Symbiosis

www.symbiosisonline.org
www.symbiosisonlinepublishing.com

Review article | Journal of Endocrinology and Diabetes | Open Access

Medical Management of Acute Foot Injury in Diabetic Patients

Marco Meloni*, Valentina Izzo, Laura Giurato, Luigi Uccioli

Department of Internal Medicine, University of Tor Vergata, Rome, Italy

Received: July 07, 2016; Accepted: July 25, 2016; Published: July 31, 2016

***Corresponding author:** Marco Meloni, Department of Internal Medicine, University of Tor Vergata, Viale Oxford 81, 00133 Rome, Italy, Tel: +39-0620902784; Fax: +39-0620902804; E-mail: meloni.marco@libero.it*

Abstract

Diabetic foot is the main cause of hospitalization in diabetic patients and the most common cause of lower extremity amputation. Infection and ischemia are the main risk factors for major amputation and death in case of critical diabetic foot ulcers. In case of acute diabetic foot, a specific limb salvage protocol should be adopted to reduce the risk of amputation and general complications. Immediate surgical approach and medical management are required. The aim of this paper is to define step by step the medical approach in case emergency acute diabetic foot patients: early diagnosis, acute offloading, antibiotic therapy, management of peripheral revascularization, treatment of general conditions. Each stage is adequately analysed and described according to scientific evidences and personal experience.

Keywords: Diabetes; Acute diabetic foot; Ischemia; Infection; Medical management

Introduction

Diabetic Foot (DF) is considered a serious complication of diabetes determined by an injury of peripheral nervous system and lower limbs arterial disease. Epidemiological data report that Diabetic Foot Ulcers (DFUs) affect up to 15% of diabetic population. This condition is considered the main reason of hospitalization and the first cause of minor and major amputation in diabetic subject [1-4]. Even, if recent papers have reported a progressive reduction of amputation rate in many developed countries, mainly Europe and USA, nowadays more than 1 million of diabetic subjects are amputees [5,6].

Acute Diabetic Foot (ADF) can be considered as a condition of acute foot injury that implies a high risk of minor or major amputation. Sometimes ADF can have a critical evolution and a systemic involvement that leads to a life-threatening condition. Ischemic and infected ulcers are the main cause of ADF and when they appear simultaneously the risk of amputation increases dramatically [7,8].

In the recent years, considerable improvements have been made both in the diagnosis and treatment of DF. The contribution of updated guidelines and the implementation of multidisciplinary approach have allowed spread knowledge in the field of DF. A standard protocol to treat ADF was not completely identified even if the approach during acute phase is usually defined by some established key points in association to clinicians' skills and individual experience [9]. The management of DFUs during acute phase is characterized by two key points: detection of ADF and treatment. The diagnosis requires the recognition of infection and/or peripheral ischemia while the treatment needs both surgical and medical management.

Diagnosis of ADF

Infection and ischemia are the two components that separately or together may be responsible for ADF.

Infected diabetic foot

To identify an infectious process and its spread along the foot, clinicians should know foot anatomical architecture and foot compartments to recognize the entry point of infection and its progression along the spaces determined by tendons ligaments and plantar fascia. This condition is often due to their anatomical structure and poor vascularization that allows an easy progression of infectious process. In some cases, the infection can move from areas of higher to lower pressure, particularly in case of neuropathic infected plantar ulcers. In fact, the pressure exerted by the weight on plantar area can allow the spread of infection on metatarsal heads and the osteomyelitis can cause the rupture of joint capsule; in this way the purulent collection get through the plantar compartment involving also the dorsum of the foot. In other circumstances plantar infection can reach the dorsal area through the interosseous compartment due to high infectious pressure developed in the central compartment. As mentioned before, when the infection causes a compartment pressure higher than microcirculation, a secondary arterial ischemia appears producing the necrosis of involved tissues; further, infectious process and inflammatory response can determine the vascular injury of digital arteries followed by the thrombosis and gangrene of affected toes [10].

Therefore, only a careful inspection of the foot allows identifying the starting point of the infection, often represented

by a foot ulcer surrounded by a red, warm and painful area. The presence of areas of redness in the plantar or dorsal aspect of the foot may help in detecting the spreading of the infection to deeper areas. Handling the foot and pushing over the areas of redness may reveal the presence of areas of fluctuation where a purulent collection may be occulted. Sometime this procedure allows that purulent material goes out from the wound, revealing the route followed by the infection to reach the deeper areas. The prompt recognition of phlegmons and abscesses is a crucial step because the delay in the drainage of purulent material and debridement of infected tissues may result in a further extension of the infection and an increased tissue loss [11,12]. Clinical assessment of infectious process may be driven by a steady international classification that identify four levels of severity (PEDIS classification: perfusion, extent/size, depth/tissue loss, infection and sensation): grade 1: no symptoms or signs of infection; grade 2: involvement of the skin and subcutaneous tissue, presence of erythema around the ulcer more than 0,5 cm and less than 2 cm; grade 3: involvement of the structures deeper then skin and subcutaneous tissue, presence of erythema > 2 cm but without signs of systemic inflammatory response; grade 4: grade 3 plus 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 > 12000 or < 4000 cell/ uL or 10% immature band. Usually this condition is characterized by systemic toxicity and metabolic instability up to shock. Attention should be paid to grade 3 and 4, two infection's levels that imply respectively the risk of limb and life-threatening [13-16].

In the identification of infection severity, imaging (x-ray, computed tomography, magnetic resonance) occupies a meaningful role mainly to detect the bone involvement and gas area in the deeper tissues. Therefore, instrumental exams should be often coupled to clinical evaluation.

Ischemic diabetic foot

Peripheral Arterial Disease (PAD) is the other risk factor for major amputation. Critical Limb Ischemia (CLI) should be identified in acute phase to allow a prompt revascularization and get limb salvage [17,18]. The study of vascular disease provides a first clinical evaluation of peripheral arterial pulses (femoral, popliteal, dorsalis pedis and posterior tibial artery) followed by first level (Ankle-Brachial Index (ABI), Toe-Brachial Index (TBI), Transcutaneous Oxygen Pressure measurements ($TcPO_2$), ultrasound color duplex (US) and second level examinations as Magnetic Resonance (MRI) or Computed Tomography (CT) if required [19-24]. ABI < 0.9 identifies a condition of PAD while values < 0.4 define a critical limb ischemia. Values > 1.3 are not reliable because of often vascular calcifications can affect the exam and in this case we cannot exclude a peripheral ischemia [25-26]. TBI defines a condition of CLI when < 0.50 [19]. $TcPO_2$ is a useful tool to know the chance of wound healing. Values < 30 mmHg identify a CLI that requires revascularization to allow wound closure. However, $TcPO_2$ values must be always associated with ulcer findings (extension, deep, infection), to assess the possibility of re-epithelialisation and the need for limb revascularization [20]. US are a sensitive and specific exam to study peripheral blood flow. It allows identifying the patency of vessels, the type and speed of the flow, providing often an accurate description of vascular disease. However, its appropriateness is related to skills operator and adequate experience is required [21,22]. MRI and CT are the gold-standard to detect PAD. They provide a whole evaluation of stenosis or obstructions driving surgeon or interventional radiologist in the revascularization [23,24]. Clinicians should define the appropriate test according to general patients' conditions, especially to kidney function. In fact, in case of CT the risk of Contrast Induced Nephropathy (CIN) need to be careful evaluated while in case of estimated glomerular filtration rate < 30 ml/min MRI ca not be performed due to the risk of nephrogenic systemic fibrosis dependent on Gadolinium administration. Further MRI cannot be indicated in patients with pace-maker, sutures and metal implants, claustrophobic [27-29].

Treatment of ADF

The management to ADF can be divided in surgical and medical. The surgical approach includes surgical debridement of infected tissues followed by antiseptic dressing and revascularization (by-pass or endovascular treatment) in case of limb ischemia. The medical management includes: medical treatment of infectious process, adequate offloading, management of revascularization, and assessment therapy in case of revascularization, treatment of systemic factors interfering on general condition and wound healing (Figure 1).

The aim of this review is to report the medical approach in the management of ADF.

Medical treatment of infectious process

Medical treatment is based on Antibiotic Therapy (AT) that will be necessarily coupled to surgical treatment in case of infection. Therefore, the selection and the management of antibiotic drugs is a key point in the treatment of ADF. In fact, AT can be considered the "second scalpel" in the treatment of infections. In case of clinical signs of infection, systemic AT should be given even if the pathogen has not been yet isolated from

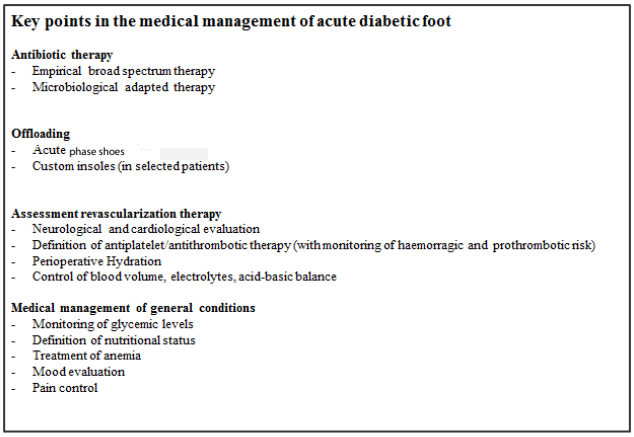

Figure 1: Summary of medical approach to diabetic foot during acute phase

ulcers [30-33]. Initially empirical broad spectrum therapy should be administered and later adapted to microbiological results. In DFUs, mainly in case of gangrene or deeper infections, several clusters of pathogens can be involved: gram-positive (especially cocci), common and less common gram-negative (*Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumanni*) and also anaerobes. Sometimes DFU may be simultaneously infected by microorganism belonging to different groups [34,35]. Therefore the initial regimen requires an association of antibiotic drugs that usually includes an agent active against Gram-positivi cocci, mainly *Staphilococcus Aeurus*. The most common and appropriate associations are fluorochinolones + daptomycin or linezolid or vancomycin, piperacillin/tazobactam + daptomycin or linezolid or vancomycin, ertapenem or meropenem + daptomicyn or linezolid or vancomycin. Tigecycline and Teicoplanine are two steady options against Gram-positive, while Colimicine is often effective against Gram-negative species resistant to common AT, particularly *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumanni* [35,36]. An increased antibiotic-resistance needs to be considered in the assessment of AT. The spread resistance to common antibiotic is generally associated to poor outcomes [37,38]. This consideration is relevant especially for the continuous development of *Meticillin Resistant Staphilococcus Aeurus (MRSA)* in hospitalized patients. Therefore, MRSA should be considered in the choice of empirical broad spectrum therapy. In the suspicious or evidence of MRSA infection, an early treatment is required and linezolid, vancomycin and daptomycin seem to be effective [36,39]. During the treatment it is useful to repeat microbiological cultures to adjust AT especially in case of failed first therapy. Tissue or bone sample are preferred for their higher sensitivity if compared to simple swab [40].

AT should be defined by adequate clinical evaluation. Initial appropriate therapy should be given according to severity of infectious process, wound characteristics, kidney and hepatic function, patient compliance, antibiotic allergy and tolerability [41]. During the treatment both wound characteristics and evolution of infectious process should be strictly followed. In case of lack of clinical improvement, empirical AT must be modified according to microbiological results [42]

There is not a single opinion on the length of treatment. Usually the severity and extension of infections, the tissues involved and the response to treatment guide the clinicians [15,30,31,43,44]. In case of severe and deeper infection with bone involvement, four-six weeks of treatment are often required. In case of longer therapy, blood counts parameters values, kidney and hepatic function need to be closely monitored. However, the management of AT is related often to medical judgment and clinical knowledge. In case of sepsis, close evaluation of skin temperature, inflammatory markers, mainly leukocytes, C-reactive protein, erythrocyte sedimentation rate and procalcitonin can help clinicians to define the course of infectious process and the management of AT [45].

Particular attention should be given to bone infection. Osteomyelitis are often the complication of infected DFUs with involvement of soft tissues that can appear in 60% of cases in severe infected wounds.[31] The most accepted criteria for diagnosis is the isolation of bacteria from adequate sample bone, minimizing contamination, associated to histological inflammation signs and/or osteonecrosis [46]. In case of any chance to perform bone sample, clinical signs (purulent secretion into the bone, exposed bone, positivity of probe to bone test, non-healing ulcer after 6 weeks of standard care), laboratory test (increased c-reactive protein and erythrocyte sedimentation rate) and imaging findings (bone disruption, osteolysis area and bone marrow edema at x-ray and MRI) should be considered [47-50].

The management of osteomyelitis is nowadays a controversial item; in fact recent report observed comparable outcomes between surgical approach through bone resection and antibiotic therapy [51-54]. Each case needs medical or surgical treatment according to clinician evaluation and medical knowledge; in case of high risk of surgical treatment (loss of foot function and transfer ulceration), confined infection without extensive involvement of soft tissues and untreatable lower limb ischemia, patients may be treated by medical therapy. Surgical approach is preferred in case of risk of infection spread, severe bone demolition, purulent bone secretion, persistence of infection, and inability to medical therapy administration, low tolerability to long antibiotic regimens and bone destruction associate to the impairment of foot function [40].

Adequate offloading

Protection of ulcer area from external injury and pressure, especially for plantar ulcers, need to be ensured. In fact, it is well known that inadequate offloading delay the wound healing [55-58]. Briefly, offloading can be usually divided in removable and non-removable. Non removable Total-Contact Cast (TCC) is absolutely contraindicated in case of limb ischemia, deep infection, abscess, phlegmon and osteomyelitis. Therefore, in case of ADF clinicians suggest the use of removable cast walkers, therapeutic shoes and custom insoles according to patients conditions, ulcer localization and tolerability [59,60]. Each orthoses or therapeutic shoes should aim to reduce pressures in the area of ulceration and remove any injury that could hamper physiological wound healing and induce local pain. In some circumstances, after extensive surgical debridement and risk of bleeding or in case of administration of some medications in particular areas of the foot with a higher risk of trauma, patients should observe a rest period.

Management of lower limb revascularization

In case of ACD, clinicians should define the best approach to treat limb ischemia. The choice is between surgical and Endovascular Treatment (ET)**.** It is well known that percutaneous angioplasty allows similar results in terms of limb salvage when compared open surgery [61-64]. However this treatment is less aggressive and reports fewer complications in patients with poor clinical conditions, therefore it is feasible also in fragile patients who cannot candidates for surgery. Further, ET showed better results in Chronic Kidney Disease (CKD) patients, especially in

dialyzed subjects, which usually report worse outcomes after open surgery [65,66]. Instead, some circumstances require surgical approach, especially the obstruction of the common femoral artery and its bifurcation. Long femoral-popliteal and infra-popliteal occlusions may be treated surgically even if there is not a single opinion on the length of the stenosis or obstructions; therefore, in these cases the choice between endovascular and surgical approach depends case by case on clinical evaluation of local expertise. In case of open surgery some elements need to be analyzed: general conditions (age, comorbidities, life expectancy), availability of suitable vein to package the by-pass, absence of tissue alteration in the distal anastomosis site, adequate vascular bed to receive increased blood flow, respect of angiosomes' theory [67].

According to our experience and scientific data, we retain that angioplasty should be considered a useful approach to treat PAD in diabetic patients, reserving surgical treatment for well defined conditions that cannot be considered for ET.

Assessment therapy in case of revascularization

In case of PAD also cerebrovascular and coronary districts are often affected by arterial disease. Therefore, in case of ADF that need lower limb revascularization, cerebrovascular and cardiology evaluation should be performed. Neurological vascular risk is usually evaluated by US of epiaortic vessels. In case of significant stenosis or ulcerated plaque, MRI or TC could be help clinician to better define arterial disease and the need of treatment. In fact, carotid stenosis > 70% or ulcerated plaque should be treated before treating limb ischemia [68].

Patients affected by ischemic or neuropathic ulcers show often silent myocardial disease that need to be detected before lower limb revascularization [69-71]. A full assessment includes clinical evaluation (detection of angina, dyspnea, rhythm modification), electrocardiogram, echocardiogram and, in case of suspected myocardial ischemia, stress test and myocardial scintigraphy (preferred in diabetic patients) [72,73]. In case of evidence of ischemic heart disease or recent changes at clinical and instrumental evaluation, coronary angiography must be performed before lower limb revascularization. Obviously each test and the operative strategy is established according to clinician judgment and hospital organization.

Once defined the need of lower limb revascularization, in case of endovascular approach adequate dual anti-platelet therapy should be given: cardioaspirin 100 mg plus Clopidogrel 75 mg or Ticlopidine 250 mg one/time a day) 2-3 days before the procedure and at least for 30 days after [67]. In case of simultaneous anticoagulant therapy (atrial fibrillation, valvuloplasty) it is mandatory to adapt therapy according to clinical evaluation and patients risk factors for thromboembolism or bleeding. Some comorbidities score to define both bleeding and thrombotic risk could help clinician in their approach (eg. Crusade and CHADVAS score) and strict control of blood coagulation is mandatory. Further perioperative management requires control of blood volume, correction of electrolytes, evaluation of acid-base balance, stabilization of vital organs [74].

In case of endovascular revascularization, the risk of Acute Kidney Injury (AKJ) related to administration of Contrast Medium (CM) must be considered. In fact, Contrast Induce Nephropathy (CIN) is responsible in 11-14, 5% of cases of AKJ, increasing the risk of dialysis treatment, the length of hospitalization, the hospital complications and the mortality rate at 1 year [75-78]. Further, in diabetic patients with pre-existing Chronic Kidney Disease (CKD) the risk can reach sometimes the 40%. Therefore clinicians should apply a defined prophylactic strategy. Adequate hydration with 0,9% NaCl is required 12 hours before the procedure and at least 12 hours after (usually 1 ml/kg/h, reduced to 0,5 ml/kg/h in case of heart failure with ejection fraction less than 35%) and nephrotoxic drugs should be discontinued at least the day of the procedure according to clinical conditions (loop-diuretics, NAIDs, angiotensin converting enzyme inhibitor, angiotensin receptors blocker, nephrotoxic antibiotics like vancomycin, aminoglycosides, amphotericin-B), a low amount of CM and low or iso-osmolar CM with appropriate dilution should be administered (< 120 ml). Serum creatinine levels need to be evaluated the day of the procedure and at least for the three days after to detect any AKJ and adopt a prompt treatment. Some nephrologists suggest the use of acetyl-cysteine and sodium bicarbonate to reduce the CM injury, however literature data are poor and these medications are not recommended but not excluded [79].

Treatment of systemic factors interfering on general condition and wound healing

ADF is a condition that can lead high glycemic levels, especially in case of infectious process. Hyperglycemia can negatively influence the wound healing process and metabolic impairment can have systemic effects. In fact, acute hyperglycemia increases the mortality rate through several mechanisms, mainly enhancing hospital infection, prothrombotic state and myocardial ischemia [80]. Usually surgical debridement with the removal of infected tissues and AT improves glycemic levels. However, to obtain adequate control, glycemic values should be observed before and 2 hours after the meal to adopt appropriate medical therapy. Usually insulin is preferred to oral medication due to its better management and lower risk of hypoglycemia [81-85]. Metformin must to be discontinued mostly for the risk of lactic acidosis mainly in cases of CM injection [79,86].

Generally extended ulcers cause a catabolic state with loss of a large amount of calories [87-89]. This condition leads a reduced regenerative capacity of injured tissues and nutritional deficiency is related usually to poor clinical condition. Therefore, malnutrition screening and adequate nutritional support should be ensured. Serum albumin < 3,5 gr/ dl, total lymphocytes < 1.800 mm3, prealbumin< 15 mg/ dl and transferrin <150 mg/ dl are useful parameters to detect a condition of malnutrition [90-93]. In particular, low values of albumin and recent weight loss have proved to be independent predictors of mortality and hospital complications [94,95]. In this context the treatment of anemia play a strong role. Even if its relationship with diabetic foot complication is not completely clear, it is well established its association with the risk of major lower limb amputation [96,97]. Further, haemoglobin levels should be careful monitored

in patients who performed surgical by-pass or endovascular revascularization due to the increased risk of operative bleeding.

Diabetic patient with DFUs usually shows major or minor depressive syndrome. This condition can influence physical condition and prognosis [98-102]. Therefore mood alteration needs to be detected and treated. In this respect also local pain should be treated to improve quality of life and psychological state. Paracetamol and opioids are the most used with good effectiveness.

Conclusions

ADF is a serious condition that leads in some cases to limb-threatening or life-threatening. Therefore, this framework requires an early diagnosis and a careful evaluation. Severe foot injury could imply a systemic impairment and in this context medical management plays a key role. Usually these patients show poor general conditions and hospitalization is often required. Although a standard protocol is not completely established, some treatment points are well defined. However medical approach is usually adapted to clinical knowledge, experience and hospital policy. In our opinion, the assessment of patient with ADF is defined by two key points: early diagnosis and tailored treatment. The diagnosis of ADF condition requires immediate recognition of infection and its possible spread along foot compartments. Further, the detection of peripheral limb ischemia should be performed. The treatment includes surgical and medical approach. Surgical approach is defined by repeated debridement to remove any infected tissues, antiseptic dressings and lower limb revascularization in case of reduced peripheral blood flow (by pass or endovascular procedure). Medical approach needs adequate antibiotic therapy, offloading, assessment therapy in case of revascularization and strict control of general conditions.

In conclusion we retain that patients affected by DFUs are complex patients the need often hospitalization, strict control of vital function, careful monitoring of wound evolution. In the management of DF global knowledge is required and the multidisciplinary approach is essential for adequate treatment and to ensure better results in terms of limb salvage and systemic complications.

Declarations

All Authors declare to not have any conflict of interest.

Disclaimers

The submitted article is a personal review of our group of study.

Sources of support

We did not receive any sources for this article.

References

1. Palumbo PJ, Melton LJ. Peripheral vascular disease and diabetes. In: Diabetes in America. Data Compiled 1984. US Government Printing Office, Washington DC, NIH publication;1985: 85-1468.
2. Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In Diabetes in America, 2nd ed. US Government Printing Office, Washington DC. NIH publication; 1995: 95-1468.
3. Frykberg RG, Haabershaw GM, Chrzan JS. Epidemiology of the diabetic foot: ulcerations and amputations. In: Contemporary Endocrinology. Clinical Management of Diabetic Neuropathy. 1998; 273.
4. Pecoraro RE, Reiber G, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. Diabetes Care. 1990;13(5):513-21.
5. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719-24.
6. Johannesson A, Larsson GU, Ramstrand N, Turkiewicz A, Wiréhn AB, Atroshi I. Incidence of lower-limb amputation in the diabetic and non diabetic general population: a 10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations. Diabetes Care. 2009;32(2):275-80. doi: 10.2337/dc08-1639.
7. Shah B, Hux J. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care. 2003;26(2):510-3.
8. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care. 1998;21(5):855-9.
9. Uccioli L, Meloni M, Giurato L et al. Emergency in Diabetic Foot. Emergency Med. 2013;3:160. doi: 10.4172/2165-7548.1000160.
10. Aragón-Sánchez J, Lázaro-Martínez JL, Pulido-Duque J, Maynar M. From the diabetic foot ulcer and beyond: how do foot infections spread in patients with diabetes? Diabet Foot Ankle. 2012;3. doi: 10.3402/dfa.v3i0.18693.
11. Shape JN. Antibiotics as an adjunct to surgical management of lower extremity ulcerations. Microsurgery. 2004;24(1):8-17.
12. Edelson GW, Armstrong DG, Lavery LA, Caicco G. The acutely infected diabetic foot is not adequately evacuate in a inpatient setting. J Am Podiatr Med Assoc. 1997;87(6):260-5.
13. Karchmer AW, Gibbons GW. Foot infections in diabetes: evaluation and management. Curr Clin Top Infect Dis. 1994;14:1-22.
14. Remington, J.S., Swartz, M.N. (Eds.). Blackwell Scientific Publications, Cambridge (USA) 1994;1-22.
15. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg. 2006;117(7 Suppl): 212S-238S.
16. Lipsky BA, Berendt AR, Deery HG. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004;39(2):104-114.
17. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. Clin Infect Dis. 2007;44(4):562-5.
18. Faglia E, Favales F, Quarantiello A, Calia P, Clelia P, Brambilla G, et al. Angiographic Evaluation of Peripheral Arterial Occlusive Disease and its Role as Prognostic Determinant for Major Amputation in Diabetic Subjects with Foot Ulcers. Diabetes Care. 1998;21(4):625-30.
19. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Journal of Vascular Surgery. 2007;45 Suppl S: S5-67.
20. Park SC, Choi CY, Ha YI, Yang HE. Utility of Toe-brachial Index for Diagnosis of Peripheral Artery Disease. Arch Plast Surg. 2012;39(3):227-31. doi: 10.5999/aps.2012.39.3.227.

21. Ballard JL, Eke CC, Bunt TJ, Killeen JD. A prospective evaluation of transcutaneous oxygen measurements in the management of diabetic foot problems. Journal of Vascular Surgery. 1995;22(4):485-490.

22. Bradbury AW, Adam DJ. Diagnosis of peripheral arterial disease of the lower limb. British Medical Journal. 2007;334(7606):1229-30. doi: 10.1136/bmj.39244.344664.80.

23. Visser K, Hunink MG. Peripheral arterial disease: gadolinium-enhanced MR angiography versus color color-guided duplex: a meta-analysis. Radiology 2000;216(1):67-77.

24. Hingorani A, Ascher E, Marks N. Preprocedural imaging: new options to reduce need for contrast angiography. Semin Vasc Surg. 2007;20(1):15-28.

25. Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJ. Diagnostic performance of computed tomography angiography in peripheral arterial disease: a systematic review and meta-analysis. JAMA. 2009;301(4):415-24. doi: 10.1001/jama.301.4.415.

26. Orchard J, Strandness DEJr. Assessment of peripheral vascular disease in diabetes. Report and recommendations of an international workshop sponsored by the American Heart association and the American Diabetes Association. Diabetes Care. 1993;16(8):1199-209.

27. Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. Diabetologia. 1993;6(7):615-21.

28. Prince MR, Zhang H, Morris M, MacGregor JL, Grossman ME, Silberzweig J, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology. 2008;248(3):807-16. doi: 10.1148/radiol.2483071863.

29. Rydahl C, Thomsen HS, Marckmann P. High prevalence of nephrogenic systemic fibrosis in chronic renal failure patients exposed to gadodiamide, a gadolinium-containing magnetic resonance contrast agent Invest Radiol. 2008;43(2):141-4. doi: 10.1097/RLI.0b013e31815a3407.

30. Wertman R, Altun E, Martin DR, Mitchell DG, Leyendecker JR, O'Malley RB, et al. Risk of nephrogenic systemic fibrosis: evaluation of gadolinium chelate contrast agents at four American universities. Radiology. 2008;248(3):799-806. doi: 10.1148/radiol.2483072093.

31. Management of diabetic foot infections. Long text. Société de Pathologie Infectieuse de Langue Francaise. Med Mal Infect. 2007 ;37(1):26-50.

32. Lipsky BA. A report from the international consensus on diagnosing and treating the infected diabetic foot. Diabetes Metab Res Rev. 2004;20 Suppl 1:S68-77.

33. Agence Francaise de Sécurité Sanitaire des Produits de Santé. [Topical antibiotic prescription in primary and secondary bacterial cutaneous infections]. Ann Dermatol Venereol. 2004;131(11):1018-21.

34. Lipsky BA, Hoey C. Topical antimicrobial therapy for treating chronic wounds. Clin Infect Dis. 2009;15;49(10):1541-9. doi: 10.1086/644732.

35. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet. 2005;366(9498):1725-35.

36. Richards Jl, Lavigne JP, Sotto A. Diabetes and foot infection: more than double trouble. Diabetes Metab Res Rev. 2012;28 Suppl1: 46-53.

37. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. Infectious Diseases Society of America. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis. 2008;46(2):155-64. doi:10.1086/524891.

38. Mantey I, Hill RL, Foster AV, Wilson S, Wade JJ, Edmonds ME.. Infection of foot ulcers with Staphylococcus aureus associated with increased mortality in diabetic patients. Commun Dis Public Health. 2000;3(4):288-90.

39. Wagner A, Reike H, Angelkort B. Highly resistant pathogens in patients with diabetic foot syndrome with special reference to methicillin-resistant Staphylococcus aureus infections. Dtsch Med Wochenschr. 2001;126(48):1353-1356.

40. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. Diabetes Care. 2003;26(4):1069-73,

41. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infection. Clin Infect Dis. 2012;54(12):1679-84. doi: 10.1093/cid/cis460.

42. Lipsky Ba, Berendt AR. Principles and practice of antibiotic therapy of diabetic foot infection. Diabetes Metab Res Rev. 2000;16 Suppl 1:S42-6.

43. Richard JL, Scotto A, Lavigne JP. New insights in diabetic foot infection World J Diabetes. 2011;15; 2(2):24-32.

44. Jeffcoate WJ, Lipsky BA, Berendt AR, Cavanagh PR, Bus SA, Peters EJ, et al. Unresolved issues in the management of ulcers of the foot in diabetes. Diabet Med. 2008;25(12):1380-1389.

45. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infection. Clin Infect Dis. 2012;54(12):e132-73. doi: 10.1093/cid/cis346.

46. Lipsky BA. Infectious problems of the foot in diabetic patients. In: Levin and O'Neal's The diabetic Foot (7th ed). In: Bowker JH, Pfeifer MA, editors. Philadelphia: Mosby Elsevier, 2008: 305-318

47. Chantelau E, Wolf A, Ozdemir S, Hachmöller A, Ramp U. Bone histomorphology may be unremarkable in diabetes mellitus. Med Klin (Munich). 2007;102(6):429-33.

48. Newman LG, Waller J, Palestro CJ, Schwartz M, Klein MJ, Hermann G, et al. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. JAMA.1991;266(9):1246-51.

49. Shults DW, Hunter GC, McIntyre KE, Parent FN, Piotrowski JJ, Bernhard VM, et al. Value of radiographs and bone scans in determining the need for therapy in diabetic patients with foot ulcers. Am J Surg. 1989;158(6):525-9; discussion 529-30.

50. Enderle MD, Coerper S, Schweizer HP, Kopp AE, Thelen MH, Meisner C, et al. Correlation of imaging techniques to histopathology in patients with diabetic foot syndrome and clinical suspicion of chronic osteomyelitis. The role of high-resolution ultrasound. Diabetes Care. 1999;22(2):294-9.

51. Armstrong DG, Lipsky BA. Diabetic foot infections: stepwise medical and surgical management. Int Wound J. 2004;1(2):123-32.

52. Lipsky BA. Osteomyelitis of the foot in diabetic patients. Clin Infect Dis 1997;25(6):1318-26.

53. Eckman MH, Greenfield S, Mackey WC, Wong JB, Kaplan S, Sullivan L, et al. Foot infections in diabetic patients. Decision and cost-effectiveness analysis. JAMA.1995;273(9):712-20.

54. Jeffcoate WJ, Lipsky BA. Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. Clin Inf Dis. 2004;39(Suppl 2):S115-22.

55. Aragón-Sánchez FJ, Cabrera-Galván JJ, Quintana-Marrero Y, Hernández-Herrero MJ, Lázaro-Martínez JL, García-Morales E, et al. Outcomes of surgical treatment of diabetic foot osteomyelitis: a series of 185 patients with histopathological confirmation of bone involvement. Diabetologia. 2008;51(11):1962-70. doi: 10.1007/s00125-008-1131-8.

56. Lebrun E, Tomic-Canic M, Kirsner RS. The role of surgical debridement in healing of diabetic foot ulcers. Wound Repair Regen. 2010;18(5):433-8. doi: 10.1111/j.1524-475X.2010.00619.x.

57. Veves A, Murray HJ, Young MJ, Boulton AJ. The risk of foot ulceration in diabetic patients with high foot pressure: a prospective study. Diabetologia. 1992;35(7):660-3.

58. Pham H, Armstrong DG, Harvey C, Harkless LB, Giurini JM, Veves A. Screening techniques to identify people at risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes Care. 2000;23(5):606-11.

59. Frykberg RG, Lavery LA, Pham H, Harvey C, Harkless L, Veves A, et al. Role of neuropathy and high foot pressures in diabetic foot ulceration. Diabetes Care. 1998;21(10):1714-9.

60. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing J Vasc Surg. 2010;52(3 Suppl):37S-43S. doi:10.1016/j.jvs.2010.06.007.

61. Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB, et al. Off-loading the diabetic foot wound: a randomized clinical trial. Diabetes Care. 2001;24(6):1019-22.

62. Ferraresi R, Centola M, Ferlini M, Da Ros R, Caravaggi C, Assaloni R, et al. Long-term outcomes after angioplasty of isolated, below-the-knee arteries in diabetic patients with critical limb ischaemia. Eur J Vasc Endovasc Surg. 2009;37(3):336-42. doi: 10.1016/j.ejvs.2008.12.001.

63. Uccioli L, Gandini R, Giurato L, Fabiano S, Pampana E, Spallone V, et al. Long-term outcomes of diabetic patients with critical limb ischemia followed in a tertiary referral diabetic foot clinic. Diabetes Care. 2010;33(5):977-82.

64. Faglia E, Mantero M, Caminiti M, Caravaggi C, De Giglio R, Pritelli C, et al. Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaenic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Inter Med. 2002;252(3);225-232.

65. Jämsén T, Manninen H, Tulla H, Matsi P. The final outcome of primary infrainguinal percoutaneous transluminal angioplasty in 100 consecutive patients with chronic critical limb ischemia. J Vasc Interv Radiol. 2002;13(5):455-63.

66. Venermo M, Biancari F, Arvela E, Korhonen M, Söderström M, Halmesmäki K, et al.The role of chronic kidney disease as a predictor of outcome after revascularisation of the ulcerated diabetic foot. Diabetologia. 2011;54(12):2971-7. doi: 10.1007/s00125-011-2279-1.

67. Lepäntalo M, Fiengo L, Biancari F. Peripheral arterial disease in diabetic patients with renal insufficiency: a review. Diabetes Metab Res Rev. 2012;28 Suppl 1:40-45.

68. Aiello A, Anichini R, Brocco E, Caravaggi C, Chiavetta A, Cioni R, et al.Treatment of peripheral arterial disease in diabetes a consensus of the Italian Societies of Diabetes (SID, AMD), radiology (SIRM) and vascular endovascular surgery (SICVE). Nutr Metab Cardiovasc Dis. 2013;24(4):355-69.

69. Aronow WS, Ahn C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women < 62 years of age. Am J Cardiol. 1994;74(1):64-65.

70. Aso Y, Fujiwara T, Inukai T. Power spectral analysis of heart rate variation in diabetic patients with neuropathic foot ulceration. Diabetes Care. 1998;21(7):1173-7.

71. Imano E, Yoshioka R, Nakatani Y, Arai K, Motomura M, Kanda T, et al. QT dispersion is increased in diabetic patients with foot ulcer. J Atheroscl Thromb. 2000;6(1): 13-7.

72. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic Autonomic Neuropathy. Diabetes Care. 2003;26(5):1553-79.

73. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. Circulation. 1999;100(10):1134-1146.

74. Penfornis A, Zimmermann C, Boumal D, Sabbah A, Meneveau N, Gaultier-Bourgeois S, et al. Use of dobutamine stress echocardiography in detecting silent myocardial ischaemia in asymptomatic diabetic patients: a comparison with tallium scintigraphy and exercise testing. Diab Med. 2001;18(11):900-905.

75. Soghomonyan N. Perioperative Management of diabetic foot. Frontiers in pharmacology. 2014;5:91.

76. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med. 1997;103(5):368-375.

77. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation. 2002;105(19):2259-2264.

78. Dangas G, Iakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol. 2005;95(1):13-19.

79. Rudnick MR, Goldfarb S, Wexler L, Ludbrook PA, Murphy MJ, Halpern EF, et al. Nephrotoxicity of ionic and non-ionic contrast media in 1196 patients: a randomized trial. The Iohexol Cooperative Study. Kidney Int. 1995;47(1):254-261.

80. Owen RJ, Hiremath S, Myers A, Fraser-Hill M, Barrett BJ, Consensus Guidelines for the Prevention of Contrast Induced Nephropathy: update 2012. Canadian Association Radiologist Journal. 2014;65(2):96-105.

81. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1159-67.

82. Preiser JC, Devos P, Van Den Berghe G. Tight control of glycaemia in critically ill patients. Curr Opin Clin Nutr Metab Care. 2002;5(5):533-7.

83. Metchick LN, Petit WA, Inzucchi SE. Inpatients management of diabetes mellitus. Am J Med. 2002;113(4):317-23.

84. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2004;27 Suppl 1:S15-35.

85. Frykberg RG, Armstrong DG, Giurini J, Edwards A, Kravette M, Kravitz S, et al. Diabetic foot disorders. A clinical practice guideline J Foot Ankle Surg. 2000;39(5 Suppl):S1-60.

86. Canadian Pharmacist Association. Glucophage. Compendium of Pharmaceutical and Specialities: The Canadian Drug Reference for Health Professionals. Canadian Pharmacist Association; 2009;1027.

87. Chernoff RS, et al. The effect of very high-protein liquid formula (Replete) on decubitus ulcers healing in long-term tube-fed istitutionalized patients: J Am Diet. 1990;90:130.

88. Breslow RA, Hallfrisch J, Guy DG, Crawley B, Goldberg AP, et al. The importance of dietary protein in healing pressure ulcers. J Am Geriatr Soc. 1993;41(4):357-362.

89. Langer G, Fink A. Nutritional interventions for preventing and treating pressure ulcers. Cochrane Database Syst Rev. 2014;12;(6):CD003216. doi: 10.1002/14651858.CD003216.

90. Yue DK, Swanson B, McLennan S, Marsh M, Spaliviero J, Delbridge L, et al. Abnormalities of granulation tissue and collagen formation in experimental uraemia and malnutrition. Diab Med. 1986;3(3):221-225.

91. Hehenberger K, Kratz G, Hansson A, Brismar K. Fibroblasts derived from human chronic diabetic wounds have a decreased proliferation rate, which is recovered by the addition of heparin. J Dermatol Sci. 1998;16(2):144-51.

92. Hehenberger K, Heilborm JD, Brismar K, Hansson A. Inhibited proliferation of fibroblasts derived from chronic diabetic wounds and normal dermal fibroblasts treated with high glucose is associated with increased formation of I-lactate. Wound Repair Rege. 1998;6(2):135-41.

93. Black E, Vibe-Petersen J, Jorgensen LN, Madsen SM, Agren MS, Holstein PE, et al. Decrease of collagen deposition in wound repair in type 1 diabetes independent of glycemic control. Arch Sur. 2003;138(1):34-40.

94. Raffaitin C, Lasseur C, Chauveau P, Barthe N, Gin H, Combe C, et al. Nutritional status in patients with diabetes and chronic kidney disease : a prospective study. Am J Clin Nutr. 2007;85(1): 96-101.

95. Combe C, Chauveau P, Laville M, Fouque D, Azar R, Cano N, et al. French Study Group Nutrition in Dialysis : Influence of nutritional factors and hemodialysis adequacy on the survival of 1,610 French patients. Am J Kidney Dis. 2001;37 (Suppl 2): S81-S88.

96. Larsson J, Agardh CD, Apelqvist J, Stenström A. Clinical characteristics in relation to final amputation level in diabetic patients with foot ulcers: a prospective study of healing below or above the ankle in 187 patients. Foot Ankle Intl. 1995;16(2):69-74.

97. Harwant S, Doshi HK, Moissinac K, Abdullah BT. Factors Related to Adverse Outcome in Inpatients With Diabetic Foot. Med J Malaysia 2000;55(2):235-241.

98. De Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med. 2001;63(4):619-30.

99. Katon W, von Korff M, Ciechanowski P, Russo J, Lin E, Simon G, et al. Behavioral and Clinical Factors Associated With Depression Among Individuals With Diabetes. Diabetes Care. 2004;27(4):914-920.

100. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, Depression, and Quality of Life A population study. Diabetes Care. 2004;27(5):1066-1070.

101. Carrington AL, Mawdsley SK, Morley M, Kincey J, Boulton AJ. Psychological status of diabetic people with or without lower limb disability. Diabetes Res Clin Pract. 1996;32(1-2):19-25.

102. Cole-King A, Harding KG. Psychological factors and delayed healing in chronic wounds. Psychosom Med. 2001;63(2):216-220.