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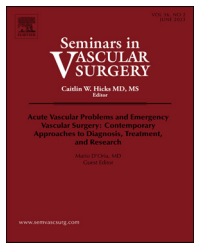

Review article

Emergent management of diabetic foot problems in the modern era: Improving outcomes

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ABSTRACT

Limb amputation is a consequence, and the leading complication, of diabetic foot ulcers. Prevention depends on prompt diagnosis and management. Patients should be managed by multidisciplinary teams and efforts should be focused on limb salvage ("time is tissue"). The diabetic foot service should be organized in a way to meet the patient's clinical needs, with the diabetic foot centers at the highest level of this structure. Surgical management should be multimodal and include not only revascularization, but also surgical and biological debridement, minor amputations, and advanced wound therapy. Medical treatment, including an adequate antimicrobial therapy, has a key role in the eradication of infection and should be guided by microbiologists and infection disease physicians with special interest in bone infection. Input from diabetologists, radiologists, orthopedic teams (foot and ankle), orthotists, podiatrists, physiotherapists, and prosthetics, as well as psychological counseling, is required to make the service comprehensive. After the acute phase, a well-structured, pragmatic follow-up program is necessary to adequately manage the patients with the aim to detect earlier potential failures of the revascularization or antimicrobial therapy. Considering the cost and societal impact of diabetic foot problems, health care providers should provide resources to manage the burden of diabetic foot problems in the modern era.

1. Introduction

The World Health Organization defines *diabetic foot* as the condition of infection, ulceration, and/or destruction of deep foot tissue associated with neurologic abnormalities and varying degrees of peripheral vascular disease of the lower extremities in a patient with diabetes mellitus. It is estimated that up to 20% of these patients will require hospitalization for diabetic foot complications. Epidemiological studies indicate the risk of developing foot ulcer is 2.5% per year [1].

The development of skin ulceration in the foot of a diabetic is a serious medical condition that can lead to amputation if not healed promptly. The result of failing to manage patients with diabetic foot ulcers (DFUs) is major amputation.

A proportion of patients with diabetes will develop peripheral neuropathy, which can lead to loss of protective sensation [2]. This, often combined with diabetes-related foot deformities, may lead to formation of DFUs caused by localized pressure and repetitive trauma. Superimposition of peripheral artery disease (PAD) compromises ulcer healing and increases the probability of infections; these are linked directly to amputations.

Therefore, prevention and early detection and management of skin lesions, prompt treatment of infection, and

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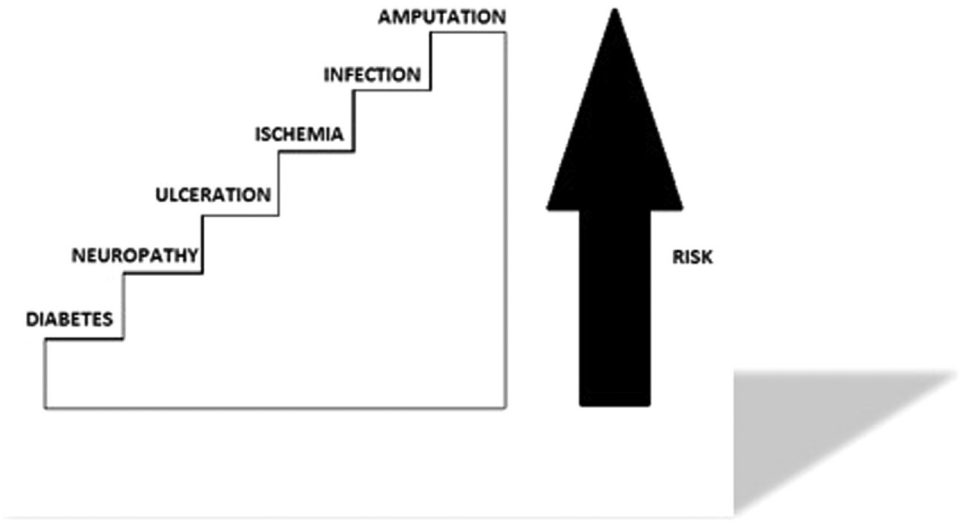

Fig. 1 – Stairway to amputation.

revascularization are the three key steps in prevention of limb amputation in these patients.

The ischemic and infectious components are time dependent factors. Elgzyri et al [3] examined the influence of time to revascularization on outcome of ischemic foot ulcers in patients with diabetes. The study concluded that shorter time to revascularization positively affects the probability of healing of ischemic foot ulcer. These findings emphasize the need for prioritization of investigations and revascularization in patients with diabetes and severe PAD to improve outcomes.

For this reason, a prompt diagnosis of chronic limb-threatening ischemia (CLTI) with adequate targeted antibiotic therapy is critical to avoid the "stairway to amputation" (Fig. 1).

The use of clinically relevant classification and grading of DFU (such as Infectious Diseases Society of America and International Working Group on the Diabetic Foot (scheme, WIfI [Wound, Ischemia, and foot Infection], and SINBAD [Site, Ischemia, Neuropathy, Bacterial Infection, and Depth]) may help determine the clinical urgency.

In patient with DFU with severe infection, microbiological diagnosis and targeted antibiotic therapy are essential. For clinically infected ulcers, obtaining a tissue specimen for culture (and Gram-stained smear, if available) as early as practical is mandatory. Tissue sampling and transportation should be standardized and a close collaboration with a reference microbiology laboratory established. *Staphylococcus aureus* is the predominant pathogen, although severe infections are often polymicrobial, with Gram-negative, Gram-positive cocci, and anaerobes [2]. Therefore, in case of severe infections, a prompt empirical, parenteral, broad-spectrum antibiotic therapy is recommended. The empirical treatment should include antibiotics against *Staphylococcus* and *Streptococcus* spp and, in some specific situations, include antibiotics against Gram-negative, methicillin-resistant *S. aureus*, *Pseudomonas* spp, multidrug-resistant bacteria, and anaerobes [4].

This antibiotic therapy can be continued and adjusted according to the culture results and the patient's clinical response. If a clinical improvement is observed, empirical treatment can be continued, and adjusted to use the ones with the best safety profile. Conversely, if the infection does not respond, the initially selected agents should be replaced with broad-spectrum antibiotics. If the infection worsens further, despite proper antimicrobial therapy, other options, such as surgery or alternative therapies should be considered [5].

Although revascularization is the primary strategy to prevent limb loss, lack of consensus regarding technical aspects remain the main obstacles to achieving satisfactory outcomes in these patients [6].

Diabetes-related CLTI is just one part of diabetic foot syndrome that includes neuropathy, Charcot foot, infection of soft tissue and bone structures, and PAD with gangrene.

Patients with CLTI have an increased incidence of coronary artery disease and cerebrovascular events, leading to a reduced 5-year survival rate [7,8]. It is known that diabetes increases the risk of myocardial infarction by 50% and stroke by 25%, but the highest risk remains the limb amputation (major or minor). The 5-year mortality rate after major amputation is 55%, although this rate decreases to 32% in patients in whom limb salvage was successful [9]. Therefore, patients with diabetic foot syndrome (diabetes plus CLTI) are fragile and very high risk [10]. A holistic, multidisciplinary approach is required to prevent complications and offer adequate and rapid treatment when ulcers occur in this patient cohort.

2. Multidisciplinary team

The paradigm that saw a solitary specialist singlehandedly managing patients with DFU is now being replaced with the multidisciplinary teams (MDT) working within a hub-and-spoke model to deal effectively and efficiently with the growing epidemic of diabetes and its complications.

A dedicated DFU-MDT with robust diagnostic and therapeutic pathways is essential. Several decades of experience have shown that a multidisciplinary approach can reduce the amputation rate by 80% [11,12]. This team should include at least a vascular surgeon with an interest in diabetic foot,

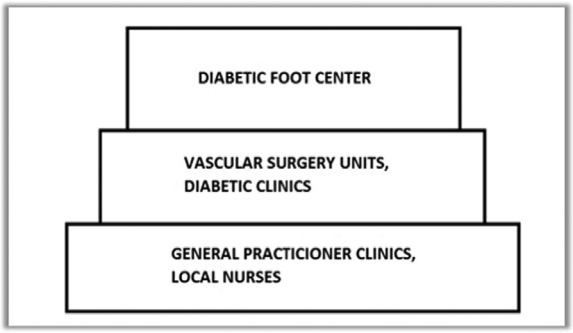

Fig. 2 – Levels of assistance.

diabetologist, microbiologist/infectious disease specialist, podiatrist, orthotist, orthopedic surgeon (foot and ankle), and a specialist tissue viability nurse. This should be complemented by a diabetic dietitian, interventional radiologists, and a plastic surgeon.

Patients with DFU should be managed in a hub-and-spoke model, with most of the care delivered close to home, in local general practitioner offices or community hospitals. Pathways, well-established policies, and procedures should be put in place to facilitate access to advanced diagnostics, and to be appropriate surgical care if, and when necessary.

The spoke centers should be able to manage the patients with DFU in the non-critical phase of the disease, with emphasis on prevention of escalation. Indeed, patients with low degree of tissue loss with or without infection, as in WIfI stages 1 to 3, and mild to moderate ischemia are often successfully managed on oral antibiotic therapy, with appropriate wound care, and input from a podiatrist. Similarly, patients who have undergone a successful revascularization and with healing wounds, could be managed locally to reduce the burden at the hub.

Accounting for differences in health care systems, regional networks should be developed linking DFU-MDT with general practitioners or primary care physicians creating integrated care systems, allowing for implementation of diagnostic and therapeutic pathways stratified according to the different burden of the disease.

All services in the community should be organized according to level of clinical burden that patients pose (Fig. 2) into the following three levels of care [13]:

1. Baseline levels (general practitioners and local nurses), whose purpose is to identify and closely follow-up patients at risk, and to involve them in educational programs. These teams would refer the high-risk patients to the intermediate care for further evaluation and management.
2. Intermediate-level DFU care (including both vascular surgery and diabetic clinics); this level should actively manage low-complexity DFU. These centers would ascertain access to adequate, timely diagnostics, and perform minor procedures (office-based).
3. Diabetic foot center (the hub): a reference level center (a tertiary referral center) specializing in the treatment of DFU, with vascular surgery and diabetology, able to manage the most severe and complex cases referred from spoke hospitals or the primary care. This level should be identified on the basis of availability of full range of open and endovascular modalities for lower limb revascularization. These centers must also have access to higher level of care (ie, high dependency unit, intensive care unit, and dialysis facilities) to provide emergency care to patients with severe sepsis.

The activities of the MDT should focus on coordinating all three levels of care.

GLOBAL Guidelines identified 9 skills for a reference center managing patients with DFU, and Fitzgerald et al suggested implementing 7 of them that are compulsory for any DFU-MDT (Table 1) [6,14].

It is vital that the patient and their family understand the problem and risks associated with DFU, and are directly involved in the management processes. This can significantly improve concordance and adherence to medications and therapy.

In a similar way to what has been in place for several years for oncologic diseases with the creation of tumor boards, the multidisciplinary group should create events for plenary discussion of the cases on a weekly basis for sharing processes and therapeutic decisions. This is also to allow sharing patient outcomes among all subjects involved in the MDT.

Another key point is the hospital management. The creation of a multidisciplinary group for the management of the DFUs increases the costs for the community. Management of patients with DFUs increases the costs per hospitalization due to the costs of advanced medications, materials for endovascular procedures, and antibiotic therapies for multiresistant bacteria [15,16]. Overall, the expenditure for the patients with DFU now requires 30% of the entire health expenditure dedicated to the treatment of diabetes mellitus [17].

At the same time, today there is also a progressive increase in limb rescue attempts in patients with multiple and severe comorbidities, and in situations that in the past would have undergone a primary major amputation, thus contributing to a further increase in costs. A well thought through business case is required with robust cost analysis in preparation for DFU-MDT. It should be noted that the initial cost can be offset due to prospective reduction in the major amputation rates.

Therefore, management of the patients with DFU within an MDT represents a standard of care and should be implemented in every community that wants to deal effectively with this complex disease [6].

3. Diagnostics

The ischemic component of DFU is the main factor leading to major amputation. A prompt diagnosis and treatment of CLTI is crucial.

Assessment of the degree of severity of the disease and choosing the best treatment approach is the first step and an integral part of treating CLTI and DFU. The WIfI classification provides a robust way to grade the disease and guide the management. The four stages of the WIfI classification seem to correlate with the risk of major amputation and wound healing

Table 1 – The nine essential skills for a reference center managing patients with diabetic food ulcers.

Essential skills	Possible team members
The ability to perform hemodynamic and anatomic vascular assessment	Vascular surgeon Interventionalist (cardiologist or radiologist) Vascular medicine
The ability to perform a peripheral neurologic workup	Neurologist Endocrinologist Podiatrist
The ability to perform site-appropriate culture technique	Infectious disease specialist Surgeon Wound nurse Physical therapist
The ability to perform wound assessment and staging or grading of infection and ischemia	Vascular surgeon Podiatrist Surgeon Infectious disease specialist Wound nurse Physical therapist
The ability to perform site-specific bedside and intraoperative incision and drainage or debridement	Podiatric surgeon Orthopedic surgeon Plastic surgeon Surgeon Vascular surgeon
The ability to initiate and to modify culture-specific and patient-appropriate antibiotic therapy	Infectious disease specialist Endocrinologist Primary care physician Vascular surgeon Podiatrist Surgeon
The ability to perform revascularization	Vascular surgeon Interventionalist (cardiologist or radiologist)
The ability to perform soft tissue or osseous reconstruction of deformities and defects	Podiatric surgeon Plastic surgeon Orthopedic surgeon Surgeon
The ability to perform appropriate postoperative monitoring to reduce risks of re-ulceration and infection	Podiatrist Wound nurse

From GLOBAL Guidelines [6], adapted with permission.

as well as the mortality rate [18]. Other studies reported that the WIfI is useful in deciding between open or endovascular treatment [19,20]. It can also be used for planning the follow-up [21].

The WIfI ischemia component is defined and described by objective parameters including ankle brachial index (ABI), ankle pressure, toe brachial index, toe pressure and transcutaneous oximetry ($TcPO_2$).

These parameters are used because they are the most often easily usable at the bedside or at the time of the examination. However, it is known that these parameters should be used with great caution and related to the clinics because they are susceptible to alterations and confounding factors [22,23] ABI, ankle pressure, and toe pressure are often falsely elevated due to the presence of calcinosis of the tunica media often present in diabetic patients or patients with chronic kidney disease, or $TcPO_2$ falsely reduced due to the presence of subcutaneous edema often present during infections or heart failure [24]. However, toe pressure and $TcPO_2$ are more sensitive than ABI and ankle pressure in identifying severe ischemic status [25,26].

These patients should still be evaluated in clinical terms with strict parameters to demonstrate a degree of ischemia that causes rest pain or that does not allow wound healing. Vascular imaging tests should also be performed to evaluate the extent and severity of PAD and to aid the physicians in the decision-making process about the type of revascularization to be performed. These tests must provide information on the vascular status from the aorto-iliac axis to the foot. Some authors still consider digital subtraction angiography as the "gold standard" because it offers dynamic information of vascular status, and computed tomography offers more precise quantification of arterial calcifications [27].

However, the first imaging method used is duplex ultrasound because it is non-invasive, more easily available, and cost-effective; it offers the possibility to obtain information on the entire peripheral vascular area, providing not only morphological data but also hemodynamic ones. The study of

Doppler waves, including hemodynamic parameters, such as peak systolic velocity, and end diastolic velocity, allows the physicians to understand the vascular status until the foot level [28,29].

4. Medical management

Diagnosis and vascular imaging are just two of the three fundamental steps for decision making about surgery [30]. Patients with diabetes and CLTI are at high risk of perioperative cardiac and cerebrovascular events. However, revascularization is necessary to treat ischemic status and PAD progression. Revascularization alone should not be performed in the absence of best medical therapy for the patient in order to decrease perioperative cardiovascular risks and improve long-term outcomes.

Best medical therapy for these patients is based on:

- lifestyle modification (such as physical activity, diet, smoking cessation, weight loss);
- antiplatelet therapy (prefer aspirin to clopidogrel in first-line treatment);
- cholesterol-lowering therapy;
- antihypertensive; and
- antidiabetic therapy.

First, CLTI is accompanied by high cardiovascular risk as mentioned, so aggressive identification and treatment of risk factors is essential. For this reason, all patients with symptomatic CLTI should be administered with antiplatelet agents from the first evaluation to reduce the risk of major adverse cardiovascular events. Aspirin should be the first-line treatment; however, there is growing evidence that alternatives to aspirin, such as clopidogrel, ticlopidine, and dipyridamole, might be effective as well. Second, concerning lipid-lower therapy, the use of moderate- or high-intensity statins is strongly recommended in both symptomatic and asymptomatic patients with CLTI with high low-density lipoprotein cholesterol, due to their effect in reducing all-cause and cardiovascular mortality. Likewise, antihypertensive and glycemic treatment should be administered to all symptomatic and asymptomatic patients from the first evaluation, thanks to the effect of reducing major adverse cardiovascular events and the risk of worsening PAD, respectively. In addition to these drugs to manage risk factors, it is necessary to encourage all patients with CLTI to adopt a healthier lifestyle from the first assessment [6].

5. Surgical treatment

Once CLTI diagnosis has been established, the GLOBAL guidelines (merging the WIfI stage with the GLASS stage, and evaluating clinical and anatomical patterns) help physicians to decide about the best possible treatment for the patients with DFU by suggesting endovascular or surgical revascularization. To improve treatment outcomes, the best option is to standardize treatments [31].

The aim is to guarantee a conduit to carry out blood continuously from the groin to the foot in what is defined as the target artery pathway. This should be the result of an open, endovascular, or hybrid surgery. To ensure that, it is necessary to guarantee good inflow and outflow status. The inflow depends on the arterial tree proximal to the superficial femoral artery, including the aorto-iliac segment and the common femoral artery. It is defined by the following criteria: absence of femoral pulsatility; rounded Doppler waves (dumping) on the common femoral; and aorta–common femoral artery gradient $>$ 10 mm Hg at rest.

Although the common femoral artery can be treated successfully with an endarterectomy, the iliac axis, in which the open surgical treatment is more challenging, can also be treated successfully with an endovascular approach using open stents to keep the iliac collaterals patent or, if necessary, covered stents [20].

Concerning the outflow, the choice of open or endovascular treatment should be suggested by the GLOBAL guidelines on the basis of the anatomic and clinical characteristics of the patient, above all taking into account the presence of an adequate great saphenous vein, which remains the conduit of choice for bypass [32]. The use of alternative venous conduits rather than prosthetic grafts is recommended in the literature, starting from the contralateral leg vein up to the cephalic veins [33]. However, it may also be reasonable in critical patients in advanced WIfI stages to attempt an initial endovascular approach, with the aim to guarantee direct-line flow to the angiosome involved in the DFU [31]. From a purely technical point of view, in recent years the increasing use of CO_2 as contrast appears to be very useful in reducing postoperative renal failure related to use of iodinated contrast mediums [34].

There is much debate in the literature about the usefulness of a direct-angiosome revascularization, according to which it is necessary to maximize the vascularization at the site of the lesion [35]; direct-angiosome revascularization seems to reduce the time to healing of DFUs [36,37]. A recent meta-analysis [38] demonstrated that direct revascularization of the tibial vessels seems to result in improved wound healing and limb salvage rates compared with indirect revascularization. Furthermore, direct-angiosome revascularization seems to be more useful in endovascular rather than open surgery. However, direct-angiosome revascularization is not always feasible.

Most patients with DFU present a multilevel disease, although a below-the-knee distribution is more frequent. For years, open bypass surgery has been the treatment of choice. The ongoing development of new diagnostic tools, endovascular technologies and equipment has led to an increased use of minimally invasive techniques, especially in fragile patients, as well as in complex disease anatomies. The ongoing BEST-CLI (Best Endovascular versus Best Surgical Therapy in Patients with CLTI) randomized controlled trial (RCT) found that among patients with a good quality of great saphenous vein, open bypass was superior as initial strategy. On the contrary, patients without adequate vein conduits might benefit from an endovascular approach first [32]. Patients lacking adequate great saphenous vein should be considered separately because they are at higher risk of limb loss. In this cohort, small saphenous veins and spliced or arm veins should

be considered as possible autologous conduits for below-the-knee bypass. Although the decision to use these conduits is highly dependent on the surgeon's experience and skills. Several studies reported the superiority of spliced/arm veins bypasses over prosthetic conduits [39]. However, these alternative conduits require a strict surveillance to guarantee satisfactory long-term patency. Concerning prosthetic grafts, a recent Cochrane review [40] comparing nine graft types (ie, autologous vein, polytetrafluoroethylene with and without vein cuff, human umbilical vein, polyurethane, Dacron, and heparin-bonded Dacron, FUSION BIOLINE, and Dacron with external support) concluded that for infrapopliteal bypass, no graft type is superior to any other in terms of primary patency. Therefore, the choice among different prosthetic conduits remains highly operator-dependent.

Another issue concerns inframalleolar disease, which constitute a major challenge in revascularization because no suitable artery for bypass crosses the ankle to the foot. A lot of endovascular techniques have been developed to overcome this problem, and open bypass surgery has been successfully employed for tarsal and plantar arteries, but again, techniques and outcomes are not well established [6].

As already mentioned, high-risk patients, such as those lacking suitable autologous conduits, might benefit from endovascular approach. Many endovascular techniques have been reported to treat infrapopliteal disease. Plain balloon angioplasty, drug-coated balloon angioplasty, bare-metal stenting, drug-eluting stenting, or covered stenting, and atherectomy may all be appropriate options on the basis of the lesion's anatomy. Plain balloon angioplasty remains the primary feasible endovascular approach for infrapopliteal disease; there is not sufficient evidence to support other more expensive techniques as first-line strategy. Technical advances in endovascular field to treat more complex lesions also include retrograde access technique [41] and "pedal loop technique," developed to achieve a complete pedal arch reconstruction [42]. Despite the increasing use of these alternative techniques, their efficacy and durability remain the main limitation.

6. Alternative treatments

Although the appropriate treatment for patients with CLTI is revascularization, a noteworthy part of patients is unsuitable for revascularization because of anatomic or physiological reasons. This cohort is defined as "no-option CLTI" [31]. This definition is based on the concept of a potential successful revascularization in patients without a suitable target artery pathway and "desert foot" (no visible arterial circulation). This type of arterial disease, mainly inframalleolar, is more common in diabetic patients and patients with end-stage renal disease. Furthermore, in the past was the main principle to perform major amputations. Currently, the broadening use of endovascular techniques contributed to relaunching the concept of no-option CLTI as an unexplored field to cross before considering a major amputation.

A lot of nonrevascularization techniques have been described, but there is still a lack of strong evidence regarding these alternative options. However, the primary goals in these patients are relieving ischemic pain, healing ulcers, avoiding limb loss, improving quality of life, and prolonging survival.

The concept of autologous cell therapy to treat no-option CLTI comes from the tumoral field. In the last few years, a lot of studies have been developed to evaluate the efficacy of bone marrow mononuclear cells and peripheral marrow mononuclear cells. Their use seems to reduce the rate of major amputation and promote wound healing. In particular, peripheral marrow mononuclear cells, which consist of a heterogenous population of lymphocytes and monocytes, seem to be the most effective autologous cells therapy, due to their easy collection and efficacy in diabetic patients [6].

Eventually, bone and dermal substitutes have become largely used, especially in large lesions with wide tissue loss, and seem to be safe and effective to promote tissue repair. A recent study [43] found that the dermal substitute Integra Dermal Regeneration Template for treatment of complicated foot lesions could be a useful option in term of limb salvage. Furthermore, available bone allograft types include cancellous or cortical bone, cadaveric bone, and demineralized and synthetic bone grafts [44]. All of these contribute in DFU and ankle reconstruction and can be used to repair large defects and enhance bone healing with promising results.

Another key point is wound management. Wound debridement is the cornerstone of ulcer management and it can be performed with different methods. Surgical debridement is used most frequently, due to its ease of application. Once debridement is performed, the choice between several dressing should consider wound features; there should be a balance between absorption of fluids if a lot of exudates are present and their release if the wound is dry. Many dressings are available to treat non-healing ulcers. Promising results have been reported with the use of the new platelet-rich plasma-fibrin glue dressing. A recent RCT showed that platelet-rich plasma-fibrin glue dressing, along with oral vitamin E and C, could be used to increase wound healing in patients with non-healing DFU by enhancing the wound healing process and reducing oxidative stress [45]. However, this RCT is based on a small sample size, so further studies will be necessary to validate these results.

Another option to improve wound healing might be hyperbaric oxygen therapy (HBOT) alone or in combination with common dressing. HBOT is based on the concept that DFUs are usually sustained by anaerobic bacteria, which preferably grow in a hypoxic environment. In addition, HBOT is able to develop neoangiogenesis, improve microcirculation, and reduce inflammation and edema. Recent data from an RCT found that HBOT significantly affected the rate of healing in DFUs in terms of wound size reduction compared with conventional wound care alone [46].

7. The importance of debridement and minor amputations

Preserving the ability to walk is an important aspect in the management of patients. Restoring independent ambulation increases quality of life and decreases costs to the health care system [47].

As we have mentioned, debridement plays a central role in DFUs management. It can be performed using several methods, such as enzymatic, autolytic, biological, mechanical, and surgical. Surgical debridement is used most frequently, due to its ease of application. Although many studies described techniques and outcomes of revascularization, very few described wound-healing outcomes after revascularization, and even fewer examined the ideal timing of foot reconstruction after surgical or endovascular revascularization. Currently, there is no evidence in the literature about the ideal timing for surgical debridement. It could be reasonable to assume that the rationale of performing debridement simultaneously with revascularization is primarily to reduce the number of patients' surgical procedures, as well as their intra- and periprocedural risks. Furthermore, debridement of foot wounds would improve the cost-effectiveness ratio of revascularization and have the potential to provide cost savings compared with local wound care alone. It might also minimize unplanned readmissions to the hospital, which occur mainly because of wound complications [48].

In any case, it may be not feasible to perform all surgical debridement in elective settings. However, emergent surgery is only necessary in specific conditions, such as gas gangrene or necrotizing fasciitis, compartment syndrome, or systemic sepsis. Surgery may range from minor debridement or drainage to extensive resections, revascularization, or major amputation. Surgical treatment of an infected DFU should be performed by a skilled surgeon with knowledge of foot anatomy and the ways in which infection spreads through fascial planes. The aim of surgical treatment is to drain any pus and minimize tissue necrosis by decompressing foot compartments and removing necrotic and infected tissues. Acute infections often spread along the tendons, therefore, infected tendons must be widely removed. Bone resection and amputation are mainly needed when there is extensive necrosis or to guarantee a more functional foot [4]. Nevertheless, a surgical approach should balance the benefits and risks of removing as much infected bone as possible against those of preserving viable tissue to aid foot function. Anyway, emergent surgery implies an aggressive and radical debridement consisting of exposing all infected tissue planes and removal of infected and necrotic bone. Any associated instability due to bone resections can be solved with temporary stabilization using threaded wires passed across the bones, external fixator, or a windowed cast [49]. In this context, the orthopedic surgeon plays a central role in providing a biomechanical perspective to avoid creating or leaving areas of hyper-pressure that would induce recurrence of ulceration with several techniques [50].

Minor amputation means digital amputation of one or more phalanges or an entire radius, transmetatarsal of the forefoot, Lisfranc, or Chopart of the midfoot. Each of these amputations may be useful for preserving ambulation in selected patients, although the rate of reinterventions still remains high [51]. Because a well-planned minor amputation offers patients a high probability of independent ambulation, this procedure should not be regarded as a failure of vascular surgery. Instead, it should be considered as an additional weapon to preserve walking ability in selected patients, but also for the immediate reduction of ischemic pain and/or infectious risk. Obviously, the success of a minor amputation is related to the good perfusion of the amputation stump.

However, there are situations when an attempted limb salvage is unlikely because it would result in too much physiological stress or would be not useful due to limb dysfunction; in such patients, primary major amputation should be considered as a viable option.

In general, *primary amputation* is defined as amputation without any previous revascularization attempts. The four goals for primary amputation are ischemic pain relief; removal of all necrotic, infected lesions from the foot; primary healing; and independent walking.

Primary amputation is therefore also indicated in those cases when there are no target arteries to revascularize, if the lesions (ulcers or gangrene) have destroyed the weight-bearing portions of the foot, or in cases when the patient has lost the ability to move the limbs (paralysis and ankylosis).

Unfortunately, some patients with DFUs in a worse scenario could benefit from primary major amputation. In those presenting with cellulitis, gas gangrene, necrotizing fasciitis, or systemic sepsis that constitutes a possible life-threatening condition, it could be reasonable to perform a primary major amputation above or below the knee, depending on the local extension of infection. Furthermore, amputation might be appropriate in patients with DFU with severe infection when conditions are not improving or even worsening, despite broaden-spectrum, parenteral antibiotic therapy and appropriate wound care [5].

Choosing the right level of amputation remains a critical and important point. Unfortunately, there are no generally accepted methods for predicting the best level of amputation, which still remains a clinical decision. Several techniques have been examined, including thermography, skin perfusion pressure, Doppler waveforms, and $TcPO_2$. $TcPO_2$ levels below 40 mm Hg increase the risk of dehiscence [52].

8. Periprocedural management and follow-up

All patients who undergo revascularization must continue with best medical therapy to slow down the atherosclerotic process and to decrease as much as possible the risks related to all other risk factors mentioned. In patients defined as being at high cardiovascular risk, the low-density lipoprotein range must be kept < 55 mg/dL, according to recent guidelines [53].

Similarly, due to the fact that glycemic fluctuation and chronic hyperglycemia can trigger the inflammatory response and increase the thrombogenicity, leading to the development of macrovascular disease, GLOBAL Guidelines fixed the hemoglobin A1c target levels at $< 7\%$ (53 mmol/mol). Antiplatelet therapy is a milestone of vascular medicine to reduce thrombotic events and to improve overall patency and limb salvage rates after vascular surgery. Acetylsalicylic acid (ASA) remains a pillar of treatment because it is cost-effective [54]; even the single-dose efficacy of clopidogrel is well-established [55]. However, it has been noted that up to 30% of patients with PAD treated with clopidogrel do not achieve the necessary antiplatelet response, leading to the conclusion that patients with PAD have greater resistance to clopidogrel than patients with coronary artery disease [56]. Although

there is no level 1 evidence, double-antiplatelet therapy is usually applied for a period ranging from 1 to 6 months after surgery [57]. Additional RCTs are needed to better define the risks and benefits of double-antiplatelet therapy in patients with PAD.

An emerging option in patients with PAD who have undergone lower-extremity revascularization is the combination of ASA 100 mg once daily plus low-dose rivaroxaban 2.5 mg twice daily [58]. Studies (such as Voyager PAD) found that this pharmacological approach is associated with a significantly lower incidence of acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, or death from cardiovascular causes in comparison with patients treated with ASA alone. The incidence of hemorrhagic complications did not differ significantly between those who were treated with ASA alone and those who received the ASA plus rivaroxaban protocol [59].

Today, this protocol still seems to be underused, but it is likely that in the near future it will become the standard of care for patients undergoing lower limb revascularization.

Follow-up is a crucial point in patients undergoing lower extremity revascularization. In many case, early detection of restenosis or occlusion reduces the risk of limb loss with a secondary procedure performed to maintain the target artery pathway open with a direct-line flow to the foot [60]. In summary, follow-up in the revascularized patient is similar to what occurs in patients with cancer; it must be continuous over time and aimed to verify whether the situation is the same as in the immediate postoperative period or if it is getting worse.

Follow-up based on clinical surveillance alone may be not sufficient because patients with stenosis may remain asymptomatic until the vessel is completely occluded, putting the patient again at a CLTI status. Recent guidelines support duplex ultrasound surveillance and prophylactic reinterventions, even for asymptomatic vein bypass stenoses [6]. Follow-up seems to be crucial, especially in the first year after index procedure [61].

An emerging issue is to carry out effective control of all revascularized patients; this involves the use of resources that are often not available in vascular surgery departments and mainly oriented toward management of the acute phase of hospitalized patients. In this field, unlike the oncological one, there is not yet a widespread culture of open-ended follow-up where the surgeon who performs the revascularization is also called to take charge of the follow-up for months and years. It becomes essential to be able to identify methods and tools that should be simple to use, even with non-medical equipment.

After both surgical and endovascular revascularization, patients should be evaluated to assess whether an appropriate revascularization has been obtained. This evaluation includes patient's clinical status and measurement of ABI and $TcPO_2$. However, noninvasive tests may not be reliable in patients with extensive wounds or severe calcifications. Thus, alternative methods have been proposed to overcome these limitations. Teso et al [62] proposed that pedal acceleration time (PAT) could be a predictor for limb salvage in patients with CTLI and seems to correlate with ABI in patients with compressible tibial vessels. This technique can be performed simply by scanning pedal arteries with a standard duplex ultrasound, available in most vascular laboratories. PAT can be measured in time over slope from the onset of systole to the peak of systole. On this basis, PAT can be categorized into the following four classes: class 1 (20 to 120 ms), class 2 (121 to 180 ms), class 3 (181 to 224 ms), and class 4 (> 225 ms). Furthermore, limb salvage is associated with a PAT of > 180 ms regardless of direct or indirect flow to the wound bed. Due to its performing simplicity, PAT might be a promising tool for the evaluation of ischemic limbs after revascularization.

Another method to assess the outcomes of revascularization is indocyanine green angiography (ICGA). The procedure provides the injection of 0.1-mg/kg dose of ICG via a peripheral venous line. Immediately after the injection of ICG, fluorescence images can be obtained using an infrared camera system. ICGA tests rapidly provide qualitative information regarding foot perfusion, and can be used to quantitatively evaluate the degree of perfusion in peripheral tissues. Despite these promising features, ICGA is more invasive, results can be subjective, costly, and not readily portable compared with PAT [63]. Lastly, because of the lack of availability in most centers and the small sample size of the studies, further research is needed to evaluate the reliability of ICGA parameters, especially in defining the severity of PAD after revascularization.

Another key point to consider in patients who have undergone revascularization is how to prevent recurrence of DFUs during follow-up. Educating patients, family, and health care professionals about foot care is widely considered to play an important role in the prevention and recurrence of DFUs. It is essential to explain to patients the need for daily foot inspection of the entire surface of both feet. Then explain that they should avoid walking barefoot and in socks without footwear or that are too tight or knee-high, and they should wear socks without seams and change them daily. Furthermore, washing feet daily (with water temperature always < 37°C) and drying them carefully, especially between the toes, is mandatory. Eventually, wearing special therapeutic footwear with offloading properties is effective in reducing the incidence and recurrence of DFUs. However, it seems that the effect may decrease gradually over time [64], probably due to the loss of patient compliance over years. For this reason, clinicians and surgeons should encourage patients to comply with a strict follow-up.

9. Myth busters

The habit of the vascular surgeon who treats a patient with PAD is to encourage him to walk "because walking favors the development of collateral circulation." Indeed, for patients with inactive DFU, mobilization with appropriate footwear and physical fitness is potentially beneficial. Conversely, in patients with DFU with active disease, this advice could be more harmful than helpful. In patients with active DFU, the neoangiogenesis is extremely reduced or totally absent. Furthermore, the cells of the tunica media mutate until they almost become real osteoblasts causing, in the worst case, what is called Mockenberg syndrome, a condition where vessels become completely inelastic and calcified [65]. Therefore, suggesting to patients with active DFU to walk as much as possi-

ble increases the risk of injuries from repeated trauma in the absence of a real advantage in terms of recruitment of new vessels.

Another point is the use of vasodilatative drugs, which are effective in reducing pain and amputation rates in selected patients [66,67]. However, the use of topical drugs in patches to be applied on the back of the foot is widely used in clinical practice. This practice is highly inadvisable because it is very high risk of creating skin lesions.

10. Conclusions

DFU is a complex disease and needs to have fast tracks and dedicated pathways in order to reduce the risk of limb loss. A correct and rapid diagnostic framework ("time is tissue") is necessary. Eradication of all possible sources of infection in the foot is mandatory, and optimization of medical therapy and modification of lifestyle appear to be essential. In addition, dedicated networks should be created to allow the long-term management of patients after revascularization. The high costs necessary to support the follow-up and management of these patients can be reduced throughout the creation of standardized protocols in dedicated organizations. In this way, it is possible to guarantee these patients an acceptable quality of life and a partial or total reintegration into social life.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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