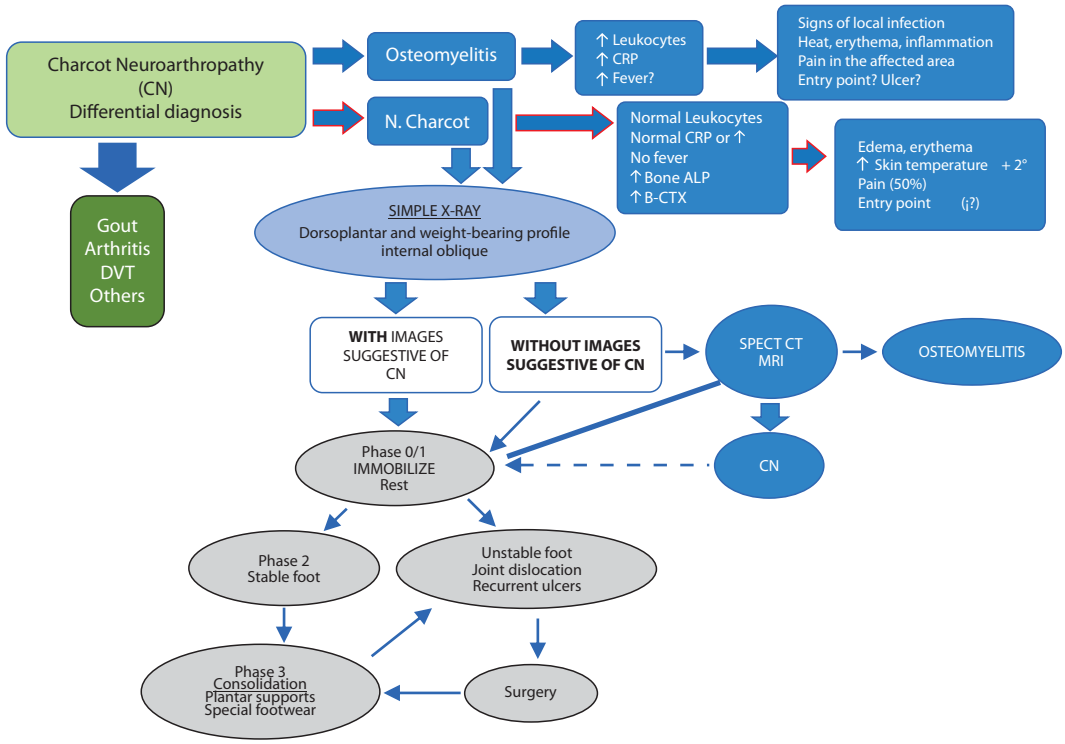

Figure 1. Diagnostic Algorithm for Charcot Neuroarthropathy .

It is recommended to use conservative treatment whenever possible. Offloading is essential and can be achieved through initial total contact casting for six to eight weeks, with changes every two weeks, until the inflammatory state is reduced, allowing for the use of adapted orthopedic footwear. This process generally takes a minimum of six months. Except for the management of metabolic and comorbid conditions in DM patients, there is no evidence of the effectiveness of specific medications for the treatment of Charcot arthropathy [27].

The goal of treatment is to achieve a plantigrade foot with an even distribution of plantar pressures. Maintaining this position can heal up to 50% of neuropathic ulcers without the need for surgical interventions, allowing the patient to return to a functional level similar to the previous one, prevent ulcerations, and reduce long-term medical costs. Chronic deformities are a significant challenge to correct due to the morphological alteration and the generation of prominent ulcers. A holistic evaluation of the patient is essential, including infection history, previous cultures, treatments, and imaging studies to determine the involved joints. The appropriate fixation material should be planned, and proper cultures taken to use antimicrobials based on the results[3,27]. Interventions may include external fixators, screw and plate fixations, exostectomies, myotendinous transfers, and lengthenings, which can be transitional until achieving a definitive construct [28].

Peripheral arteriopathy

Macrovascular disease in patients with diabetes mellitus (DM) is characterized by being a diffuse atheromatous process, affecting not only the arteries of the lower extremities but also the coronary and carotid arteries. The involvement of the arterial territory in peripheral arterial disease (PAD) varies according to the presence of DM. In patients without DM, it preferably affects the aortoiliac and femoropopliteal territory. In contrast, PAD in patients with DM is characterized by more frequent involvement of the tibial and inframalleolar arteries, specifically affecting the infragenicular territory and the area below the ankle. DM is the most common cause of non-traumatic lower limb amputation. Seventy-five percent of lower limb amputations in our setting are performed on patients with DM [29]. In fact, amputation is 15 to 40 times more frequent in patients with DM than in those without this condition[30].

Approximately 85% of amputations in patients with DM are preceded by a foot ulcer. Between 7% and 20% of patients with DM who develop a foot ulcer will eventually require a more or less extensive limb amputation [31]. Additionally, patients with DM have twice the risk of a second amputation if they have a history of a previous amputation compared to patients without DM. Major amputations are associated with increased mortality in patients with DM. Short-term mortality is approximately 10%, increasing to 30% at one year, 50% at three years, and 70% at five years [32]. Regarding the prevalence of PAD in patients with diabetic foot (DF), current data shows it is present in approximately half of the patients.

The presence of PAD in a patient with DF increases the risk of ulcer infection and complicates its healing[33]. This phenomenon is partly due to the difficulty in the delivery of nutrients and oxygen to the tissue, as well as poor penetration of the antibiotic into the infected tissue. Regarding the costs associated with the care of these patients, it should be noted that the presence of an infected ulcer in a patient with PAD multiplies the costs fourfold compared to patients with a foot ulcer without PAD or infection. This increase is mainly due to hospitalization expenses, the use of antibiotics, amputations, and other surgical procedures[34].

Finally, it is important to mention that the treatment of DF ischemia is still suboptimal, according to the data described in the Eurodiale study. This study, which involved fourteen hospital centers, aimed to analyze the characteristics of 1,229 patients with DM who had a foot ulcer. Only 40% of patients with severe ischemia underwent angiography, and only 43% with critical ischemia underwent a revascularization procedure[34].

Comprehensive management of diabetic patients with foot ulcers

The management of ulcers in diabetic patients is complex due to the need for intervention from multiple professionals. This complexity lies in the coordinated execution of the proposed treatment. To facilitate this multidisciplinary approach, we propose using the "Diabetic Foot Evaluation and Treatment System," published in November 2023 in the journal Foot and Ankle Research. This system (Table 2) consists of a main table that evaluates two fixed variables: the presence of infection and the depth of the ulcer, classifying them into five grades (from 0 to 4). Grade 0 excludes Charcot foot or underlying infections without the presence of an ulcer; grade 1 encompasses superficial ulcers (epidermis/dermis) without sign s of infection; grade 2

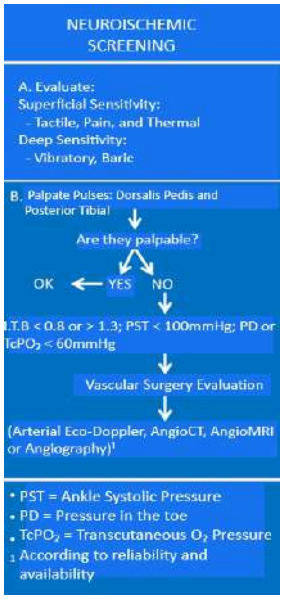

Figure 2. Neuroischemic Screening Algorithm.

includes ulcers that reach the subcutaneous tissue with signs of superficial infection; grade 3 comprises deep ulcers that reach the subcutaneous tissue or bone, with signs of deep but localized infection; and grade 4 considers deep ulcers as in grade 3, but also presents critical ischemia, areas of necrosis, and/or systemic involvement. When an ulcer is ischemic in nature, it is considered and treated as an additional grade due to the significantly worsened prognosis. Additionally, the system includes nine supplementary tables or algorithms that address different aspects of DF management: diagnosis of Charcot neuroarthropathy (Figure 1), neuroischemic screening (Figure 2), diagnosis of osteomyelitis (Figure 3), obtaining samples for microbiological culture (Figure 4), microorganisms to consider (Figure 5), oral antibiotics (Figure 6), topical treatment (Figure 7), offloading systems (Figure 8), and surgical techniques (Figure 9). Each of these algorithms provides guidelines for the required examination, differential diagnosis, and the most appropriate treatment for each situation. The implementation of this system allows for a more structured and effective management of ulcers in diabetic patients, optimizing collaboration among the various specialists involved.

Table 2. Proposed evaluation and treatment system.

Evaluation and Treatment System for Diabetic Foot					
Ulcer Grade	**0**	**1**	**2**	**3**	**4**
CHARACTERISTICS **Depth** **Infection?**	NO ULCER Hot foot, edema, erythema. DISMISS	EPIDERMIS/DERMIS SIGNS OF ISCHEMIA** No	GI+ SUBCUTANEOUS TISSUE SIGNS OF ISCHEMIA** Superficial	GII+ FASCIA/MUSCLE/BONE SIGNS OF ISCHEMIA** Deep/localized	GIII ISCHEMIA? YES/NO NECROTIC AREAS Systemic involvement Deep/localized
Evaluation	Screening/ Thermometry Neuroarthropathy? Nuclear Medicine?	Neuroischemic screening	Neuroischemic screening Microbiological culture Discard osteomyelitis	Neuroischemic screening Microbiological culture Discard osteomyelitis	Neuroischemic screening Microbiological culture Discard osteomyelitis
Treatment	If suspected of Charcot neuroarthropathy: immobilize: boot or synthetic cast Surgery?	Offloading Topical treatment	Offloading Topical treatment Oral antibiotics	Debridement, surgery Oral/IV antibiotics Topical treatment Offloading Relative rest	Debridement and/or revascularization IV antibiotics Topical treatment Absolute rest
Care level **Patient education**	Primary care/ UPD/ Hospital Review	Primary care Review	Primary care/ UPD Review	UPD/ Hospital Review	Hospital/UPD
****SIGNS OF ISCHEMIA**: Consider as an additional grade**					

Infections and antibiotic therapy in diabetic foot

Infection in diabetic patients can be a serious complication. Although most infections are superficial, up to 25% can extend to deeper tissues, even affecting the bone. It is important to remember that an infected foot ulcer precedes 60% of amputations [35]. Antibiotic treatment of infections in the diabetic foot requires a deep understanding of the lesion's pathogenesis, with explicit mention of the biofilm and the microorganisms involved. This is essential for selecting the appropriate antibiotic based on the microorganism's sensitivity and various pharmacokinetic characteristics. Bone infection, or osteomyelitis, is a common complication of diabetic foot ulcers. To rule out contiguous infection, the bone contact test is performed. Any exposed bone at the base of an ulcer, whether visible or that can be contacted by inserting a sterile blunt-tipped probe, has a high probability of being infected, with a specificity of 83% and a sensitivity of 87% [36]. The following algorithm (Figure 3) assists in the correct interpretation of the bone contact test and the precise diagnosis of osteomyelitis.

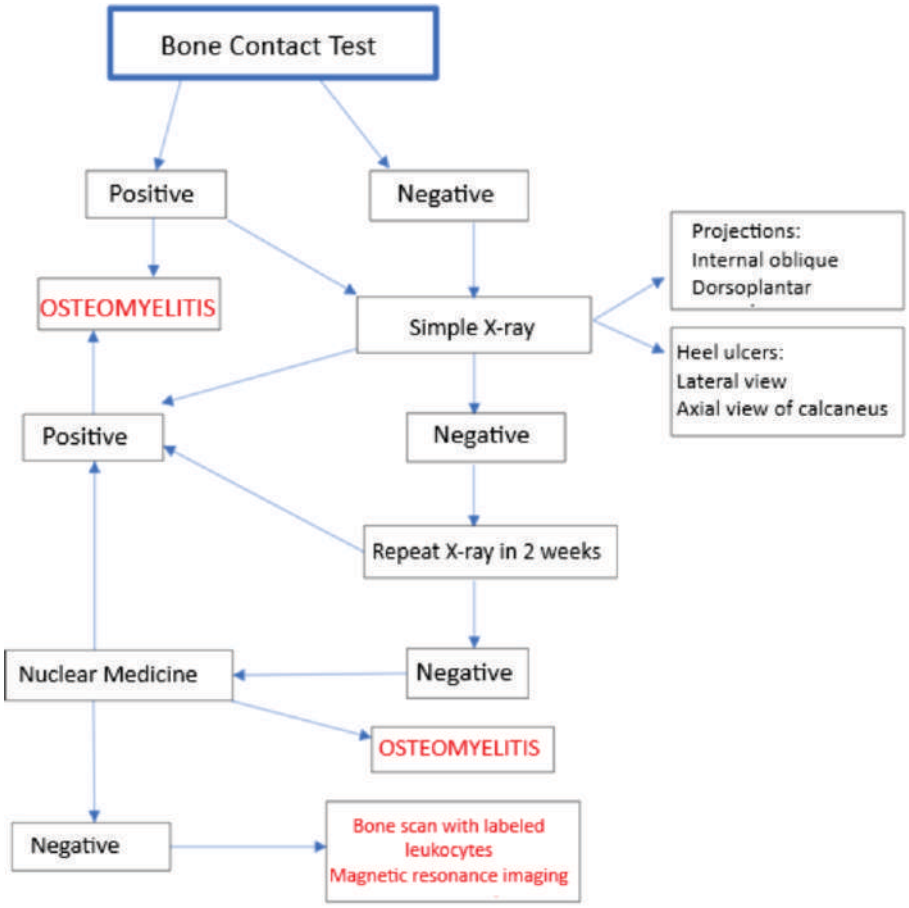

Figure 3. Bone Contact Test for Osteomyelitis Diagnosis.

Biofilm and microbiological culture

The presence of biofilm in diabetic foot ulcers complicates antibiotic therapy. The biofilm, a biofilm generated by the interaction of cells covering the ulcer and physicochemical and bacterial factors, hinders the penetration and activity of antibiotics, as well as the isolation of the microorganisms responsible for the infection.

This latter issue, with poorly collected samples, makes it difficult to differentiate between contamination and infection [37]. To etiologically identify the responsible microorganism, it is mandatory to clean and debride the wound before obtaining the sample. This can be obtained by scraping the ulcer with a scalpel, curettage, or surface biopsy. Aspiration of purulent secretions with a sterile needle and syringe can also

be useful. All samples should be promptly placed in a sterile container or appropriate medium and sent to the laboratory for Gram staining and aerobic and anaerobic culture[38].

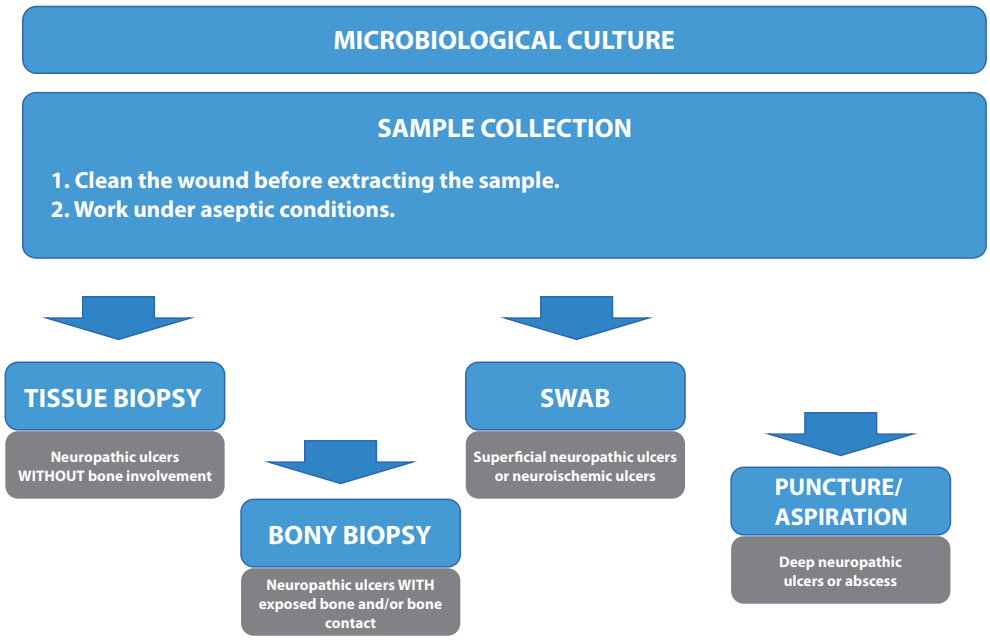

Figure 4. Procedure for obtaining samples for microbiological culture.

On the contrary, non-infected ulcers should not be cultured, nor should samples be obtained without prior cleaning or debridement, or by swabbing the wound or purulent secretions. Table 3 presents the microorganisms responsible for diabetic foot infection according to various series[35,39-41].

Table 3. Microorganisms responsible for infection.

GRAM POSITIVE	
S aureus	72 (30)
S. coagulasa negativos	4 (1.7)
Enterococcus spp	8 (3.3)
Streptococcus pyogenes	4 (1.7)
GRAM NEGATIVE	
E coli	24 (10)
Klebsiella pneumoniae	22 (9.2)
Enterobacter spp	22 (9.2)
Proteus spp	
Pseudomonas aeruginosa	28 (11.7)
Acinetobacter spp	12 (5.2)
S. maltophilia	2 (0.8)
ANAEROBES	21 (2)
OTHERS	(>5.2)

Adapted from the references[35,39-41].

However, depending on the characteristics of the wound, certain microorganisms must be particularly taken into account (Table 4).

Table 4. Wound characteristics and responsible microorganisms.

Type of wound	Microorganisms responsible for infection
Cellulitis or open skin wound	S. aureus / β-hemolytic Streptococcus
Infected ulcer (NO previous antibiotics)	S. aureus / β-hemolytic Streptococcus
Chronically infected ulcer (previous antibiotics)	S. aureus / β-hemolytic Streptococcus / Enterobacteriaceae
Macerated ulcer	Pseudomonas aeruginosa
Long-standing ulcers with previous antibiotics	Aerobic Gram-positive cocci, Enterobacteriaceae, Pseudomonas spp, and other non-fermenting Gram-negative bacilli
Foul-smelling, extensive necrosis, or gangrene	Polymicrobial flora: Gram-positive cocci, Enterobacteriaceae, non-fermenting Gram-negative bacilli, anaerobes

Adapted from the references [35,39-41].

Depending on the severity of the ulcer, according to the criteria of our classification system, the microorganisms indicated in FIgure 5 should be considered.

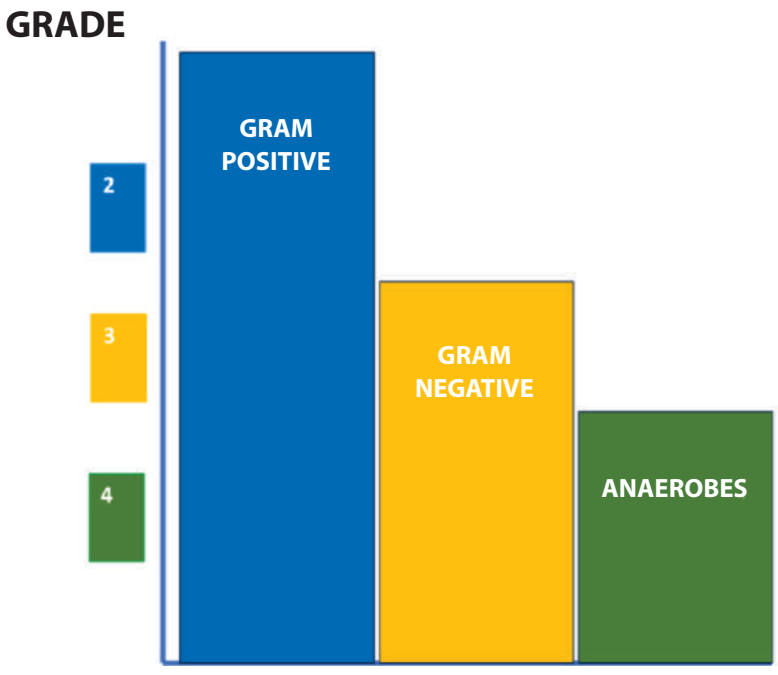

Figure 5. Microorganisms to consider according to ulcer severity.

As shown in Figure 5, Gram-positive cocci are usually present in all stages of severity, so it will always be necessary to cover them with appropriate antibiotics. Anaerobes, on the other hand, are observed in severe ulcers and always associated with other microorganisms. In these cases, broad-spectrum antibiotic treatment is required, also considering the possibility of multi-resistant enterobacteria producing extended-spectrum beta-lactamases.

Antibiotic therapy

Before administering antibiotics, it is crucial to consider several characteristics inherent to the microorganism and the pharmacokinetics of the antibiotic. This includes the sensitivity of the microorganism to the tested antibiotics according to the antibiogram, the bioavailability of the antibiotic when administered orally, and its volume of distribution[42]. Oral bioavailability is a fundamental characteristic for selecting effective antibiotics via this route. Some antibiotics, such as fluoroquinolones, have a bioavailability close to 100%, while amoxicillin does not reach 70%. Both are useful in diabetic foot, but doses must be adjusted appropriately [43].

The volume of distribution is also important, as some antibiotics are preferentially distributed in the vascular compartment, reaching the interstitium and the cellular compartment in low concentrations. In diabetic foot, antibiotics with a high volume of distribution are preferred to ensure they adequately reach the site of infection[44]. Table 6 presents a scheme detailing the use and considerations of oral antibiotics in the treatment of infections in diabetic foot. The figure is divided into several sections addressing critical aspects of antibiotic therapy, such as antibiotic selection, oral bioavailability, and volume of distribution.

Table 6. Oral antibiotic therapy for diabetic foot infections.

Antibiotic	Microorganisms	Dose (mg)	Dose interval (hours)	Bioavai-lability (%)	Distribution (L/kg)	Renal elimination	Side effects
Amoxicillin	GP/GN	500-1000	8	60	0.2	No	Gastrointestinal
Amox-Clavulanic	GP/GN/AN	875	8	60	0.2	No	Gastrointestinal
Levofloxacin	GP/GN	750	24>90		1.5	Yes	Tendinopathy, Qt, CNS
Moxifloxacin	GP/GN	400	24>90		2.0	No	Qt, CNS
Clindamycin	GP/AN	300-450	8>90		1.1	No	Gastrointestinal, CD
Cotrimoxazole	GP/GN	160-800	12>90		1.8	Yes	Nephrotoxicity, AL
Linezolid	GP	600	12	100	0.7	No	Hematological
Doxycycline	GP	100	12>90		0.7	Yes	Gastrointestinal
Metronidazole	AN	500	8>90		0.8	No	Gastrointestinal, CNS
Rifampicin	GP	600	24>90		1.6	No	Hepatotoxicity

GP: Gram positive. GN: Gram negative. AN: Anaerobes. Qt: QT Interval prolongation.
CNS: Central Nervous System. CD: Clostridioides difficile-associated diarrhea. AL: Allergic reactions.
H: Hepatotoxicity. HE: Hematological effects.
Taken from references [42–44]

Duration of antibiotic treatment

The duration of antibiotic treatment varies according to the severity of the infection. Most ulcers will be sterilized with one to two weeks of oral treatment. In more complicated cases, treatment can start with intravenous antibiotics followed by oral antibiotics to complete two weeks. Suspected osteomyelitis requires treatments of three to four weeks, and after debridement, if viable bone remains, the treatment should continue for approximately three months. In any case, the clinical evolution will determine the exact duration of the antibiotic treatment [31,42].

Topical treatment

In recent years, new technologies and products have been developed to accelerate the healing of foot ulcers in patients with diabetes.

Currently, there is a wide range of products and devices for topical treatment. The choice of the appropriate product depends on several factors, including the depth and extent of the ulcer, the presence of infection and/or necrotic tissue, and the degree of exudation [45]. It is important to consider that the disease itself can slow down the healing process due to the presence of vasculopathy, neuropathy, humoral immunodeficiency factors, smoking, among others [3].

In ulcers located on the plantar surface of the foot, where the stratum corneum is thicker, the use of adhesive dressings is not recommended to avoid maceration. If the degree of exudation is significant or a graft is required, negative pressure therapy may be an effective therapeutic option [46]. Figure 7 provides guidance on topical treatment based on the grade of the ulcer.

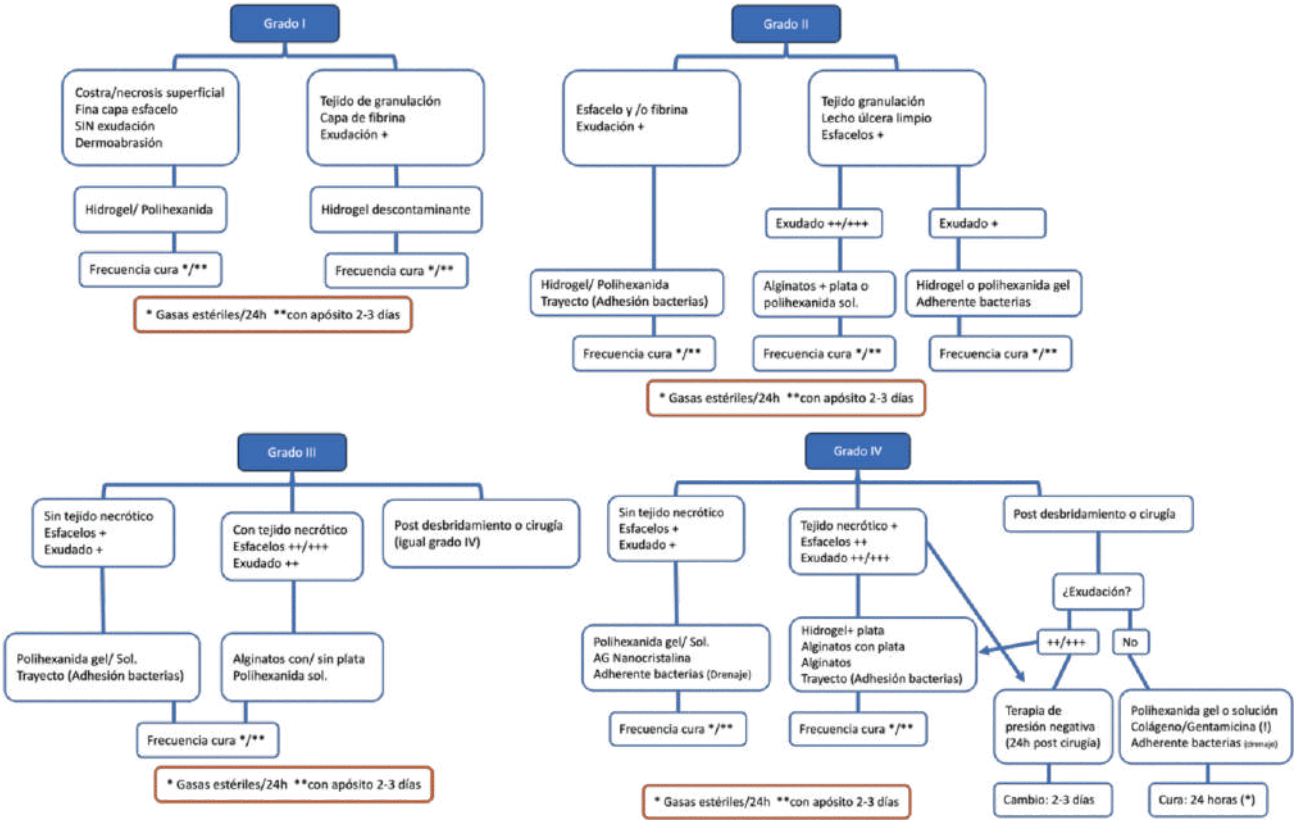

Figure 7. Guidance on topical treatment of ulcers according to grade.

Offloading systems

Offloading is essential for the prevention or treatment of pressure areas or active ulcers. Various materials and systems are available for this purpose, requiring knowledge in biomechanics and skills for proper fabrication and application. The general objective of offloading, whether provisional (adhesive felt, plastic cast, functional orthosis) or definitive (plantar support, silicone orthosis, special footwear), is to evenly distribute the forces and pressures acting on the foot, protecting healthy areas and isolating ulcerated or susceptible areas [3]. Structural alterations of the foot, along with high plantar pressure, are major factors influencing the formation of plantar ulcers in diabetic patients[47]. For the fabrication of provisional offloading systems, adhesive felt and polyurethane bandages are preferably used. The functional orthosis (Walker) can be used in combination with adhesive felt for offloading or to control edema and prevent deformities in patients with Charcot neuroarthropathy in phase 0-1 or suspected[48].

The use of plantar supports is indicated when the ulcer is healed or as a prevention for areas of high pressure that, if not corrected, could become ulcers, as well as to prevent recurrences [3,49]. Figure 8 presents a detailed scheme of the different offloading systems used in the management of diabetic foot ulcers. These systems are crucial for reducing pressure on the affected areas and promoting healing.

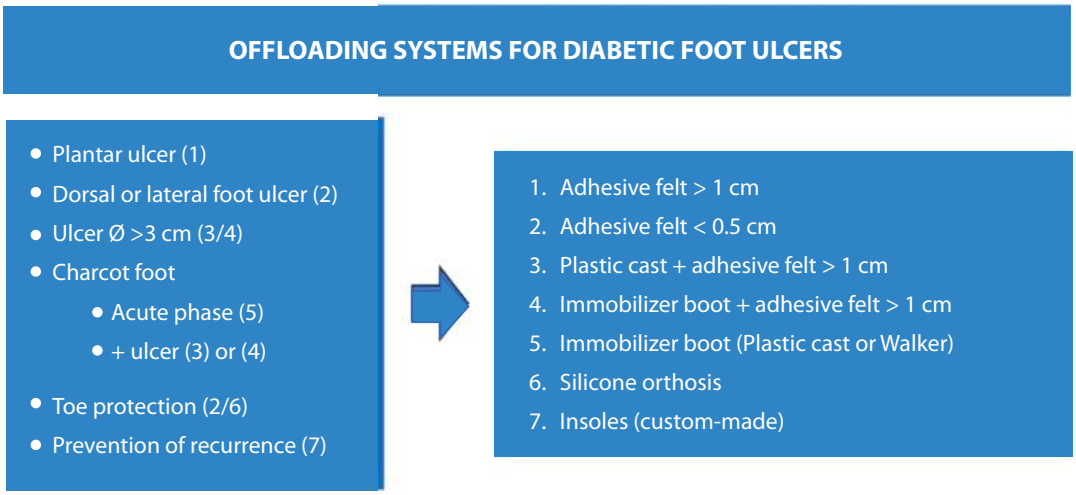

Figure 8. Offloading system for diabetic foot ulcers.

Surgical treatment

Surgery is often necessary in diabetic patients to address a variety of issues such as ulcers, infections, and severe deformities. Various surgical techniques are used to correct deformities, eliminate areas of high pressure, improve foot support, heal or prevent ulcers, revascularize the limb, or perform some type of amputation[50]. (Figure 9).

<table>
<tr>
<td colspan="2">MINIMALLY INVASIVE SURGERY
Osteotomies
• Oblique of the head and neck of the central metatarsals
• Base of the first metatarsal
• Base of the proximal phalanx of the 1st toe
Soft tissues
• Achilles tendon lengthening
• Partial gastrocnemius section
• Tenotomies (digital)</td>
<td>CHARCOT FOOT
• Arthrodesis
• Bone resections
• Internal/external fixators

REVASCULARIZATION
• Endovascular
• Open
• Hybrid</td>
</tr>
<tr>
<td>CONVENTIONAL SURGERY
• Ostectomy / Curettage / Drainage
• Septic arthritis
○ Interphalangeal
○ Metatarsophalangeal
○ Others</td>
<td>RECONSTRUCTIVE SURGERY
• Grafts
• Flaps</td>
<td>AMPUTATIONS
• Major
○ Supracondylar
○ Infracondylar
• Minor
○ Toes
○ Transmetatarsal
○ Syme</td>
</tr>
</table>

Figure 9. Surgical techniques for the treatment of diabetic foot.

The fundamental principle of surgical interventions in diabetic foot is osteotomies. These interventions allow for the correction of bone deformities that can contribute to ulcer formation. Surgery in these cases involves cutting and repositioning bones to relieve pressure and improve load distribution on the foot [51]. Osteotomies are especially indicated in neuropathic ulcers without underlying osteomyelitis that do not respond to conventional treatment.

Among the most common osteotomies are: the base osteotomy of the first metatarsal [52], indicated in cases of hyperpressure on the head of the first metatarsal caused by cavus feet, adducted feet, posterior leg compartment muscle shortening, or biomechanical alterations; the base osteotomy of the proximal phalanx of the first toe[3], indicated for treating ulcers located on the plantar area of the first toe's interphalangeal joint; and the distal oblique osteotomy of the lesser metatarsals (second to fifth) [53], indicated for ulcers located in the plantar metatarsal area without the presence of osteomyelitis. The decision on the number and type of osteotomies is based on clinical and radiological criteria, considering the morphology of the metatarsal formula and the ulcer location, with the Leventen formula recommended to guide these interventions [3].

Surgical techniques

When an infected foot is found, the most common surgical techniques initially include surgical debridement, which consists of removing dead or infected tissue around an ulcer. This procedure not only cleans the wound and promotes healing but also allows for sample collection for study and microbiological culture. Debridement may need to be repeated as necessary[3,50,54].

Once debridement is performed, various surgical techniques can be carried out depending on the specific problem. Partial or complete exostectomies allow for skin closure and prevent ulcer recurrence[3,55]. In cases of joint instability or major deformities, arthrodesis, which involves the fusion of a joint, is performed. By fusing a joint, its natural mobility is eliminated, thereby reducing the risk of new ulcer

formation. Arthrodesis can be performed using internal fixation with plates and screws or external fixation [56], known as osteotaxis. Due to the biological complexity of diabetic patients, arthrodesis is not always effective and may result in fibrous arthroplasty. Although not the ideal scenario, fibrous arthroplasty provides relative stability compatible with ambulation and a plantigrade foot [57]. To avoid this scenario, current trends favor performing arthrodesis and osteosynthesis with "superconstruct" techniques, which use a greater amount of osteosynthesis material and screws to ensure more robust and durable fixation[58].

Revascularization techniques and indications

In situations where the results of other interventions are unsatisfactory and the evolution is unfavorable, compromising the limb or the patient's life [59], amputations are resorted to. In severe cases, where ulcers or infections are extensive and unresponsive to other treatments, amputation may be the only option to prevent infection spread and save the patient's life. Additionally, in cases where the arterial system is obstructed, revascularization of the diabetic foot may be necessary to restore blood flow. This may include techniques such as angioplasty, stent placement, or vascular bypass[3].

Reconstruction techniques: plastic surgery

Regarding plastic surgery, various techniques such as grafts, flaps, and artificial dermis are useful for ulcer coverage in patients with diabetic foot. Reconstruction of the distal lower extremity is a surgical challenge, especially in those cases with a high risk of complications such as diabetes or advanced vasculopathy. Several types of local and regional flaps have been described, such as the sural flap or the extensor digitorum flap. However, the main problem lies in the lack of reliability of their vascularization, especially in patients with underlying vasculopathy or loss of tissue quality due to chronic pathologies or the high thickness of the flap, creating contour defects[60].

Final recommendations for the diagnosis of diabetic foot

·The diagnosis of diabetic foot infection should be primarily based on clinical criteria.

·A visible bone with a positive bone test is highly suggestive of osteitis/osteomyelitis.

·It is crucial to clean and debride before culturing.

·Biopsy is the most cost-effective procedure from a microbiological standpoint.

·For outpatient treatment, use antibiotics with good oral bioavailability and good compartmental distribution.

·An antibiotic window is recommended in case of poor evolution or recurrence (do not treat while selecting microorganisms).

·The microbiological documentation of diabetic foot infections is very helpful for antibiotic prescription, always accompanied by clinical information (especially appearance and evolution).

·The Microbiology laboratory should know, inform, and detect local bacterial resistance patterns.

·Gram staining as a rapid test provides valuable information. The quantification of cultures has not shown added value.

Final recommendations for the treatment of diabetic foot

·The treatment of diabetic foot infections should include empirical antibiotics covering Staphylococcus aureus (SSA, MRSA, CA-MRSA) and Streptococcus spp.

·It is essential to clean and debride the wound before taking samples for microbiological culture.

·Use antibiotics with good oral bioavailability and adequate compartmental distribution for outpatient treatment.

·In case of poor evolution or recurrence, an antibiotic window is recommended instead of continuously adjusting the treatment.

·Select products for topical treatment according to the ulcer's depth, extent, presence of infection or necrotic tissue, and exudate level.

·Implement offloading systems, such as adhesive felt, polyurethane bandages, and functional orthoses, to

reduce pressure on the affected areas.

·Use plantar supports to prevent ulcer recurrence once healed and correct areas of hyperpressure.

·Perform surgical debridement to remove dead or infected tissue and promote healing, allowing sample collection for microbiological culture.

·Consider performing partial or complete exostectomies to allow skin closure and prevent recurrence.

·Employ arthrodesis to fuse joints in cases of instability or severe deformities, using internal or external fixation as needed.

CONCLUSIONS

Every patient diagnosed with diabetic foot should receive treatment through a multidisciplinary team [7-9,61]. It is essential to coordinate the different specialties with a common goal and establish a link between all specialists. The "System for the Evaluation and Treatment of Diabetic Foot" brings together in one document all the necessary variables for the proper management of these patients.

This system can be used in any work setting, from primary care and diabetic foot units to hospitals and emergency services. Its implementation simplifies multidisciplinary management, facilitates collaboration among professionals, and significantly contributes to reducing the number of amputations. The results obtained over more than 20 years support its effectiveness and usefulness in clinical practice.

REVIEW ARTICLE

Authorship contributions: JVJ, JLL, MNP, MSL, MLV, FJMC, XMA, MSG, CRH, CCL, RPA, and ARB participated in the conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, original draft writing, supervision, validation, writing, review, and editing. All authors approved the final version to be published.

Funding: Self-funded.

Correspondence: *Jordi Viadé Julià.*
Address: *C/ Lacy 184. 08202. Sabadell. Barcelona.*
Telephone: *+34 630403613*
Email: ***jviadej@gmail.com***

Conflict of interest: The authors declare no conflict of interest.

Received: January 05, 2024.
Approved: April 29, 2024.

REFERENCES

1. Hébert-Blouin M-N, Tubbs RS, Carmichael SW, Spinner RJ. Hilton's law revisited. Clin Anat NY N. 2014;27(4):548–55. doi:10.1002/ca.22348

2. Shaping embryonic development. Nat Chem Biol. 2017;13(6):559. doi:10.1038/nchembio.2403

3. Viadé, J. Royo, J. Pie diabético. Guía para la práctica clínica. 2a. Editorial Médica Panamericana; 2013. 187 p.

4. Bekele F, Kelifa F, Sefera B. A male's foot is being shot by an ulcer, not a gunshot! The magnitude and associated factors of diabetic foot ulcer among diabetes mellitus patients on chronic care follow-up of southwestern Ethiopian hospital: A cross-sectional study. Ann Med Surg 2012. 2022;79:104003. doi:10.1016/j.amsu.2022.104003

5. Nather A, Cao S, Chen JLW, Low AY. Prevention of diabetic foot complications. Singapore Med J. 2018;59(6):291–4. doi:10.11622/smedj.2018069

6. Lim JZM, Ng NSL, Thomas C. Prevention and treatment of diabetic foot ulcers. J R Soc Med. 2017;110(3):104–9. doi:10.1177/0141076816688346

7.Systematic Review of Multidisciplinary Teams to Reduce Major Amputations for Patients with Diabetic Foot Ulcers. J Vasc Surg. 2020;71(4):1433-1446.e3. doi:10.1016/j.jvs.2019.08.244

8. Blanchette V, Brousseau-Foley M, Cloutier L. Effect of contact with podiatry in a team approach context on diabetic foot ulcer and lower extremity amputation: systematic review and meta-analysis. J Foot Ankle Res. 2020;13:15. doi:10.1186/s13047-020-0380-8

9. Viadé J, Nicolás M, Bundó M, Sirvent M, Riera C, Sabriá M. A novel assessment, diagnostic and treatment system for diabetic foot. J Foot Ankle Res. 2023;16:84. doi:10.1186/s13047-023-00687-z

10. Ziegler D, Strom A, Lobmann R, Reiners K, Rett K, Schnell O. High prevalence of diagnosed and undiagnosed polyneuropathy in subjects with and without diabetes participating in a nationwide educational initiative (PROTECT study). J Diabetes Complications. 2015;29(8):998–1002. doi:10.1016/j.jdiacomp.2015.09.008

11. Pirart J. [Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (2nd part) (author's transl)]. Diabete Metab. 1977;3(3):173–82. https://pubmed.ncbi.nlm.nih.gov/913749/

12. Pirart J. [Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (3rd and last part) (author's transl)]. Diabete Metab. 1977;3(4):245–56. https://pubmed.ncbi.nlm.nih.gov/598565/

13. Pirart J. [Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (author's transl)]. Diabete Metab. 1977;3(2):97–107. https://pubmed.ncbi.nlm.nih.gov/892130/

14. Mundet X, Pou A, Piquer N, Sanmartin MIF, Tarruella M, Gimbert R, et al. Prevalence and incidence of chronic complications and mortality in a cohort of type 2 diabetic patients in Spain. Prim Care Diabetes. 2008;2(3):135–40. doi:10.1016/j.pcd.2008.05.001

15. Yovera-Aldana M, Velásquez-Rimachi V, Huerta-Rosario A, More-Yupanqui MD, Osores-Flores M, Espinoza R, et al. Prevalence and incidence of diabetic peripheral neuropathy in Latin America and the Caribbean: A systematic review and meta-analysis. PloS One. 2021;16(5):e0251642. doi:10.1371/journal.pone.0251642

16. Longa López JCM. Physicians' attitudes towards the approach to diabetic neuropathy in public and private health facilities, 2023. Rev Fac Med Hum. 2023;23(4):54-61. doi:10.25176/RFMH.v23i4.6109

17. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. Pharmacol Ther. 2008;120(1):1–34. doi:10.1016/j.pharmthera.2008.05.005

18. Humphrey LL, Palumbo PJ, Butters MA, Hallett JW, Chu CP, O'Fallon WM, et al. The contribution of non-insulin-dependent diabetes to lower-extremity amputation in the community. Arch Intern Med. 1994;154(8):885–92. doi:10.1001/archinte.1994.00420080085009

19. Papanas N, Ziegler D. Risk Factors and Comorbidities in Diabetic Neuropathy: An Update 2015. Rev Diabet Stud RDS. 2015;12(1–2):48–62. doi:10.1900/RDS.2015.12.48

20. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017;40(1):136–54. doi:10.2337/dc16-2042

21. Carmichael J, Fadavi H, Ishibashi F, Shore AC, Tavakoli M. Advances in Screening, Early Diagnosis and Accurate Staging of Diabetic Neuropathy. Front Endocrinol. 2021;12:671257. doi:10.3389/fendo.2021.671257

22. Madan SS, Pai DR. Charcot neuroarthropathy of the foot and ankle. Orthop Surg. 2013;5(2):86–93. doi:10.1111/os.12032

23. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. J Clin Invest. 2007;117(5):1219–22. doi:10.1172/JCI32169

24.Nazimek-Sieweniak B, Moczulski D, Grzeszczak W. Risk of macrovascular and microvascular complications in Type 2 diabetes: results of longitudinal study design. J Diabetes Complications. 2002;16(4):271–6. doi:10.1016/s1056-8727(01)00184-2

25.Newman JH. Non-infective disease of the diabetic foot. J Bone Joint Surg Br. 1981;63B(4):593–6. doi:10.1302/0301-620X.63B4.7298692

26. Hastings MK, Johnson JE, Strube MJ, Hildebolt CF, Bohnert KL, Prior FW, et al. Progression of foot deformity in Charcot neuropathic osteoarthropathy. J Bone Joint Surg Am. 2013;95(13):1206–13. doi:10.2106/JBJS.L.00250

27. Waibel FWA, Böni T. Nonoperative Treatment of Charcot Neuro-osteoarthropathy. Foot Ankle Clin. 2022;27(3):595–616. doi:10.1016/j.fcl.2022.05.002

28. Sammarco VJ. Superconstructs in the treatment of charcot foot deformity: plantar plating, locked plating, and axial screw fixation. Foot Ankle Clin. 2009;14(3):393–407. doi:10.1016/j.fcl.2009.04.004

29. Frykberg RG, Zgonis T, Armstrong DG, et al.; American College of Foot and Ankle Surgeons. Diabetic foot disorders: a clinical practice guideline (2006 revision). J Foot Ankle Surg. 2006;45(Suppl)–S66. doi:10.1016/S1067-2516(07)60001-5

30. Almaraz MC, Gonzalez-Romero S, Bravo M, Caballero FF, Palomo MJ, Vallejo R, et al. Incidence of lower limb amputations in individuals with and without diabetes mellitus in Andalusia (Spain) from 1998 to 2006. Diabetes Res Clin Pract. 2012;95:399–405. doi:10.1016/j.diabres.2011.10.035

31. Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA, et al. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3266. doi:10.1002/dmrr.3266

32. Armstrong DG, Wrobel J, Robbins JM. Guest Editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J. 2007;4:286–7. doi:10.1111/j.1742-481X.2007.00392.x

33. Gibbons GW, Shaw PM. Diabetic vascular disease: characteristics of vascular disease unique to the diabetic patient. Semin Vasc Surg. 2012;25(2):89–92. doi:10.1053/j.semvascsurg.2012.04.005

34. Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabet Med J Br Diabet Assoc. 2008;25(6):700–7. doi:10.1111/j.1464-5491.2008.02445.x

35. 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. doi:10.26355/eurrev_201904_17471

36. Senneville EM, Lipsky BA, van Asten SAV, Peters EJ. Diagnosing diabetic foot osteomyelitis. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3250. doi:10.1002/dmrr.3250

37. Pouget C, Dunyach-Remy C, Pantel A, Schuldiner S, Sotto A, Lavigne J-P. Biofilms in Diabetic Foot Ulcers: Significance and Clinical Relevance. Microorganisms. 2020;8(10):1580. doi:10.3390/microorganisms8101580

38. Peters EJG, Lipsky BA. Diagnosis and management of infection in the diabetic foot. Med Clin North Am. 2013;97(5):911–46. doi:10.1016/j.mcna.2013.04.005

39. Bansal E, Garg A, Bhatia S, Attri AK, Chander J. Spectrum of microbial flora in diabetic foot ulcers. Indian J Pathol Microbiol. 2008;51(2):204–8. doi:10.4103/0377-4929.41685

40. Hatipoglu M, Mutluoglu M, Turhan V, Uzun G, Lipsky BA, Turk-Day Study Group, et al. Causative pathogens and antibiotic resistance in diabetic foot infections: A prospective multi-center study. J Diabetes Complications. 2016;30(5):910–6. doi:10.1016/j.jdiacomp.2016.02.013

41. Abdulrazak A, Bitar ZI, Al-Shamali AA, Mobasher LA. Bacteriological study of diabetic foot infections. J Diabetes Complications. 2005;19(3):138–41. doi:10.1016/j.jdiacomp.2004.06.001

42. Lipsky BA, Uçkay İ. Treating Diabetic Foot Osteomyelitis: A Practical State-of-the-Art Update. Medicina (Mex). 2021;57(4):339. doi:10.3390/medicina57040339

43. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg. 2006;117(7 Suppl):212S-238S. doi:10.1097/01.prs.0000222737.09322.77

44. Ray A, Malin D, Nicolau DP, Wiskirchen DE. Antibiotic Tissue Penetration in Diabetic Foot Infections A Review of the Microdialysis Literature and Needs for Future Research. J Am Podiatr Med Assoc. 2015;105(6):520–31. doi:10.7547/14-036.1

45. Jiang P, Li Q, Luo Y, Luo F, Che Q, Lu Z, et al. Current status and progress in research on dressing management for diabetic foot ulcer. Front Endocrinol. 2023;14:1221705. doi:10.3389/fendo.2023.1221705

46. Nather A, Chionh SB, Han AYY, Chan PPL, Nambiar A. Effectiveness of vacuum-assisted closure (VAC) therapy in the healing of chronic diabetic foot ulcers. Ann Acad Med Singapore. 2010;39(5):353–8. https://pubmed.ncbi.nlm.nih.gov/20535423/

47. Chatwin KE, Abbott CA, Boulton AJM, Bowling FL, Reeves ND. The role of foot pressure measurement in the prediction and prevention of diabetic foot ulceration-A comprehensive review. Diabetes Metab Res Rev. 2020;36(4):e3258. doi:doi.org/10.1002/dmrr.3258

48. Yalla SV, Crews RT, Patel NA, Cheung T, Wu S. Offloading for the Diabetic Foot: Considerations and Implications. Clin Podiatr Med Surg. 2020;37(2):371–84. doi:10.1016/j.cpm.2019.12.006

49. Bus SA, Sacco ICN, Monteiro-Soares M, Raspovic A, Paton J, Rasmussen A, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev. 2023;e3651. doi:10.1002/dmrr.3651

50. Sohrabi K, Belczyk R. Surgical Treatment of Diabetic Foot and Ankle Osteomyelitis. Clin Podiatr Med Surg. 2022;39(2):307–19. doi:10.1016/j.cpm.2021.11.003

51. Frykberg RG, Wukich DK, Kavarthapu V, Zgonis T, Dalla Paola L, Board of the Association of Diabetic Foot Surgeons. Surgery for the diabetic foot: A key component of care. Diabetes Metab Res Rev. 2020;36 Suppl 1:e3251. doi:10.1002/dmrr.3251

52. Gil Boix JV, Lladó Vidal M, Mena Ribas E, Viadé Julià J, Fanjul Losa FJ, Tofé Povedano S. Minimally invasive offloading osteotomy in the treatment of diabetic foot ulcer: Analysis of 25 patients. Med Clin (Barc). 2024;S0025-7753(23)00757-1. doi:10.1016/j.medcli.2023.11.024

53. Mehlhorn AT, Harrasser N, Walther M. [Treatment of plantar, neuropathic and metatarsal ulcers by minimally invasive metatarsal osteotomy]. Orthopade. 2020;49(7):625–31. doi:10.1007/s00132-019-03848-w

54. Dayya D, O'Neill OJ, Huedo-Medina TB, Habib N, Moore J, Iyer K. Debridement of Diabetic Foot Ulcers. Adv Wound Care. 2022;11(12):666–86. doi:10.1089/wound.2021.0016

55. Myerson MS, Edwards WH. Management of neuropathic fractures in the foot and ankle. J Am Acad Orthop Surg. 1999;7(1):8–18. doi:10.5435/00124635-199901000-00002

56. Badahdah HM, Zgonis T. External Fixation for Surgical Offloading of the Diabetic Foot. Clin Podiatr Med Surg. 2022;39(2):351–6. doi:10.1016/j.cpm.2021.11.007

57. Yammine K, Assi C. A Meta-Analysis of the Outcomes of Resection Arthroplasty for Resistant Hallucal Diabetic Ulcers. J Foot Ankle Surg Off Publ Am Coll Foot Ankle Surg. 2021;60(4):795–801. doi:10.1053/j.jfas.2020.04.025

58. Ramanujam CL, Zgonis T. An Overview of Internal and External Fixation Methods for the Diabetic Charcot Foot and Ankle. Clin Podiatr Med Surg. 2017;34(1):25–31. doi:10.1016/j.cpm.2016.07.004

59. Slahor L, Iselin L. [Diabetic foot syndrome]. Ther Umsch Rev Ther. 2020;77(7):339–46. doi:10.1024/0040-5930/a001201

60. Poyatos J, Senosiain O, Suñe C, Malagón-López P, Duque P. Manejo y reconstruccion microquirúrgica de extremidad inferior distal con colgajo SCIP libre. Cir Plástica Ibero-Latinoam. 2019;45:189–95. doi:10.4321/S0376-78922019000200012

61. Bundó M, Vlacho B, Llussà J, Bobé I, Aivar M, Ciria C, et al. Prediction of outcomes in subjects with type 2 diabetes and diabetic foot ulcers in Catalonian primary care centers: a multicenter observational study. J Foot Ankle Res. 2023;16(1):8. doi:10.1186/s13047-023-00602-6. doi:10.1186/s13047-023-00602-6