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Diabetic foot infection: pathophysiology, diagnosis and treatment

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Diabetic foot infection: pathophysiology, diagnosis and treatment

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Resumo

Introdução

O Pé Diabético é uma das complicações catastróficas da diabetes e é considerado um problema de saúde global em crescimento com um enorme impacto financeiro. A neuropatia periférica diabética e a doença arterial periférica são os principais fatores de risco para o desenvolvimento de úlceras do Pé Diabético, que geralmente surgem na região anterior do pé. O atraso na cicatrização das feridas inerente ao Pé Diabético predispõe para infeções graves, que resultam frequentemente em hospitalização e amputação nos casos extremos. Por este motivo, a atempada avaliação do risco do pé e as medidas preventivas precoces são preditoras de um desfecho clínico satisfatório.

Objetivos

A presente revisão literária tem como objetivo compilar o conhecimento científico atualizado acerca da Infeção do Pé Diabético, focando na sua fisiopatologia, diagnóstico e tratamento.

Metodologia

A pesquisa foi realizada na base de dados do PubMed, utilizando os seguintes termos médicos (MeSH): “diabetic foot”, “pathophysiology”, “diagnosis” and “treatment”. Foram selecionados artigos de investigação e de revisão indexados nos últimos 5 anos, escritos em inglês e português. Os projetos de experimentação animal e relatos de caso clínico isolado foram excluídos. Outros materiais pesquisados incluíram livros de referência na área de Cirurgia Vascular, nomeadamente Rutherford Vascular Surgery - 9th Edition, 2018.

Desenvolvimento

O Pé Diabético é caracterizado por uma complexa e multifatorial fisiopatologia. A perda de sensação de proteção resulta em trauma despercebido do pé e ulceração subsequente. A cicatrização das feridas é comumente comprometida pela co-existência de isquemia do pé. Como tal, as recomendações atuais propõem ferramentas de avaliação do risco que são baseadas no exame do pé, exame vascular, exame neurológico e comorbilidades associadas à doença. Além disso, vários sistemas de classificação de úlceras foram desenvolvidos para avaliar o prognóstico clínico adequadamente e gerir os problemas associados às úlceras eficazmente. A gestão do Pé Diabético requer uma abordagem multidisciplinar, que inclui educação do doente, medidas de alívio de pressão, controlo da infeção, desbridamento e tratamento local da ferida e revascularização do pé isquémico. Recentemente, cuidados avançados de feridas estão a ser

desenvolvidos como terapêuticas adjuvantes promissoras, que respondem aos défices do micro-ambiente das feridas.

Conclusões

O Pé Diabético permanece a principal causa global de amputação não traumática. Como tal, o diagnóstico precoce, a monitorização regular e o tratamento adequado são cruciais para a prevenção da morbilidade do Pé Diabético.

Palavras-chave

"diabetic foot", "pathophysiology", "diagnosis", "treatment".

Abstract

Background

Diabetic foot is one of the catastrophic complications of diabetes and is considered a growing global health care problem with a heavy financial burden. Peripheral diabetic neuropathy and peripheral arterial disease are the major risk factors for diabetic foot ulcers development, which generally occur in the forefoot region. Delayed wound healing inherent to diabetic foot can predispose to serious infection, frequently resulting in hospitalization and amputation in extreme cases. For this reason, prompt risk foot assessment and early preventive interventions are predictors of satisfactory clinical outcomes.

Objectives

The present literature review aims to compile updated scientific knowledge about diabetic foot infection, focusing on its pathophysiology, diagnosis and treatment.

Methods

Search was performed in PubMed database, using the following medical subjects heading (MeSH) terms: “diabetic foot”, “pathophysiology”, “diagnosis” and “treatment”. Research and review articles indexed in the last 5 years, written in English and Portuguese, were selected. Animal experimentation works and single case-reports were excluded. Other materials searched comprised reference books in the area of Vascular Surgery, namely Rutherford Vascular Surgery - 9th Edition, 2018.

Development

Diabetic foot is characterized by a complex and multifactorial pathophysiology. Loss of protective sensation results in unperceived foot trauma and subsequent ulceration. Wound healing is commonly compromised by the co-existence of foot ischemia. Thereby, current guidelines propose risk assessment tools that are based on foot examination, vascular status assessment, neurologic examination and disease-related comorbidities. Moreover, several ulcer classification systems were developed to properly evaluate clinical prognosis and effectively manage ulcer-related problems. Management of diabetic foot requires a multidisciplinary approach, including patient

education, offloading, infection control, wound debridement and novel dressings and foot revascularization. Recently, advanced wound treatments have been developed as promising adjunctive therapy, that targets wound microenvironment deficiencies.

Conclusions

Diabetic foot remains the main global cause of non-traumatic amputations. Thereby, early diagnosis, regular follow-up and adequate treatment are crucial to prevent diabetic foot morbidity.

Key words

“diabetic foot”, “pathophysiology”, “diagnosis”, “treatment”.

Abbreviations

ABI – ankle brachial index

ADM – acellular dermal matrix

AGE – advanced glycation end-product

DF – diabetic foot

DFI – diabetic foot infection

DFU – Diabetic foot ulcer

dHACAs – dehydrated human amnion and chorion allografts

EGF – epidermal growth factor

EPC – peripheral endothelial progenitor cell

FGF – fibroblast growth factor

IDSA – Infectious Diseases Society of America

IWGDF – International Working Group of Diabetic Foot

LEAD – lower extremity arterial disease

LOPS – loss of protective sensation

MRSA – Methicillin-resistant *Staphylococcus Aureus*

NICE – National institute for health and care excellence

NPWT – Negative pressure wound therapy

PAD – Peripheral arterial disease

PDGF – platelet-derived growth factor

PEDIS – perfusion, extent, depth, infection and sensation

PKC – activation of protein kinase C

RAGE – AGE-receptor

ROS – radical oxygen species

SA – *Staphylococcus Aureus*

SINBAD – site, ischemia, neuropathy, bacterial infection, area and depth

TCC – total contact cast

TcpO2 – transcutaneous pressure of oxygen

TGF – transforming growth factor

SDF-α1 – stromal cell-derived growth factor-α1

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INTRODUCTION

Diabetic foot (DF) is one of the main complications of diabetes. It is characterized by the need of multidisciplinary management, high complexity pathophysiology and associated premature mortality. [1-4] In 2013, 382 million people were diagnosed with type 2 diabetes and it is estimated to affect 592 million individuals by 2035. [2] Following rising diabetes prevalence, DF is a growing public health problem [2, 5, 6] related to a severe financial burden on healthcare services. [4, 6-9]

Peripheral diabetic neuropathy is responsible for the loss of protective sensation (LOPS) that predisposes to repetitive micro traumatisms of the foot. [4] Moreover, around half of diabetic patients present lower extremity arterial disease (LEAD) with an increased incidence of infra popliteal arteries involvement. [8] Combination of peripheral neuropathy and LEAD results in diabetic foot ulcer (DFU) development, that occurs in 15% to 25% of these patients during their lifetime. [3] DFU are commonly located in forefoot region, due to a greater exposure to pressure and shear stress.[1]

DFU is marked by a retarded healing process predisposing to infectious pathogens invasion that often results in limb or life-threatening infection. In fact, diabetic foot infection (DFI) is the most frequent cause of hospitalization among diabetic patients [10-12] and the leading cause of non-traumatic amputation worldwide. [6, 11, 13, 14]

Despite of current knowledge about DF pathophysiology, late foot evaluation and delayed treatment still explain the severity of some DFUs. Thereby, prompt risk foot assessment and early preventive interventions are predictors of a successful clinical outcome. [5] DFU prevention and treatment requires a multidisciplinary approach, in which the patient must have an active role. [2, 4, 15]

The present literature review aims to compile updated scientific knowledge about diabetic foot infection, focusing on its pathophysiology, diagnosis and treatment.

METHODS

Search was performed in PubMed database, using the following medical subjects heading (MeSH) terms: “diabetic foot”, “pathophysiology”, “diagnosis” and “treatment”. Research and review articles indexed in the last 5 years, written in English and Portuguese, were selected. Animal experimentation works and single case-reports were excluded. Other materials searched comprised reference books in the area of Vascular Surgery, namely Rutherford Vascular Surgery - 9th Edition, 2018.

PATHOPHYSIOLOGY

Diabetic foot (DF) is a syndrome caused by multiple factors that interact between each other. Diabetes is a chronic hyperglycemic state that promotes overproduction of radical oxygen species (ROS). Oxidative stress induces a pro-inflammatory environment that increases tissue damaged. Additionally, there is an increased production of advanced glycation end-products (AGEs), activation of protein kinase C (PKC) and polyol pathway. [16, 17]

Hyperglycemia induces the production of glycated proteins that undergo multiple reactions, such as oxidation, dehydration and condensation, and eventually culminate in AGEs. [17, 18] These proteins have the power to enhance monocytes migration to subendothelial space and subsequent differentiation into macrophages, reduce nitric oxide production and disrupt extracellular matrix components, and so indirectly promoting atherosclerosis. [17] In addition, studies demonstrated that AGE and activation of AGE-receptor (RAGE) activates NF-kB pathway in nervous system cells, which is implied in inflammatory process and apoptosis. [17]

PKC is a family of protein kinases that are involved in many cellular activities, including cell proliferation, differentiation, and apoptosis. [18] In addition, PKC is a major regulator of vasomotor function, thus being upregulated in diabetes contributes to an increased vascular tonus. [19] Furthermore, different authors have found that PKC is overexpressed in diabetic nervous system cells. [18]

Activation of polyol pathway stimulates aldose reductase and sorbitol dehydrogenase. These enzymes convert glucose in sorbitol and fructose, which diminish myoinositol production in nerve cells, impairing nerve conduction. [20]

This pathophysiologic cascade is implied in the two major factors of DF, namely peripheral neuropathy and LEAD. [6, 21] Moreover, other “minor” risk factors contribute to the recrudescence of DF, including increased body mass index, [22] absence of self-efficacy behavior, [2] poor glycemic control, longer disease duration, [23] and co-existence of retinopathy and nephropathy. [8]

Diabetic foot ulcer (DFU) consists of an ulceration in a foot that has baseline neuropathy and/ or LEAD. [10] These conditions increase foot vulnerability to delayed wound healing in the presence of trauma. In fact, 25 % of diabetic patients develop an ulcer at some point of their lives. [1] Non healed

ulcer promotes the vulnerability to several pathogenic microorganisms, leading to the development of a diabetic foot infection (DFI). [3]

Diabetic peripheral neuropathy

Diabetic peripheral neuropathy is a distal symmetrical polyneuropathy, that predominantly affects sensitive nerve fibers. [24] Approximately half of diabetic patient develop peripheral neuropathy. [25] In the context of sensorial neuropathy, studies found that small fibers were affected in early stages of the disease. This involvement was predominantly associated to thermal sensation disturbances. [26, 27] Moreover, progress to large fiber was related to other neurologic symptoms, including numbness, tingling and formication. [26] Eventually, sensory neuropathy leads to the inability to sense light pressure, known as loss of protective sensation (LOS), which greatly increases the risk of unperceived foot trauma and ulceration. [26, 28, 29] In the absence of this protective sensation, forefoot is the most vulnerable foot region as it is where plantar loads and shear stress are increased. [1]

At the same time, motor neuropathy leads to intrinsic foot muscle weakness and subsequent flexor and extensor tendons imbalance [30] that contribute to foot deformities, namely hammer toe, responsible for the pressure increase in the metatarsal heads. [31] Indeed, the most frequent location of neuropathic ulcers is in cutaneous tissue underneath metatarsal heads, since it is the maximum point of pressure and shear stress induced by gait cycle. [30, 31] In addition, AGEs accumulate in different human tissues, including tendons and ligaments. A paradigmatic example of diabetic patients is the thickness of Achilles tendon, which is the strongest tendon of the human body and has a major influence in gait cycle. This biomechanical abnormality was widely described in diabetic individuals, as well as its impact in plantar pressure and subsequent foot ulceration. [30] Furthermore, it is also known that diabetes is implied in the calcification of the insertion of Achilles tendon, which is responsible for posterior group muscle weakness. [32] Both biomechanical abnormalities contribute to a decreased ankle joint mobility that exacerbates plantar pressure. [30, 32] Additionally, atrophy of the lumbricals and interosseous muscles result in hyperextension of the metatarsophalangeal joint combined with a flexion deformity of the proximal interphalangeal joint, which is known by claw toes deformity. Thereby, this deformity causes distal migration of sub metatarsal fat pads, increasing vulnerability to pressure of metatarsal heads. [33] Motor neuropathy together with lack of proprioception (sensory neuropathy) disturb gait cycle and patient balance, which again increases plantar pressure. [30]

Concomitantly involvement of the small cholinergic sympathetic C-fibers, implied in autonomic function, results in sudomotor disfunction. Thereby, sudor production is decreased, skin becomes drier, thus increasing the risk of cracks and fissures. [34, 35]

All things considered, foot deformities and subsequent plantar pressure, unperceived sensitivity to trauma and skin dryness increase the risk of diabetic foot ulcers. [36]

Lower extremity arterial disease (LEAD)

Chronic hyperglycemia leads to endothelial dysfunction that is characterized by endothelial cells proliferation, thickening of basement membrane, decreased endothelium-derived vasodilators and nitric oxide production and disruption of microvascular tone. Endothelial dysfunction in combination with smooth muscle cells disturbances as well as oxidative stress result in burden of atherosclerosis, which result in calcified arteries. Moreover, hyperglycemia is also associated to thromboxane A2 increasing with subsequent hypercoagulability. Arteriolar-venular shunting due to autonomic neuropathy also contributes to impaired blood supply.

LEAD is a combination of microvascular and macrovascular diabetic disease that is present in 50% of diabetic foot ulcers. [8, 37, 38] In contrast to general population, peripheral arterial disease of diabetic patients is bilateral and rapidly progressive. [39] Classic pattern of diabetic peripheral arterial disease is characterized by the involvement of infra-popliteal arteries, including anterior tibial artery, posterior tibial artery and peroneal artery. [39, 40] Peroneal artery and dorsalis pedis artery are less affected, allowing frequently bypass revascularization. [41]

Several studies demonstrated that lower extremity arterial disease is a predictor of poor clinical outcome in diabetic foot ulcer due to impaired wound healing. [6, 37, 38, 42] For this reason, restoration of foot blood supply is the cornerstone ulcer treatment. Unfortunately, diabetic vascular disease distribution remains a challenge to revascularization procedures, revealing poor patency rates. [23, 39] In fact, infra popliteal arterial disease was considered an independent predictor of not healing, minor amputation and revascularization failure. [39] Impaired blood flow in wound bed is responsible for chronic diabetic foot ulcers, which are more vulnerable to infection. [13, 43]

Infection

In addition to peripheral neuropathy and LEAD, immunologic system is also affected in diabetic patients. Studies found that an impaired leukocyte function and apoptosis defects were related to poor glycemic control. [44] Furthermore, LEAD not only compromises healing process but also decreases the concentration of antibiotic that reach infected tissues. [45]

Diabetic foot ulceration is a mixture of neuropathy, vasculopathy and immunopathy, that enables rapid bacterial proliferation. [13] In fact, 20% of diabetic infected ulcers evolve to osteomyelitis, if not properly treated, leading to limb-threatening infection requiring amputation or even to sepsis. [45] Notably, diabetic foot infection is the main cause for hospitalization of diabetic subjects. [8, 10, 11]

Diabetic foot infections are mostly polymicrobial and the most isolated microorganisms are skin commensal agents. [45, 46] Several studies demonstrated that most of infections are caused by aerobic gram-positive cocci, particularly *Staphylococcus Aureus* (SA) and *Streptococcus* species, but more chronic ulcers were found to be associated to aerobic gram-negative and obligate anaerobic bacteria. Furthermore, SA is mostly related to monomicrobial infections while gram-negative bacteria are isolated in polymicrobial infections, mainly in chronic and deep wounds. [10, 14, 47] A recent study described the evolutionary trend in bacteria isolated from diabetic foot infections in a Portuguese tertiary center. *Machado et al.* found that in 2010/11 most commonly isolated pathogen was SA, whereas in 2016/7 most isolated pathogens were from Enterobacteriaceae family. Authors proposed that this tendency could be related to the switch of specimens sampling, which was initially done by swab while recently is done by tissue samples. Another plausible explanation was the increase of neuro-ischemic foot, which is related to more chronic wounds and consequently mixed microbial environment. Additionally, the rate of *Pseudomonas Aeruginosa* increased as did the rate of *Pseudomonas Aeruginosa* resistant to fluroquinolones. Despite the decrease of SA, prevalence of Methicillin-resistant *Staphylococcus Aureus* (MRSA) remains around 40%. In addition, authors found an increase of extended spectrum beta lactamase-producing *Enterobacteriaceae* (see Table I). [10]

Several studies demonstrated that the frequency of resistant strains is associated with recent antibiotic therapy, particularly broad-spectrum antibiotics, and previous hospitalizations. Moreover, resistant pathogens were found to increase the risk of life-threatening infection and subsequent amputation. [10, 14, 47]

RISK ASSESSMENT OF DIABETIC FOOT

Diabetic foot ulcer risk factors must be preciously identified, and respective preventive interventions must be adopted. [48, 49] Thereby, risk assessment of diabetic foot is recommended at the time of type 2 diabetes diagnosis. [50, 51] Studies demonstrated that ulceration of diabetic foot is inherent to various risk factors, including LOPS, changes in foot structure, poor glycemic control, smoking, and history of previous ulcer or amputation. [52] Interestingly, *Hangaard et al.* found that, in type 2 diabetic patients, increased first time foot ulcer development was associated to age > 60 years, history of cardiovascular disease, and long diabetes duration. [48]

Clinical history

To begin with, patient must be inquired about duration of the disease, diabetes-related comorbidities (e.g. end stage renal disease) [53] and previous ulceration and/ or amputation. [5, 50] Other cardiovascular risk factors must be explored as well as systemic cardiovascular disease. Moreover, symptoms related to foot neuropathy and lower limb vasculopathy might be present. Reported neuropathic symptoms include numbness, tingling, formication and pain, [24, 26, 28] whereas ischemic symptoms include cramps, claudication and pain walking or at rest and ulcers. [54] In addition, foot-care knowledge, and socio-economic conditions are also relevant topics of clinical history. [5, 50]

Foot examination

Diabetic foot skin might have a dryness appearance, which is frequently associated to fissures. Hypertrophic calluses are commonly present in points of pressure, particularly underneath metatarsal heads. Brittle or broken toenails may be a port of entrance for infectious microorganisms. Bony prominences and other deformities, such as claw toe or hammer toe, are potential ulceration sites. Reduced foot joints mobility might exacerbate plantar pressure. [5]

Vascular status assessment

Clinical signs of LEAD may be present, such as pale or cyanotic skin, thinning skin, hair loss, unpalpable distal pulses, increased capillary refill time and trophic lesions among others. [54, 55] In fact, signs and symptoms of lower limb ischemia demonstrated low sensitivity. Non-invasive examination must be included in vascular status assessment. [54] Doppler ultrasonography is the first line of investigation for diabetic-related peripheral arterial disease. Ankle pressure and ankle brachial index (ABI) as well as plethysmography waveforms are examined. ABI between 0.9-1.4, triphasic pedal pulse waveform and toe brachial index $\geq$ 0.75 generally exclude symptomatic LEAD [8, 40, 54] Unfortunately, these patients have often calcified vessels, that not only lead to unreliable pulse palpation but also might overvalue the results of ABI (incompressible ABIs). [8, 40, 54] In fact, a recent study found that more than one third of patients with critical limb ischemia and severe popliteal disease have normal or incompressible ABIs. [40] For this reason, recent guidelines recommend the establishment of toe pressure or transcutaneous pressure of oxygen ($TcpO_2$) as a more accurate LEAD diagnosis method. Toe pressure < 30 mmHg or $TcpO_2$ < 25 mmHg are indicative of severe foot impaired blood flow. [40, 56, 57]

Neurologic examination

LOPS is defined as the inability to sense light pressure. According to International Working Group of Diabetic Foot (IWGDF) practical guidelines, peripheral neuropathy can be detected with 10-gram Semmes-Weinstein monofilament, 128 Hz tuning fork or light test touch. [50]

Ten-gram Semmes-Weinstein monofilament test must be applied at least in three different regions of the plantar surface of both foots, including skin under first metatarsal phalangeal joint (great toe joint), second metatarsal head and fifth metatarsal head. Callus and ulcer sites should be avoided. [58] In addition, vibration perception is tested with 128 Hz tuning fork, which is applied in the bony prominence of distal interphalangeal (DIP) joint of the first toe. [27] For both tests, application is repeated three times for each region, though one of the applications is done in a “false location” effectively testing sensation. Protective sensation and vibration perception are confirmed if the patient answers correctly to at least two of three applications of monofilament on each foot site and tuning fork application on DIP joint, respectively. [27, 58] When previous mentioned tests are not available, light touch test can be performed. Using the tip of second finger, the examiner softly

touches the first, third and fifth toes. Test is confirmative when light touch is absent in at least two of the toes. [50]

During foot examination, loss of deep tendon reflexes, muscle atrophy as well as deformities, such as claw toes (DIP joint flexion) and hammer toes (hyperextension of metatarsal-phalangeal joint), might be suggestive of sensory and motor neuropathy. [50]

Diabetic foot follow-up

Frequency of diabetic foot reassessment depends on the risk of developing diabetic foot problems. IWGDF and National institute for health and care excellence (NICE) guidelines propose different intervals of screening according foot risk stratification (see Table II). [50, 51] Nevertheless, opinion of the health care provider that follows the patient prevails over guidelines indications.

DIABETIC FOOT ULCER ASSESSMENT

Diabetes is a chronic disease that in addition to specialized follow-up must also be managed in primary care services. For this reason, a need to formulate risk classification system of diabetic foot ulcers was relevant. The aim of these classifications systems was to help communication between the different health care providers that participate in the multidisciplinary treatment of diabetic foot, evaluate the clinical prognosis of the ulcer, manage the approach to infected diabetic foot, decide whether or not lower limb revascularization is needed and simplify the procedure of external [59] and internal audits of health care systems. [60]

Classification systems must be easy and fast to use, not require specialized diagnostic exams and allow patients triage in a timely manner. In this respect, assessment must consider potential life-threatening conditions, namely infection, ischemia and ulcer size (area and depth). [60]

Different classification systems have been proposed, which reflects that none fulfills the conditions required. The most commonly applied are the Wagner-Meggit Classification System, University of Texas Classification System, [59] PEDIS - perfusion, extent, depth, infection and sensation system and SINBAD - site, ischemia, neuropathy, bacterial infection, area and depth system. [60] In fact, each one has pros and cons that should be considered when choosing risk assessment classification system (see Table III). [13, 36, 59-61]

Several studies attempted to compare the different classification systems, however there is no consensus between authors. [36, 61, 62] *Chuan et al.* found that PEDIS system was more accurate in predicting ulcer clinical outcome than Wagner-Meggit Classification System and SINBAD system. [62] In contrast, *Ugwu et al.* demonstrated that higher Wagner grades were accurate to predict lower extremity amputation risk. [61] Moreover, *Jeon et al*. reported that Wagner-Meggit Classification System and the University of Texas Classification System were better predictors of lower extremity amputation comparing to other classifications system, including SINBAD. [36]

According to IWGDF guidelines, there are eight factors that predict diabetic foot ulcer patient clinical outcomes, namely end stage renal disease (patient factors), peripheral arterial disease and LOPS (limb factors) and area, depth, location (forefoot or hindfoot), number and infection (ulcer factors) (see Table IV). As a matter of fact, there is no classification system yet that gathered these factors, thus IWGDF guidelines consider that no classification system that has been proposed should be used to evaluate the individual prognosis of the patient. [60]

The Society for Vascular Surgery recommends that neuro-ischemic ulcers should be stratified with WIfI staging system, which considers wound size, presence of peripheral arterial disease and underlying infection. [40, 52] Given these points, authors demonstrated that ankle pressure of 65 mmHg with an infected, large wound may benefit more of revascularization than a similar ankle pressure value with a noninfected minor wound. [40] WIfI system has been broadly used in daily practice.

INFECTION DIAGNOSIS

Diabetic foot infection mainly occurs when pathogens enter through active ulcers. According to IWGDF guidelines, clinical diagnosis of diabetic foot infection is based on the presence of two or more of the following signs: local swelling or induration, erythema < 2 cm around the ulcer, local tenderness or pain, local warmth or purulent discharge and fever. In addition, high area and depth ulcer size and positive probe-to-bone (sterile blunt metal probe) might be suggestive of extended diabetic foot infection. [13]

If ulcer infection is suspected, microbiological material for culture must be collected. Tissue or bone samples were found to be more sensitive by identifying more pathogens when compared to wound swabs. These are frequently contaminated. Preferably, tissue samples should be obtained before initiating empiric antibiotic however antibiotic administration must not be delayed. [3]

Chronic ulcers, particularly deep wounds with positive probe-to-bone (touch bone with a sterile metal probe) or exposed bony structure are risk factors for develop an osteomyelitis. Plain radiographs can demonstrate destructive bone changes or tissue gas. Absence of radiology findings do not exclude the diagnosis of osteomyelitis. If diagnosis remains uncertain, further imaging test can be done, such as magnetic resonance imaging or nuclear medicine scans. [63]

Additionally, IWGDF and IDSA proposed a clinical-decision score for infected foot ulcer which allows identification of patients that require in-patient hospital care with intravenous antibiotics (see Table V). [60]

MANAGEMENT OF DIABETIC FOOT

Management of diabetic foot requires a multidisciplinary approach, including infection control, surgical debridement, appropriate dressings, offloading of pressure, revascularization in the presence of LEAD, treatment of comorbidities, metabolic control and patient education. [64] Treatment goal of diabetic foot ulcers is to achieve healing as quickly as possible to prevent the onset of serious complications. [21, 65]

Antibiotic therapy

Presence of diabetic foot infection requires prompt antibiotic therapy. Conversely, there is no evidence that prophylactic antibiotic therapy decreases the risk of diabetic foot infection. After microbiologic material collection (tissue or bone samples), empiric antibiotic therapy is initiated, with a switch to target-antibiotic regimen when the results of microbiologic study and antimicrobial agent's sensitivity test are available. [50, 51]

Limb-threatening and life-threatening conditions must be identified and immediately referred to hospital. These conditions include ulceration with fever or any signs of sepsis, ulceration with limb ischemia, suspected deep-seated soft tissue or bone infection or gangrene. [51]

Empiric antibiotic therapy depends on the infection severity and frequent microorganisms involved (see Table VI). Antibiotic regimen should cover gram positive bacteria, particularly SA, and the most commonly isolated gram-negative agents. Additionally, in moderate to severe infections of ischemic or neuro-ischemic foot, antibiotic should also cover anaerobes pathogens, especially in the presence of necrosis and recent antibiotic therapy. Considering the common polymicrobial infection etiology, guidelines recommend the use of broad-spectrum antibiotics alone or in combination.[10, 66]

In mild or moderate infections without systemic affection or hospitalization criteria, guidelines recommend oral Amoxicillin/ Clavulanic Acid or Fluroquinolones as empiric antibiotic regimen. In Portugal, the use of Fluroquinolones must be used with caution due to recent emerging of resistant bacteria species, namely Fluoroquinolones-resistant *Pseudomonas Aeruginosa*. [10]

Other moderate to severe infections are managed in patient care with intravenous broader-spectrum antibiotics, such as Piperacillin/ Tazobactam or Carbapenems. [10]

Piperacillin/ Tazobactam has a shorter spectrum comparing to Carbapenems, thus is safely used in neuropathic foot without ischemia. If the patient is allergic to beta-lactam antibiotics, combination of Metronidazole, Levofloxacin and Vancomycin is used. [66]

Ischemic or neuro-ischemic diabetic foot infection require intravenous Carbapenem treatment. Imipenem is mostly used whereas Ertapenem and Meropenem are reserved for specific situations.[66] Ertapenem does not cover *Pseudomonas spp* and *Enterococcus spp*, thus it is used when the risk for *Pseudomonas spp* is low and/ or absence of recent hospitalizations. [12] Meropenem is used in high convulsive risk cases, chronic kidney disease > grade 3 or previous stroke. [66]

In limb-threatening and life-threatening infections, empirical antibiotic therapy is a combination of a carbapenem (meropenem) and vancomycin. Vancomycin is added considering the possibility of MRSA. Linezolid is a preferable option if vancomycin is contra-indicated and/ or extended osteomyelitis is present. In fact, these anti-MRSA agents should be added to antibiotic regimen in case of a recent isolation or high suspicious of MRSA regardless of infection severity. [66]

Duration of antibiotic therapy is defined based on infection severity, adequate blood flow and response to treatment. [67] In-patients receiving intravenous antibiotics, need reassessment after 48 hours from intravenous treatment initiation. Switch to oral administration is possible when clinical response to treatment is evidenced. [51] In general, guidelines consider a 7 days mean duration for oral antibiotic therapy in patients with indication for outpatient clinic or in-patients after switch of intravenous antibiotics. [51] Bone involvement requires longer antibiotic regimen, that might be prolonged up to 6 weeks of duration. [51]

Debridement

Removal of any obstacle that prevents new tissue formation is an important principle of wound bed preparation. [21, 68] DFUs chronicity depend on various factors, including impaired immune system activity, biofilm development, [69] and vascular insufficiency. [68]

Debridement is an important element of local ulcer care, since it transforms a stagnant wound into an acute healing process. [68] In addition, debridement, physical or chemical, removes biofilm from chronic infected wounds. [69]

There are different debridement techniques, and the most used are surgical (sharp), mechanical, enzymatic, biologic, and autolytic. Surgical debridement removes non-viable tissue with sharp instruments and must be done by an expert practitioner. This procedure can be repeated as often as needed (even weekly) until unhealthy tissue is completed removed. Generally, mechanical debridement is done prior to surgical debridement. This method includes wet-to-dry dressings, hydrotherapy and pulsed lavage. [70]

Topical application of enzymes is an active debridement technique due to enzymatic digestion of extracellular matrix components from devitalized tissue. Usually, this technique is done after surgical debridement and should be avoided in the presence of extended necrotic tissue. Papain-urea combinations in a cream base and collagenase in a petrolatum base are the most used enzymatic agents. [70]

Autolytic debridement consists in inherent capacity of the body to remove necrotic tissue through endogenous enzymes and phagocytosis; [68] it can be enhanced by applying hydrogel or hydrocolloid dressings. [68, 71]

Maggot therapy (larva therapy) is a biological debridement technique that is known to reduce bacterial load through digestion of *Lucilia Sericata* (most used larva specie), which secretes antibacterial products, thus destroying biofilms. Moreover, this method demonstrated to reduce the malodor of infected diabetic foot ulcers. [72-74]

Despite the variety of debridement techniques, current guidelines recommend surgical debridement as it remains the only technique with demonstrated efficacy.[51, 55]In general,

aggressive debridement can be performed with no anesthetic administration due to sensory neuropathy. [72-75]

Dressings

Dressings are a crucial component of wound treatment, since they protect ulcer from external aggressions and promote healing. The concept of simple physical barrier was overtaken with the development of dressings that actively promote wound healing and prevent infections. [71]

Diabetic foot ulcers are a dynamic process that might require distinct types of wound care. [76] In diabetic foot infections, aerobic and anaerobic bacterial proliferation is responsible for inflammatory wound exudation and characteristic malodor. Dressings not only promote wound healing but also reabsorb exudate and unpleasant odor. [77] Different types of dressings were designed to target different ulcer characteristics (see Table VII). [68, 71, 76, 77]

ADVANCED WOUND TREATMENT

Despite optimal wound care, wound closure is not always achieved. In this context, emerging advanced wound treatments might be promising. Nevertheless, guidelines recommendations refer that these novel treatments are adjunctive to standard care, thereby should only be considered after standard care is attempted. [50, 51]

Negative pressure wound therapy

Negative pressure wound therapy (NPWT) is an adjuvant treatment that uses a vacuum system to remove excess fluid and promote healing in acute or chronic wounds. The therapy uses a sealed wound dressing connected to a vacuum pump, that applies a controlled negative pressure, continuously or intermittently. [65, 78, 79]

NPWT benefits are improvement of wound bed supply, reduction of ulcer size, wound exudate removal and local edema resolution, and decreasing of bacterial load in infected ulcers. [65] Several trials have shown that NPWT is safe and effective in the treatment of ischemic or neuro-ischemic diabetic foot ulcers. Presence of osteomyelitis and necrotic tissue are contraindications to NPWT.[65, 78, 79]

Chiang et al. demonstrated that NPWT promotes higher reduction of wound depth comparing to standard wound care. [80] *Mu et al.* found an increase of peripheral endothelial progenitor cells (EPCs) after NPWT in diabetic patients with mild to moderate degrees of ischemia. Authors proposed that EPCs increase was related to the upregulation of vascular endothelial growth factor (VEGF) and stromal cell-derived growth factor-α1 (SDF-α1). [78] Moreover, *Borys et al.* found that NPWT stimulates differential expression of genes that are involved in re-epithelization and angiogenesis of diabetic foot ulcers. [65] Furthermore, studies have demonstrated that NPWT reduces bacterial count to less than 10^5 bacteria per gram of tissue and increases granulation tissue formation. [79]

Sucrose octasulfate impregnated dressing

Diabetic foot ulcers environment is characterized by a pro-inflammatory activity, fibroblasts dysfunction and upregulation of matrix metalloproteinases (MMP). MMP are known to destroy growth factors and disrupt extracellular matrix, being implied in impaired wound healing. [64, 81, 82]

Sucrose octasulfate impregnated dressing main component is potassium salt of sucrose octasulfate that is known to inhibit MMP. [64, 81, 82] Thereby, guidelines recommend this dressing as an adjuvant therapy of non-infected neuro-ischemic diabetic foot ulcers that fail to heal after 4-6 weeks despite optimal clinical care. [50]

The "Explorer" study demonstrated that TLC-NOSF dressing (UrgoStart Contact, Laboratoires Urgo, France), a polyester mesh enriched of sucrose octasulfate potassium salt, was associated to higher closure rates (48%) than a neutral dressing (30%), after 20 weeks of treatment of non-infected neuro-ischemic diabetic foot ulcers. [64] Pos-hoc analysis of the Explorer's data confirmed that TLC-NOSF treatment improved wound closure rate compared to neutral dressing regardless of initial wound duration. [82]

Placental membrane allografts

Placental membrane allografts are aseptically processed dehydrated human amnion and chorion allografts (dHACAs). dHACAs accelerate wound healing, by providing extracellular matrix proteins, growth factors and cytokines to poor diabetic foot ulcers microenvironment. Use of dHACAs has been studied in the treatment of uninfected diabetic foot ulcers with or without moderate ischemia. [83-86]

dHACAs have been compared to standard of care treatments in non-infected diabetic foot ulcers. [83, 84] *DiDomenico et al.* demonstrated that, after 12 weeks of treatment, AmnioBand® (dHACA) plus standard of care had higher complete wound healing rates compared to standard of care alone (85% versus 33%, respectively). [83] *Zelen et al*. found that, after 6 weeks of treatment, EpiFix ® (dHACA) presented higher complete wound closure rates than standard of care presented (95% versus 35%, respectively). [84]

Furthermore, studies showed that dHACAs had higher healing rates compared to acellular dermal templates (bio-engineered skin). [84, 86] *Glat et al.* found that mean time to heal at 12 weeks was 32 days for AmnioBand ® compared to 63 days for Apligraf ® (tissue-engineered skin substitute). [86] Similarly, *Zelen et al.* demonstrated that EpiFix ® had significantly greater rates of complete healing and more rapid time to healing than Apligraf ® (complete wound closure within 4 and 6 weeks 85% and 95% versus 35% and 45%; median time to healing 13 days versus 49 days, respectively). [84]

Platelet-rich topical treatment

Platelets derived from peripheral blood were found to increase levels of VEGF and fibroblast growth factor (FGF), stimulating formation of new vessels and promoting healing process. [87, 88] When compared with Suile® wound dressing alone (contained mostly Vaseline), the addiction of autologous platelet-rich gel improved healing grades (69.0% versus 85.4%, respectively). Additionally, an antibacterial activity, particularly against SA, was reported. [88] Moreover, 30 days treatment with cord blood platelet gel application showed higher mean ulcer's area reduction (79%) when compared with traditional dressings (46%), in diabetic patients with critical limb ischemia who underwent revascularization. [87] Recently, a multicenter trial randomized 269 individuals to receive standard care or care plus weekly application of LeucoPatch ® (disc comprising autologous leucocytes, platelets, and fibrin). From 132 ulcers treated with this device 45 healed in 20 weeks while 134 ulcers treated with standard care alone only 29 healed at the same time. [89] No relevant side effects were found in these studies. Presence of local and systemic signs of infections are contraindications to these treatments. [87-89]

Biologically active products

Collagen is a major component of extracellular matrix, providing strength and flexibility to tissues. [90, 91] *Babu et al.* demonstrated that exogenous collagen particles in the form of powder application on diabetic foot ulcer had a higher wound contraction rate than saline dressing alone (day 7, 15 and 30, respectively; 2.45 cm^2 versus 2.15cm^2; 2cm^2 versus 1.73cm^2; 1.67cm^2 versus 1.05cm2). [91] Recently, a prospective study evaluated the effectiveness of 100% porcine type I collagen dressing material. *Park et al.* found that collagen group had a higher rate of complete healing compared to control group, foam dressing alone (82.4% versus 38.5%, respectively).[90] In both studies, patients with infectious or inflammatory diseases were excluded and no relevant side effects were reported.[90, 91]

Growth-factors

Growth factors have been proposed as promising adjunctive wound treatments, including platelet-derived growth factor (PDGF), FGF, transforming growth factor (TGF) and epidermal growth factor (EGF). EGF has been the most studied for DFU treatment. Studies found that EGF promotes epithelial cell growth on wound bed, stimulates epidermal regeneration and increases epithelization. *Park et al.* demonstrated that a novel spray-applied growth factor therapy containing recombinant human EGF had a higher complete wound healing comparing to placebo (73.2% versus 50.6%, respectively). [92]

Bioengineered skin

Bioengineered skin is a biological skin substitute, which is composed by an epidermal and/ or dermal layer inserted to an acellular matrix. These allograft tissues have been widely used as adjunctive therapy of chronic non-infected DFUs. [84, 93, 94] The mechanism of wound healing promoting depends on their components. For example, Apligraf ® is a bi-layered cultured skin substitute, in which the epidermal layer is formed by human keratinocytes and has well-differentiated stratum corneum; the dermal layer is composed of human fibroblasts in a bovine Type I collagen lattice. The presence of fibroblasts and keratinocytes trigger a paracrine reaction, that promotes epithelization and angiogenesis. [84] Moreover, acellular dermal matrixes (ADMs) have been studied not only as scaffolds but also as allografts. ADMs are generated by decellularization process that removes potentially immunogenic material and preserves the intact extracellular skin matrix. Studies have shown that ADMs enhance wound healing of chronic DFUs. [93, 94]

CO-ADJUNTIVE MEASURES

Patient education

Patient education is a cornerstone of diabetic foot problems prevention. Foot care education aims to improve foot-care knowledge, patient's skills and confidence to unable self-care behavior. [2, 4, 95]

Recently, different patient education programs have been published. The Social Cognitive Theory or Self-efficacy Theory of Bandura has been the most studied theory-based intervention. This intervention is based on promoting patient's beliefs about his capability of perform a certain skill. In diabetic foot context, self-efficacy enhancing programs have demonstrated that not only improves foot self-care knowledge but also promotes preventive foot care behavior. [2, 95]

Education includes instructions for foot hygiene and self-inspection, skin and nail care, appropriate footwear, injury prevention, and when to seek a healthcare provider. [2, 95] Moreover, other self-care activities should be considered, such as healthy diet, exercise and self-monitoring of blood sugar.[15] Health education programs alone do not prevent the development of diabetic foot problems, thereby must be integrated with other diabetic foot interventions. [4, 15]

Offloading

Offloading consists in minimizing plantar pressure on the active ulcer or potential ulceration sites, thus is a mainstay for the prevention and treatment of neuropathic diabetic foot ulcers. [28, 33, 96, 97] Ischemic and infected foot ulcers also benefit of offloading; however, perfusion restoration and infection control are firstly required. [51, 97]

Non-removable knee-high offloading device, including total contact cast (TCC) or removable walker rendered irremovable, remains gold standard offloading device. [98] Several studies demonstrated that non-removable knee-high offloading device is more effective in redistributing plantar pressure.[97, 98] Authors suggested that non-removable knee-high offloading device efficacy is partially attributed to its irremovable character. Despite great efficacy in decreasing plantar pressure, this device does not allow daily ulcer assessment, and is associated with muscle atrophy.[97]

If non-removable knee-high offloading device is contra-indicated or not tolerated, removable knee-high offloading device is indicated. Knee-high devices demonstrated more efficacy in reducing plantar pressure than ankle-high devices, owing to high capacity to uphold lower limb weight. [98] Eventually, removable ankle-high offloading (cast shoe) device might be considered. Patient education is crucial to warrant device adherence. [97, 98] Walking insoles are considered last line offloading device owing to minimal plantar pressure decreased compared. Nevertheless, rigid rocker sole demonstrated higher ulcer recurrence-free survival timer than semi-rigid walking sole. [28] Different offloading devices are documented in Table VIII.

Above all, patients' preferences also play a role in offloading device decision. Non-removable offloading device was more frequently related to negative impact on quality of life, thereby patients prefer removable devices. Patients must be informed of the non-removable devices' benefits. Still, if removable device is preferred, patient adherence must be promoted. [97]

Neuropathic complications management

At present, treatment of diabetic neuropathy is limited. Glycemic control is considered the basis of treatment, since it is known to prevent microvascular complications, including neuropathy. [23] Neuropathic pain is responsible for a great negative impact on diabetic patients' quality of life. Therefore, guidelines recommend the use of antidepressants (duloxetine), anticonvulsants (pregabalin and gabapentin), and opiods to control painful diabetic neuropathy. [99, 100]

Moreover, studies found that might exist an association between diabetic peripheral neuropathy and hypovitaminosis, such as vitamin D and complex-B vitamins. Authors demonstrated that intramuscular vitamin D treatment improves quality of life of patients with painful diabetic neuropathy. [101, 102] *Alvarado et al.* reported that complex B vitamins plus gabapentin was associated to a greater reduction of pain intensity compared to gabapentin alone. [96]

Peripheral neuropathy induces biomechanical abnormalities that contribute to balance deterioration and gait disturbances. Recent studies have found that structured program exercises might improve proprioception and somatosensory inputs restoring patients' mobility. [103, 104] *Ahmad et al.* revealed that sensorimotor training improved static and dynamic balance as well as proprioception measures. [104] *Monteiro et al.* are conducting a study that aims to assess the clinical

outcomes of a foot-ankle strength and flexibility program, including gait speed and biomechanics while walking. [103]

REVASCULARIZATION

Although not being a part of the aim of this review, it should be noted that revascularization is the cornerstone of ischemic DFUs treatment. [11, 39, 105] The goal of revascularization is to prevent limb loss, timely healing and control pain. Patients with an ankle pressure < 50 mmHg, an ABI < 0.5, a toe pressure < 30 mmHg or a $TcpO_2$ < 25 mmHg should undergo arterial imaging study to determine the extension of the disease. [39] Endovascular procedure is becoming standard owing to good technical results as well as being less invasive. Nevertheless, choice of revascularization technique depends on patient-related factors (pattern and extension arterial involvement and patients' co-morbidities) and center experience. [11, 39, 105]

CONCLUSION

Diabetic foot infection is a major concern in the management of diabetic patients. For this reason, scientific community has made a great investment on diabetic foot field. It is known that chronic hyperglycemic state is responsible for the cascade of events that culminates in neuropathy, vasculopathy and immunopathy resulting in chronic diabetic foot ulcers. In this respect, different guidelines recognized the importance to preciously identify diabetic foot in risk of ulceration. Preventive interventions, such as patient education, offloading of pressure and glycemic control, constitute the basis of diabetic foot management. Presence of diabetic foot infection is a medical urgency that requires prompt diagnosis and empirical antibiotic therapy. Afterwards, wound healing requires debridement, appropriate dressings, offloading and restoration of foot perfusion. Physical exercise not only proved to be promising in improving foot circulation but also demonstrate to play a role in improving peripheral neuropathy-related gait disturbances. All mentioned above, a regular foot follow-up and a multidisciplinary care, can mitigate the risk of ulcerations and reduce diabetic foot morbidity.

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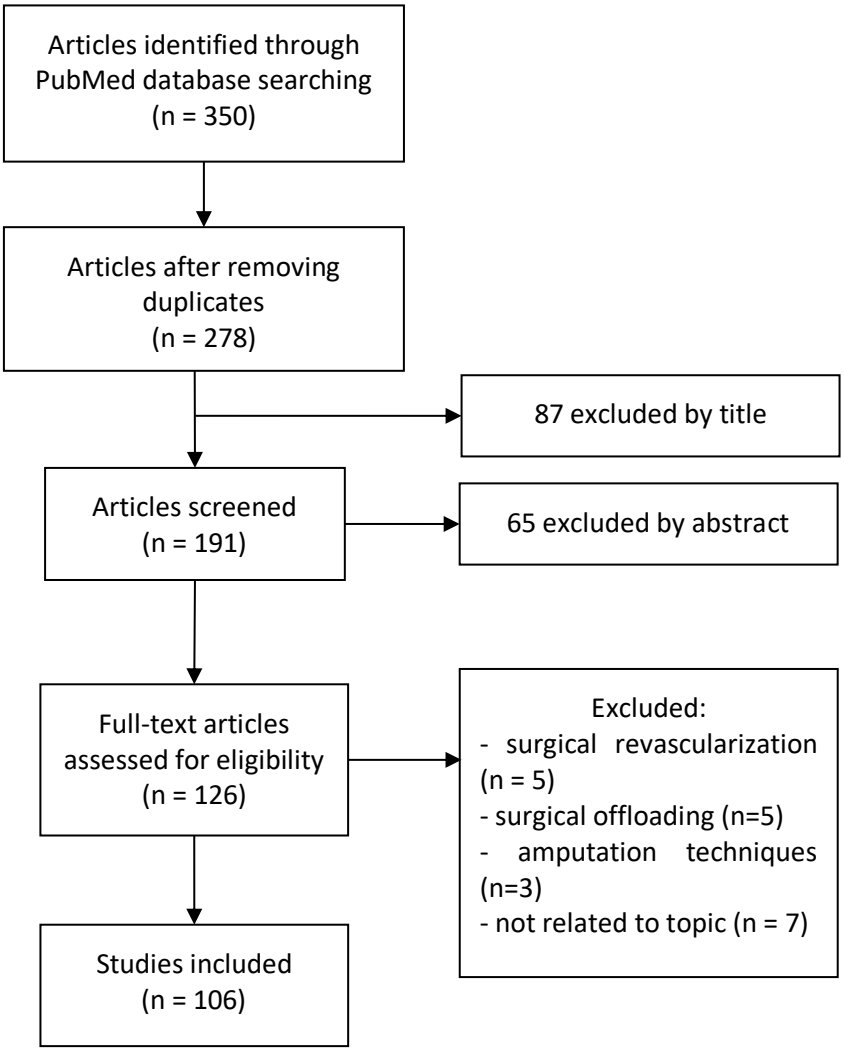
Prisma Flow Diagram



Tables list

Table I - Characteristics of isolated pathogens [10] ***(adapted from C Machado et al, Evolutionary trends in bacteria isolated from moderate and severe diabetic foot infections in a Portuguese tertiary center)***		
	2010/11	**2016/ 17**
Gram-positive bacteria	**68.2 %**	**50.3 %**
Staphylococcus Aureus	26.7 %	19.7 %
- Methicillin-sensitive *Staphylococcus Aureus*	14.2 %	11.5 %
- Methicillin-resistant *Staphylococcus Aureus*	12.5 %	8.2 %
Other *Staphylococcus* spp	9.1 %	4.4 %
Streptococcus spp	11.9 %	9.8 %
Enterococcus spp	14.8 %	14.2 %
Other Gram-positives	5.7 %	2.2 %
Gram-negative bacteria	**31.3 %**	**48.6 %**
Enterobacteriaceae	15.9 %	30.6 %
Pseudomonas Aeruginosa	9.1 %	13.7 %
- Fluoroquinolone sensitive	6.3 %	6.6 %
- Fluoroquinolone resistant	2.8 %	7.1 %
Enterobacteriaceae	1.1 %	1.6 %
Other Gram-negatives	5.1 %	2.7 %

Table II - Guidelines of IWGDF (*International Working Group of Diabetic Foot)* and NICE (*National institute for health and care excellence). ***PAD - peripheral arterial disease; LOPS -Loss of protective sensation.***

Practical guideline	Ulcer risk	Characteristics	Screening intervals
IWGDF [50]	**Very low**	No LOPS and no PAD	Annual
	Low	LOPS or PAD	Once every 6-12 months
	Moderate	LOPS + PAD, or LOPS + foot deformity or, PAD + foot deformity	Once every 3-6 months
	High	LOPS or PAD, and one or more of the following: - History of a foot ulcer - A lower extremity amputation (minor or major) - End-stage renal disease	Once every 1-3 months
NICE [51]	**Low**	No risk factors, except callus	Annual
	Moderate	Deformity or neuropathy or non-critical limb ischemia	Frequently (e.g. every 3-6 months)
	High	Previous ulceration or previous amputation or on renal replacement therapy or neuropathy and non-critical limb ischemia together or neuropathy in combination with callus and/ or deformity or non-critical limb ischemia in combination with callus and/ or deformity	More frequently (e.g. every 1-2 months)

Table III - Ulcer classification systems. ***ABI (ankle brachial index), IWGDF (International Working Group of Diabetic Foot), $TcPO_2$ (Transcutaneous oxygen pressure) and TP (Toe Pressure)***

Classification system	Characteristics	Advantages	Disadvantages
Wagner-Meggit Classification System [55, 59, 60]	Ulcer depth, presence of gangrene and level of tissue necrosis [59]	Simple application [60]	Does not consider loss of protective sensation, ischemia and infection [55, 59, 60, 62]
University of Texas classification system [59, 60]	Depth (grade 0-3) [59, 60] Infection (stage B), ischemia (stage C) or both (stage D) [59, 60]	Identification of potential for infection at each ulcer depth [60]	Requires ≥ 1 non-invasive criteria ($TcPO_2$, ABI or TP) [59, 60] Does not consider loss of protective sensation and size (area) [59, 60] No difference in organisms or required antibiotic selection [60]
PEDIS [62]	Perfusion, extent, depth, infection and sensation [59, 60]	High relevance to pathophysiology of ulcer [55]	Useful for research, not for prognostic value [60]
SINBAD [60]	Site, ischemia, neuropathy, bacterial infection, area and depth [60]	Simple and quick to use; no specialist equipment; necessary information to allow patient triage [60]	Does not gathered the 8 patient prognosis factors proposed by IWGDF [60]

Table IV - Eight predictors factors of diabetic foot ulcer patient [60]

Patient factor	End stage renal disease
Limb factors	Peripheral arterial disease and loss of protective sensation
Ulcer factors	Area Depth Location Number Infection

Table V - IWGDF/ IDSA system [60] ***IDSA (Infectious Diseases Society of America), IWGDF (International Working Group of Diabetic Foot) and PEDIS (Perfusion, Extent, Depth, Infection and Sensation)***

Clinical manifestations	IDSA Infection severity	PEDIS grade
Infection present, as defined by presence of ≥ 2 of the following: - Local swelling or induration - Erythema between 0.5-2 cm around the ulcer - Local tenderness or pain - Local warmth or purulent discharge	Mild	2
Local infection with erythema > 2 cm around the ulcer, or involving structures deeper than skin and subcutaneous tissues (e.g. bone, joint, tendon, muscle) and no systemic signs or symptoms	Moderate	3
Local infection with ≥ 2 of the following systemic signs or symptoms: - Temperature > 38° C or < 36° C - Heart rate > 90 beats/ min - Respiratory rate > 20 breaths/ min or $PaCO_2$ < 32 mmHg - White cell count < 4 x 10^9/ L or > 12 x 10^9/ L	Severe	4

Table VI - Empiric antibiotic regimen for diabetic foot infection [66] *IV (intravenous)*	
Severity of infection	**Empiric antibiotic regimen**
Mild infection **Moderate infection without systemic affection and/or hospitalization criteria**	Amoxicillin/ Acid clavulanic *500 mg 8/ 8 h per os* Ofloxacin *200-400 mg 12/ 12 h per os* Ciprofloxacin *500-750 mg 12/ 12 h per os*
Moderate infection with systemic affection and/ or hospitalization criteria **Severe infection**	**<u>Neuropathic foot</u>:** Piperacillin/ Tazobactam 4.*5 g 8/8 h IV* Beta-lactam allergy: metronidazole + levofloxacin + vancomycin **<u>Ischemic or neuro-ischemic foot</u>:** Carbopenem IV: Imipenem *500 mg 6/ 6 h IV or* Ertapenem *1g qd IV (low risk of Pseudomonas Aeruginosa isolation and/ or absence of recent hospitalization)* or Meropenem *1g 8/ 8h IV (risk of convulsions, chronic kidney disease > grade 3, previous stroke*)
Limb or life-threatening infection	Meropenem *1g 8/ 8h IV + Vancomycin 1 g 12/ 12h IV or* Meropenem *1g 8/ 8h IV* + Linezolide *600 g 12/ 12h IV* (more severe cases, contra-indications to vancomycin use and/ or extended osteomyelitis)

Table VII - Wound dressings

TYPE	EXAMPLE	CHARACTERISTICS	INDICATIONS
Hydrogels	Hydrogel dressings include ActiformCool® (Activa) and Aquaflo® (Covidien, Dublin, Ireland) [76]	- Three-dimensional structure of hydrophilic substances [71] -Stimulates autolytic debridement [71] -Absorbent [68, 71] - Typically, transparent enables wound assessment [71] - Maintain the wound moist, thus might cause maceration [68, 71]	Moderate-to-high exudative wounds (infected) [71]
Hydrocolloids	Aquacel Hydrofiber® (ConvaTec, Reading, UK) [76]	- Hydrogel mixed with synthetic rubber and sticky materials [71] - Stimulates autolytic debridement [71] - Absorbent (10% to thousands fold their equivalent weight) [71] - Maintain the wound moist, thus might cause maceration [71]	Severe exudative wounds (infected) [71]
Foams	Tegaderm™ (3 M Health Care) [76]	- Composed of polyurethane or silicone[71] - Semipermeable [71] - Antimicrobial activity [71] - Thermal insulation and maintain moisture to the wound [71] - Also used as secondary dressings with hydrogel or alginate dressings [71]	Infected wounds [71]
Alginates	Algosteril ® (calcium alginate) (Les Laboratoires Brothier, S.A., Nanterre, France) [71, 76]	- Fibrous products derived from brown seaweed, which can form a gel after binding to wound exudate [71] - Can be freely cut according to the shape of the wound [71] - Excellent exudate absorption properties (used in dry wounds or wounds with minimal exudate should be avoided) [71] - Alginate hydrogel (bioglass and desferrioxamine); hydrogel optimizes wound humidity – better outcomes in diabetic foot ulcers [68, 71] - Hemostatic proprieties [68]	Infected and non-infected wounds with a large amount of exudate (exudate is necessary to transform alginate into gel) [68, 71]

Films	Meliplex Ag (Molnlych Health Care, Gothenburg, Sweden) [76] GranuDerm™ and Sentry™ (Acute Care Sollutions, LLC, Canton, OH, USA) [76]	- Adhesive, porous, and thin transparent polyurethane [71] - Oxygen, carbon dioxide, and water vapor from the wound pass through the dressing, whereas liquids and bacteria are well-isolated [71]	Epithelializing wounds and superficial wounds with few exudates (non-infected) [71]
Silver-impregnated	AQUACEL ® Hydrofiber ® (ionic silver) (E. R. Squibb & Sons, L.L.C., Princeton, NJ, USA) [71] Silverlon® (Argentum Medical, LLC, Geneva, IL, USA) [76] Allevyn (Smith & Nephew, London/Hull, UK) [76] Dermacol/Ag™ (DermaRite Industries, North Bergen, NJ, USA) [76]	- Silver ion releasing dressings[77, 106] - Anti-microbial activity [77, 106] - Pain control [77, 106] - Faster wound contraction (accelerated proliferation of fibroblasts and differentiation into myofibroblasts) [106] - Odor absorption [77, 106]	Infected exudative wounds [77, 106]

Table VIII - Comparison of casting devices [97, 98] ***VAS (Visual Analogue Scale)***

CASTING DEVICES	ADVANTAGES	DISADVANTAGES
Non-removable knee-high offloading device	-Lowest peak pressure (Pedar X-system) [98] - Total adherence [97]	- Not enables ulcer daily assessment [97] - Muscle atrophy [97] - Lower perceived walking comfort (VAS) [98]
Removable knee-high offloading device	- Lower peak pressure than cast shoe (Pedar X-system) [98]	- Higher peak pressure than non-removable knee-high offloading device (Pedar X-system) [98] - Reduced adherence [97]
Removable ankle-high offloading device (cast shoe)	- Lower impact on contralateral limb (Pedar X-system) [98]	- Lower redistribution of pressure from forefoot to more proximal regions compared to knee-high offloading devices (Pedar X-system) [98] - Reduced adherence [97]
Walking soles	- Walking comfort [98] - Leg-length discrepancy [98] - Costs [98]	- Minimal effects on plantar pressure [98] - Reduced adherence [97]