Treatment of Diabetic Foot Ulcer: An Overview Strategies for Clinical Approach

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Abstract: Diabetic foot disease is a major health problem, which concerns 15% of the 200 million patients with diabetes worldwide. Major amputation, above or below the knee, is a feared complication of diabetes. More than 60% of non-traumatic amputations in the western world are performed in the diabetic population. Many patients who undergo an amputation, have a history of ulceration. Major amputations increase morbility and mortality and reduce the patient's quality of life. Treatment of foot complications is one of the main items in the absorption of economic and health resources addressed to the diabetic population. It is clear that effective treatment can bring about a reduction in the number of major amputations.

Over recent years, we have seen a significant increase in knowledge about the physiopathological pathways of this complication, together with improvements in diagnostic techniques, but above all a standardized conservative therapeutic approach, which allows limb salvage in a high percentage of cases. This target has been achieved in specialized centers.

An important prelude to diabetic foot treatment is the differing diagnosis of neuropathic and neuroischemic foot. This differentiation is essential for effective treatment.

Ulceration in neuropathic foot is due to biomechanical stress and high pressure, which involves the plantar surface of toes and metatarsal heads. Treatment of a neuropathic plantar ulcer must correct pathological plantar pressures through weight bearing relief. Surgical treatment of deformities, with or without ulcerations, is effective therapy. A neuropathic ulcer that is not adequately treated can become a chronic ulcer that does not heal. An ulcer that does not heal for many months has a high probability of leading to osteomyelitis, for which treatment with antibiotics is not useful and which usually requires a surgical procedure. Charcot neuroarthropathy is a particular complication of neuropathy which may lead to fragmentation or destruction of joints and bones. A well-timed diagnosis of Charcot neuroartropathy is essential to avoid deformities of chronic evolution.

In the diabetic population peripheral vascular disease (PVD) is the main risk factor for amputation. If peripheral vascular disease is ignored, surgical treatment of the lesion cannot be successful. In diabetic patients, PVD is especially distal, but often fully involves the femoral, popliteal and tibial vessels. It can be successfully treated with either open surgical or endovascular procedures.

Infection is a serious complication of diabetic foot, especially when neuroischemic: phlegmon or necrotizing fascitis are not only limb-threatening problems, but also life-threatening ones. In this case, emergency surgery is needed.

Primary and secondary prevention of foot ulceration is the main target. Prevention programs must be carried out to highlight risk factors, lowering amputation incidence.

Keywords: Diabetic foot, Amputation, Diabetic ulceration, Critical limb ischemia, Diabetic foot surgery, Revascularization.

INTRODUCTION

Diabetic foot must be considered a syndrome. Two aspects are recognised: neuropathic foot and neuroischemic foot [1]. Both entities have different pathophysiological moments, diagnostic-therapeutic phases and outcomes. These two distinct entities involve two time-frames, justifying a methodologically integrated but essentially different approach. In 1990, Pecoraro outlined the pathways that take a diabetic subject with neuropathic and ischemic complications through the chain of defined events to develop an infective progression that consequently leads to an elevated risk of having to undergo amputation [2]. It is useful to clarify the importance of defining essential steps in diagnostic and therapeutic strategies when treating diabetic foot aimed at saving the limb. It is only by recognising the factors capable of negatively influencing prognosis and correcting them (e.g. critical ischemia and revascularization, osteomyelitis and its surgical treatment, compartmental syndrome, emergency surgery) that we can reduce the number of amputations in the target diabetic population. The objective of this review is therefore to define therapeutic strategies in the various types of diabetic foot syndrome.

Various classification systems have been proposed to classify diabetic foot ulcers. The most popular classification systems have long been the Wagner and Texas University Classifications [3,4].

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Table 1. PEDIS Classification System

Perfusion	**Grade 1** No symptoms or signs of PAD -Palpable dorsal pedal and posterior tibial artery -ABI 0.9 to 1.1 -TBI >0.6 -tcpO2>60 mmHg	**Grade 2** Symptoms and signs of PAD, but not of critical limb ischemia -Presence of intermittent claudication -ABI <0.9 and ankle pressure >50 mmHg -TBI <0.6 and systolic toe blood pressure >30 mmHg -tcpO2 30-to 60 mmHg	**Grade 3** Critical limb ischemia -Systolic ankle pressure <50 mmHg -Systolic toe blood pressure <30 mmHg -tcpO2 <30 mmHg	
Extent/Size				
Depth/tissue loss	**Grade 1** Superficial full- thickness ulcer, not penetrating any structure deeper than dermis	**Grade 2** Deep ulcer, penetrating below dermis to subcutaneous structures, involving fascia, muscles or tendons	**Grade 3** All subsequent layers of the affected foot, including bone and/or joint (exposed bone, probing to bone)	
Infection	**Grade 1** No symproms or signs of infection	**Grade 2** Infection involving the skin and the subcutaneous tissue only (at least two of following items are present: -swelling -erythema >0.5 to 2 cm -local tenderness -warmth -purulent discharge	**Grade 3** Erythema >2 cm plus one of following items: -swelling -tenderness -warmth -discharge	**Grade 4** Any foot infection with following signs of a systemic inflammatory response syndrome: -Temperature >38° or <36°C -Heart rate >90 beats/min -Respiratory rate >20 breaths/min -PaCO2 <32 mmHg -WBC count >12,000 or <4000/cu mm -10% of immature (band) forms
Sensation	**Grade 1** No loss of protective sensation	**Grade 2** Loss of protective sensation on affected foot		

The International Working Group of the Diabetic Foot has recently developed a classification system for research purposes: in the PEDIS system, ulcers are classified in five categories: perfusion, extent/size, depth/tissue loss, infection, and sensation (Table **1**) [5,6].

GOAL OF TREATMENT: THE REDUCTION OF AMPUTATIONS

In 1989, the St Vincent Declaration cited, amongst its most important objectives, the reduction by 50% of the number of major amputations in 5 consecutive years. This was in addition to improving the quality of care worldwide for patients affected by Diabetes Mellitus [7]. Although some population figures of amputation have not shown a fall in diabetic patients [8,9], reports from Sweden [10], Denmark [11], Italy [12-14] and the United Kingdom [15] have shown a reduction in major amputation.

During the last 20 years, physiopathological knowledge and treatment methods for diabetic foot have progressively increased. The percentage increase in limb salvation in patients treated in multidisciplinary units is linked to improved treatment technique of an acutely infected foot, neuropathic foot, and the critical ischemic conditions of neuroischemic foot [16]. Some notable physiopathological knowledge concerning the development of ulcers has been important in putting into effect certain therapeutic behavior which has, in turn, shown itself to be particularly effective.

EPIDEMIOLOGY

Around 15% of diabetics encounter a foot ulcer at some point in their lives [16]. The incidence and prevalence of the diabetic ulcer in literature varies, depending on the population and the method of survey used. Studies carried out in the UK have highlighted a prevalence of this lesion between 5.3% and 7.4% [17,18]. In the USA, Ramsey highlighted a cumulative incidence of 5.8% of ulcerated lesions in patients discharged from hospital over a period of 3 years [19]. In Sweden, a yearly incidence of 3.6% of ulceration was recorded [20], and in Holland a yearly incidence of 2.1% of ulcers in type II diabetic patients was shown [21]. In a large community survey in the UK, the annual incidence of foot ulceration was slightly more than

2.0 % among all patients [22] and between 5.0% and 7.5% among patients with peripheral neuropathy [23].

More than 60% of non-traumatic amputations in the western world are performed in the diabetic population. The incidence of major amputations varies from 0.5 to 5 per 1000 patients [24,25].

Rates of amputation vary between countries, racial groups, and within countries, and may exceed 20 per 100.000 people [26-31]. Ulcerations and above all amputations are made worse by incorrect prognosis [32,33]. Morbility and mortality rates are higher in the population with ulcerations. Mortality in the peri-operative period is high: 9% in a Dutch study [34] and 10-15% in the UK [35]. A recent retrospective paper by Aulivola *et al.* has shown the rate of mortality within 30 days of a major amputation (above or below the knee), reaching 10% [36]. In a follow-up study of an amputated population, we have shown a 5-year survival rate of 50% [37].

PATHOPHYSIOLOGY AND TREATMENT OF NEUROPATHIC FOOT

Neuropathy is associated with an 8- to 18- fold higher risk of ulceration and a 2- to 15- fold higher risk of amputation. Peripheral neuropathy is considered the basic pathophysiological alteration leading to Charcot's neuro-arthropathy. The mechanisms through which neuropathy acts as a pathogenetic event for ulceration and thus to amputation are complex and different. Above all, the reduction of protective sensitivity (including sensitivity to pain and heat) leads to a reduction in the perception of pain stimuli. Moreover, the motor component of neuropathy involves a progressive weakening of the intrinsic muscle component made up of interosseous and lumbrical muscles. It reveals itself as a deformation in toe flexion and the formation of overloaded plantar areas, identifiable from under the metatarsal heads and the tips of the toes. Thirdly, the autonomous component of neuropathy causes anhydrosis and dry, flaky skin, as well as an increase in arterio-venous shunting, leading to altered skin and bone perfusion.

It has been widely demonstrated that a biomechanical foot alteration, which includes an increase in plantar pressures, bone abnormalities, mobility limitations, and equinus, are all linked to an significant increase in the risk of ulceration.

A patient develops a neuropathic lesion due to pathological plantar pressures. The pathological overload is immediately detected in a foot that maintains complete sensitivity. However, in a neuropathic subject, repeated environmental traumas (poorly fitting shoes, sharp objects, environmental surfaces) go unnoticed. The ulcer therefore develops due to the lack of perception of the repeated trauma linked to movement. The clinical characteristics of the neuropathic lesion are as follows: development of an overloaded area, surrounded by a callous formation before the development of the lesion, without painful symptoms. Like pressure ulcers, neuropathic plantar lesions tend to be undermined, with a small opening toward the skin surface, compared with the true involvement of deeper tissues.

The risk of the lesion worsening in terms of both progressive deep tissue destruction and infection, is linked to the co-existence of an ischemic component. Therefore, peripheral vascular disease must be excluded in the initial assessment of an ulcerated lesion with clinical characteristics proper to those of a neuropathic lesion.

Proper debridement must follow the evaluation of an ulcer. It should completely remove the callus that surrounds the lesion and all non-healthy tissues, until healthy bleeding edges are revealed. Sharp debridement allows for thorough removal of all necrotic material and diminishes the bacterial load, thus promoting healing. It is then necessary to carry out an accurate "probe to bone" maneuvre in order to establish the involvement of deeper structures such as tendons, joint capsules and bones.

In the majority of cases, the 'probe-to-bone' maneuvre with a sterile blunt instrument is enough to diagnose osteomyelitis. It is therefore only necessary to use more complex methods (such as Nuclear Magnetic Resonance and/or radio-labeled leukocyte scanning) in a small percentage of cases [38-44].

The literature clearly highlights how offloading is essential in cases of plantar neuropathic lesion. Simple offloading techniques are multi-faceted and include casts and boots, sandals, half shoes or felted foam dressings. The use of a non-removable cast has recently been shown by Caravaggi to be faster treatment for plantar neuropathic ulcers than a half- shoe (Fig. **1**) [45].

These data were been confirmed by Armstrong [46]. The best effect is probably linked to the greater therapeutic adherence of a non-removable device, which brings about reduction of weight-bearing and walking times compared with other devices.

Piaggesi *et al.* have recently shown that the inflammatory component of ulcerated lesions, surgically removed after treatment with a leg cast, was reduced compared with other kinds of treatment. In addition, the parameters of tissue repair (production of collagen, angiogenesis, quantity of granulation tissue) were better in the group treated with total-contact casts [47].

In order to prepare a TCC (Total Contact Cast), staff with experience are needed, to minimize the risk of iatrogenic lesions. This involves a high level of cost and takes time.

A TCC usually remains in place for 5-7 days and must then be removed, the wound inspected, and the cast re-moulded.

Absolute contraindications to the use of a TCC include ischemia with Transcutaneous Oxygen Pressure (TcPO2) less than 30-50 mmHg measured on the dorsal aspect of the forefoot, active infection, involvement of deep tissue and/or osteomyelitis, and walking difficulties due to neurological and/or hypovision complications. We treat patients with low-molecular weight heparins concomitantly. Armstrong *et al.* have recently reported the efficiency of other offloading devices such as AIRCAST® REMOVABLE WALKER [48]. Incorrect diagnostic planning, incorrect staging of the wound, and therefore an erroneous therapeutic approach, involves a higher risk of the wound becoming chronic and an

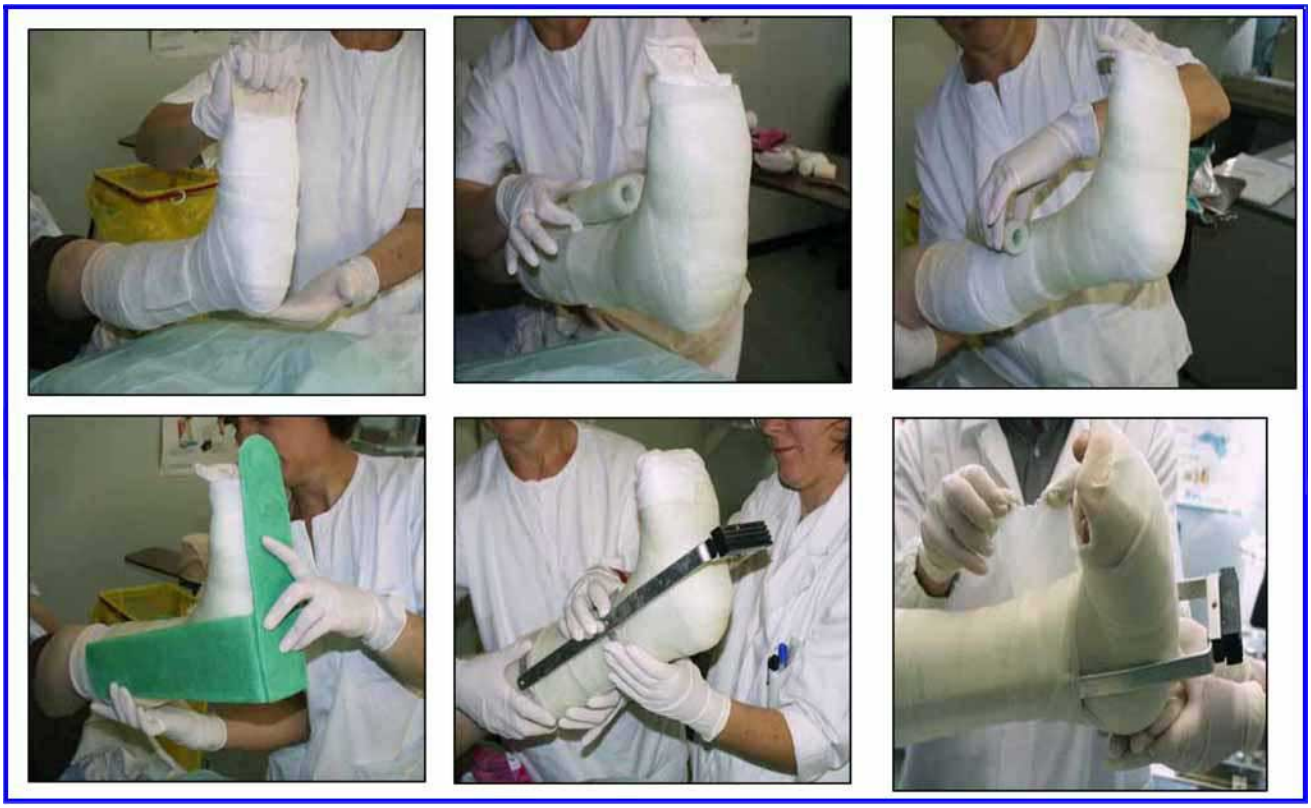

Fig. (1). Preparation of a non-removable cast.

elevated risk of infection spread. The first step in treating an uncomplicated ulcerated neuropathic lesion is local debridement, dressing, and off-loading. However, clinical conditions exist in which surgery becomes the treatment of choice. Armstrong and Frykberg have provided a classification of diabetic foot surgery that correlates classes of treatment with a risk of amputation score [49]. Indications for surgical treatment of plantar neuropathic ulcers are essentially: 1) co-existence of osteomyelitis 2) plantar exostosis which puts healed wound at a high risk of recurrence 3) chronically ulcerated wounds resistent to conservative therapy.

In these situations, surgery allows two important results to be achieved. The first is that of healing the ulcerated wound in a significantly shorter time. The second is surgical correction of the pathological overload by means of anatomic correction of the exostosis [50]. Piaggesi *et al*. have shown that surgical treatment of a wound (ulcerectomy), accompanied by modification of the pathological overload (exostectomy) in a population of diabetic patients affected by plantar neuropathic ulcers allows significantly shorter healing times and a fewer percentage of ulcerative repetition, compared with conservative treatment (Fig. **2**) [51].

Microbiological assessment is made to choose appropriate antibiotic treatment before ulcerectomy. It is necessary to establish any involvement of bone (such as a metatarsal head) so as to plan the best type of surgery for the wound.

Surgery is usually carried out under local anesthetic with a peripheral anesthesiological block.

We generally remove the whole thickness of the ulcerated wound [1]. Should clinical or radiological evidence show the involvement of a bone, the bone segment in question is exposed and cleared [2]. The most common locations are metatarsal heads, tips of the toes or phalangeal joints at the forefoot, cuboid bone or medial cuneiform at the midfoot in Charcot neuroarthropathy. When a metatarsal head is involved, it must be exposed after ulcerectomy and removed totally with a sagittal saw. The proximal epiphysis of the basal phalanx is only removed when radiological or clinical findings reveal osteomyelitis. The removed bone portion is sent for microbiological and histological checks. Before using the pulsated irrigation stitch technique with antiseptic and physiologic solution [3], we carry out careful hemostasis to avoid the formation of hematoma. We place suction drainage or gauze [4] and suture points of surgical access with a nylon 3-0 4-0 or prolene monofilament [5]. We usually avoid using soluble stitches in order to avoid ischemia of tissues and infection.

This is certainly the simplest procedure and we reserve the most complex techniques of coverage such as rotational or advancement flaps, for cases involving larger ulcerated wounds.

The involvement of more than one metatarsal head or the presence of a vast plantar lesion may indicate the need for

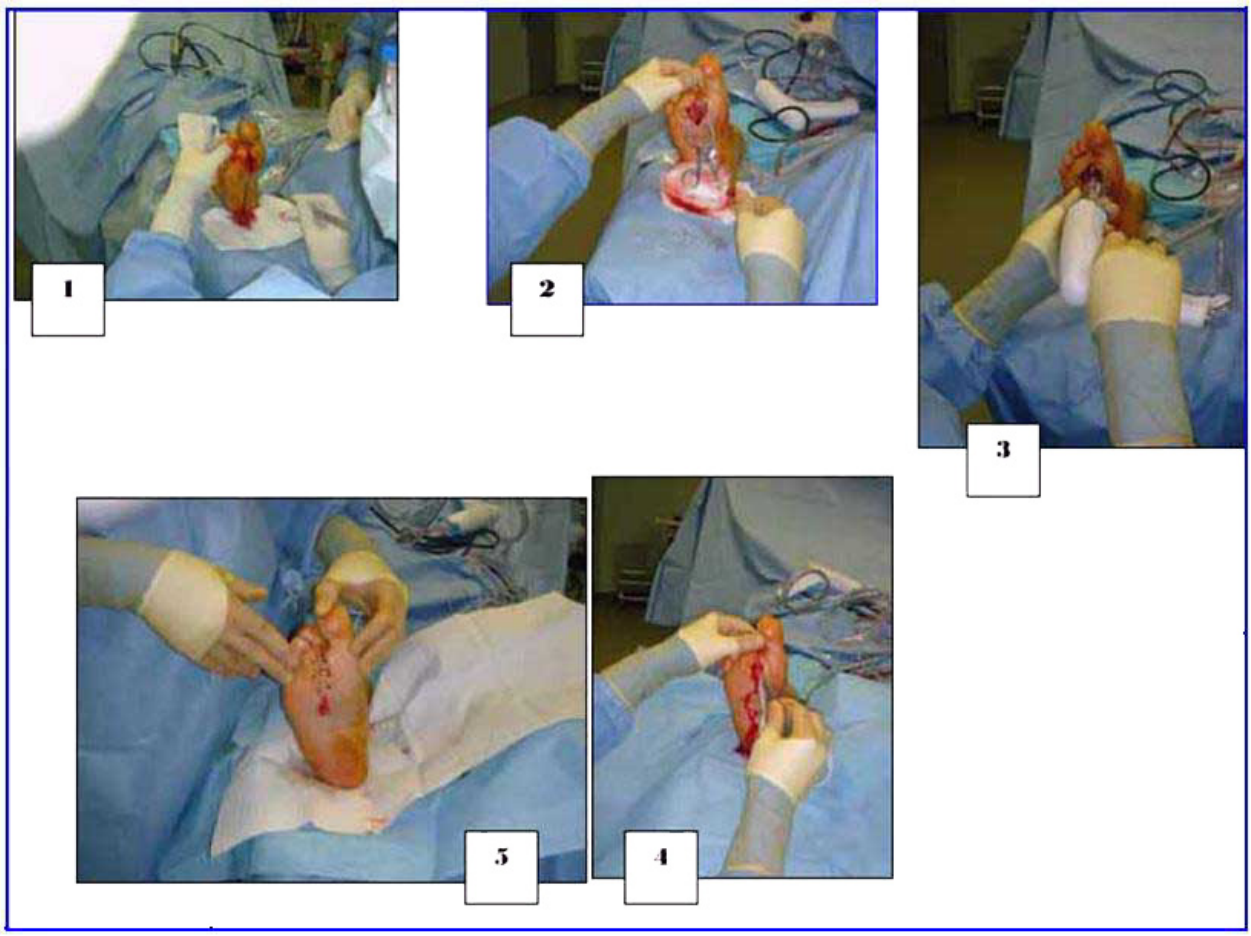

Fig. (2). Surgical treatment of neuropathic plantar ulcer.

Table 2. Eichenholtz Phases in Charcot Foot

Stage 0: **"At risk" foot and ankle**. Patient with diabetes and peripheral neuropathy who has had an acute sprain or fracture.
Stage 1: **Development**. Patients presents with an acute inflammatory process; X-rays show bone fragmentation with debris and occasional joint disruption or dislocation.
Stage 2: **Coalescence**. Swelling, warmth and redness regress, and X-rays show bone surrounding the joint as sclerotic; absorption of fine debris occurs, and most of the large fragments fuse together.
Stage 3: **Reconstruction**. Continued resolution of inflammation, and X-rays show persistent remodeling with some reformation of joint architecture. This is the best time for surgical fusion.

more complex surgical techniques including panmetatarsal head resection or minor amputation.

Surgical treatment of an ulcer (ulcerectomy and exostectomy) carries significant risks of transferring pathological plantar pressure to other metatarsal heads. In such cases, treatment of repeated ulceration is different from that already being treated, depending on possible osteomyelitic involvement of the adjacent metatarsal head. A conservative method of healing through debridement with a leg cast may be considered, if the lesion does not present osteomyelitis. This is followed by rebalancing through increasing osteotomy and/or lengthening the Achilles' tendon. In cases of osteomyelitis, treatment may involve pan-metatarsal head resection or trans-metatarsal amputation.

Surgery should not only be curative but also effective in preventing new ulceration. Orthesis is sometimes not possible higher plantar overload of the forefoot due to equinus. In such cases, surgery should be considered. Treatment of the overload by lengthening the Achilles' tendon, has been shown [52] to be effective both in reducing the plantar pressures of the forefoot and the primary risk of ulceration and recurrent infection. It can be carried out with traditional open surgery or via the skin.

CHARCOT NEUROARTHROPATHY

Charcot neuroarthropathy is certainly the clearest demonstration of the dominant role which neuropathy may play in progressive physiological loss in the foot of a diabetic patient.

Eichenholtz codified the phases of development (Table **2**) and Frykberg and Sanders listed several affected areas in a 5-stage classification (Fig. **3**).

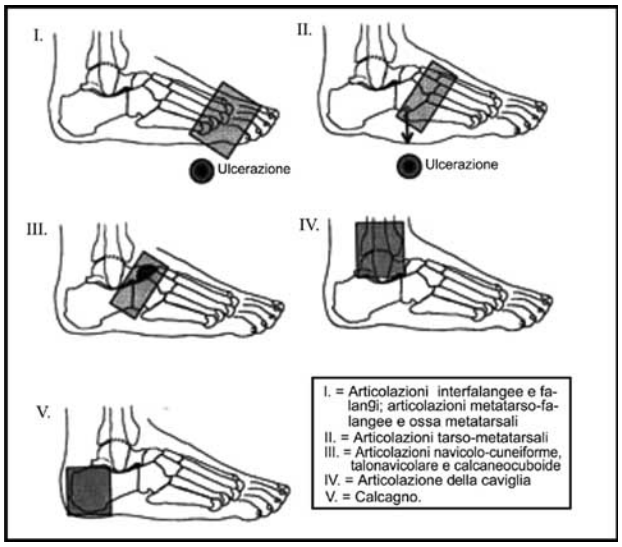

Fig. (3). Sanders and Frykberg classification of Charcot foot.

The aims of treatment are: 1) to create and maintain a plantigrade, stable foot; 2) to heal an ulcerated wound; 3) to heal fractures; 4) to prevent deformities.

The choice of treatment depends on the Eickenholtz stage and location of the disease. The elective treatment of acute Charcot foot is prolonged immobilization. The principles of this approach are control and treatment of edema, providing skeletal stability and protecting soft tissues. Immobilization time varies depending on site. For the midfoot, 10-12 weeks of total offloading are forecast, followed by a further 4-10 weeks of protected weight-bearing with a cast or boot. Regards the hindfoot, 10-12 weeks of total offloading followed by 6-12 months of protected weight-bearing. Once clinical stabilization has been reached, the patient should be treated with special preventive footwear. Clinical stabilization is proven by a fall in skin temperature and resolution of oedema.

Very precise clinical conditions indicate a surgical approach (Table **3**).

Table 3. Indications for Surgical Treatment in Charcot Neuroarthropathy

• Plantar ulcerative wound on exostosis, with or without osteomyelitis;
• Recurrent wound;
• Severe deformity not manageable with orthotics or accommodative footwear;
• Severe joint instability not manageable with orthotics and accommodative footwear;

Ulceration is usually found at the midfoot level and is followed by osteo-joint dislocation, with collapse of the plantar fascia and onset of plantar exostosis. In the majority of cases this occurs at the Lisfranc line. The clinical characteristics of these ulcerations are usually persisting exostosis, its large size, a callus surrounding the wound, torpidity, and lack of healing. The risk of osteomyelitis is very high.

In the case of superficial wounds (grade I-II of the Texas classification), the treatment of choice is offloading of pathological pressures, together with local dressings, which vary depending on the state of the wound. Once the wound has healed, the decision is taken as to whether to place the patient in a prevention program or not. Through education, insoles and rocker bottom soles, the patient can keep the risk of recurrent infection under control. If the patient has to be operated on, this tends to minimalize the risk of recurrent ulcerations.

When the ulcerated wound involves joints and/or bones, surgical treatment is indicated, usually entailing removal of the lesion, exposure and clearing of exostosis. The bones involved are usually those in the medial aspect of the foot, the navicular and/or medial cuneiform and/or base of the first metatarsal; in the lateral aspect of the foot, bones involved are the base of the fifth metatarsal or the cuboid.

There are three techniques for performing exostosectomy for plantar wound:

- The first (Fig. **4A**) requires removal of the bone through skin different from that a plantar wound, in order to minimize contamination of the bone beneath. It is possible to perform an ulcerectomy later in order to achieve quick healing of the chronic lesion, which is thus transformed into an acute one. An example is a plantar ulcer of the forefoot, with resection of the adjacent metatarsal heads through a dorsal incision.
- The second technique (Fig. **4B**) consists of removing the ulcer and, through the same incision, performing an exostosectomy, before the wound is closed. The advantage of removing an ulcer is that soft tissue is often so fibrous that sufficient granulation tissues are difficult to reach, despite bone restoration. An ulcerectomy allows healthy tissue to heal quickly.
- The third technique involves an ulcerectomy and removal of bone. This is done without closing the wound, which is then treated daily. Closure is postponed to a later date. We use this approach when treating infected ulcers.

The unstable deformities of Charcot neuroarthropathy make up the largest indications of arthrodesis, the aim of which is to achieve stability of the joints involved, reducing the risk of further ulcerations and the entire collapse of the foot. Reconstruction is considered in patients with deformities and instabilities, in whom surgical stabilization is the only alternative to major amputation [53].

An in-depth assessment of international literature has highlighted some key points which must be followed in surgical treatment of Charcot foot [25,53]. It is absolutely essential to wait for the quiescent state, which is characterized by the disappearance of signs of inflammation. Only when the foot is in the quiescent stage (reduced oedema, normal skin color, lower temperature with symmetrical comparison in the contralateral limb) can surgery be considered. However, Simon recently reported good results with

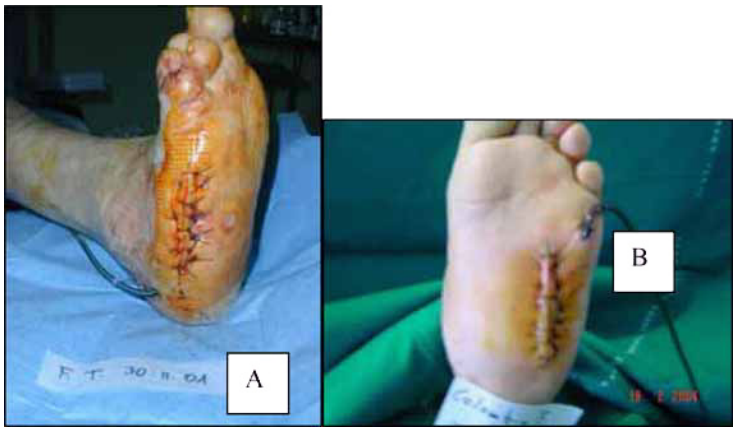

Fig. (4). A-B Plantar esostectomy in Charcot foot.

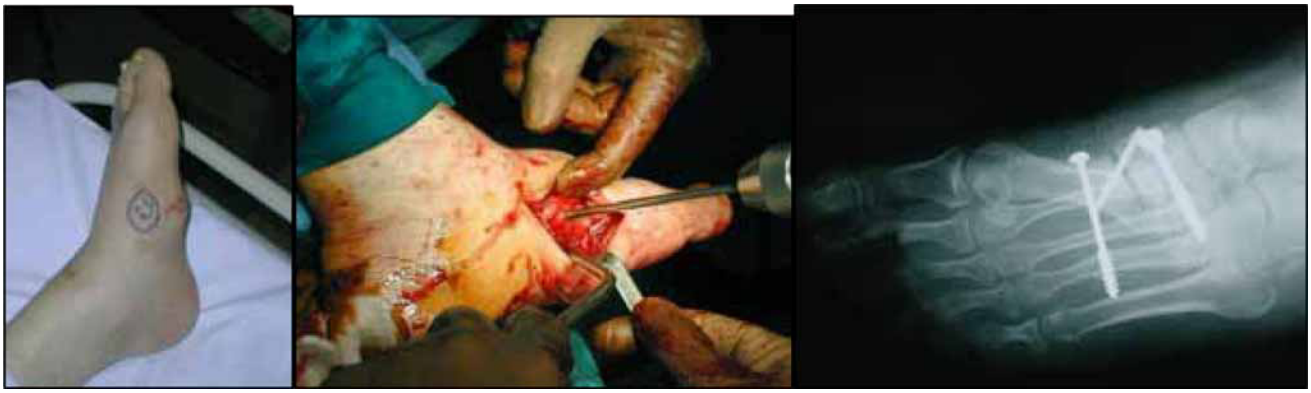

Fig. (5). Medial column fusion in instable Charcot foot.

early arthrodesis as an alternative to non-operative treatment [54]. The main problem of this study is the lack of follow up.

Fusion procedures are carried out traditionally with internal fixation (Fig. **5**). Studies showing positive results can be found in the literature, although with significant complication rates, varying between 30% and 70%. These figures are due to failure of fixation, infections, and sepsis which may lead to amputation. Unfortunately, these works are not comparable, as they all have differing methods of patient selection, types of operation and operative time-frames.

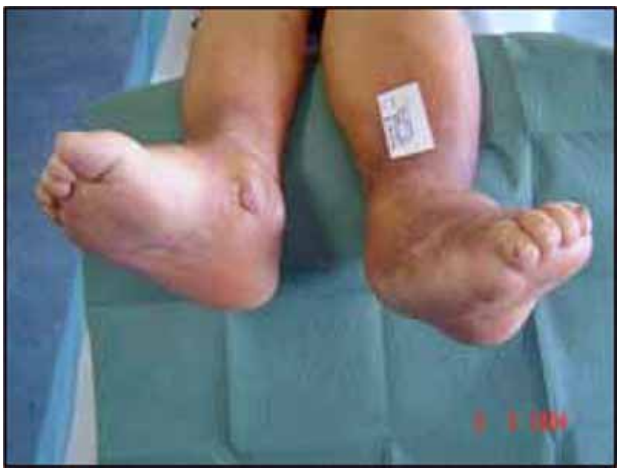

Fig. (6). Ankle instability in Charcot foot.

Ankle instability is a major challenge in limb salvage procedures (Fig. **6**). Good results have been reported by our group and others, showing significant percentages of limb salvation through the use of intramedullary nail (Fig. **7**) [55,56].

These are used to stabilize the ankle in patients presenting a high risk of ulceration and therefore possible amputation. External fixation (Fig. **8**) is an alternative in patients with osteomyelitis or infective complications from internal fixation. More importantly, external fixation allows earlier mobilization.

PRINCIPLES OF TREATMENT OF THE NEURO-ISCHEMIC FOOT

The epidemiological characteristics of peripheral vascular disease (PVD) are more obvious in diabetics than in the general population [57-59]. The main characteristic of PVD in diabetics is he morphological and clinical presentation

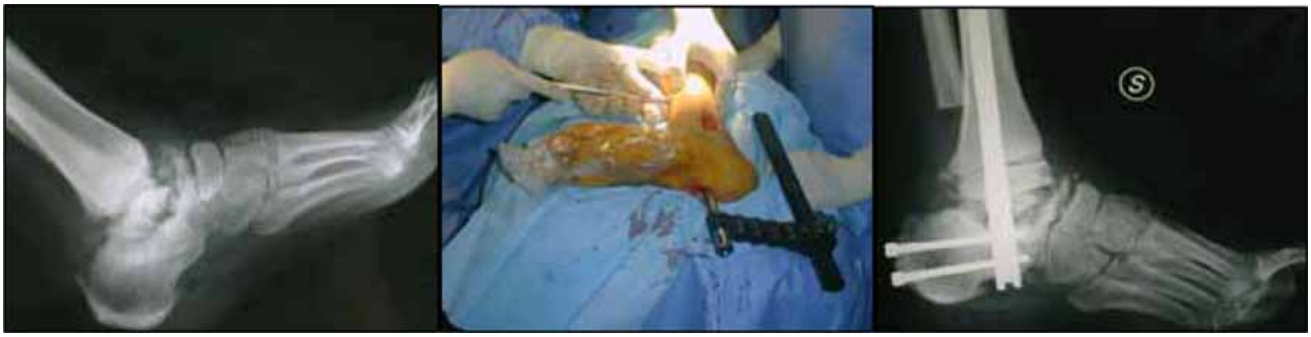

Fig. (7). Ankle fusion using intramedullary nail.

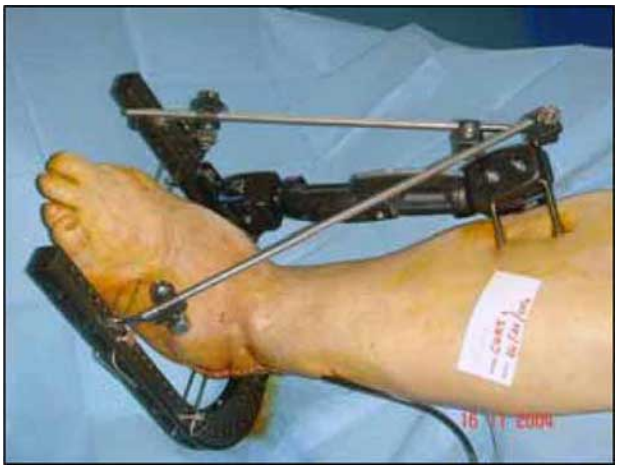

Fig. (8). External fixation in Charcot foot involving the ankle.

[59,60]. Obstructions are mainly located below the knee; occlusions prevail, compared with stenoses [61]; painful symptoms are often reduced or absent, due to the co-existence of neuropathic sensitivity, and medial arterial calcinosis (MAC) is common [62]. These characteristics make PVD in diabetics more difficult to diagnose and therapy more problematic than in non-diabetics. They also means that PVD plays a fundamental role in the prognosis of major amputation. Nevertheless, since the 1990's, revascularization procedures have been proved feasible options compared with initial thinking. Procedures ranging from distal revascularization to angioplasty and by-pass interventions have all been able to change the original prognosis of amputation [13].

The fundamental problem of diabetic PVD is precision of diagnosis. These patients often suffer little or no pain when walking or at rest. The frequent presence of arterial calcifications is another confusing element, sometimes giving rise to incorrect evaluation of the importance of pressure parameters, as both ankle-pressure and ankle-brachial index. These typical diabetic characteristics are the primary factors that lead to underestimation of the presence of PVD. This mistake plays a major role in delayed wound healing and possible gangrene, and is a contributing factor to many amputations [63]. This is true in the case of minor amputations when the foot lacks sufficient blood flow, wounds cannot heal, and an amputation is necessary at a more proximal level [64].

The TASC (TransAtlantic Inter-Society Consensus) [65] was published in 2000 (Table **4**). This Consensus introduced a useful diagnostic tool- transcutaneous oxygen tension ($TcPO_2$)- and gave higher cut-off pressures than those determined previously [66]. Some parameters cannot be applied to the diabetic population. Rest pain is often absent, ankle pressure is not feasible or erroneously high. In our experience, around 50% of patients with foot ulcer present incompressible arteries of erroneously high figures, as reported by Gibbons [67].

Table 4. Critical Limb Ischemia: Diagnostic Criteria (TASC)

Chronic ischemic rest pain, ulcers or gangrene,
attributable to objctively proven arterial occlusive disease,
with
ankle < 50-70 mmHg or toe pressure < 30-50 mmHg
or
transcutaneous oxygen tension< 30-50 mmHg

The pressure of the big toe is even less useful, not only because calcifications often include inter-digital arteries, but above all because the wound often involves the big toe.

We rely on the TcPO2 in our clinical practice, since it is feasible in all patients. Duplex scanning is an accessible and widespread diagnostic tool, which provides two types of information at the same time. One is morphological and regards the presence of stenosis or occlusions, and one is functional, and deals with the rate of blood flow. This type of diagnostic investigation is highly sensitive and specialised in the large vessels of the thigh. Even without arteriography, some authors consider this examination sufficient for choosing reconstructive therapy. The main limitation of duplex scanning is its dependency on operator ability. All too often defective examinations are made, unreliable for a diagnosis of PVD. Fig. **9** shows our clinical and instrumental protocol to assess PVD [12,14,68]. Arteriography is the gold-standard diagnostic instrument, which fully responds to the need for precise definition of the existence, extent, location and morphology of arterial lesions, even in diabetics. In diabetics, arteriography is often described as risking more severe complications compared with non-diabetics. This is true above all as regards the renal toxicity of the contrast medium. From this point of view, current contrast media must be considered. The digital technique and non-ionic

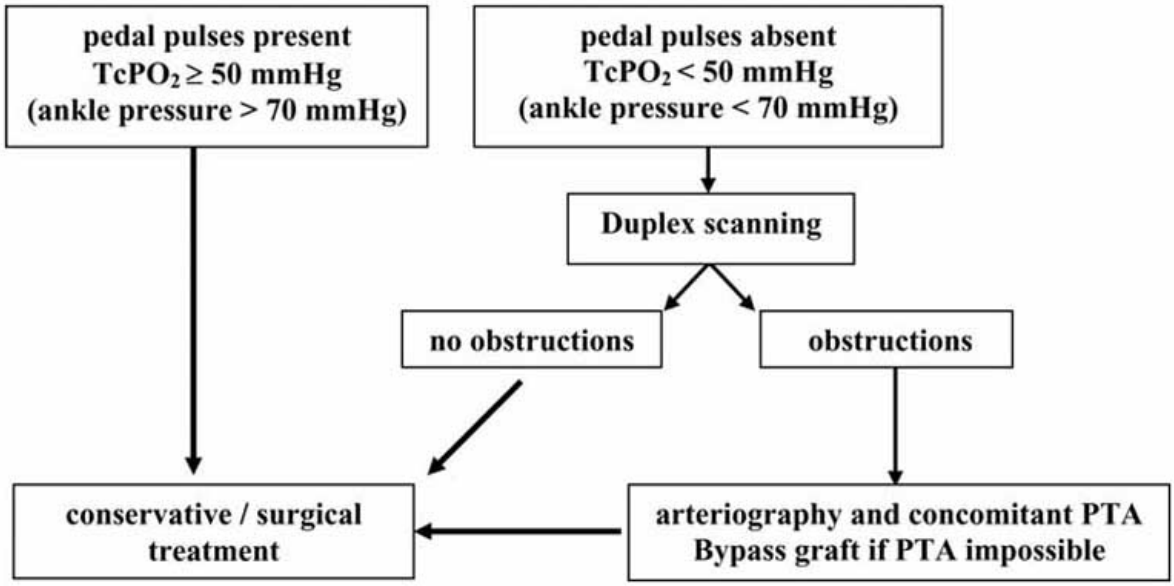

Fig. (9). Flow chart of diagnostic-therapeutic procedure in PVD.

contrast medium require lower dosages and concentrations of contrast media. Both literature and our experience has confirmed that hydration procedures, both pre- and post-examination, drastically reduce the risk of renal toxicity [69]. In cardiopathic patients with cardiac ejection fraction < 40% we use furosemide at the start and end of daily hydration in order to avoid possible effects of overloading liquids. This procedure has allowed us practically to eliminate the risk of nephropathy due to contrast media, even in patients suffering from serious kidney insufficiency.

Vascular investigations with excellent imaging obtained by angio-CT or angio-MRI are currently considered. Despite the high cost and poor accessibility of the equipment, we do not believe that such instrumentation provides a feasible method for routine use at the present time. The double time required when using such methods- the first diagnosis, followed by a second intervention- does not have a place in a procedure like ours. We maintain that arteriography forms a 'bridge' between diagnosis and PTA therapy (carried out whenever possible) during an angiographic examination. However, we would welcome the double time if it were useful in revascularizing patients with PVD.

Certainly endoluminal or surgical revascularization is the only treatment capable of reducing the number of major amputations significantly. This is amply shown in literature [12-14,57-60,65,68-80]. Revascularization can restore direct arterial flow where it has been interrupted or significantly reduced. This is an indispensable condition for healing a wound in an ischemic foot without resorting to amputation.

This procedure is essential in cases of pain at rest. It is vital when corrective surgery of a wound of part of the foot is necessary. We consider it incorrect to perform surgical amputation without carrying out an exhaustive diagnosis of PVD and (where appropriate) without considering revascularization [81-83].

A vascular procedure is controversial as regards claudication [59]. We avoid proposing revascularization procedures for this state and prefer to correct risk factors and plan clinical follow-up. We consider revascularization in cases of tight claudication with a free interval of < 50 mt, but only if the patient requests it and is well informed of the risks connected with such procedures. Uncertainties remain as to the most efficient and safe approach for these patients.

In our protocol percutaneous transluminal angioplasty (PTA) was the first-choice revascularization procedure [12] yelding outcomes similar to by-pass grafting (BPG) [84]. It does not require general or spinal anesthetic, is well tolerated, does not pose problems of local surgical treatment of the wound, hospitalization is very short, and the possibility of BPG in the event of failure is not ruled out [67-76]. In the hands of experts PTA is a feasible approach for distal, long and multiple obstructions (Fig. **10**) [12,14], as noted in recent guidelines [85]. However, when critical limb ischemia (CLI) is present any procedure is welcome to save the foot.

It is often believed that PTA is a useless approach, due to immediate and unavoidable restenosis. This is not so since it is necessary to distinguish between clinical and morphological restenosis [86]. Morphological restenosis, visible by Duplex scanning or transcutaneous oxygen tension and with ankle-pressure values lower than 15% of pre-PTA values [73], in the absence of returning pain or worsening or relapse of foot wounds, is an irrelevant clinical condition. The absence of a foot wound and of pain when resting does not indicate the need for revascularization. It is clinical restenosis that is important, as it shows itself through investigatory procedures and the reappearance of pain or foot wounds. In our experience, clinical restenosis has a frequency of around 10-14% of treated cases. Efficient PTA is possible in about 80% of cases of restenosis [12,14].

In our protocol, PTA is carried out at the same time as angiography [12,14]. If PTA is not considered feasible, the angiographic study is used to evaluate the possibility of surgery. PTA may be associated with a BPG at the same

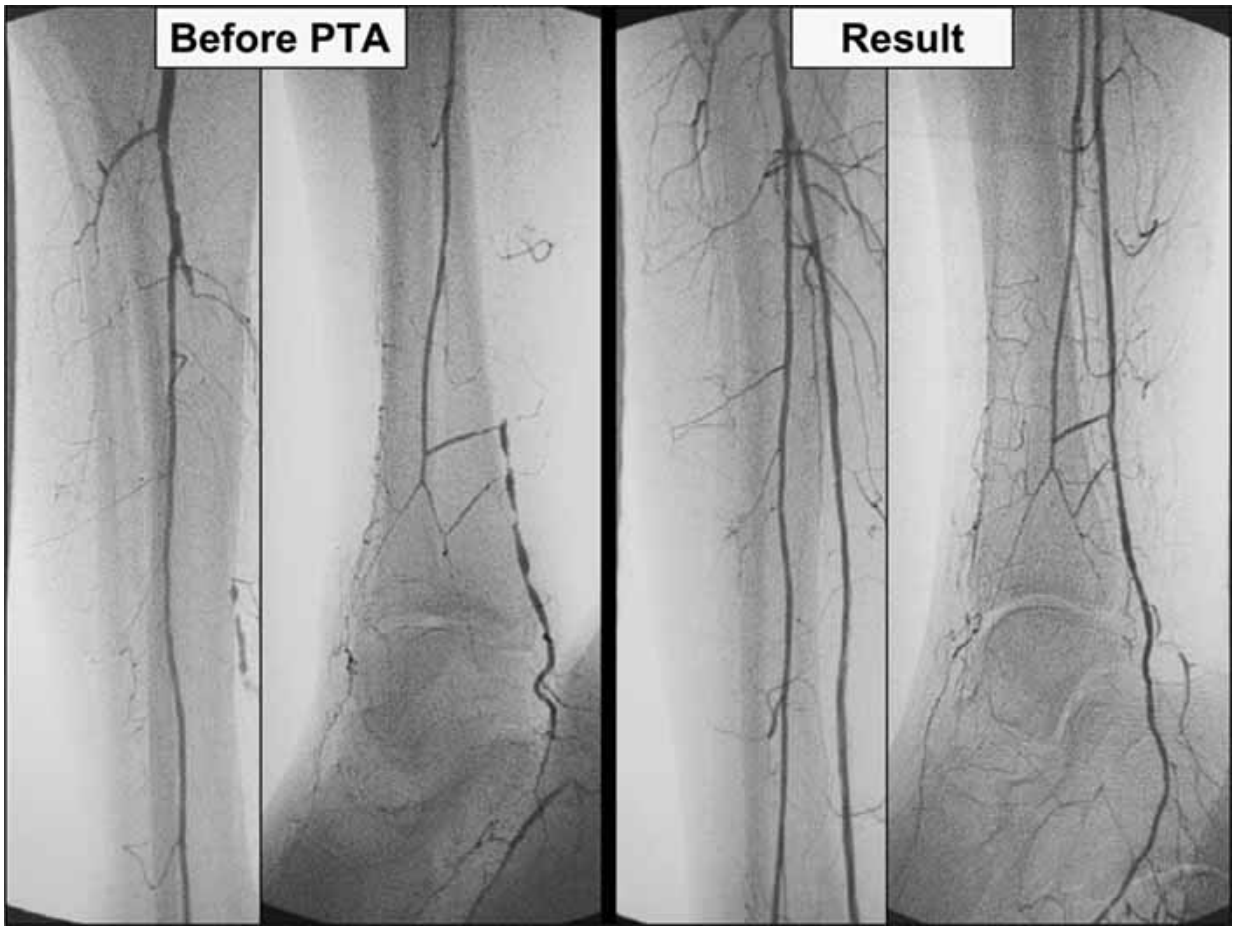

Fig. (10). Below the knee endovascular procedure.

time as surgery or immediately afterwards. An example is a femoral-popliteal bypass giving the PTA the task of recanalizing distal (tibial) stenosis. This allows a 'short' bypass to be carried out instead of a 'long' one. The former has a shorter surgical time and better chances of patency in the long term. Distal PTA allows a good run-off to bypass.

In our clinical practice, a surgical bypass is only carried out when PTA is deemed impossible or ineffective. It has been widely shown that distal bypasses are both possible and effective in diabetics [87,88].

As in restenosis, non-recanalizable closure during a bypass does not always lead to limb amputation. If bypass closure happens after the wound has healed, in some cases the patient remains asymptomatic.

The objective is always revascularization as regards the foot. We have often seen femoral-popliteal bypasses or PTA of the superficial femoral which have left infragenicular arteries occluded. In a recent analysis of 420 PTAs judged to be technically successful procedures, the probability of major amputation increased 8 times for every non-recanalized infragenicular artery (personal data, unpublished data). In a few cases, recanalization of the peroneal artery was not enough to save the limb. Recanalization of at least one of the tibial arteries is the optimum to salvage a limb. However, in some diabetic subjects neither endoluminal nor surgical revascularization of the arteries below the popliteal is possible, and amputation is often resorted to although the patency of at least one artery to the foot is an optimal guarantee of limb salvage, revascularization with PTA or BPG of the arteries upstream can lead to an increase in collateral circles, with an improvement in distal perfusion. Such procedures sometimes allow wound healing and pain remission. Even if the foot cannot be saved, a leg amputation can be performed instead of a thigh amputation, thus creating a distinct advantage for ambulation with a prosthesis.

The extensive use of revascularization undoubtedly allows a very high percentage of limb salvage. The ability to revascularize, with PTA and BPG, is an essential requisite for a diabetic foot center.

INFECTED FOOT: TIMING AND THERAPEUTIC PROTOCOL IN ACUTE AND CHRONIC INFECTION

An ulcerated wound may start as a uncomplicated case, but infection may develop and lead to compromise of soft tissues and even bone involvement. In diabetic subjects this is due to the development of hyper-pressure plantar areas, primarily at the forefoot, whereas in neuroischemic cases it is due to contact with the environment or to inadequate footwear. Cases of serious soft tissue destruction, osteomyelitis and compartmental syndrome (progressive infection through plantar and dorsal compartments) are true medical and surgical emergencies [89].

Table 5. Clinical Characteristics of Diabetic Foot Infections

Clinical manifestations of infections	Severity
Wound without purulence or any signs of inflammation	**Uninfected**
≥ 2cm manifestation of inflammation (purulence or erythema, pain, tenderness, warmth, induration) but any cellulitis/erythema extending ≤ 2 cm around ulcer and infection is limited to superficial tissues. No local complications or systemic illness.	**Mild**
Infection in patient who is systemically well and metabolically stable but who has ≥ 1 of following: cellulitis extended > 2 cm; lymphangitis; spread beneath fascia; deep tissue abscess; gangrene; muscle, tendon, joint, bone involved	**Moderate**
Infection in patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycaemia)	**Severe**

In these cases the ischemic stage is not an initial risk element of ulceration, but it is certainly the least favorable event in determining the prognostic risk of amputation.

TREATMENT OF INFECTION

Infection of soft tissues, progressive compromise of deep tissues, and the development of osteomyelitic foci are the points which separate conservative treatment from a more aggressive surgical approach. This stage must include careful therapeutic planning, which should rely upon microbiological examination after exclusion of the ischemic component. Clearly revascularization must be postponed until after acute treatment of infection.

Infections that do not pose an immediate threat of limb loss are defined as 'non limb-threatening', and are generally characterized by the absence of signs of systemic intoxication. In a superficial lesion cellulitis of >2 cm is generally not present, nor are deep abscesses, osteomyelitis or gangrene. Infections defined as 'limb-threatening' show extended cellulitis, deep abscesses, osteomyelitis or gangrene. Ischemia characterizes a superficial lesion as limb-threatening [90]. Lipsky provided a more specific classification of infection, shown in tab.5 [91]. Infected ulcers are sometimes unrelated to important local and general signs and symptoms in diabetics.

Table 6. Recommended Evaluation of a Diabetic Patient with a Foot Infection

- Describe lesion (cellulitis, ulcer, etc.) and any drainage (serous, purulent, etc)
- Enumerate presence or absence of various signs of inflammation
- Ascertain whether or not infection is present, and attempt to define probable cause
- Examine soft tissue for evidence of crepitus, abscesses, sinus tracts
- Probe any skin breaks with sterile metal probe to see if bone can be reached
- Measure the wound(length x width; estimate depth); consider photograph
- Palpate and record pedal pulses; use Doppler instrument if necessary
- Evaluate neurological status: protective sensation; motor and autonomic functions
- Cleanse and debride wound; remove any foreign material and eschar
- Culture cleansed wound (by curettage, aspiration, or swab)
- In most cases order plain radiographs of infected foot

In the majority of clinical studies in the literature, antibiotic treatment does not improve the outcome of non-infected ulcers [92]. A follow-up, including close monitoring of local conditions, is necessary, to ensure that dangerous signs and/or symptoms of local infection are highlighted [90]. The diagnosis of infection is clinical. The presence of purulent secretions of two or more signs of inflammation (erythema, warmth, tenderness, heat, induration) should be used in diagnosing an infection. Faced with a clinical case of non-limb-threatening infection, it is best to start antibiotic treatment early on. For mild infections, antibiotic therapy is administered orally. Oral treatment is less expensive, easier to manage and usually sufficient for this type of patient. Parenteral treatment (difficulty in intestinal absorption, gastrointestinal allergies, isolation of bacteria resistent to oral antibiotic therapy) can only be chosen in cases. The chosen antibiotic must reach good serous levels and provide good coverage against gram-positive cocci bacteria.

ACUTE INFECTED FOOT

Acute infection (phlegmon, abscess, necrotizing fasciitis) is an emergent condition that can threaten not only the limb but also the patient's life. It requires evaluation, and immediate hospitalization and treatment. The infection may be due to progressive destruction of soft tissues, involvement of bone, the need for surgical treatment, and possibly amputation [92,93].

In many cases, rapid treatment is absolutely essential in effectively treating an acute wound in a diabetic foot. It is often necessary to turn to debridement surgical treatment, carried out in emergency, without considering limiting factors such as metabolic compensation, patient's nutritional state or vascular condition [94-96]. In this specific environment, surgical debridement presents advantages over other forms of debridement (enzymatic, physical, chemical). In less urgent cases, patients can be treated on the ward or in bed, without need of anesthesiologic support. In cases of wider and deeper infections an operating theatre is required for adequate debridement and drainage. This is especially true in cases with bone involvement.

Surgical treatment, antibiotic treatment and support should all be decided after thorough general and local examination of the patient (Table **6**) [91].

Other than causing a negative prognosis, infection alone can lead to ischemia through inflammatory and thrombotic mechanisms which involve the terminal digital arteries (increase in oxygen consumption, oedema, septic thrombo-angioitis). It is precisely for this reason that debridement allows a reduction of the infected mass, and improvement in local circulatory conditions.

From a clinical point of view, the acute phase of infected diabetic foot is divided into four main stages: cellulitis, abscess, necrotizing fascitis, gangrene. Cellulitis is usually treated with antibiotics; the other three need surgical treatment.

ABSCESS

Deep-space abscess is a limb-threatening infection: international guidelines state that incision, drainage and debridement, together with broad-spectrum antibiotic therapy, is the most effective method to eliminate pus and infected tissues totally [97]. However, in deep-space abscesses, the involvement of deep tissues is greater than may be clinically apparent upon examination [98]. This may lead the physician to prescribe only antibiotic treatment and postpone radical surgical debridement [99-101]. Delay in radical surgical treatment may lead a high percentage of minor amputations and also of above-the-ankle amputations, because it allows the infection to proliferate and destroy tissues [102]. Literature data confirm that medical treatment of deep-space abscesses solely with antibiotics is insufficient [103] and that surgical debridement plus broad-spectrum antimicrobial therapy is the best treatment for deep foot infection. Our experience emphatically indicates that delay in surgical debridement increases the risk of a more proximal level of amputation, including above-the-ankle amputation [104].

Operatively, if purulent drainage is observed from an ulcerated wound, or if movement of subcutaneous or deep soft tissues is noted during the probing-to-bone maneuvre, an abscessed mass should be suspected. In this case, the suspected area should be pierced and the tissues involved drained, allowing removal of the purulent mass. A series of

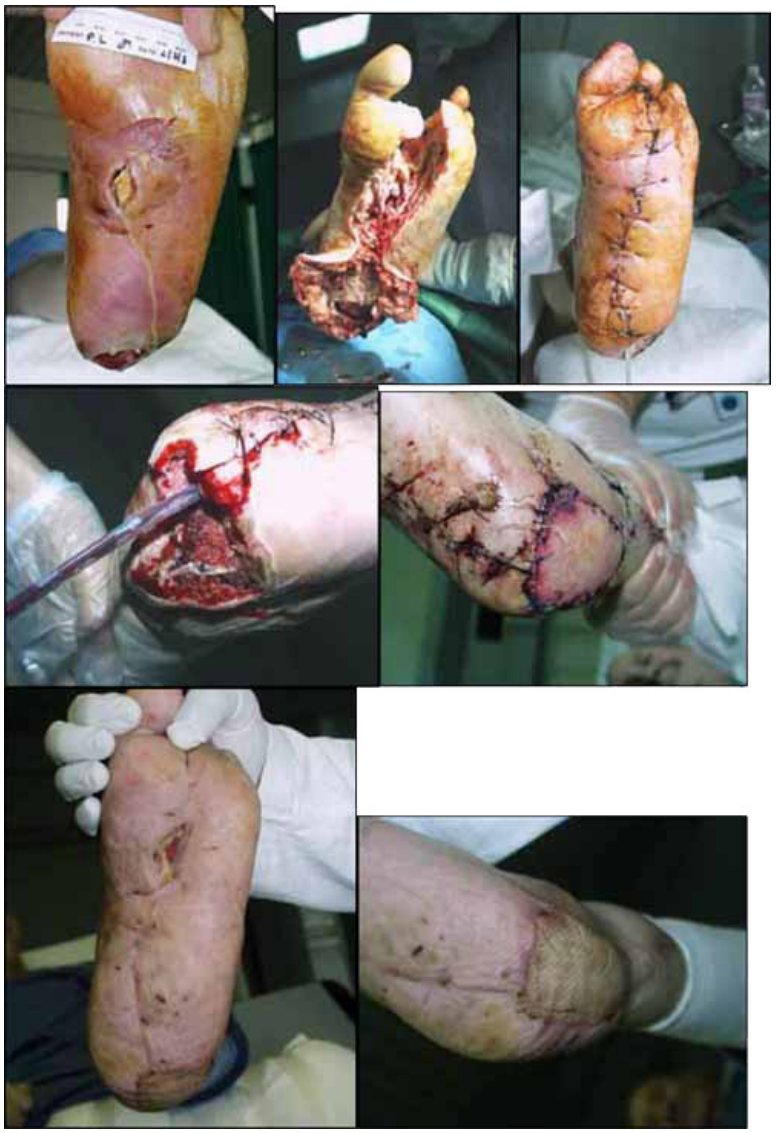

Fig. (11). Drainage of extended abscess on whole foot, starting from ulcer on heel. Drainage of collected pus, partial calcanectomy for osteomyelitis, and secondary transplantation of sural muscle.

incisions is sometimes necessary through plantar and dorsal areas in order to reach deeper locations. Pressure on a proximal point may lead to an additional burst and the total exit of pus (Fig. **11**).

All necrotic and infected tissues must be gradually removed until healthy bleeding tissues are reached. From a microbiological point of view, many organisms can contaminate the surface of the wound and therefore only samples taken deep below the skin surface can give reliable indications for antibiotic therapy.

NECROTIZING FASCITIS

Necrotizing fascitis is a life-threatening disease [105]. It may occur spontaneously, especially in patients with diabetes and/or occlusive vascular pathologies. The most frequent isolated anaerobic pathogen is *Peptostreptococcus*, but *Clostridium* and *Bacteroides* may also be involved, e.g. *Staphylococcus Aureus* and *Streptococcus Pyogenes*. The infection starts quickly in the 24-72 hours following surgery or minor trauma with ample diffusion deeply through the area and necrosis of tissue below the skin. great Extensive separation and destruction of the most superficial tissues below the skin may be observed. The area appears gray and necrotic, but muscles are not involved (Fig. **12**).

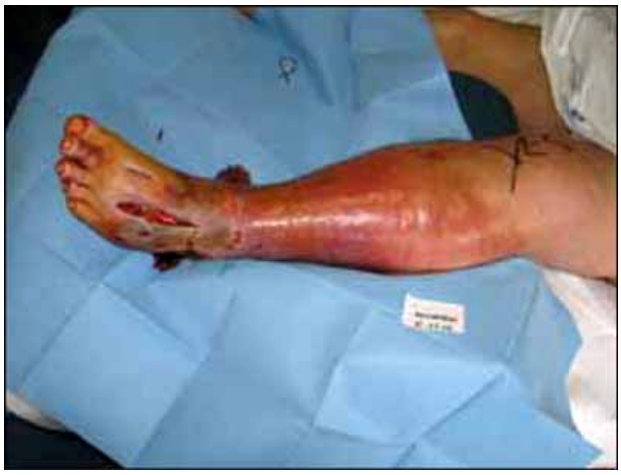

Fig. (12). Necrotizing fascitis.

The treatment of choice is extensive surgical debridement of the tissues involved, until healthy bleeding tissues are reached. This procedure must be carried out in emergency. Antibiotic therapy should be started as soon as possible, without waiting for the results of microbiological cultures. As ancillary treatment, hyperbaric oxygen therapy can be used.

GANGRENE

Gangrene is a very frequent complication, of both neuropathic and neuroischemic ulcers. In a neuropathic foot, this pathology often involves one or more toes without compromising the whole foot. Involvement of the digital arteries leads to the rapid onset of gangrene (septic vasculitis). In the dissemination and progression of an infection involving vessels of the half-foot, the situation may worsen, and lead to gangrene and involvement of the entire foot, with indications for a greater amputation. The evolution of gangrene is generally quicker and more destructive in a diabetic subject with an ulcerated wound presenting an occlusive vascular disease.

In both situations, the surgical approach is debridement, which must be as extensive and as thorough as possible, to remove all non-healthy tissues. We recommend surgical removal of necrotic tissue in cases of occlusive vascular processes (avoiding definitive surgical intervention), followed by angiography to evaluate the feasibility of revascularization.

Once the acute phase has been resolved, most appropriate step must be chosen, taking into account the patient's clinical state.

LOCAL TREATMENT OF DIABETIC FOOT ULCERS

Local treatment of an ulcerated wound is considered indispensable ancillary treatment in a suitable overall protocol of care. By local treatment, we mean periodic inspection, cleansing, removal of surface debris, bacteria control, and the creation of a suitable environment to facilitate endogenous processes of wound healing. Many options and new dressings are available but clearly local management of the ulcer must be integrated in a multidisciplinary care program.

The choice of local treatment depends on general assessment, evaluating etiological factors such as PVD and biomechanical alterations that can lead to pathological plantar overloading. Costly dressings to treat plantar wounds are ridiculous if the problem of offloading is not considered.

The state of the wound is improved through appropriate local treatment. In the initial stages, when problems of infection predominate, antiseptic dressings must be used as well as debridement. Together with general antibiotic treatment, local antiseptic products can help to control bacterial load. At this stage, dressings with antiseptic components such as povidone iodine, clorexidine and hydrogen peroxide are used. Novel agents have recently been produced, containing silver compounds which act as antiseptics in a chemical-physical way by guaranteeing slow release and lower toxicity, while maintaining their bactericidal effect. The same philosophy of gradual release of antiseptic to wounds is the basis of iodine cadexomer. This is a formulation of iodine which not only allows chemical sterilization, but also disinfects bacterial residues absorbed inside the granules of the product.

New dressings have enabled effective victory over the so-called "bio-burden", i.e. the bacterial load of the wound which even when metabolically scarcerly active can negatively influence the repair process of the wound itself. "Wound bed preparation" is used to refer to the period of wound management, which allows a safe and speedy arrival at the point of granulation tissue formation through the use of few histiotoxic yet bactericidal substances.

Although controlled studies of diabetic foot still do not exist, other studies of chronic lesions (e.g., burns, pressure sores, leg ulcers) have been carried out, making this type of medication highly promising, even in such a specialized sphere.

Other than classic antiseptic dressings, silver-based dressings have recently been made available. They have been proven to produce effective control of bacteria and reduced healing times. A new local antiseptic, based on highly ionized water, has also recently been shown to be superior to povidone iodine in treating infected ulcers [106]. Tests have shown the product to have excellent bactericidal, fungicidal and virucidal activity [107]. Many trials are in progress to test its effectiveness in various spheres.

New equipment for debridement has been produced, with the intention of providing wound preparation devices which together with antiseptics, control infections.

Following infection control, the aim is to disinfect and clear the wound of debris and necrotic tissue allowing the granulation tissue to proliferate. Autolytic methods may be used, combining the rationale of autolytic enzyme activation of exposed tissues in a wound with particular conditions of pH, humidity and temperature. These enzymes gradually destroy necrotic material and reach healthy tissue, where they are inactive. Suitable materials for this technique are hydrogels, coated with transparent semi-permeable membranes. Advantages of this approach include absence of pain, ease of application, and the possibility of treating the patient in bed. Disadvantages include impossible application in patients who are mobile or who have infections or ischemia, maceration of tissue surrounding the wound, and cost.

Enzymatic methods consist of the applying of topical preparations of collagenase, protease, desoxyribonuclease and fibrinolysin to the wound, in order to debride its base and edges with enzymes. Advantages of this technique include ease of application and the possibility of the patient managing it alone. Disadvantages are the possibility of sensitivity to components in the products, inactivation of enzymes, and cost. Stimulation of repair processes finds applications in the anabolic phases of tissue repair: the proliferative and reconstructive phases. Semi-occlusive or occlusive medicines are found in this phase as well as 'advanced' methods such as growth factors or bio-engineered tissues. Usable advanced dressings in this phase are those based on hyaluronic acid, hydrofibers and foams.

Of the *growth factors*, PDGF (Platelet Derived Growth Factor) is the most deeply studied. It has been evaluated clinically for use in diabetic foot lesions in randomized studies [108]. The effectiveness of this approach has already been tested on other types of chronic ulcers. The main limitations include high cost and possible allergic reactions to the product.

Bio-engineered products have recently been developed. Autologous and heterologous fibroblasts and keratinocytes on various kinds of scaffolding are now available. Effectiveness has been studied in randomized controlled studies [109-111]. When applied repeatedly, these materials stimulate tissue regeneration through the liberation of growth factors. The philosophy of this approach is to use cells which produce growth factors, rather than the growth factor alone. In this way, it is possible to prolong therapeutic action, even in the presence of multiple growth factors and their temporal sequence, connected to the healing process of the wound. Negative Pressure Wound Therapy (NPWT) has recently been proven to be effective treatment for both complicated and non complicated ulcerated wounds. The system consists of reticulated foam which is placed into the wound and sealed with an occlusive dressing. A suction tube is secured over a hole cut in the dressing, allowing contact with the sponge, and the other end of the tube is attached to a machine that delivers negative pressure as suction, in a continuous or intermittent fashion. Negative pressure wound therapy is indicated for use with various types of ulcers, and has been shown to help wound healing in various ways. Tests on animals have shown that NPWT decreases the bacterial burden in wounds, changing them wounds from infected to colonized after 4 to 5 days [112]. Oedema is reduced, thus stimulating the formation of granulation tissue, compared with wet-to-moist dressings [113]. Intermittent NPWT is even more effective in granulation tissue formation. Some evidence suggests that removing inhibitory cytokines and activated polymorphonuclear leucocytes may also help. NPWT has also been shown to decrease the depth of deep wounds faster than wet-to-moist dressings [114]. Specific guidelines are now available for the use of NPWT in treating diabetic foot wounds [115]. In a multicenter randomized study carried out recently, Armstrong *et al*. examined NPWT applied to open amputations. The control group was treated with advanced dressings, depending on the standard of the participating centers. NPWT treatment, used as advanced dressing, led to a statistically significant reduction in healing time [116].

CARE ORGANIZATIONS

The diagnostic paths and treatments examined above are certainly the fruit of a multidisciplinary approach. The optimal way of improving prevention and treating patients with diabetic foot complications is to create an independent and dedicated multidisciplinary team [117,118]. In many situations, where the social health impact of the problem has occurred, the decisive step toward facing the problem in a new way has been the creation of specialized centers.

The so-called 'foot clinics' have various characteristics depending on the healthcare enviroment in which the various specialists work [119]. They are professionals dedicated to the problem of diabetes and experts in prevention techniques and treatment. In the Italian case, the role of coordination is usually assigned to a diabetologist, with the collaboration of vascular and orthopedic surgeons, radiologists, cardiologists, podologists, and specialized nurses. The organisation of care should offer the possibility of treating non-complicated wounds in a ward environment, using modern offloading techniques, local therapy, and advanced dressings. Admittance to a care structure managed by a foot clinic should be arranged for complex wounds. In such a structure, overall treatment should be possible: from revascularization to emergency and/or elective surgical treatment, to rehabilitation [120].

REFERENCES

[1] Edmonds M. Progress in care of the diabetic foot. Lancet 1999; 354:270-272.

[2] Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care 1990; 113(5): 513-521.

[3] Wagner FW. The disvascular foot: a system for diagnosis and treatment. Foot Ankle 1981; 2: 64-122.
[4] Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system: contribution of depth, infection and vascular disease to the risk of amputation. Diabetes Care 1998; 21: 855-859.
[5] Apelqvist J, Bakker K, van Houtum WH, Nabuurs-Franssen MH, Schaper NC. International Working Group on the Diabetic Foot. International Consensus on the Diabetic Foot. Maastricht, 1999.
[6] Peters EJ, Lavery LA. Effectiveness of the diabetic foot risk classification of the International Working Group on The Diabetic Foot. Diabetes Care 2001; 24: 1442-1447.
[7] The St. Vincent Declaration, Diabet. Med. 1990; 7:360, 89.
[8] Trautner C, Giani G, Haastert B, *et al.* Unchanged incidence of lower limb amputations in a German city, 1990-1998. Diab Care 2001; 24: 855-59.
[9] Stiegler H, Standl E, Frank S, Mendler G. Failure of reducing lower extremity amputation in diabetic patients: results of two subsequent population based survey 1990 and 1995 in Germany. Vasa 1998; 27 (1):10-14.
[10] Larsson J, Apelqvist J, Agardh CD, Stenstrom A. Decreasing incidence of major amputations in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabet Med 1995; 12: 770-776.
[11] Holstein P, Ellitsgaard N, Olsen BB, Ellitsgaard V. Decreasing incidence of major amputations in people with diabetes. Diabetologia 2000; 43: 844-847.
[12] Faglia E, Dalla Paola L, Clerici G, *et al.* Peripheral angioplasty as the first choice revascularization procedure in diabetic patients with critical limb ischemia: prospective study of 993 consecutive patients hospitalized and followed between 1999 and 2003. Eur J Vasc Endovasc Surg 2005; 6: 620-627.
[13] Faglia E, Favales F, Aldeghi A. Change in major amputation rate in a center dedicated to diabetic foot care during the 1980's: prognostic determinants for major amputation. J Diabetes Complications 1998; 12: 96-102.
[14] Faglia E, Mantero M, Dalla Paola L, *et al.* Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive subjects. J Intern Med 2002; 252: 225-232.
[15] Edmonds M, Forster AVM. Reduction of major amputations in the diabetic a strategy to "take control" with conservative care as well as revascularization. Vasa 2001; 58: 6-14.
[16] Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers Am J Surg 1998; 176: 5S-10S.
[17] Kumar S, Asche HA, Parnell LN. The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. Diabet Med 1994; 11:480-84.
[18] Walters DP, Gatling W, Mullee MA. The distribution and severity of diabetic foot disease: a community study with comparison to non-diabetic group. Diabet Med 1992; 9: 354-58.
[19] Ramsey SD, Newton K, Blough D. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diab Care 1999; 22: 382-387.
[20] Henriksson F, Agardh C-D, Berne C. Direct medical costs for patients with type 2 diabetes in Sweden J Intern Med 2000; 248: 387-396.
[21] Muller IS, de Grauw WJC, van Gerwen WHEM. Foot amputation and lower limb amputation in type 2 diabetic patients in Dutch primary health care. Diab Care 2002; 25: 570-574.
[22] Abbot CA, Carrington AL, Ashe H. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med 2002; 19: 377-84.
[23] Abbot CA, Vileykite L, Williamson S, Carrington AL, Boulton AJM. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diab Care 1999; 22: 382-7.
[24] Van Houtum,WH, Lavery LA, Harkless LB. The impact of diabetes-related lower extremity amputations in The Netherlands. J Diabetes Comp. 1996; 10(6): 325-30.
[25] Witsø E, Rønningen H. Lower limb amputations: registration of all lower limb amputations performed at the University Hospital of Trondheim, Norway, 1994-1997. Prosthet Orthop Int 2001; 25: 181-85.
[26] Group TG. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia: the global lower extremity amputation study group. Br J Surg 2000; 87: 328-37.
[27] Spichler ERS, Spichler D, Lessa I. Capture-recapture method to estimate lower extremity amputation rates in Rio de Janeiro, Brazil. Pan Am J Public Health 2001; 19: 334-40.
[28] Trautner C, Giani G, Haastert B. Unchanged incidence of lower limb amputations in a German city, 1990-1998. Diab Care 2001; 24: 855-59.
[29] Wrobel JS, Mayfield JA, Reiber GE. Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. Diab Care 2001; 24: 860-64.
[30] Van Houtum WH, Lavery LA. Regional variation in the incidence of diabetes-related amputation in the Netherlands Diabetes. Res Clin Pract 1996; 31: 125-32.
[31] Canavan R, Connolly V, Airey CM. Risk of diabetes-related amputation in South Asians vs Europeans in the UK. Diabet Med 2002; 19: 99-104.
[32] Boyko EJ, Ahroni JH, Smith DG. Increased mortality associated with diabetic foot ulcer. Diabet Med 1996; 13: 967-72.
[33] Moulik P, Gill G. Mortality in diabetic patients with foot ulcers. Diabetic Foot 2002;5:51-53.
[34] Lavery LA, van Houtum WH, Harkless LB. In-hospital mortality and disposition of the diabetic amputees in The Netherlands. Diabet Med 1996; 13: 192-97.
[35] da Silva AF, Desgranges P, Holdsworth J. The management and outcome of critical limb ischemia in diabetic patients: results of a national survey. Audit Committee of the Vascular Surgical Society of Great Britain and Ireland. Diabet Med 1996; 13: 726-28.
[36] Aulivola B, LoGerfo FW, Pomposelli FB. Major lower extremity amputation: outcome of a modern series Arch Surg 2004; 139 (4): 395-9.
[37] Faglia E, Favales F, Morabito A. New ulceration, new major amputation and survival rates in diabetics subjects hospitalised for foot ulceration from 1990 to 1993: a 6.5year follow-up. Diab Care 2001; 24: 78-83.
[38] Karchmer AW, Gibbons GW. Foot infections in diabetes: evaluation and management. Curr Clin Top Infect Dis; 1994;14:1-22.
[39] Remedios A, Valabhji J, Oelbaum R, Sharp P, Mitchell R. 99m Tc-nanocolloid scintigraphy for assessing osteomyelitis in diabetic neuropathic feet. Clin Radiol 1998; 53:120-5.
[40] Newman LG. Imaging techniques in the diabetic foot. Clin Podiatr Med Surg 1995;12: 75-86.
[41] Mushlin A, Littemberg B, and the Diagnostic Technology Assessment Consortium. Diagnosing pedal osteomyelitis. J Gen Intern Med 1994;9:1-7.
[42] Elgazzar A, Abdel-Dayem H, Clark J, Maxon H. Multimodality imaging of osteomyelitis. Eur J Nucl Med 1995; 22: 1043-63.
[43] Gold R, Tong D, Crim J, Seeger L. Imaging the diabetic foot. Skeletal Radiol 1995; 24: 563-71.
[44] Grayson M, Gibbons G, Balogh K, Levin E, Karchmer A. probing to bone in infected pedal ulcers: a clinical sign of underlying osteomyelitis in diabetic patients. JAMA 1995; 273: 721-3.
[45] Caravaggi C, Faglia E, De Giglio R, *et al.* Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus therapeutic shoein the treatment of neuropathic foot ulcers. Diab Care 2000; 23(12): 1746-51.
[46] Armstrong DG, Nguyen HC, Lavery L, van Schie CHM, Boulton AJM, Harkless LB. Off loading the diabetic foot wound. Diab Care 2001; 24: 1019-1022.
[47] Piaggesi A, Viacava P, Rizzo L, *et al.* Semiquantitative analysis of the histopathological features of the neuropathic foot ulcer: effects of pressure relief. Diab Care 2003; 26 (11): 3123-8.
[48] Armstrong DG, Lavery LA, Wu S, Boulton AJ. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diab Care 2005; 28 (3): 551-4.
[49] Armstrong DG, Frykberg RG. Classifying diabetic foot surgery: toward a rational definition. Diabet Med 2003; 20; 329-331.

[50] Blume PA, Paragas LK, Sumpio BE, Attinger CE. Single-stage surgical treatment of non infected diabetic foot ulcers. Plas Reconstr Surg 2002; 109 (2) : 601-9.
[51] Piaggesi A, Schipani E, Campi F, *et al.* Conservative surgical approach versus non-surgical management of diabetic neuropathic foot ulcers. Diabet Med 1998;15(5): 412-7.
[52] Armstrong DG, Stacpoole-Shea S, Nguyen H, Harkless LB. Lenghtening of the Achilles tendon in diabetic patients who are at high risk for ulceration of the foot. J Bone Joint Surg Am 1999; 81 (4): 535-8.
[53] Group TG. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia: the global lower extremity amputation study group. Br J Surg 2000; 87: 328-37.
[54] Simon SR, Tejwani SG, Wilson DL, Santner TJ, Denniston NL. Arthrodesis as an early alternative to nonoperative management of Charcot arthropathy of the diabetic foot. J Bone Joint Surg Am 1992; 74: 261-269.
[55] Pinzur MS, Kelikian A. Charcot ankle fusion with retrograde locked intramedullary nail. Foot Ankle Int 1997; 18: 699-704.
[56] Caravaggi C, Cimmino M, Caruso S, Dalla Noce S. Intramedullary compressive nail fixation for the treatment of severe charcot deformity of the ankle and rear foot. J Foot Ankle Surg 2006; 45 (1): 20-4.
[57] LoGerfo FW, Gibbons GW, Pomposelli FB Jr, *et al.* Trends in the care of the diabetic foot. Expanded role of arterial reconstruction. Arch Surg 1992; 127: 617-20.
[58] Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. N Engl J Med 1994; 29: 854-60.
[59] Ouriel K. Peripheral arterial disease. Lancet 2001; 358: 1257-64.
[60] Reiber GE. The epidemiology of diabetic foot problems. Diabet Med 1996; 13 Suppl: S6-11.
[61] Kansal N, Hamdan A. Clinical features and diagnosis of macrovascular disease. In: The diabetic foot: Medical and surgical Management. Ed A. Veves, JM Giurini, and FW Lo Gerfo, Humana Press Inc, Totowa, NJ, 113-125, 2000.
[62] Emanuele MA, Bauchanan BJ, Abraira C. Elevated leg systolic pressure and arterial calcifications in diabetic occlusive vascular disease. Diab Care 1981; 4: 289-292.
[63] Lepantalo M, Biancari F, Tukiainen E. Never amputate without consultation of a vascular surgeon. Diab Metab Res Rev 2000; 16 Suppl 1: S27-S32.
[64] Yeager RA, Moneta GL, Edwards JM, *et al.* Predictors of outcome of forefoot surgery for ulceration and gangrene. Am J Surg 1998; 175:388-390.
[65] TranAtlantic Inter-Society Consensus (TASC). Management of peripheral arterial disease(PAD). Eur J Vasc Endovasc Surg; 2000; 19 Suppl.
[66] European Working Group on critical leg ischemia. Second European consensus on chronic critical leg ischemia. Eur J Vasc Surg 1992; 6 Suppl A: 1-32.
[67] Gibbons GW, Wheelock Fc Jr, Hoar CS Jr, Rowbotham JL, Siembieda C. Predictive success of forefoot amputations in diabetics by noninvasive testing. Arch Surg 1979; 114:1034-1036.
[68] Fraser SC, al-Kutoubi MA, Wolfe JH. Percutaneous transluminal angioplasty of the infrapopliteal vessels: the evidence. Radiology. 1996; 200: 33-6.
[69] Merten GJ, Burgess WP, Gray LV, *et al.* Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 2004; 291: 2328-34.
[70] Melliere D, Berrahal D, Desgranges P, *et al.* Influence of diabetes on revascularisation procedures of the aorta and lower limb arteries: early results. Eur J Vasc Endovasc Surg. 1999; 17: 438-41.
[71] Spence LD, Hartnell GG, Reinking G, Gibbons G, Pomposelli F, Clouse ME. Diabetic versus nondiabetic limb-threatening ischemia: outcome of percutaneous iliac intervention. AJR Am J Roentgenol. 1999; 172: 1335-41.
[72] Pentecost MJ, Criqui MH, Dorros G, *et al.* Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels. A statement for health professionals from a special writing group of the Councils on Cardiovascular Radiology, Arteriosclerosis, Cardio-Thoracic and Vascular Surgery, Clinical Cardiology, and Epidemiology and Prevention, the American Heart Association. Circulation. 1994; 89: 511-31.
[73] Grollman J, Levin DC, Bettmann MA, *et al.* Recurrent symptoms following lower extremity angioplasty: claudication and threatened limb. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000; 215 Suppl: 95-9.
[74] Kumpe DA, Rutheford RB. Percutaneous transluminal angioplasty for lower extremity ischemia. In: Rutheford RB eds Vascular Surgery, 3rd edition. Philadelphia PA: WB Saunders. 1992: 759-61.
[75] London NJ, Varty K, Sayers RD, Thompson MM, Bell PR, Bolia A. Percutaneous transluminal angioplasty for lower-limb critical ischemia. Br J Surg. 1995; 82: 1232-5.
[76] Rhodes JM, Gloviczki P, Bower TC, Panneton JM, Canton LG, Toomey BJ. The benefits of secondary interventions in patients with failing or failed pedal bypass grafts. Am J Surg. 1999; 178: 151-5.
[77] Gschwandtner MF, Minar F, Ahmadi A, *et al.* Impact of different therapeutic alternatives in treatment of severe limb ischemia: Experiences on 190 consecutive patients at a department of medical angiology. Vasa 1999; 28: 271-278.
[78] Melki JP, Fermand M, Riche MC, Lazareth I, Priollet P, Cormier JM. Treatment of diabetic arteriopathy. Importance of transluminal angioplasty. J Mal Vasc 1993; 18: 37-41.
[79] Soder HK, Manninen HI, Jaakkola P, *et al*. Prospective trial of infrapopliteal artery balloon angioplasty for critical limb ischemia: angiographic and clinical results. J Vasc Interv Radiol 2000; 11: 1021-31.
[80] Wagner HJ, Rager G. Infrapopliteal angioplasty: a forgotten region? Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr. 1998; 168: 415-20. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care. Diab Care 1999; 22: 1354-60.
[81] Treiman GS, Oderich Gustavo SC, Ashrafi A, Schneider PA. Management of ischemic heel ulceration and gangrene: an evaluation of factors associated with successful healing. J Vasc Surg 2000; 31: 1110-1118.
[82] Yeager RA, Moneta GL, Edwards JM, Williamson WK, Taylor LM Jr, Porter JM. Predictors of outcome of forefoot surgery for ulceration and gangrene. Am J Surg 1998; 175: 388-390.
[83] La Fontaine J, Reyzelman A, Rothenberg G, Husain K, Harkless LB. The role of revascularization in transmetatarsal amputations. J Am Podiatr Med Assoc 2001; 91: 533-535.
[84] Bypass versus angioplasty in severe ischemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005; 366: 1925-1934.
[85] Hirsch AT, Haskal ZJ, Hertzer NR, *et al.* ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006; 113(11): e463-654.
[86] Isner JM, Rosenfield K. Redefining the treatment of peripheral artery disease. Role of percutaneous revascularization. Circulation 1993; 88: 1534-1557.
[87] Pomposelli FB Jr, Marcaccio EJ, Gibbons GW, *et al*. Dorsalis pedis arterial bypass: durable limb salvage for foot ischemia in patients with diabetes mellitus. J Vasc Surg 1995; 21: 375-384.
[88] Panneton JM, Gloviczki P, Bower TC, Rhodes JM, Canton LG, Toomey BJ. Pedal bypass for limb salvage: impact of diabetes on long-term outcome. Ann Vasc Surg 2000; 14: 640-647.
[89] Eneroth M, Larsson J, Apelqvist J. Deep foot infections in patients with diabetes and foot ulcer: an entity with different characteristics, treatments, and prognosis. J Diab Comp 1999; 13: 254-263.

[90] American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care. Diab Care 1999; 22: 1354-60.

[91] Lipsky BA Infectious problems of the foot in diabetic patients In: Bowker JH, Pfeifer MA (eds): Levin and O' Neal's The Diabetic Foot 6th edition Mosby 2001.

[92] Chantelau E, Tanudjaja T, Altenhofer F. Antibiotic treatment for uncomplicated neuropathic forefoot ulcers in diabetes: a controlled trial. Diabet Med 1996; 13: 156-159.

[93] Boiko EJ, Lipsky BA Infection and diabetes mellitus. In: Harris MI (ed), Diabetes in America, 2nd ed. Diabetes data compiled 1995. Bethesda, MD: National Institutes of Health. NIH publication No 95-1468,1995: 485-499.

[94] Rosemblum BI, Pomposelli FB, Giurini JM, *et al.* Maximizing foot salvage by a combined approach to foot ischemia and neuropathic ulceration in patients with diabetes. A 5-year experience. Diab Care 1994; 9: 983-987.

[95] Holstein P. Limb salvage experience in a multidisciplinary diabetic foot unit. Diab Care 1999; 22: 97-103.

[96] Gibbons GW. The diabetic foot:amputations and drainage of infection. J Vasc Surg 1987; 5: 791-793.

[97] Frykberg RG, Armstrong DG, Giurini J, *et al.* American College of Foot and Ankle Surgeons. Diabetic foot disorders: a clinical practice guideline. J Foot Ankle Surg 2000; 39: 31-33.

[98] Epstein DA, Corson JD. Surgical perspective in treatment of diabetic foot ulcers. Wounds 2001; 13: 59-65.

[99] Edelson GW, Armstrong DG, Lavery LA, Caicco G. The acutely infected diabetic foot is not adequately evaluated in an inpatient setting. Arch Intern Med 1996; 156: 2873-2878.

[100] Van Baal JG. Surgical treatment of the infected diabetic foot. Clin Infect Dis 2004; 39: 123-128.

[101] Shape JN. Antibiotics as an adjunct to surgical management of lower extremity ulcerations. Wiley InterScience 14 January 2004.

[102] Armstrong DG, Lipsky BA. Diabetic foot infections: stepwise medical and surgical management. Int Wound J. 2004; 1: 123-132.

[103] Sanders LJ. Surgical approach to the diabetic foot. In: Edmonds ME, Foster AVM, Sanders L (Eds.) A practical Manual of Diabetic Footcare, BlacKwell Publishing 2004; 183-219.

[104] Tan SJ, Friedman NM, Hazelton Miller C, Flanagan JP, File TM Jr. Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation? Clin Infect Dis 1996; 23: 286-291.

[105] Brandt MM Corpron CA, Wahl WL. Necrotizing soft tissue infections: a surgical disease. Am J Surg 2000; 66: 967-970.

[106] Dalla Paola L, Brocco E, Senesi A, Ninkovic S, Merico M. Use of Dermacyn, a new antiseptic agent for the local treatment of diabetic foot ulcers. Journal of wound healing 2005; 2: 201.

[107] Landa-Solis C, Gonzalez-Espinoza D, Guzman B, *et al.* Microcyn: a novel super-oxidized water with neutral pH and disinfectant activity J Hosp Infect 2005; 61 (4): 291-299.

[108] Wieman TJ. Efficacy and safety of a topical gel formulation of recombinant human-platelet derived growth factor-BB (beclapermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-bind study. Diab Care 1998; 21(5): 822-7.

[109] Caravaggi C, Faglia E, Dalla Paola L, *et al*. HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial. Diab Care 2003; 26(10): 2853-9.

[110] Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a Human Skin Equivalent, is Effective in the Management of Non Infected Neuropathic Ulcers: a prospective multicenter rdomized clinical trial. Diab Care 2001; 24 (2): 290-5.

[111] Richard A. A Human Dermal Replacement for the Treatment of Diabetic Foot Ulcer. Wounds 1997; 9(1): 175-183.

[112] Morykwas M, Argenta L, Shelton-Brown E, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plas Surg. 1997; 38; 6: 55-6.

[113] Kieswetter K. Mechanism of action for NPWT. Presentation at the National VAC Educational Conference. New York, NY: May 2004.

[114] Joseph E, Hamori C, Bergman S, Roaf E, Swann N, Anastasi G. A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. Wounds 2000; 12: 60-67.

[115] Armstrong DG, Attinger CE, Boulton AJ, *et al.* Guidelines regarding negative wound therapy (NPWT) in the diabetic foot. Ostomy Wound Manage 2004; 50 (4B Suppl): 3S-27S.

[116] Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. Lancet 2005; 12: 1704-1710.

[117] Donohoe ME, Fletton JA, Hook A, *et al.* Diabetic foot care for people with diabetes mellitus--a randomized controlled trial of an integrated care approach. Diabet Med 2000; 17: 581-7.

[118] Driver VR, Madsen J, Goodman RA. Reducing amputation rates in patients with diabetes at a military medical center: the limb preservation service model. Diab Care 2005; 28: 248-53.

[119] Gottrup F A. Specialized wound-healing center concept: importance of a multidisciplinary department structure and surgical treatment facilities in the treatment of chronic wounds. Am J Surg 2004; 187: 38-43.

[120] Wraight PR, Lawrence SM, Campbell DA, Colman PG. Creation of a multidisciplinary, evidence based, clinical guideline for the assessment, investigation and management of acute diabetes related foot complications. Diabet Med 2005; 22: 127-36.

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