

Grey-zone in the treatment of patients with Diabetic Foot. The results of an Italian multidisciplinary Delphi survey conducted among a group of experts

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ABSTRACT

Diabetic foot is one of the most severe complications of Diabetes Mellitus (DM) and the leading cause of non-traumatic amputation of the lower limbs, with an estimated one million people with DM undergoing radical treatment each year as a result of this condition. Despite the existence of national and international guidelines on diabetic foot management, in some aspects of management the recommendations given are not supported by a strong body of evidence. This can be a potential source of uncertainty in decision-making, but also a starting point for clarification of aspects related to diabetic foot management in Italian practice. The objective of this document is, therefore, to recalibrate the international recommendations on diabetic foot management in the light of the opinions of Italian experts.

INTRODUCTION

Every year more than one million people with Diabetes Mellitus (DM) undergo non-traumatic lower limb amputation as a result of this condition. There are several areas of uncertainty in decision-making related to diabetic foot management. This review collects the opinions of Italian experts on aspects for which the guideline recommendations are not supported by strong evidence.

DIABETES MELLITUS: CLASSIFICATION OF THE PATHOLOGY AND ITS ASSOCIATED COMPLICATIONS

DM is a metabolic disease, characterised by hyperglycaemia as a consequence of a complex interaction between genetic, immunological and environmental factors. Underlying the pathology is the loss of pancreatic beta cells and insulin deficit in type 1 diabetes, insulin resistance, altered insulin secretion and increased liver glucose production in type 2 diabetes.

The hyperglycaemia that characterises diabetes mellitus causes, over time, the onset of micro and macro-vascular complications, often severe, which can cause disability and have a significant impact on the patient and the health care system.

These complications are divided into microvascular (retinopathy, nephropathy and neuropathy), macrovascular (coronary artery disease, peripheral obliterative arteriopathy and cerebrovascular disease) and non-vascular (skin changes and infections) complications. The complications of diabetes mellitus are the main cause of morbidity and mortality associated with the disease, in fact they can lead to the development of chronic renal failure, blindness, non-traumatic amputations of the lower limbs, heart attack and stroke. The incidence of DM is increasing worldwide with about 250,000 new cases per year. The increase is mainly due to the ageing of the population and some risk factors (overweight, obesity and sedentariness). According to the World Health Organisation (WHO), 52 million people are affected by DM in Europe and 346 million

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worldwide, with considerable variations depending on the geographical area. According to the Italian National Statistics Institute, in 2015, 5.4% of the population was affected by diabetes:^{1,2} 90% by DM type 2 and 10% by DM type 1. Recently published data from the Arno Observatory indicates the incidence of diabetes in Italy at 6.2%.³

DIABETIC FOOT: PREVALENCE, PATHOGENESIS AND RELATED COMPLICATIONS

Diabetic foot, one of the most severe complications of DM, is defined by the presence of ulceration and/or destruction of deep tissues associated with a variable degree of peripheral neuropathy and arteriopathy. Diabetic foot is the leading cause of non-traumatic amputation of the lower limbs (which in 85% of cases is preceded by ulceration) as well as a frequent reason for hospitalisation^{3,4} and a negative prognostic factor for mortality. In particular, in a prospective multicentre study of 917 foot ulcers in diabetic patients, wound healing was found to be an independent predictor of life expectancy and risk of amputation.⁵ The prevalence and incidence of ulcers in the diabetic foot are variable and often discordant in the various studies reported in the literature. Overall, it is estimated that in Europe the prevalence of ulcerative foot lesions in diabetic patients is 5.5%. Two thirds of these lesions heal while just under 30% of these lesions are amputated.⁶ It is estimated that globally, every 20 seconds a patient loses a limb due to diabetes complications.⁴ Risk factors for the development of ulcerative foot lesions include male sex, smoking, type 2 DM, advanced age, duration of illness over 10 years, peripheral neuropathy and/or obliterative arteriopathy of the lower limbs, hypertension, diabetic retinopathy, diabetic nephropathy, poor glycemic control, a positive history of previous ulcerations, the presence of structural alterations of the foot (presence of bone alterations, callosity, nail thickening), the use of inappropriate footwear. The pathogenesis of lower limb complications in diabetic patients is multifactorial with several factors playing a role, but fundamentally including neuropathy and peripheral vasculopathy. Peripheral neuropathy, interfering with nociception, causes hypoesthesia and therefore predisposes to inadvertent trauma because it is not associated with pain. In addition, the alteration of proprioceptive capacity, causing an abnormal load during walking, leads to biomechanical stress, dermal suffering with consequent cell hypoxia, subcutaneous bleeding and tissue ulcerations. Finally, autonomic neuropathy, which occurs with anhydrosis and alterations in the microcirculation predisposes to skin dryness and fissures. Peripheral arteriopathy is present in 50% of patients with diabetic foot ulcers and is generally caused by atherosclerosis with decreased or interrupted blood flow in one or more lower limb arteries.⁷ However,

only a small percentage of these ulcerations are purely ischemic, most of them being neuropathic or neuro-ischemic (*i.e.* caused by the simultaneous presence of neuropathy and ischemia).⁸ Neuropathic ulcerations are typically located in hyperload areas such as metatarsal heads, have irregular contours with hyperkeratotic perilesional margins and are characterised by absence of pain. Ischemic lesions are typically localised on the heel, apex and back of the toes, interdigital spaces, have regular, well-defined margins with atrophic perilesional skin, and most often are accompanied by intense pain.⁸

A rapid nosological classification of the ulcer is essential for proper management of ulcerative lesions and their associated complications. In addition, ulcer infection is associated with a marked increase in the risk of amputation. A clinical diagnosis of infection can be made in the presence of at least 2 classic signs of local inflammation including redness, swelling, pain, hardening/edema, warmth on palpation or purulent exudate. In the most serious cases the infection and exudate can spread to the deepest soft tissues, extending along the tendon sheaths until a phlegmon develops, involving the subfascial spaces of the back or sole of the foot.

A CLOSER EXAMINATION OF CRITICAL ISSUES/GREY ZONES EMERGING FROM THE DELPHI CONSENSUS

The Delphi method is an interactive survey method that facilitates a discussion between a panel of experts with the primary objective of collating the opinions of each member into a more complete common position (*consensus*). The points on which a *consensus* position is not reached reflect the complexity of DM, particularly in relation to aspects of the multidisciplinary management and treatment of diabetic foot conditions. The critical issues that have emerged, defined by the term “grey zones”, correspond to topics for which the data in the literature is insufficient and the guidelines do not appear to be a point of reference. The survey that was conducted previously was designed to explore the views of a panel of Italian experts on diabetic foot management.⁹

RESULTS

The results of the survey highlight critical issues arising from 7 areas of non-consensus. Non-consensus tables 1-3-4-6-8 are presented, for the others see the previously published survey results.⁹

The first element of non-consensus, albeit with a trend towards agreement among experts, concerns the pathophysiology of diabetic foot lesions (item 1.4, Table 1). In particular, it is not unanimously agreed that diabetic foot

lesions are predominantly caused by peripheral neuropathic neuropathy. This may be due to the extreme pathogenetic complexity of the diabetic foot syndrome. In fact, although the neuropathic component plays a fundamental role, the vascular aspect is often perceived by clinicians as the primary reason why ischemic patients are considered to be at a more advanced stage of disease than purely neuropathic patients. Moreover, at least in part, the formal approach of the statement may have been a harbinger of disagreement. In particular, the term “macro-vascular impairment” seems to include a broader concept, which is open to different interpretations. Of these, there is the viewpoint of the vascular surgeon, for whom the distal peripheral arteriopathy, typical of the diabetic patient, determines an involvement of the collateral circulation and the small arteries of the vascular arches of the foot, conditioning the run-off bed for revascularisation procedures. However, the revision of the most recent Guidelines on the subject⁸ stresses that most ulcerations are predominantly neuro-ischemic, thus underlining the etiopathogenetic importance of neuropathy.

The second element of non-consensus concerns two items related to the role of the antiseptic (Table 2).

The first item (3.5) documents the absence of consensus on the view that it is essential to apply an antiseptic to prevent diabetic foot infection and guarantee healing within physiological time frames. The panel of experts believes that a possible explanation for the lack of consensus lies in the unclear formulation of the question, which results in an ambiguous interpretation of the concept of “physiological time frames”. The role of the antiseptic depends on the type of lesion: in the case of a

superficial lesion, an irrigation with saline solution is sufficient. However, in the case of a deep lesion, a phlegmon, or where there are evident signs of infection, the use of an antiseptic is recommended in order to prevent the extension of the infectious process to the deep tissues, since this would expose the patient to an increased risk of osteomyelitis and, in extreme cases, to the need to proceed with minor or major amputation surgery. On this issue, it also emerged that in cases of biofilm lesions, careful disinfection is necessary before any treatment. It was also acceptable to use an antiseptic in complex lesions¹⁰ to allow the removal of exudate and the reduction of bacterial load, thus accelerating healing times, which tend to slow down when there is a full-blown local infection. In addition, the use of an antiseptic appears to be crucial in two specific contexts: during the initial dressings when the patient is taken on (a phase in which the risk of having to deal with an infection of the lesion is greater, as it was probably not treated until then) and in the case of operations with skin grafts (a phase in which the presence of infection could result in a failure of plastic surgery due to the failure of the graft). Recently, in doubtful cases, fluorescence diagnostics have shown that wounds with a bacterial load $>10^4$ CFU can be detected. On the other hand, the use of antiseptic is not recommended in phases where the bottom of the lesion appears to be dominated by the production of active granulation tissue. In these cases a simple cleansing with crystalloids and/or physiological solution is preferable. It is documented that the coexistence of an infectious state and arterial insufficiency of the lower limb triples the risk of an ulcer not healing compared to cases with neuropathy or vasculopathy but with-

Table 1. Definitions and classifications - I consider that:

	1	2	3	4	5	TOTAL
1.1. diabetic foot lesions are a local manifestation rather than the evolution of a general syndrome	23	7	1	1	0	32
	94%		6%			100%
1.2 the classifications of lesions currently used are necessary for the proper management of diabetic foot lesions	0	0	5	17	10	32
	0%		100%			100%
1.3. it is useful to classify diabetic foot infections as mild, moderate (class A and B) and severe for proper diagnostic therapeutic management, according to IDSA 2012.	0	2	4	13	13	32
	6%		94%			100%
1.4. the physio-pathogenesis of a diabetic foot lesion is predominantly sustained by a substrate of peripheral neuropathy versus macrovascular impairment	4	8	10	9	1	32
	36%		64%			100%

out infection.¹¹ It is, therefore, essential to type the patient and the type of lesion in order to personalise the timing of intervention, the professionals involved and the most appropriate treatment.

Item 3.6 documents a second aspect on which there is no consensus, concerning the view that it is essential to apply an antiseptic to facilitate healing in physiological time frames (the response trend tends towards positive consensus). On this item also, the panel of experts considers that the formulation of the question makes different interpretations possible, despite the fact that it was intended merely to “provoke” each clinician to describe their daily approach, focusing on personal experience and the tools available, especially in cases where the Guidelines are difficult to apply. Considering the term “physiological time frames” as an aspect on which there is no consensus, it was decided to interpret it as synonymous with “expected time frames”.

With regard to the critical aspects concerning the phase of taking on a patient with diabetic foot-related lesions and monitoring them over time, item 4.8 (Table 3) documents the absence of consensus on the view that the assessment of inflammation is essential for the classification of diabetic foot infection. The panel of experts agreed that the subjective interpretation of the term “classification” should not be confused with the concept of “diagnosis”. In fact, there are validated criteria for the diagnosis of diabetic foot lesion infection. In particular, hyper-

glycemia states, apparently unjustified but actually linked to an inflammatory state, and alterations in the inflammation indicators (reactive C protein and procalcitonin) are crucial elements for evaluating the effect of treatment, the need for a change in the therapeutic procedure and follow-up, while their role in the diagnostic phase is considered marginal.

Item 6.4 (Table 4) describes the absence of consensus on the view that in wound care the choice of advanced dressing is decisive for wound healing. Doubts were raised as to the interpretation by the panel of experts, as clinical reasoning should have led to a positive consensus, given that advanced dressings are differentiated and have indications for use in relation to particular stages of the healing process, serving as aids to correct wound bed preparation according to the concept summarised in the acronym TIME (correct tissue management, treatment of the infection, maintenance of a moist environment and facilitation of regeneration of the epithelial margin of the lesion). Moreover, the five therapeutic approaches considered (“standard wound care”, biological drugs, platelet growth factors, cell therapy and hyperbaric therapy) are not uniformly applied by panel clinicians. This lack of consensus on approach could be due to the fact that there is little scientific evidence on the role of each of these interventions. The board agrees that an advanced dressing accelerates the healing process by creating a moist, adequate and more physiological microenvironment than

Table 2. Role of antiseptic - I consider that:

	1	2	3	4	5	TOTAL
3.1. initial disinfection of diabetic foot lesions is essential prior to any diagnostic-therapeutic approach, in order to ensure subsequent optimal management of the lesion	0	6	6	10	10	32
	18%		82%			100%
3.2. the ideal characteristics of an antiseptic to be used in this setting are speed of action and broad spectrum	0	1	5	17	9	32
	3%		97%			100%
3.3 cytotoxicity is a criterion to be considered when choosing the antiseptic	0	1	9	13	9	32
	3%		97%			100%
3.4. the absence of colouration is a key characteristic of an antiseptic	0	5	9	7	11	32
	15%		85%			100%
3.5. it is essential to apply an antiseptic to prevent diabetic foot infection in order to guarantee healing within physiological time frames	1	14	10	4	3	32
	48%		52%			100%
3.6. it is essential to apply an antiseptic to facilitate healing within physiological time frames	1	11	10	8	2	32
	36%		64%			100%

would be achieved with traditional dressings. Given the lack of guidelines based on authoritative scientific evidence regarding the use of advanced dressings with antibacterial products, the board believes that the use of these dressings, in particular negative pressure wound therapy (NPWT) and sucralfate-based dressings, should be based primarily on experience and clinical judgement. In fact, the most recent IWGDF Guidelines⁴ confirmed that NPWT is indicated as a “best standard of care” (BSC) ad-

juvant treatment to reduce the size of post-surgical lesions, but suggest that it not be used as a substitute for BSC in non-surgical wounds. The same guidelines, in a recommendation rated WEAK, and evidence quality MODERATE, invite clinicians to consider the use of sucralfate-based dressings in non-infected neuroischemic ulcers that have not responded to BSC treatments.

The statement also specifies that in the healing process, it is not only the dressing applied that is decisive, but also

Table 3. Diagnosis - I consider that:

	1	2	3	4	5	TOTAL
4.6 it is useful to take a superficial swab of the ulcer by surface rolling	11	15	4	2	0	32
	82%		18%			100%
4.7 alternative methods such as needle-mediated aspiration of wound secretions are useful	0	9	14	2	7	32
	27%		73%			100%
4.8 it is essential to assess the phlogosis indices to grade the diabetic foot infection	2	11	10	3	6	32
	39%		61%			100%
4.9 haemocultures must be performed where there is a diabetic foot ulcer	4	19	5	3	1	32
	73%		27%			100%

Table 4. Other therapeutic approaches - I consider that:

	1	2	3	4	5	TOTAL
6.1. after 4 weeks of “standard wound care” without having achieved at least a 50% reduction, staging of the lesion should be reconsidered	0	0	8	16	8	32
	0%		100%			100%
6.2 where the lesion is not improving, biological medications, platelet growth factors, cell therapy, and hyperbaric therapy should be used.	3	18	9	2	0	32
	67%		33%			100%
6.3 where the lesion is not improving, vascular reassessment is essential.	0	0	3	14	15	32
	0%		100%			100%
6.4 in wound care the choice of advanced medication is key to its healing	1	15	9	3	4	32
	48%		52%			100%
6.5 the presence of a severe infection requires hospitalisation to guarantee correct diagnostic and therapeutic management	0	1	2	10	19	32
	3%		97%			100%

adequate management of the TIME wound bed and the patient as a whole, according to a holistic approach.¹²

Statement 8 on surgery has two aspects on which there is no consensus (Table 5).

Item 8.3 describes the absence of consensus on the view that primary major amputation is a valid surgical option in case of systemic signs of infection. However, the term “option” does not seem adequate and the board agrees that primary amputation is not “an option” but should be considered as a last resort in cases of systemic infection with typical clinical manifestations including fever, intense pain, general discomfort, metabolic imbalance and organ impairment (individual signs of infection, such as the presence of persistent isolated hyperpyrexia, are not, in the opinion of the panel, an indication for amputation). In the case of an infected wound, the experts agree that conservative management (preparation of the wound bed, accurate debridement and management of systemic signs) is the first choice approach. Of extreme importance is the presence of a multidisciplinary team that adequately manages timely and prolonged conservative treatment.

Item 8.4, on the other hand, highlights the absence of consensus (albeit with a trend towards negative consent) on the view that major amputation should be preferred to repeated and prolonged conservative treatment of a severe lesion. The correct management of a severe lesion is conditioned by two critical issues: on the one hand, the health care costs¹³ related to conservative treatment, which often do not take account of the direct costs of prosthetisation and rehabilitation of the patient and the indirect costs borne by the family, and on the other hand data in the lit-

erature showing an increased mortality rate among patients undergoing major amputation. Despite the lack of homogeneity of approaches and resources available in the territory, the panel of experts stresses the need to follow the Guidelines, which are a tool for good clinical practice, as well as protection for a clinician who is required to manage complex situations that have medical-legal implications.

OPINION OF EXPERTS IN DIABETIC FOOT MANAGEMENT

The factors leading to the development of foot ulcers in diabetic patients are complex and require the intervention of various professionals, with multiple treatments to be performed over a prolonged period of care. Accordingly, healthcare professionals with experience in various specialities should be involved in the management of the diabetic foot in order to make a specific contribution in relation to their field of experience. Of the health professionals involved in the treatment of diabetic foot, the podiatrist plays a fundamental role. In fact, the podiatrist intervenes when a patient is taken on, putting the first dressings on when the risk of infection of the lesion is greatest. At a more advanced stage, infection in patients undergoing surgery involving skin grafts may result in a failure of the graft to take root and are therefore a contraindication to the performance of this surgical procedure requiring further clinical action for its elimination. From the vascular surgeon’s standpoint, given that revascularisation procedures in these patients often allow primary patency of only a few months,

Table 5. Surgery - I consider that:

	1	2	3	4	5	TOTAL
8.1 the presence of gases in the tissues surrounding the ulcer with the presence of necrotised fasciitis is an appropriate indication for urgent surgery	0	0	2	4	26	32
	0%		100%			100%
8.2 In the presence of severe infected lesions (cellulitis, fasciitis, phlegmon or abscess) urgent surgery is warranted	0	0	2	3	27	32
	0%		100%			100%
8.3 major primary amputation is a valid surgical option in case of systemic signs of infection	6	13	4	5	4	32
	61%		39%			100%
8.4 major amputation should be preferred to repeated and prolonged conservative treatment of a severe peripheral lesion	5	14	3	5	5	32
	61%		39%			100%

attention should be paid to the correct timing for revascularisation surgery. Although revascularisation procedures are effective in the treatment of vascular insufficiency/ischemia, their extensive use is likely to be overestimated when compared to the improvements achieved with correct and less invasive wound management, especially in the case of the neuroischemic foot.

DIABETIC FOOT MANAGEMENT: NEED FOR MULTIDISCIPLINARY MANAGEMENT

The primary objective of diabetic foot management is the prevention of ulcers and amputations (secondary to the presence of an ulcer in 85% of cases) in order to reduce the inevitable economic and psychosocial impact. Due to the complexity and heterogeneity of the clinical pictures, multidisciplinary management is required to ensure effective collaboration between the professionals involved.^{14,15}

The recent publication of the Position Statement of the Italian Study Group on the Diabetic Foot sought to identify the specific tasks and responsibilities of individual team members, while at the same time indicating who does what when taking care of a patient with diabetic foot.¹⁶

Added to this is the need to involve and educate the patient in self-management through foot care and the use of appropriate footwear. The desirable care model should therefore provide for cooperation between the various professionals (general practitioner, diabetologist, neurologist, orthopaedist, general surgeon, vascular surgeon, nurse, dietician, podiatrist, orthopaedic technician, psychologist and/or psychiatrist) who work to ensure that the patient is cared for in a holistic sense, using adequate communication and relational techniques.¹⁷ The available evidence, starting from a series of Italian observational studies, shows that the active participation of diabetes centres, alongside general medicine, is associated with a significant reduction in mortality.¹⁸⁻²² Finally, the presence of a multidisciplinary team for diabetic foot care has shown a reduction in the amputation rate of between 49 and 85%.¹⁷ For team operators it is therefore necessary, through the creation of dedicated interdisciplinary university masters, to introduce a common basic training and approach to the patient and the lesion, with an awareness of the need for a timely referral to the various specialists in the field.

THE “IDEAL” ANTISEPTIC: ROLE IN DIABETIC FOOT MANAGEMENT

With respect to the polymicrobial aetiology of diabetic foot infections, the role of antiseptics is crucial. Between 40% and 60% of DM patients treated for a foot ulcer receive antibiotic treatment. Although the use of antiseptic

is recommended for the treatment of infected ulcers, incongruous use is frequently associated with local adverse effects and bacterial resistance. Therefore the essential characteristics of the “ideal” antiseptic include rapid and broad-spectrum action, no interference with the healing process, no provoking of local irritation, being colourless to enable monitoring of the wound bed over time, and not inducing bacterial resistance in the treated strains.

GUIDELINES: SUPPORT TOOL OR TO LEARN MORE

Despite the variety of clinical approaches and resources available in Italy territory, the Guidelines represent both a tool for good clinical practice and a means of protection for the clinician called on to manage complex situations that often also have medical-legal implications. However, although the management of the diabetic foot is the subject of specific recommendations, there remain open questions of wound management in relation to which the guidelines do not provide strong evidence, or for which individual experiences are particularly uneven. A potential future objective is the organisation of international trials that focus on the critical issues that are not sufficiently dealt with in the literature.

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