The Management of Diabetic Foot

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Abstract: Diabetes is a chronic disease with a worldwide increasing trend. Foot complications, closely related to neuropathy and obstructive peripheral vascular disease, are responsible for more than 1 million of leg amputations every year. Foot infection can dramatically increase the risk of amputation. Although many ulcer classification systems have been proposed to stratify the severity of the infectious process, the definition of a specific therapeutic approach still remains an unsolved problem. A Diabetic Foot Triage and an Integrated Surgical Protocol are proposed to identify a diagnostic flow-chart and a step-by-step surgical protocol that can be applied in the treatment of diabetic foot infection. Considering the rapid climbing of multidrug resistant strains it is very important to rationalize the use of antibiotics utilizing them only for the treatment of true infected ulcers. PAD is widely considered the most important factor conditioning the outcome of a diabetic foot ulcer. Currently no randomized control trials are reported in the international literature directly comparing open versus endovascular revascularisation in diabetic patients with CLI. Insufficient data are available to demonstrate whether open bypass surgery or endovascular interventions are more effective in these patients. A decisional flow chart in choosing the best revascularization strategy in diabetic patients with CLI is proposed.

Goals and technical aspects of emergency and elective surgical procedures in diabetic foot are analysed to evaluate critical aspects and to suggest proper surgical choices.

Keywords: Charcot Neuroarthropaty, Diabetic foot, Diabetic foot infection, Diabetic foot surgery, Diabetic foot ulcer, Ischemic diabetic foot.

INTRODUCTION

Diabetes is a worldwide common chronic disease caused both by genetic and environmental factors with an epidemic evolution in developing countries. It is estimated that approximately 346 million people worldwide (6.5%) have diabetes and this trend is expected to increase to some 440 million (7.8%) by 2030 [1]. Every year more than 1 million people undergo a lower-limb amputation as a consequence of diabetes and 85% of all amputations are preceded by a foot ulcer [2]. Prevalence of lower-extremity amputations in people with diabetes ranges from 0.2 to 4.8% while annual incidence ranges from 46 to 936 for 100.000 diabetic patients [3]. Differences in prevalence and incidence are mainly related to demographic factors, local prevalence of diabetes and different data collection criteria.

Diabetic people are 25 times more likely to lose a leg than non-diabetic and throughout the world up to 70% of leg amputations are performed in people with diabetes [4]. Diabetic foot complications result in huge costs for diabetics, their families and society and foot problems consume from 15% to 40% of the healthcare resources for diabetes [1,2,5].

DEFINITION, CHARACTERISTICS AND PATHOPHYSIOLOGY

Diabetic foot has been defined as an infection, ulceration or destruction of deep tissues of the foot associated with neuropathy and/or peripheral arterial disease [4]. Ulcers may involve any part of the foot: approximately 50% are located on the planter surface of the foot while remaining 50% may involve other areas. Diabetic foot lesions frequently result from a combination of many risk factors occurring together as listed in Table 1 [6]. Diabetic foot ulcers can be divided into neuropathic, neuro-ischemic and pure ischemic lesions [7].

Neuropathy

Diabetic peripheral neuropathy is characterized by the involvement of all fibers (sensory, motor and autonomic). Motor neuropathy results in atrophy and weakness of the
muscles of foot and leg and joint rigidity with consequent abnormal walking pattern resulting in increase of peak pressure on the plantar aspect of the foot. Foot deformities as consequence of muscle impairment and joint rigidity may cause ulcer on both plantar and dorsal side of the foot [8,9].

Autonomic neuropathy results in reduced or absent sweating leading to dry skin with cracks and fissures. The involvement of sympathetic nerve fibers causes increased arteriovenous shunting which leads to a warm and edematous foot with distended dorsal foot veins [10].

Sensory neuropathy may reduce pain perception, increasing the risk of ulceration secondary to repetitive trauma during walking [11-13]. Insensitive callus on plantar foot surface, caused by peak of pressure, frequently anticipates the onset of a neuropathic plantar ulcer [8,9,11].

Charcot neuro-osteoarthropathy is a devastating complication of diabetic foot syndrome. Acute Charcot usually presents with a hot, inflamed, swollen and sometimes painful foot without skin lesions. Clear differentiation from infection is essential to ensure appropriate management. Progression is often rapid with bone fragmentation and joints destruction followed by exuberant periosteal reaction. Collapse of the medial longitudinal arch of the foot is a common evolution leading to typical 'rocker bottom' deformity with a high risk of deep infected ulcer [14-16].

**Peripheral Arterial Disease**

PAD is the most important factor conditioning the outcome of a diabetic foot ulcer and is the only independent prognostic factor for amputation [7]. PAD can be approximately found in 50% of the patients presenting a foot ulcer [17]. In diabetics PAD is more common, affects younger individuals, is equally divided between genders, has a multisegmental and more distal localization with a faster progression [4].

Less than 25% of diabetic patients affected by PAD reports intermittent claudication due to the concomitant sensory neuropathy [4,18]. Diagnostic procedures include ankle and toe pressure measurements and ankle-brachial index. The cut off for diagnosis of CLI in patients with ulcers or gangrene is considered an ankle pressure less than 70 mmHg or a toe pressure less than 50 mmHg [18]. High or a toe pressure less than 50 mmHg [18]. High incidence of arterial wall calcification in diabetic patients renders ankle and toe pressure often unreliable due to overestimation of the intravascular pressure [19]. TcPO2 measurement is more valuable in diabetic patients, the critical level of TcPO2 for the diagnosis of CLI is considered < 30 mmHg; however Faglia et al. demonstrated that TcPO2 levels < 34 mmHg indicate the need for revascularization, while for values ranging from 34 to 40 mmHg it appears less pressing, although there remains a considerable probability of amputation. TcPO2 levels greater than 40 mmHg suggest that the revascularization is dependent on the severity of the tissue loss and on the possible morbidity caused by the procedure [20].

### Infection

Foot infection is a common complication in patients with diabetes and is associated with a dramatic increase of the risk of lower extremity amputation. Patients with diabetes are particularly susceptible to foot infection [21] because of neuropathy, vascular insufficiency and diminished neutrophil function [22-24]. Several studies have demonstrated that in diabetic subjects there was a consistent reduction in apoptosis and consequently neutrophil failed to down regulate the production of TNFα over time. The failure to limit the production of mediators potentially causing tissue injury might contribute to the extensive tissue damage observed during infections in diabetic patients. DFIs are classified as mild, moderate, or severe (Table 2) [4,25].

### Osteomyelitis

Osteomyelitis is a frequent and serious complication of diabetic foot ulcers and infection. Bone infection may be difficult to detect on a clinical basis [26]. A delay in the diagnosis of osteomyelitis increases the risk of amputation considering that imaging techniques are not enough specific and sensitive [27-29]. Diagnostic criteria for the diagnosis of osteomyelitis have been recently proposed (Table 3) [30].

### Diabetic Foot Triage: A New Therapeutic Approach to Diabetic Foot Problems

In case of a foot ulcer in a diabetic patient, the assessment of the extent and depth of the lesion, of the presence of PAD and infection is crucial for the diagnosis, the therapeutic approach and the prognosis. Many staging systems have been proposed, currently the most widespread and validated system is the University of Texas Wound Classification System that combines the depth of the lesion and the presence or absence of ischemia and infection (Fig. 1) [31, 32]. TUC stages demonstrate a positive correlation between ulcer size, ischemia and infection and the increase of the relative amputation risk. Although this classification permits to stratify accurately the severity of the infectious process, the problem of defining a correct therapeutic approach for different clinical conditions remains unsolved. From a clinical point of view it is clear that the severity of an infectious process indicates the need for immediate treatment, but unfortunately there are few data in the literature that specify which treatment is appropriate according to the different degrees of infection and ischemia. In 2004 Van Baal et al.
Table 2. Clinical Classification of Diabetic Foot Infection.

<table>
<thead>
<tr>
<th>Clinical Manifestations of Infection</th>
<th>Infection Severity</th>
<th>PEDIS Grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound lacking purulence or any manifestations of inflammation.</td>
<td>Uninfected</td>
<td>1</td>
</tr>
<tr>
<td>Presence of ≥2 manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends &lt;2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness.</td>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>Infection (as above) in a patient who is systemically well and metabolically stable but which has ≥1 of the following characteristics: cellulitis extending ≥2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)</td>
<td>Severe</td>
<td>4</td>
</tr>
</tbody>
</table>

From Lipsky BA et al. [25]
*PEDIS: perfusion, extension/size, depth/tissue loss, infection, and sensation [4]

Table 3. Proposed Criteria for Diagnosing Osteomyelitis in the Diabetic Foot.

<table>
<thead>
<tr>
<th>Category</th>
<th>Probability Osteomyelitis</th>
<th>Management Advice</th>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>&gt;90%</td>
<td>Treat for osteomyelitis</td>
<td>• Bone sample with positive culture AND positive histology OR</td>
<td>Sample must be obtained at surgery or through uninvolved skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Purulence in bone found at surgery OR</td>
<td>Definite purulence identified by experienced surgeon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Atraumatically detached bone fragment removed from ulcer by podiatrist/surgeon OR</td>
<td>Definite bone fragment identified by experienced surgeon/podiatrist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intraosseous abscess found on MRI OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Any two probable criteria OR one probable and two possible criteria OR, any four possible criteria below</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>51-90%</td>
<td>Consider treating, but further investigation may be needed</td>
<td>• Visible cancellous bone in ulcer OR</td>
<td>Sinus tract; sequestrum, heel or metatarsal head involved; cloaca</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MRI showing bone oedema with other signs of osteomyelitis OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bone sample with positive culture but negative or absent histology OR</td>
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<td></td>
<td></td>
<td></td>
<td>• Bone sample with positive histology but negative or absent culture OR</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Any two possible criteria below</td>
<td></td>
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</tbody>
</table>
Table 3. contd….

<table>
<thead>
<tr>
<th>Category</th>
<th>Probability Osteomyelitis</th>
<th>Management Advice</th>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible</td>
<td>10-50%</td>
<td>Treatment may be justifiable, but further investigation usually advised</td>
<td>• Plain X-rays show cortical destruction OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MRI shows bone oedema OR cloaca, OR</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Probe to bone positive OR, Visible cortical bone OR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• ESR &gt;70mm/h with no other plausible explanation OR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Non-healing wound despite adequate offloading and perfusion for &gt;6 weeks OR</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Ulcer of &gt;2 weeks duration with clinical evidence of infection</td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>&lt;10%</td>
<td>Usually no need for further investigation or treatment</td>
<td>• No signs or symptoms of inflammation AND normal X-rays AND ulcer present for &lt;2 weeks or absent AND any ulcer present is superficial OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Normal MRI OR</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Normal bone scan</td>
<td></td>
</tr>
</tbody>
</table>

From Berendt AL et al. [30]

**University of Texas Wound Classification System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No infection or ischemia</td>
<td>0A</td>
<td>IIA</td>
<td>IIIB</td>
<td>IIID</td>
</tr>
<tr>
<td>B</td>
<td>Infection present</td>
<td>0B</td>
<td>IB</td>
<td>IIIB</td>
<td>IIID</td>
</tr>
<tr>
<td>C</td>
<td>Ischemia present</td>
<td>0C</td>
<td>IC</td>
<td>IIIC</td>
<td>IIID</td>
</tr>
<tr>
<td>D</td>
<td>Infection and ischemia present</td>
<td>0D</td>
<td>ID</td>
<td>IIID</td>
<td>IIID</td>
</tr>
</tbody>
</table>

**Grade**

- 0: Pre or postoperative infection completely eradicated
- I: Superficial wound, not involving tendon, capsule, or bone
- II: Wound penetrating to tendon or capsule
- III: Wound penetrating to bone or joint

**Fig. (1).** University of Texas Wound Classification System Adapted from Armstrong DG et al. [32]. Colors were inserted to create a link with figure 2 “Diabetic Foot Triage”.

demonstrated that the delay in the radical surgical treatment is correlated with an high percentage of major and minor amputations because it allows the infection to proliferate and destroy the tissues [33]. Faglia et al. demonstrated that, in case of CLI, an early surgical treatment of a severe infection followed by an early revascularization procedure, is able to achieve limb salvage or a more distal level of foot amputation [34]. The International Guidelines on Diabetic Foot Treatment have clearly indicated which is the treatment of choice to be applied in different situations to achieve the best clinical outcome [4]. Unfortunately these guidelines have been applied in only a few specialized Centres and have remained unknown and not enforced by most physicians who deal occasionally with diabetic foot lesions. Patients with an infected diabetic foot are often sent to an Emergency Department where only rarely they can be subjected to an evaluation by a diabetic foot specialist for proper diagnosis and treatment. In our clinical experience anything resulting in a dramatic delay in the diagnosis and treatment of DFI increases not only the risk of amputation but also the risk of death. We therefore considered appropriate, based on a ten-year experience in emergency medicine and surgery of diabetic foot, to propose a specific “diabetic foot triage” (Fig. 2) envisaged as a codified set of procedures that allows the evaluation of the priorities of patient care. We think that this diagnostic approach could be of great therapeutic utility not only for the diabetic foot specialists but also for all physicians who have to deal, even occasionally, with diabetic foot problems.
**ANTIBIOTIC THERAPY FOR DIABETIC FOOT INFECTIONS**

**Etiology**

DFI is one of the most frequent complications of diabetes mellitus and represents a major cause of morbidity and mortality; it is the first cause of diabetes-related admission to the hospital and one of the primary causes of lower limb amputations [2, 25,35-38]. The commonest etiology of infection is actually represented by Gram-positive bacteria, such as *Staphylococci* and *Streptococci*, but the isolation of Gram-negative strains is not unusual in chronic ulcers and in patients previously treated with antimicrobials. The most frequent isolated bacterial strains resulting from a seven-year study of an European and American surveillance were: *S. aureus*, *P. aeruginosa*, *E. coli* and *Enterococcus spp* [39]. During the observation period it was noticed a growth in the incidence of multi-resistant bacteria, especially MRSA. However, recent data demonstrate a decreasing trend in the prevalence of MRSA in several European countries, except in Italy, where an increasing trend has been noted probably related to an inadequate hospital infection control policy; Gram-negative bacteria with a warning resistance pattern represented the 30% of isolates in the same study [40].

### Rationale of Antibiotic Therapy

Compared to the climbing of multidrug resistant strains, there are no new antimicrobials, especially active against Gram-negatives [40], consequently, it is very important to rationalize the use of antibiotics which have to be used only for the treatment of true infected ulcers, that must be differentiated from colonized ulcers (Table 2). An ulcer can be defined as infected when there are at least two signs: surrounding cellulitis and inflamed wound and/or drainage. In fact, the antibiotic treatment is mandatory only if there is clinical and microbiological evidence of infection (local or systemic). Bacteriological sampling is only indicated if the DFI is clinically confirmed, corresponding to grade 2-4 infections (3). Microbiological samples must be collected prior to the initiation of the antimicrobial therapy, by cutaneous biopsy, ulcer curettage or deep aspiration of pus. Superficial swabs must be discouraged, because of the low diagnostic accuracy of this technique [41]. The imaging studies (ultrasounds and MRI) are useful to evaluate depth of the infection and can also demonstrate the involvement of the bone (CT, MRI, FDG-PET, bone scintigraphy with technetium-99m-labeled diphosphonates or leucocyte scanning with radiolabeled blood cells).

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**Fig. (2).** Diabetic Foot Triage Lesions code refers to figure 1; colors were inserted to create a link with figure 1 “University of Texas Wound Classification System”.

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<table>
<thead>
<tr>
<th>Code</th>
<th>Lesion</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>Ulcer 0A-1A</td>
<td>1. daily wound dressings 2. dressing shoe 3. LMWH</td>
</tr>
<tr>
<td>Green</td>
<td>Ulcer 0-B</td>
<td>1. Total off-bearing of the foot with rigid cast (Gibergen or plastyr) 2. LMWH</td>
</tr>
<tr>
<td>Yellow</td>
<td>Ulcer 0-CD 1-CD 2-BCD 3-ABCD</td>
<td>1. Broad-spectrum antibiotic therapy 2. LMWH 3. Emergency surgery according to the severity of the local infectious process</td>
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</tbody>
</table>

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### Table 2

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**Diagnostic tools** foot radiograph in three projections 2) MRI (Charcot, osteomyelitis) 3) vascular assessment: is early revascularization needed?
Antimicrobial Treatment

The appropriate antimicrobial treatment must be chosen on the basis of the type of infection (depth of the infection, presence of ischemia, systemic symptoms, metabolic alterations). Usually the commonest isolates in patients who have not been treated in the past and whose ulcer’s TUC grade is 2-3 are single Gram-positive pathogens. Patients with severe ulcers (TUC grade 4), or previously exposed to antimicrobial therapy, frequently have more than one pathogen responsible of the infection (either Gram positive or negative pathogens), potentially drug-resistant. Anaerobic bacteria must be suspected in every case of ischemic lesions (negative pathogens), potentially drug-resistant. Anaerobic bacteria must be kept between 15-20 mg/ml. The therapy can be taken orally, given the high bioavailability of this drug. Alternative regimens can be represented by fluoroquinolones (moxifloxacin 400 mg q24 hours or levofloxacin 500 mg q12 hours or 750 mg q24 hours), cotrimoxazole (900 mg q8 hours) or ceftriaxone (2 g q24 hours). If MRSA infection is suspected, the choice is among linezolid (600 mg q12 hours), daptomycin (6-8 mg/kg q24 hours), or vancomycin (2g q24 hours). In severe DFI (grade 4), the therapy must cover a broader spectrum of pathogens (both gram positive and gram negative strains) and be administrated intravenously. The appropriate treatment can be one of the following:

- Piperacillin/tazobactam (4,5 g q6hours) + daptomycin (6-8 mg/kg q24 hours) / linezolid (600 mg q12 hours) /vancomycin (2 g q24 hours).
- Ciprofloxacin (400-mg q8 hours) / levofoxacin (500 mg q 12 hours or 750 mg q24 hours) + daptomycin (6-8 mg/kg q24 hours) / linezolid (600 mg q12 hours) / vancomycin (2 g q24 hours).
- Ertapenem (1 g q24 hours) + daptomycin (6-8 mg/kg q24 hours) / linezolid (600 mg q12 hours) / vancomycin (2 g q24 hours).
- Meropenem (1 g q6 hours) + daptomycin (6-8 mg/kg q24 hours) / linezolid (600 mg q12 hours) / vancomycin (2g q24 hours).
- Tigecycline (100 mg q24 hours)

An MRSA infection must always be considered on the basis of the local epidemiology and the previous antibiotics exposure. Although vancomycin and teicoplanin are considered the first choices in case of MRSA infection, failure with these options occurs due to the growing number of strains with higher MIC to glycopeptides [42-44]. The main disadvantages of old glycopeptidase are the renal toxicity and the need of monitoring blood levels to obtain the most favorable ratio between toxicity and effectiveness: blood levels must be kept between 15-20 µg/ml.

New molecules active on MRSA and useful in DFI are linezolid and daptomycin (both active only on Gram positive strains) and tigecycline (active even against gram negative bacteria). Linezolid is an oxazolidione, has a bacteriostatic effect against all Gram-positive bacteria and a very good penetration in skin and bone tissue. The drug is available both as intravenous and oral formulations, allowing the planning of sequential therapies, even for prolonged time. Daptomycin is a cyclic lipopeptide, characterized by a rapid bactericidal and concentration-dependent activity against all Gram positive bacteria. Daptomycin is approved at a dose of 4 mg/kg for the treatment of complicated skin and soft-tissue infection and at a dose of 6 mg/kg for S. aureus bloodstream infection, including treatment of right-sided endocarditis.

Although prospective randomized clinical studies have claimed that these dosage regimens are safe and effective for their respective indications, the optimal dose level has not been firmly established yet. In recent years, reports of clinical failures and emergence of resistant strains following daptomycin treatment have raised great concern. As a result, higher doses of daptomycin are being proposed as an alternative for some difficult-to-treat infections such as complicated bacteremia and osteomyelitis [45-48]. On the basis of published data and personal experience, daptomycin at higher doses (> 8 mg/kg/day) seems safe and might be more effective than standard dosage in S. aureus infections.

Tigecycline is actually approved in complicated skin and soft tissue and intra-abdominal infections, but not in the therapy of DFI. It has a broad antimicrobial spectrum [49] and its usage must be limited in cases of multi-resistant strains [50]. In fact, its use in case of P. aeruginosa infections is not adequate. In infections sustained by Gram-negative multi-drug resistant bacteria, it may be mandatory the use of colistin, a re-emerging antibiotic which use had been abandoned in the last years because of its high nephrotoxicity (Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, Paterson DL).

Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis. 2006;6(9):589-601). It has been rediscovered recently, since it maintains an high activity versus P. aeruginosa, carbapenemase- producers K. pneumoniae and A. baumannii.

It is difficult to establish the best treatment duration of colistin, however at least of 1-2 weeks appear appropriate for mild to moderate infections and 2-4 weeks for severe infections. In some cases longer treatment times are needed, depending on the site of infection and local vascularization.

In conclusion, in view of the growing prevalence of multi-resistant bacteria, the correct and appropriate use of antimicrobials and the knowledge of the local resistance pattern must always be taken into consideration. There is also a need for continuous microbiological surveillance of resistant bacteria to provide the basis for empirical therapy and reduce the risk of complications. The best way to stem the phenomenon of multidrug resistance is the use of molecules with low selective pressure and high efficacy and the planning of reasonable combination therapies.
Involvement of BTK arteries, calcifications and prevalence of CTOs over stenosis [18,51,52]. The majority of diabetic patients with CLI have a femoro-popliteal obstruction associated with BTK vessels disease and less than 20% of the patients present pure BTK vessels disease [51,53]. Iliac and common femoral arteries obstruction is generally related to other associated cardiovascular risk factors such as smoking and hypercholesterolemia [54]. The first manifestation of CLI can be caused by the natural progression of the vascular obstructive disease, leading to an unbearable ischemic condition of the distal tissues evolving in necrosis. In most cases, the initial lesion follows a mechanical trauma: neuropathy and bone deformity cause recurring trauma, burns and ulcerations [13]. When the tissue loss is established in an ischemic foot, the treatment becomes a challenge because healing is a blood flow dependent process.

**Targets of the Revascularization Therapy**

Peregrin *et al.* analyzed the clinical success of PTA in diabetic patients with CLI considering the number of BTK vessels successfully treated [55]. The emerging concept is that “complete” revascularization is better than “partial” revascularization: limb salvage rate at one year was 56% without direct blood flow to the foot (0 BTK vessels open), and, respectively, 73%, 80% and 83% with 1, 2 or 3 BTK vessels open (Fig. 3). Faglia *et al.* also found that PTA of tibial arteries had a better outcome than PTA of the peroneal artery alone [56]. Another emerging concept is the “wound related artery” revascularization: following the angiosome concept [57], the revascularization of the artery directly feeding the wound region leads to higher rate of limb salvage and wound healing [58,59]. Figure 4 summarizes the concept of complete and WRA revascularization. Also in the case of distal bypass surgery, Neville demonstrated that revascularization of the artery directly feeding the ischemic angiosome leads to a higher rate of healing and limb salvage [60]. Complete and WRA revascularization must not be uncritically pursued: the procedure must be tailored on technically realistic strategies and on the general patient status.
Type of Revascularization

There are currently no randomized control trials directly comparing open versus endovascular revascularization in diabetic patients with CLI, therefore, there are insufficient data to demonstrate whether open bypass surgery or endovascular interventions are more effective in these patients [61]. Pedal bypass grafting is generally considered the gold standard therapy for CLI in diabetics, providing good outcomes in terms of limb salvage and patency rate [62,63]. Nevertheless an increasing number of studies propose an “angioplasty first strategy”, advocating the minor invasiveness of percutaneous procedures and the possibility to revascularize patients that cannot be treated surgically due to poor general status, extensive foot tissue damage, unavailability of an adequate vein conduit or of a target vessel for distal anastomosis [64-73]. To achieve a long-term benefit, however, multiple revascularization procedures may be required in diabetic patients, and a dedicated interdisciplinary surveillance program is mandatory; while the choice of the initial revascularization modality (surgical or endoluminal) seems not to influence the clinical success [74]. Figure 5 summarizes the decisional flow chart in choosing the best revascularization strategy in diabetic patients with CLI. While waiting for future studies to better clarify the selection criteria for surgical or percutaneous revascularization according to the clinical and anatomical variables, the personal expertise plays a key role in the decision making [61].

Surgical Revascularization

If the decision to revascularize is in favor of the open surgical procedure, there are some key points to be considered: the graft inflow and outflow, the availability of autologous material for grafting [75], the absence of contamination at the surgical incision sites and the forecast of possible adverse events for a long procedure in a fragile patient [76].

Choice of the Anastomosis Site

The optimal bypass graft starts from an healthy artery and ends in an artery which must be less diseased as possible. To approach such condition when atherosclerosis involves proximal arteries it is sometimes necessary to perform an endarterectomy of the donor artery (common femoral, less frequently profunda or superficial femoral artery), on the contrary it is better to avoid the endarterectomy of the distal site due to the general poor result. One must find the segment of artery relatively spared from calcium, with an ade-
Diabetic Foot Management

**Step-by-step approach in CTOs**

- **Antegrade approach**
  1. Endoluminal
  2. Subintimal

- **Retrograde puncture**

- **Transcortial**
  1. Pedal-plantar loop technique
  2. Peroneal artery branches PTA

![Step-by-step approach in CTOs](image)

**Fig. (6).** Step-by-step approach in CTOs crossing strategies.

|quate lumen and a direct flow line to the ankle (peroneal artery) or to the foot (anterior and posterior tibial arteries). Due to the disease pattern in diabetic patients, the distal anastomosis is rarely performed in the proximal popliteal artery (above the knee graft). In the majority of the cases, the anastomosis site is chosen on the distal popliteal, tibial or pedal arteries. BTK bypass grafts have significantly inferior patency rates than above the knee grafts [77], whereas distal and ultradistal BTK bypass have comparable outcomes [78].

**Choice of Bypass Graft Material**

It is generally accepted that an autologous vein should be used wherever possible; there are observations that autologous vein bypass grafts in patients with diabetes have better 30-day limb salvage rates than in patients without diabetes [79]. The vein must be free of disease (varicosis, fibrosis) with a diameter > 3 mm; if the caliber is not uniform (distally smaller) it is better to graft it “in situ”; anyway there is no significant difference between in situ and reversed saphenous vein bypass at any time interval [80]. In case of unavailability of an autologous vein, a prosthetic Dacron or PTFE bypass can be performed, possibly with a distal cuff [81].

A trend towards an improved primary patency using PTFE versus Dacron bypass was observed. A significant benefit for a PTFE bypass with a vein cuff when compared with PTFE alone [was underlined [82].

**Surveillance of the Graft**

Vigilant ongoing surveillance of infringuinal grafts may be resource-demanding but it is essential to obtain a high graft patency in order to obtain an good limb salvage rate. Revision of graft stenoses identified by duplex scanning is required in up to 40% of diabetic patients [83]. For venous grafts acetylsalicylic acid treatment is preferred; clopidogrel in association with acetylsalicylic acid confers benefit in patients receiving prosthetic grafts [84].

**Percutaneous Revascularization**

**The Approach**

In the majority of diabetic patients with CLI, the obstructive disease involves below-the-groin vessels, sparing the iliac and the common femoral artery and enables the antegrade femoral approach. In diabetic CLI this is the favored approach because it provides adequate device control, maximizes angiographic resolution, and enables access to foot vessels to achieve complete and WRA revascularization [53,56,66]. However, the antegrade access is more technically demanding, it is fraught by an increased risk of access site failure or complications and it requires an adequate learning curve [85-87].

**CTOs Crossing Strategy**

The first step in percutaneous recanalization is to cross the long CTOs typical of diabetics CLI. Different techniques are now available: endoluminal approach, subintimal, transcortial, pedal-plantar loop technique and retrograde puncture of the vessel beyond the CTO [88-98]. Figure 6 summarizes the role of these different techniques in a step-by-step approach.

**Acute Result Optimization**

Long, thin-profiled, high pressure balloons are the key point in BTK vessel PTA [64-70,99]. Traditionally a 1-2 minutes inflation is recommended, longer time in case of dissection, but there are not studies comparing results using different inflation times in BTK vessel PTA. Bailout stenting in case of flow limiting dissection or poor result is recommended [18]. Atherectomy, cryoplasty, laser, scoring balloons, cutting balloons, are all promising devices which
value have to be clarify, especially regarding the cost-to-benefit ratio [100,101].

Prevention of Restenosis

Restenosis remains the Achille’s heel of percutaneous revascularization. Restenosis is higher for small arteries and long lesion [18], reaching a 69% rate in BTK vessel three month after PTA [102]. Figure 7 shows the length of treated lesions in studies regarding the patency after BTK angioplasty performed with balloon expandable stents, nitinol self expandible stents and plain old uncoated and drug-coated angioplasty balloons [103]. The good results in terms of prevention of restenosis by stenting, particularly DES, are confined to short BTK lesions (<5cm) that are a minority of the lesions seen in diabetic CLI patients. In long, diffuse lesions (majority of CLI patients) the optimal endovascular treatment remains the balloon angioplasty with dedicated BTK balloons and bailout stenting. In these type of lesions DEBs are promising devices in the prevention of restenosis [104]. Apart from these data, it is well known that patency after BTK PTA and limb salvage are not strongly correlated [105,106] therefore further studies are needed to clarify the importance of BTK vessels patency in terms of wound healing, time-to-walking, target vessel revascularization and cost-to-benefit ratio.

THE SURGICAL TREATMENT OF AN INFECTED DIABETIC FOOT INJURY

Surgical Classification of Diabetic Foot Infection

The diabetic foot infections can be classified, from a surgical point of view, as superficial, intermediate and deep. A specific diagnostic and therapeutic approach with a different risk of amputation corresponds to each of these clinical conditions.

Superficial infections are those that affect epidermis and dermis and that have no tendency to spread by contiguity or by the lymphatic and venous network. The amputation risk is extremely low. Such infections are mostly supported by Gram-positive pyogenic cocci, with a prevalence of Staphylococcus aureus. Intermediate infections are those that affect the dermis up to the external muscular fascia with tendency to spread locally by contiguity and by active transport through the lymphatic network of the district, without involvement of deep structures but being associated with a risk of minor amputations. Intermediate infections are supported mostly by pyogenic cocci but they can also be associated with Gram-negative bacteria such as Pseudomonas aeruginosa. The most frequent clinical forms of intermediate infections are the deep infected bacteria such as Pseudomonas aeruginosa. The combination of different microbial species has a potentiating effect on the aggressive-
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Fig. (8). Deep infection of forefoot-midfoot.

Fig. (9). Ulcer debridement by Hydrosurgery.

ness of each strain, creating a true pathogenetic synergy. The evolution of the clinical condition is abruptly progressive, spontaneously turning into wet gangrene, with putrefactive phenomena if proteolytic strains predominate.

Necrotizing fasciitis is the most severe infective clinical condition in the diabetic population, very often it is highly correlated to previous incorrect surgical procedures. In these patients the risk of major amputation is up to 50%

Surgical Approach to the Treatment of Infected Diabetic Foot Lesions

As previously pointed out, the extent and depth of infection correlates with an increased risk of amputation. A rapid control of the early infective process is the cornerstone of treatment of infected diabetic foot lesions. In 2003 Armstrong and Frykberg [107] have classified the diabetic foot surgery into 4 groups showing increasing risks of surgical failure and amputation when surgical procedures are performed in emergency clinical conditions. The objective of emergency surgery in an infected diabetic foot is to gain a rapid control of local and systemic effects of infection. It should be stressed that the time factor must be considered of paramount importance in the surgical treatment approach of the infected diabetic foot. Faglia et al. [36] have recently shown that the early treatment of both the infection by emergency surgery and the CLI by endoluminal or surgical revascularization procedures, are able to obtain a tremendous increase in limb salvage or a distalization of the amputation level of the foot.

Surgical Treatment of Infected Superficial Ulcers of the Foot

The goal of surgical treatment of infected superficial ulcers is the debridement of the lesions and their management until healing. Debridement of the ulcer consists in the removal of all necrotic or non vital tissue with exposure of an healthy and bleeding wound bed. The ulcer debridement methods basically surgically remove by physical means (scalpels, scissors, curette) dead, infected or necrotic tissue and open all sinuses that may be present. The advantages of this approach are its speed, direct control by the operator, versatility on different anatomical sites and cost-effectiveness. The need to perform local anaesthesia often and the risk of surgical complications like bleeding and injury to deep structures are the main disadvantages. In any case, the surgical debridement should always be performed by skilled operators in a suitable environment. Surgical debridement can be performed by an ultrasound debrider. This technique allows to modulate the aggressiveness of the surgical intervention therefore sparing as much as possible the viable tissue Another surgical debridement tool is represented by the Hydrosurgery system, which employs the "Venturi" effect. Thanks to a jet of saline solution at very high speed it is possible to obtain the removal of the necrotic or infected tissue with very high selectivity (Fig. 9). By virtue of its highly aggressiveness, the hydrosurgery system can be used only by specially trained medical and nursing staff (109).

Once the infected and/or necrotic tissue has been removed, NPWT is generally used to guarantee the cleansing of the wound bed and the quick removal of all exudates which could be still be contaminated by residual deep bacterial colonies. The primary treatment goal in the application of NPWT to DFU is to progress towards a wound closure either by secondary intention or by surgical closure (109). Once the control of infection by surgical means has been obtained (110), the NPWT therapy is a useful aid in the preparation of the wound bed, either in case of a chronic or surgical lesion The application of NWPT may be considered as a bridge to obtain a healthy wound bed suitable for a surgical closure by suture, flaps or skin graft) or by secondary healing in combination with a dermal substitute or an advanced dressings.

Surgical Treatment of Deep Infection of the Foot

Phlegmon

The complications of a superficial ulcer incorrectly treated can be the collection of purulent material in the dermis and in deeper tissues. The clinical signs that point to the presence of a phlegmon of the deep tissues are the classic signs of local infection (rubor, tumor, calor, dolor and functio laesa) accompanied by an area of fluctuation interesting the skin and the subcutaneous tissues. In the most favourable case, the infection progresses to a spontaneous drainage of the purulent material through a skin ulcer with partial remis-
sion of local and systemic signs of inflammation. In case of spread of the infection into other deep foot compartments, a clinical evolution into an infective compartmental syndrome can be observed, which places patients at risk of sepsis and major limb amputation. The surgical treatment includes incision of the skin and deep tissues with drainage of purulent material and removal of all infected tissues (Fig. 10). When the infective process involves skeletal structures, it is mandatory to remove the infected bone exposing the vital subcutaneous tissues and the bone which are macroscopically healthy. Frequently, an open forefoot or midfoot amputation has to be performed in order to allow the daily cleaning and dressing of the wound (Fig. 11). It is recommended not to expose the cancellous bone until the infection is under control, to prevent the resorption of the infected material with a consequent risk of bacteraemia and sepsis.

**Infective Compartmental Syndrome**

A deep foot infections in a diabetic patient is a disaster both in terms of local and systemic effects. In fact, the foot structure consists of four main compartments: medial, central (superficial and deep), lateral and interosseous, which are separated by fascial structures. This division into compartments is strictly independent and is responsible for the onset of the infective compartmental syndromes. The increase of pressure inside the compartments, caused by tissue oedema due to the infective process, causes the compression of the small arteries resulting in tissue ischemia and worsening of tissue blood perfusion. From a clinical point of view, patients may present with systemic signs of infection (fever, leucocytosis, elevated erythrocyte sedimentation rate) accompanied by signs of inflammation and pain of varying intensity.

The surgical approach to deep wound infection of the foot requires a careful inspection of foot compartments. It should be underlined that, although the different compartments of the foot are anatomically separated, the infective process can disseminate with the involvement of the adjacent compartment, particularly if the infection is not quickly treated. Frequently a phlegmon of the central compartment of the foot, originating from a dorsal ulcer, deepens through the intermetatarsal area, reaching the plantar compartments. A floating and painful plantar area in the midfoot often represents the only clinical sign of a plantar involvement (Fig. 12). From the surgical point of view, the infective compartmental syndromes of the foot is treated by performing a decompression fasciotomy. It is very important to follow such decompression fasciotomy with an accurate inspection of the deep tissues. It is mandatory to check carefully the integrity of the adjacent anatomical compartments to exclude their involvement in the infectious process. After opening the infected compartment and performing a meticulous debridement, cleansing of wound bed should be done with hydrogen peroxide and povidone iodine solution. After wound bed rinsing, a biopsy of the deep tissue should be performed to obtain a suitable specimen for the microbiological examination and culture. The residual tissue cavity obtained after surgical debridement should be dressed with iodoform gauze. The edges of the surgical incision must be approached with stitches to avoid retraction of the skin, which may complicate the surgical wound closure at a later time. The dressing should be replaced once or twice a day to achieve a complete control of the infective process.
Necrotizing Fasciitis

Necrotizing fasciitis is a frequent complication of the surgical treatment of a severe diabetic foot infection. It is characterized by a particular aggressiveness and devastating evolution of the infective process (111). In the initial stage, the infection tends not to involve the underlying muscular structures. Given the rapid evolution of the infective process, the surgical treatment has to be applied as soon possible.

A careful examination of all infected tissues must be performed, followed by an extensive fasciotomy and open minor amputation to allow the drainage of all infected materials. The result of the surgical debridement must be monitored daily as it may be necessary to carry out further debridements to achieve the full infection control.

Gangrene

Wet gangrene is often the final evolution of a superficial ulcer in presence of CLI not underwent to a correct diagnostic and treatment approach (Fig. 13). Although an antibiotic treatment can sometimes gain control of the infection turning a wet gangrene into a non infected dry one, the evolution toward the auto amputation of a necrotic segment is absolutely not indicated due to the high risk of subsequent infection, unless the patient is confined to bed for a chronic illness.

A proper surgical treatment involves removing the necrotic tissue including the infected bone segment. The demolition of part of the foot can result in an open amputation of the forefoot, midfoot, or rear foot at different levels depending on the spread of the infective process. As previously noticed, the extent of the surgical debridement does not depend on the vascular condition but only on the severity of the infection. The objective remains the complete removal of the infected tissue. Obviously, in case of critical ischemia of the foot, following the surgical debridement the patient will be immediately subjected to the most appropriate revascularization procedure (surgical or endoluminal).

RECONSTRUCTIVE SURGERY OF THE INFECTED DIABETIC FOOT

While the goal of emergency surgery is the control of the local and systemic infection, the role of elective surgery is primarily the reconstruction of the foot and the correction of foot deformity and joint instability (107). It is extremely important to underline that the objective of the diabetic foot surgery, both in emergency and elective conditions, is to allow the patient to return to walk with an improved quality of life. On deciding which surgical approach has to be applied on a patient, some questions have to be answered beforehand.

First of all, it should be considered whether the patient has maintained its residual walking attitude. Patients often come to clinical observation after a long period of chronic infection of the foot that has greatly undermined the possibility of a functional recovery. The peripheral vascular disease in diabetes populations is frequently associated with heart disease which greatly reduces the workload of the heart, while the cerebrovascular disease puts the major limitations to the recovery due to the residual functional deficits of the lower limbs. These patients, after a long period of bed rest, frequently have an irreducible flexion of the knee on the thigh, which undermines any attempt of limb salvage. In this clinical situation the choice of major amputations (mostly above the knee) can be the best option as it allows a rapid healing thus avoiding further risks of infection. The choice of the definitive surgical treatment is completely different if the patient has a good chance to return to walk. No doubt that the main goal of reconstructive surgery of the foot is obtaining a foot or a stump useful for a proper gait and for easy fitting. From the biomechanical point of view, the residual foot or the stump should have some basic features: 1) a lever long enough in order to maintain stability during the boost phase of the gait cycle, 2) proper alignment of the foot with the leg, 3) proper motion of pronation and supination of the forefoot and dorsiflexion of the ankle joint, 4) a suitable subcutaneous tissue in the plantar region of the foot that can withstand pressure trauma on the plantar surface of the foot during walking. These biomechanical and functional characteristics are often present after minor surgery of the forefoot (toe or ray amputation) and of the midfoot (Transmetatarsal amputation). Having to decide the definitive surgical treatment in a patient with good residual ability to walk, the reconstructive surgery of the forefoot and the midfoot is indicated. Several precautions must always be taken into account. From a biomechanical and functional point of view, amputation of the hallux and of the 5th toe does not pose any serious problems unless after surgical treatment the patient wears a protective shoe with an unloading insole. These shoes are characterized by a rigid rocker bottom sole and a moulded insole with the aim to control the redistribution of pressure level on the plantar surface (Fig. 14).

The amputation of the intermediate toes (2nd, 3rd, 4th) poses serious problems both in terms of functional and biomechanical aspects. Amputation of the 2nd, 3rd or 4th toe

Fig. (13). Forefoot wet gangrene.
will cause unequivocally a varus or valgus deviation of the other toes with severe metatarsal head loading and subsequent serious risk of insensitive plantar ulcer. When possible, it is better to perform a partial amputation of the toe. In the case of an ulcer with osteomyelitis of the phalanges, instead of performing a toe amputation it is advisable to try to remove the infected bone thus saving part of the toe. Amputation of a single ray (in the proximal third metatarsal) is also a correct surgical choice that allows to have a foot with remaining 4 fairly symmetrical and stable rays (Fig. 15). From a biomechanical point of view amputation of the 5th ray doesn’t create any problem while 1st ray may be responsible for walking impairment. Even in this case it is essential to wear proper protective shoes.

In recent years the availability of different kinds of dermal substitutes has greatly changed the reconstructive surgical approach of severe diabetic foot infection. The massive loss of soft tissue after demolitive surgery for the control of infection can now be restored using a Hyaluronic acid derived dermal substitute that is able to stimulate the process of soft tissue reconstruction (Fig. 16). The final closure of the surgical wound may ultimately be obtained by secondary intention or by a skin graft (Fig. 17). However, the need for a stable foot, well aligned with the leg and functionally valid must be pointed out.

Transmetatarsal amputations are certainly the surgical procedures most frequently performed in cases of severe infection of the forefoot. To reduce dramatically the risk of a relapsing ulcer, a metatarsal amputation must be performed at the base of the metatarsals (very proximally) to obtain a stable and symmetrical forefoot stump. A more distal resection of the metatarsals may cause an increase of pressure on the plantar surface of the stump because of its tendency to the equinus deformity with a high risk of ulcer recurrences (Fig. 18).

Lisfranc amputation is performed disarticulating the forefoot at the base of the metatarsals (Lisfranc joint) saving only the cuneiform. Although, from a surgical point of view, Lisfranc Amputation can be considered an “elegant” amputa-
tion, from a biomechanical point of view it poses serious problems of stability and alignment of the forefoot. The removal of the base of the 5th metatarsal, and the consequently loss of the peroneus brevis insertion, leads to a supination deformity of the forefoot causing serious problems of gait. To avoid the deviation of the forefoot, the base of 5th metatarsal must be spared and fixed to the cuboid bone with a screw when performing Lisfranc Amputation.

Chopart Amputation, which saves only the talus and calcaneus, is the most proximal midfoot amputation (Fig. 19). This surgical option is sometimes the only alternative to leg amputation in case of severe infection of the forefoot and midfoot.

The question that arises when suggesting this surgical choice to the patient is whether, from biomechanical and functional points of view, the Chopart amputation can be considered a good solution. From a functional point of view, the Chopart Amputation shows some disadvantages: 1) a very short residual lever; 2) the boost phase of the walking cycle is completely lost; 3) the deviation of the stump in equinovarus is frequent. Prostheses also pose serious problems because the neck of the foot is completely lost and consequently the stump tends to turn into the shoe with a high risk of ulceration. Chopart amputation can be considered a good surgical choice in elderly patients because in these patients the ability to use a prosthesis in case of major amputation is very low. Great part of elderly patients submitted to leg amputation frequently lose the ability to walk with total loss of autonomy in daily living activities. In elderly diabetic patients with important comorbidities such as heart disease, kidney disease and vision impairment, the Chopart amputation should be considered a rescue choice that allows an acceptable walking ability with discrete autonomy in daily activities. In particular patients with severe dysfunction of heart may not tolerate the increase in load on cardiovascular system correlated with the use of a prosthesis for major amputation (BKA-AKA). The risk of ulceration of the stump can be dramatically reduced by replacing the protective shoe with a custom-built brace that is inserted into a dedicated shoe thus avoiding any twisting and bending of the stump (Fig. 20). Since, from a functional point of view, the Chopart amputation does not allow a valid gait, it may be appropriate to suggest a below-the-knee amputation to a young patient because modern prostheses provide a high level of physical activities. In any case, the choice of the amputation level must be always agreed with the patient.

**LIST OF ABBREVIATIONS**

- AMS = absorbable metal stent
- BMS = bare metal stent
- BTK = below-the-knee
- CABG = coronary artery bypass graft
- CLI = critical limb ischemia
- CT = computed tomography
- CTO = chronic total occlusion
- DEB = drug eluting balloon
- DES = drug eluting stent
- DFC = diabetic foot center
CONFLICT OF INTEREST

Dr. Roberto Ferraresi has a consultant agreement with Medtronic Invatec, Abbott, EV3.

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None

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Carlo Caravaggi, MD; Francesco Grigoletto, ScD; Nicolò Scuderi, MD Wound Bed Preparation With a Dermal Substitute (Hyalomatrix® PA) Facilitates Re-epithelialization and Healing: Results of a Multicenter, Prospective, Observational Study on Complex Chronic Ulcers (The FAST Study) Wounds 2011;23(8):228–235