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Emergency in Diabetic Foot

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Abstract

Diabetic foot is the main cause of hospitalization in diabetic patients and the most common cause of lower extremity amputation. The risk of a diabetic subjects to develop a foot ulceration during his life is 15%. When infection and ischemia are present the risk of major amputation increases dramatically. Therefore it is crucial a correct diagnosis and approach. Unfortunately a specific protocol treatment for emergency in diabetic foot lesion is not completely defined. In this paper we try to identify the state of emergency in diabetic foot and we suggest a proper treatment. We define this condition as critical diabetic foot that represents a risk of limb or life threatening. It requires an immediate multidisciplinary approach to treat the infection and also the peripheral ischemia if necessary. We propose an operative strategy that can be divided in four consecutive phases or frequently simultaneous: surgical approach to remove infected tissues, aggressive antibiotic therapy, revascularization by angioplasty first approach or by-pass and finally the management of general conditions. Each stage is adequately analyzed. The aim is to emphasize the necessity of a careful evaluation in the emergency of the diabetic foot and to define a useful treatment strategy.

Keywords: Diabetic foot; Emergency; Surgical approach; Revascularization

Introduction

Diabetes is a metabolic disease that affects approximately 346 million people worldwide, with a prevalence of 6% in general population [1]. Epidemiological data suggest that the disease is rapidly increasing and predict that about 440 million people will be affected in 2030 (7.5%) [2]. Diabetic Foot (DF) is one of the diabetic complication and a foot lesion appears in 15% of cases during the course of the disease [3-5]. Further, DF is the most common cause for hospitalization in diabetic patients and the main reason of lower limbs amputation [4,6]. The prevalence of major amputation among diabetic subjects affects up to 4,8%, interesting more than 1 million people [2,7]. In more than 85% of cases lower limb amputation is a complication of a foot lesion after a trivial injury of the foot negatively evolved [8,9].

Definition of Diabetic Foot

Usually DF is classified in neuropathic, ischemic and neuroischemic according to the cause of ulcer [10]. Diabetic neuropathy can be divided into sensory, motor and autonomic. Motor neuropathy represents the cause of deformed foot, depending from atrophy of intrinsic muscle of the foot. This condition promotes the protusion of metatarsal heads, resulting in an alterated biomechanics and peak plantar pressure [11]. Sensory abnormalities reduce the perception of pain and trauma during walking with a high risk of ulceration [12-14]. Further patients can lose the thermal discrimination with an easy risk of burns [11]. Autonomic neuropathy causes an alteration in skin hydration resulting in a higher risk of fissures [15]. Moreover, it creates a dysregulation of blood flow opening the arteriovenous shunts that cause edema with a secondary obstruction of small arteries and an abnormal inflammatory response to foot injuries [16,17].

Ischemic lesions are caused by a basic condition of Peripheral Arterial Disease (PAD), that is the most significant and independent risk factor for both negative outcome and major amputation [10].

PAD in diabetic patients is usually more distal interesting the district below the knee, affects more arterial segmental and also the collateral vessels and shows a rapid progression [18,19]. Under a condition of poor peripheral blood flow, infection becomes a common complication, increasing the risk of major amputation [20]. Moreover the diabetes per se increases the risk of foot infection. In fact, in addition to vascular disease and neuropathy, the immune system may be compromised and the defenses against infections reduced [21-23].

Critical Diabetic Foot

Critical Diabetic Foot (CDF) can be defined as a condition of limb or life threatening that requires an immediate multidisciplinary treatment to limit the evolution of the critical clinical state. Therefore, it is essential to characterize the lesion for a correct diagnosis and approach. A standard classification of diabetic foot lesion is the University of Texas Wound Classification (TWC) where depth of the lesion, ischemia and infection are considered. This classification shows as both ischemia and infection are related to the severity of the lesion and when they appear simultaneously the risk of amputation increases dramatically [24].

According to this classification, CDF can be considered when ischemia and infection coexist and the lesion affects the deeper tissues. Another recent classification of DF is the Diabetic Foot Triage (DFT) of Caravaggi et al. It allows identifying the level of emergency and how to treat the patient in relation to the different severity codes [25]. Following the DFT, yellow and red code can be defined as CDF that requires an immediate treatment based on surgical, infectious and general approach. The yellow code identifies a foot lesion that needs urgent surgery without impairment of vital functions; the red code represents a foot lesion with partial impairment of circulatory and respiratory systems which need an emergency treatment for a hemodynamic stabilization and subsequently a surgical treatment. Considering these elements, it is clear how the infectious process plays a key role and its severity must guide the clinicians in the operative strategy. Usually, according to Infectious Disease Society of America (IDSA) and International Working Group on the Diabetic Foot (IWGDF) classification, the infections are classified based on depth and clinical signs. According to the depth of the lesion, deeper infections are most aggressive and represent the condition of increased risk of amputation. When they involve muscle, tendons, joint and bones, they can determine a state

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of CDF. They can advance along the foot compartments destroying the anatomical structures that they meet. The implication of some vital structures can result in loss of functionality of the foot and increases the risk of amputation. In relation to clinical manifestations the IWGDF identified four levels of severity defined by PEDIS [perfusion, extent/size, depth/tissue loss, infection and sensation] degrees: grade 1 characterized by no symptoms or signs of infection; grade 2 defined by the involvement of the skin and subcutaneous tissue and the presence of erythema around the ulcer more than 0.5 cm and less than 2 cm; grade 3 identified by the involvement of the structures deeper then skin and subcutaneous tissue, the presence of erythema >2 cm but with signs of systemic inflammatory response; grade 4 when the condition of grade 3 is associated at least 2 signs of systemic inflammatory response [temperature >38°C or <36°C, Heart rate >90 beats/min, Respiratory rate >20 breaths/ min or $PaCO_2$ <32 mmHg, White blood cell count >2000 or <4000 cell/uL or 10% immature [band] forms. This condition is usually characterized by systemic toxicity with vomiting, confusion, metabolic instability and shock. Moderate and severe infections, defined respectively by the grade 3 and 4 of PEDIS classification, require an immediate treatment and can be considered as a condition of CDF [26,27]. While the grade 3 identifies a risk of lower limb loss, the grade 4 is a condition of life-threatening [28,29].

Therapeutic Approach in Limb and Life Threatening

Unfortunately there are few data in literature that define the right treatment for the different patterns of foot lesion. The therapeutic approach to CDF can be divided into four stages that must be sequential and often simultaneous: surgical treatment of infected tissues, aggressive antibiotic therapy, revascularization in case of critical limb ischemia [CLI], and management of general conditions (Figure 1).

Surgical Approach in CDF

As previously underlined, the infection can evolve rapidly and a delay in the local treatment may facilitate its extension and increase the risk of minor and major amputation [30]. Only an immediate surgical treatment, with an accurate debridement of infected tissues, can limit the progression of infections. These can occur in several ways. In case of phlegmon the infection is localized in the dermis and in deeper tissues. Often, beyond the classical signs of infection, it is possible to recognize an area of fluctuation over the collection of purulent material that can guide the surgical approach. International guidelines support the effectiveness of a surgical treatment, opening one or more area of the skin, removing infected and non-vital tissues and draining purulent collection [31,32]. The structural architecture of the foot divided into different compartments increases the risk of infective compartmental syndrome. When an infectious process develops within a compartment, the edema, due to inflammation response, causes a compression of small arteries with a secondary ischemia of the affected tissues. Although the compartments are separated by fascial structures, the progression of the infection can involve the closer compartments. Sometimes it happens that the abscesses are not visible externally and can bring clinicians to prescribe only antibiotic therapy delaying the drainage [33,34]. Therefore it requires a careful evaluation of the foot, researching the suspicious areas, identified as red, warm, tender or floating zone. After an incision of the suspicious area, the surgical approach is characterized by an evaluation of deep tissues and the extension of infection with particular attention to fistulas. Successively it is necessary a decompression fasciotomy opening the infected compartments, the removal of infected tissues and an accurate disinfection of the cavities. Necrotizing fasciitis is a condition of CDF life-threatening that evolves rapidly accompanied by a systemic signs and symptomes [35]. It is characterized by an involvement of the skin and subcutaneous tissues up to the fascia. It is mandatory a prompt treatment with an extended surgical debridement. After a first approach it is necessary a daily monitoring and the treatment of possible area of new infection. The gangrene is frequently associated to a CLI with a reduction of peripheral blood flow. Even if these patients require a lower limb revascularization, an appropriate debridement must be performed

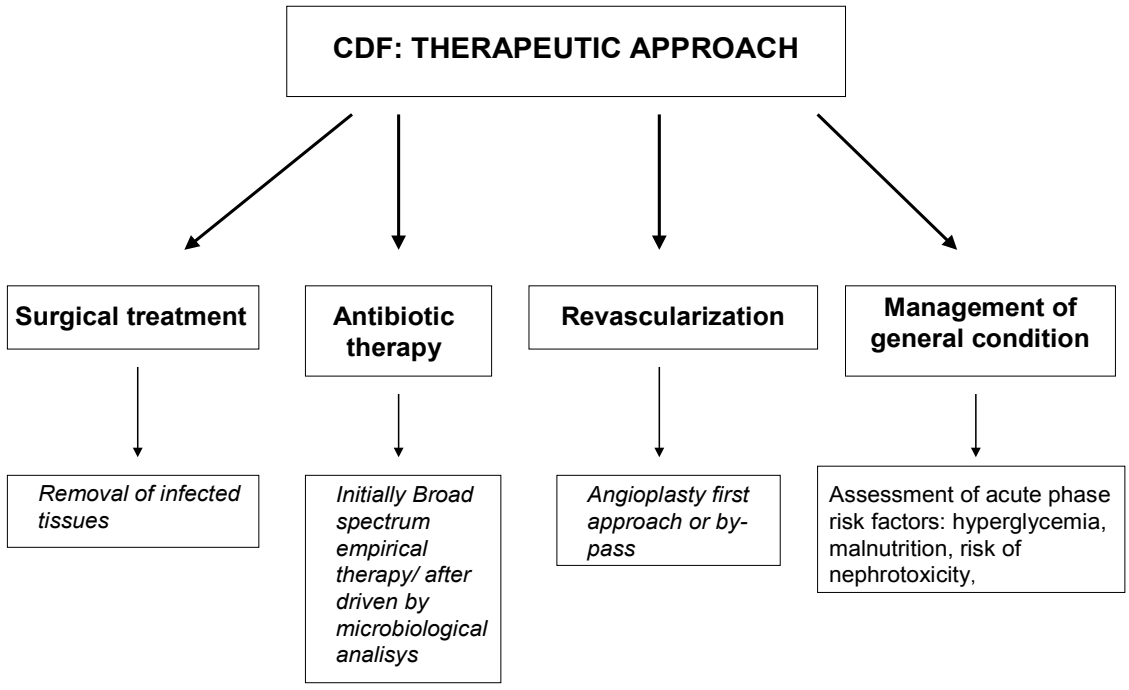

Figure 1: Therapeutic approach in critical diabetic foot.

regardless of vascular impairment to reduce the risk of amputation and death [36-38]. Obviously these patient need a rapid revascularization to allow a sufficient blood flow in the area of the lesion and it should be done as soon as possible.

Imaging can provide more information to clinical evaluation. X-ray, magnetic resonance imaging and computed tomography become a useful adjunct especially when there is a suspicion of bone involvement and to assess if all purulent collections were drained by surgical debridement.

It's clear that patients with CDF require an immediate hospitalization for repeated surgical treatment, intravenous antibiotic therapy, possible lower limb revascularization and adequate management of general conditions.

Antibiotic Therapy

In presence of a CDF it is mandatory to start an antibiotic therapy, initially empirical and after based on microbiological isolates. Infection involving deeper tissues, gangrene and moderate or severe infection according to IDSA classification need a broad-spectrum regimen therapy. The treatment should cover all types of pathogens involved in diabetic foot infection, gram-positive cocci, especially *S. aureus*, common gram-negative and also anaerobes. In fact in chronic ulcers it is possible found a polymicrobial flora while in deeper infection or gangrene it is easy to find anaerobic bacteria [39,40]. In CDF, where moderate and severe infections play a key role, internationals guidelines indicates one of these associations of antibiotic therapy: fluorochinolones daptomycin or linezolid or vancomycin, piperacillin/tazobactam+daptomycin or linezolid or vancomycin, ertapenem or meropenem+daptomicyn or linezolid or vancomycin, tygecycline. Particular attention should be given to MRSA infections that present a high resistance to several antibiotic regimens. In this case the choice is between linezolid, vancomycin or daptomycin. Teicoplanina also can be considered a useful treatment against Gram-positive bacteria [41]. In case of multidrug-resistant Gram-negative bacterial infections, colistina is an excellent option [42]. Obviously the dose of drugs must be adjusted according to renal and hepatic function. A correct choice of antibiotic therapy is related to clinical evaluation, bacteria found in cultures and hospital resistance. It is recommended to start with parenteral treatment and only later to shift to oral therapy. Several microbiological analyses of infected tissues [deep buffer, tissue and bone culture] can be useful to guide antibiotic therapy. Each result of microbiological testing must be considered after a careful evaluation of clinical response to empiric treatment. In fact, when initial therapy determines an improvement of infection pattern it could be not necessary to modify antibiotic therapy. The duration of treatment should be defined by clinical evaluation. Usually moderate and severe infections require from two to four weeks of treatment, but when there is a bone involvement or the infection is not completely resolved, the treatment is longer. The factors that influence the duration of therapy are the severity and the extension of the infection, the effectiveness of the surgical approach, the clinical response to antibiotic therapy and the general conditions. It is also useful to evaluate inflammatory markers as leukocytosis, C-reactive protein, erythrocyte sedimentation rate and procalcitonin that can help clinical assessment [43].

Revascularization

When CDF is accompanied by a condition of CLI it is mandatory a lower limb revascularization that can be performed by open surgery or endovascular treatment. Artery disease in diabetic patients affects commonly the vessels below the knee, it is symmetric and multisegmental and also collateral arteries are involved [18,19]. PAD in diabetes is a high risk factor for major amputation and the non revascularization is a negative predict factor for limb salvage [44,45]. Therefore it is crucial to obtain a diagnosis of PAD and CLI to treat them as soon as possible. The first non invasive evaluation is the detection of peripheral arterial pulses (femoral, popliteal, dorsalis pedis and posterior tibial artery). However the absence of pulses cannot add more information on the perfusion deficit and its presence cannot exclude completely a peripheral ischemia [46]. It is therefore necessary to use instrumental methods that are more sensitive. They can be divided into first and second level examinations. Among first-level exams there are: Ankle- Brachial Index (ABI), Toe- Brachial Index (TBI), Transcutaneous Oxygen Pressure measurements (TcPO2) and US color duplex. The second-level exams are Magnetic Resonance (MRI) and Computed Tomography (CT). ABI defines a condition of vascular disease when the value is <0.9. A value <0.4 identifies a severe ischemia. When ABI >1.3 it is possible there are several calcifications and we cannot exclude an ischemic disease [47,48]. TBI <0.50 indicates a CLI that usually requires a vascular treatment [49]. A useful tool is certainly the $TcPO_2$ that gives us information on the possibility of wound healing. Values <30 mmHg identify a CLI that doesn't allow a wound healing without revascularization. Of course higher values must be correlated with clinical findings, such as size and depth, to assess the need for revascularization [50]. Edema or local inflammation can falsify the final results. Thus, with a foot infection we can find unreliable values. US color duplex is a sensitive and specific exam that allows to obtain several data about peripheral flow [51]. Its limits are determined by the operator dependence and the patient collaboration [52]. MRI and CT are the gold-standard for the evaluation of vascular tree. They provide an accurate description of stenosis or obstructions and help the operator who will perform the revascularization [53]. MRI cannot be indicated in patients with pace-maker, sutures and metal implants, claustrophobic. Further the exam cannot be done when estimated glomerular filtration rate is <30 ml/min per 1.73 m^2 due to the high risk of nephrogenic systemic fibrosis [54-56]. Also CT allows an optimal evaluation of examined arterial district. It is limited by the use of iodinated contrast organ that increases the risk of nephro toxicity in patients with severe chronic kidney disease specially if performed at short distance from a revascularization [57,58]. Arteriography never must be considered a diagnostic examination. In CDF, when a rapid revascularization could be necessary, it should be useful to perform diagnostic angiography together with an endovascular revascularization in the same session. It saves time and reduces the toxicity of the iodinated contrast organ.

The choice of the kind of revascularization is between vascular by-pass and endovascular treatment. Even if it is reported that the by-pass maintains a longer vessel patency [59,60], in our policy we prefer the angioplasty first approach. Several studies highlight as percutaneous angioplasty allows a rate of limb salvage at least similar to that obtained with open surgery [61-65]. However this treatment is less aggressive, has fewer complications, may be repeatable in case of re-stenosis and also feasible in patients with poor clinical conditions who cannot candidates for surgery. Even in patients with chronic kidney disease on dialysis treatment, which have in general worse outcomes, the angioplasty shows better results in terms of limb salvage and survival [66,67]. Based on angiosome theory, it is current the concept of "wound related artery", according to which it is advantageous a revascularization targeted artery that perfuses the area affected by the lesion [68,69]. In fact this strategy reported better rates of limb salvage compared to a not addressed revascularization [70,71]. There are some cases of PAD that require a surgical approach. According to the Italian Consensus on the treatment of PAD in diabetic patients, the obstruction of the common

femoral artery and its bifurcation should be treated surgically. Also the long femoro- popliteal and infra- popliteal occlusions may be treated by surgical approach. In this regard there is no clear advice on the length of the stenosis or obstruction and the choice should be assessed case by case from the local expertise. In choosing the by-pass option is important to evaluate some critical elements: general conditions [age, comorbidities, life expectancy]; the distal anastomosis site [absence of tissue alteration or no subsequent surgical procedures at the same site]; availability of suitable vein; presence of adequate vascular bed defined as "landing zone" [acceptable diameter of the vessel, absence of severe vascular disease or calcifications]; respect of angiosome theory; absence of small vessel disease that could affect the distal run off. Therefore it is essential to perform a revascularization in case of CDF complicated by a CLI and the treatment should be quick to obtain a good therapeutic success [72].

Management of General Conditions

CDF can be accompanied by a systemic impairment of general conditions. So it is right to consider all aspect that can influence the general and local status. In addition to the risk factors associated with diabetes that need to be treated in primary and secondary prevention, as hypertension, dyslipidemia and smoke, there are some elements that need attention in the acute phase of the disease. In the big part of patients affected by a severe wound infection it is easy to find a metabolic failure characterized by a hyperglycemia that can reach very high values. This can negatively influence the management of the infection and the healing of the lesion. Next to drug treatment an accurate surgical debridement can improve the glycemic values by an extended removal of the infection [31,38]. In fact after a surgery treatment of infectious focus it is possible to observe a stabilization of glycemic levels. An extended infectious wound causes a catabolic state with loss of a large amount of calories [73-75]. Therefore it is necessary a malnutrition screening and an optimal nutritional treatment. In case of vascular study and angioplasty treatment it is crucial an adequate hydration before and after the infusion of iodinate contrast to reduce the risk of nephrotoxicity [76,77]. Further, if the patient undergoes the lower limb angioplasty, it is crucial a dual antiplatelet therapy [Cardioaspirin 100 mg one time/day + Clopidogrel 75 mg one time/day or Ticlopidin 250 mg one/time day] for 30 days [78]. In addition, fever, local pain and mood alteration must be treated.

Conclusion

CDF identifies a clear emergency in DF. It represents a condition of limb or life threatening that requires an immediate and multidisciplinary approach. Among diabetic foot teams the expression "time is tissue" is current. In fact only a careful evaluation with an early diagnosis allows a rapid treatment that can limit the extension of the infection and reduce the risk of loss of foot or limb.

Obviously the management of this clinical complexity requires a hospitalization in a specialized centre of reference. Although there are not several data in literature that describe a right approach, it is well know that the treatment is defined by a surgical debridement to remove all infected tissues, an aggressive antibiotic therapy, initially a broad-spectrum regimen and after driven by microbiological results of analyzed tissues and revascularization in case of CLI. Moreover also general condition that could prevent the healing process need to be checked and treated.

When the acute phase and infection are treated, the lost tissue reconstruction can be performed by conventional or advanced medications, negative pressure therapy or dermal substitutes according to characteristics of the lesion and medical evaluation. It should be underlined that, even if a correct and immediate treatment allows optimal results in terms of limb salvage, the prevention is crucial to avoid the emergency conditions that imply a high risk of major amputation.

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