

Approach to Infection models

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Important aspects during management of diabetic foot infection

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ABSTRACT

Diabetic foot is a complex disease. One of its most important complications is infection with risk of limb loss. In severe cases it is also a life-threatening condition. Several guidelines are available in order to achieve the implementation of some standard of care strategies. However, these consensus documents do not address all controversial issues arising during diabetic foot infection. The present article aims to review some of these controversial aspects.

Key words: diabetic foot, infection, empirical treatment, osteomyelitis, comorbidity.

BACKGROUND

Diabetic foot is a complex and heterogeneous disease. One of its most important complications is infection with risk of limb loss. In severe cases it is also a life-threatening condition [1].

Management of these types of infections is not easy since many different specialities are involved on it. In addition, perception, knowledge and awareness of this condition is quite heterogeneous between different physicians. Several guidelines are available in order to achieve the implementation of some standard of care strategies [2,3]. However, these consensus documents do not address all controversial issues arising during diabetic foot infection attention. When to treat resistant bacteria empirically, the duration of this treatment and which is the best dose to achieve high concentrations at the site of infection are aspects that guidelines do not always explain. Some comorbidities play also an important role in the management of prognosis of diabetic foot infections. The present article aims to review some of these controversial aspects:

CHOICE OF EMPIRICAL ANTIBIOTIC

Regarding medical treatment of infection, the choice of an empirical antibiotic is quite difficult, especially in moderate or severe infections, where polymicrobial involvement is frequent. In this clinical scenario, early administration of correct antibiotics improves prognosis and results in lower amputation and mortality rates. On one hand, delay on antibiotic treatment can lead to adverse outcomes, which means that there is often no time to wait until results of cultures are available. But on the other hand, bad evolution and lack of improvement could be the consequence of an incorrect empirical choice.

Mild infection. In general terms, mild infections (less than two centimetres of redness of skin with depth affecting only subcutaneous tissue) of acute lesions with a course of no longer than two weeks and without prior antibiotic are usually caused by gram-positive bacteria and do not need coverage against gram negative bacteria, anaerobes or resistant microorganisms. However, this is only a general approach [2,3]. It is necessary to take into account that some patients are at high risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infections despite having non-complicated disease. So, prior MRSA infections or colonization by this microorganism, nasal carriers, peripheral vasculopathy and chronic kidney disease (most of all in dialyzed patients) are risk factors for being infected by this virulent bacterium and are described in medical literature. It is important to rule out these circumstances for the correct treatment of mild infections because when they are present, coverage against MRSA should be, at least, considered [4-6].

At this point it is important to notice that correct evaluation of both vascular status and infection depth is mandatory. For example, small cellulitis areas are sometimes present in deep lesions including osteomyelitis so that they seem to be less severe infections than they really are. That is why this evaluation should be done by trained professionals. When phy-

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sicians have doubts about these facts prompt referral to specialized diabetic foot units is recommended. This shows that correct diabetic foot infection management requires a complex and multidisciplinary approach. In addition, it is important to mention that sharp debridement at site of infection and revascularization when needed is as important as the correct choice of antibiotic, making teamwork crucial to achieve successful outcomes [1,2].

Moderate and severe infection. Moderate diabetic infections have cellulitis areas that are usually bigger than 2 cm and affect deeper structures beyond subcutaneous tissue such as fascia, muscle, joints or bone. In this scenario, wider antibiotic coverage should be considered including gram negative bacteria and anaerobes. However, multidrug resistant bacteria are not always responsible [2,3].

Severe infection with systemic toxicity signs or sepsis, is a life-threatening condition and needs to be treated covering resistant gram-positive and resistant gram-negative bacteria. In these cases, in which broad spectrum antibiotics are prescribed, it is also mandatory to obtain tissue samples correctly in order to switch to a narrow spectrum antibiotic when possible. Swab samples do not offer reliable results and should not be taken.

Following Basetti, M et al. [7] in general population, host factors in general population for multidrug resistant gram-negative infections are older age (more than 70), diabetes mellitus, chronic obstructive pulmonary disease, malignancy, immunosuppression (including neutropenia and corticosteroid use) Charlson comorbidity index greater than 3, indwelling devices, need of haemodialysis, recent surgery or exposure to antibiotics within previous three months. Poor hygiene, recent hospital stay or transfer from another healthcare

facility and prior colonization are also epidemiological factors that must be taken into account when assessing treatment for gram-negative bacteria. Probably, the presence of only one of these risk characteristics is not enough to support treatment against resistant Gram-negative bacteria. However, when some of them are present at the same time, wide spectrum antibiotics need to be considered.

Regarding specifically diabetic foot syndrome population, enterobacteria producing extended-spectrum beta-lactamases (ESBL) play an important role. In addition to the risk factors mentioned above, previous treatment with cephalosporines and presence of osteomyelitis are also risk factors for infection [4].

Importance of Osteomyelitis in diabetic foot infection. As mentioned above, ruling out bone infection in diabetic foot patients is always necessary. Long-time non-healing ulcers usually fail to respond to several antibiotic schemes. When this happens, many different causes could be responsible. Wrong local management, need of revascularization, low antibiotic dosages, bad treatment adherence or the failing of discharge strategies are possible causes. However, when ulcers do not heal or infection does not improve despite an apparently correct treatment, it is crucial to rule out diabetic foot osteomyelitis. Bone penetration of antibiotics is a difficult issue and higher doses could be needed. Bone removal, when possible, is another option that helps to improve infections. When not possible, longer antibiotic courses are needed (as long as six weeks). As it has been explained before, osteomyelitis is an independent risk factor for multi-drug resistant bacteria such as MRSA or ESBL enterobacteria. For all those reasons the classical diabetic foot infection classification [2] (Table 1) is presently very much discussed. Although severe infection with

Table 1	Classical diabetic foot infection classification by IWGDF in 2019 update [2]	
Definition		Grade
No signs of infection.		1
- Infection limited to skin or superficial subcutaneous tissues without local complication or systemic signs AND		2
- Erythema does not extend > 2 cm around the wound.		
Infection with no systemic manifestations		3 (add "0" if infection involves bone)
- Erythema extending > 2 cm from the wound margin AND/OR		
- Infection deeper than skin and subcutaneous tissues (deep tissue abscess, lymphangitis, tendon, muscle, joint and/or bone involvement)		
Any foot infection with associated systemic signs as manifested by 2 or more of the following:		4 (add "0" if infection involves bone)
- Temperature > 38 °C or <36°C		
- Heart rate > 90 beats/min		
- Respiratory rate > 20 breaths/minute or PaCO2 < 32 mmHg		
- White blood cell count >12.000/mm ³ or < 4000/mm ³ or > 10% immature (band forms)		

IWGDF: international working group of diabetic foot

Table 2		Revised IDSA diabetic foot classification by Lavery et al [8]	
Definition			Grade
Diabetic foot ulceration without any manifestation of infection			No infection
Infection limited to skin or superficial subcutaneous tissue without local complication or systemic illness with 2 or more of the following signs:			
<ul style="list-style-type: none"> - Local swelling or induration - Erythema (extending <2 cm around the wound) - Local tenderness or pain - Local warmth - Purulent discharge 			Mild soft tissue infection
Either systemically stable or unstable patients with 1 or more of the following:			
<ul style="list-style-type: none"> - Erythema extending > 2 cm from ulceration - Lymphangitis - Spread beneath fascia - Deep tissue abscess - Gangrene - Can involve muscle tendon and joint but not bone 			Moderate/severe soft tissue infection
This category includes patients with moderate or severe soft tissue infection. Severe infection is defined by 2 or more of the following:			
<ul style="list-style-type: none"> - Temperature > 38 °C or <36°C - Heart rate > 90 beats/min - Respiratory rate > 20 breaths/minute or PaCO2 < 32 mmHg - White blood cell count >12.000/mm³ or < 4000/mm³ or > 10% immature (band forms) 			
Any bone infection of the foot			
This category includes patients with moderate or severe bone infection. Severe infection is defined by 2 or more of the following:			
<ul style="list-style-type: none"> - Temperature > 38 °C or <36°C - Heart rate > 90 beats/min - Respiratory rate > 20 breaths/minute or PaCO2 < 32 mmHg - White blood cell count >12.000/mm³ or < 4000/mm³ or > 10% immature (band forms) 			Moderate/severe diabetic foot osteomyelitis

IDSA: infectious disease society of America.

systemic toxicity is always a reason for concern, it seems that the presence of osteomyelitis has important prognosis implications, and a new classification [8] has been proposed by Lavery et al (Table 2).

One meta-analysis published in 2019 by Pinar Sen et al showed [9] the importance of osteomyelitis as an independent risk factor for amputation. In pooled OR analysis, the presence of gangrene/necrosis (OR: 9.9, 95% CI, 6.243-15.699; *P* < 0.001), presence of osteomyelitis (OR: 4.5, 95% CI, 2.277-8.885; *P* < 0.001), and length of hospitalization (SMD: 0.70, 95% CI, 0.45-0.95; *P* < 0.001) were the main associations with an increased risk of lower extremity amputations in patients with diabetic foot infections. Results showed also that the risk of amputation increased 1.7-fold with an IWGDF grade 3 classification and 2.5-fold with an IWGDF grade 4 classification (95%

CI, 1.398-2.061; *P* < 0.001 and 95% CI, 1.647-3.823; *P* < 0.001, respectively)

This study showed that diagnosis of diabetic foot infection is not only based on clinical suspicion and bacterial-isolation. Correct depth assessment and identification of affected structures are obligatory actions to be done before performing any therapeutic strategy. It is particularly important to rule out the presence of gangrene/necrosis and osteomyelitis since they seem to be the most important predictors of amputation.

Bone cultures still remain as an essential procedure in order to diagnose diabetic foot osteomyelitis [10] In addition, in patients with chronic osteomyelitis, which are often overtreated, cultures could be less reliable and bone biopsy should be considered [11].

Table 3 Clinical situations in which nonsurgical treatment could be considered in patients with diabetic foot osteomyelitis [13]

Clinical situation
Infection confined to the forefoot
Adequate limb perfusion
No tissue necrosis
Contraindication to surgery AND/OR high surgical risk
Patient preference to avoid surgery

DURATION OF TREATMENT

Although guidelines make some recommendations about this issue, the decision of stopping antibiotics should be made on the basis of clinical evolution. For example, for mild infections, 1-2 weeks antibiotic courses are recommended [2]. Whether 7 or 14 days of antibiotic treatment are required should be assessed individually taking into account the improvement or absence of infection signs, the possibility of removing infected tissue with sharp debridement, side effects, vascular status, etc. Again, it is particularly important to rule out osteomyelitis because removal of infected bone can reduce dramatically the duration of antibiotic treatment. In cases where bone removal is not possible or surgery is not indicated (Table 3) six weeks of medical therapy alone are recommended [12,13]. However, this medical approach is not preferred since long antibiotic courses are associated with higher risk of side effects such as renal failure, *Clostridioides difficile* infection, candidiasis, bone marrow toxicity, etc. One prospective, randomized non-inferiority pilot trial suggests that 3 weeks of medical treatment could be enough. However, in this study surgical debridement was performed before medical treatment [14].

In addition, in cases of infection that do not improve despite apparently correct medical treatment, just prolonging the same antibiotic scheme seems not to be a good option. Checking treatment adherence and antibiotic dose in order to achieve high concentrations at infection site, revising cultures results, evaluating dressing and offloading devices, assessing vascular status and ruling out bone involvement taking samples are essential aspects to be regarded in order to achieve success during management and avoid amputations, which is the most important objective of diabetic foot infection management.

COMORBIDITIES

Some comorbidities have demonstrated to have prognostic implications in diabetic foot infections [15-21]. Chronic kidney disease, haemodialysis, heart failure, ischaemic heart disease, malnutrition and poor glycaemic control are conditions which are frequently present in diabetic foot patients and have shown to increase the risk of adverse outcomes such

as mortality after amputation, amputation risk or delay of the healing process.

If these comorbidities are not detected, treated and controlled, diabetic foot infection will have more systemic repercussion and prognosis will worsen. This shows again the need of a multidisciplinary, collaborative and communicative approach between different specialties involved on diabetic foot management. Nurses, vascular surgeons, podiatrists, orthopaedic surgeons, internal medicine, endocrinology, microbiology and infectious diseases specialists are professionals that contribute to improve diabetic foot infection management and it seems difficult that they can achieve their objectives separately. The objective of successful diabetic foot infection management can only be achieved by efficient teamwork.

CONFLICT OF INTEREST

Authors declare no conflict of interest

REFERENCES

- García-Klepzig JL, Sánchez-Ríos JP, Manu C, Ahluwalia R, Lüdemann C, Meloni M, et al. Perception of diabetic foot ulcers among general practitioners in four European countries: knowledge, skills and urgency. *J Wound Care*. 2018 May 2;27(5):310-319. doi: 10.12968/jowc.2018.27.5.310. PMID: 29738299.
- Lipsky BA, Senneville É, Abbas ZG, Aragón-Sánchez J, Diggle M, Embil JM, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020 Mar;36 Suppl 1:e3280. doi: 10.1002/dmrr.3280.
- Blanes JI; Representatives of Spanish Society of Surgeons (ACS); Representatives of Spanish Society of Angiology and Vascular Surgery (SEACV); Representatives of Spanish Society of Emergency Medicine (SEMES); Spanish Internal Medicine Society (SEMI); Representatives of Spanish Society of Critical Care Medicine and Coronary Units (SEMICYUC); Representatives of Spanish Society of Chemotherapy (SEQ). Consensus document on treatment of infections in diabetic foot. *Rev Esp Quimioter*. 2011 Dec;24(4):233-62. PMID: 22173195.
- García Zafra V, Hernández Torres A, García Vázquez E, Soria Cogollos T, Canteras Jordana M, Ruiz Gómez J, et al. Risk factors for methicillin-resistant *Staphylococcus aureus* and extended-spectrum β -lactamase producing Enterobacterales in patients with diabetic foot infections requiring hospital admission. *Rev Esp Quimioter*. 2020 Dec;33(6):430-435. doi: 10.37201/req/101.2020.
- Feng SH, Chu YJ, Wang PH, Jun X, Min D, Li XM. Risk factors and gene type for infections of MRSA in diabetic foot patients in Tianjin, China. *Int J Low Extrem Wounds*. 2013 Jun;12(2):106-12. doi: 10.1177/1534734613489991.
- Lavery LA, Fontaine JL, Bhavan K, Kim PJ, Williams JR, Hunt NA. Risk factors for methicillin-resistant *Staphylococcus aureus* in diabetic foot infections. *Diabet Foot Ankle*. 2014 Apr 10;5. doi: 10.3402/dfa.v5.23575.

7. Bassetti M, Vena A, Giacobbe DR, Castaldo N. Management of Infections Caused by Multidrug-resistant Gram-negative Pathogens: Recent Advances and Future Directions. *Arch Med Res*. 2021 Nov;52(8):817-827. doi: 10.1016/j.arcmed.2021.09.002.
8. Lavery LA, Ryan EC, Ahn J, Crisologo PA, Oz OK, La Fontaine J, Wukich DK. The Infected Diabetic Foot: Re-evaluating the Infectious Diseases Society of America Diabetic Foot Infection Classification. *Clin Infect Dis*. 2020 Apr 10;70(8):1573-1579. doi: 10.1093/cid/ciz489.
9. Sen P, Demirdal T, Emir B. Meta-analysis of risk factors for amputation in diabetic foot infections. *Diabetes Metab Res Rev*. 2019 Oct;35(7):e3165. doi: 10.1002/dmrr.3165.
10. Lázaro-Martínez JL, Tardáguila-García A, García-Klepzig JL. Diagnostic and therapeutic update on diabetic foot osteomyelitis. *Endocrinol Diabetes Nutr*. 2017 Feb;64(2):100-108. English, Spanish. doi: 10.1016/j.endinu.2016.10.008
11. Tardáguila-García A, Sanz-Corbalán I, García-Morales E, García-Álvarez Y, Molines-Barroso RJ, Lázaro-Martínez JL. Diagnostic Accuracy of Bone Culture Versus Biopsy in Diabetic Foot Osteomyelitis. *Adv Skin Wound Care*. 2021 Apr 1;34(4):204-208. doi: 10.1097/01.ASW.0000734376.32571.20.
12. Tone A, Nguyen S, Devemy F, Topolinski H, Valette M, Cazaubiel M, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care*. 2015 Feb;38(2):302-7. doi: 10.2337/dc14-1514.
13. Lipsky BA, Uçkay İ. Treating Diabetic Foot Osteomyelitis: A Practical State-of-the-Art Update. *Medicina (Kaunas)*. 2021 Apr 1;57(4):339. doi: 10.3390/medicina57040339.
14. Gariani K, Pham TT, Kressmann B, Jornayvaz FR, Gastaldi G, Stafylakis D, et al. Three Weeks Versus Six Weeks of Antibiotic Therapy for Diabetic Foot Osteomyelitis: A Prospective, Randomized, Noninferiority Pilot Trial. *Clin Infect Dis*. 2021 Oct 5;73(7):e1539-e1545. doi: 10.1093/cid/ciaa1758.
15. Margolis DJ, Hofstad O, Feldman HI. Association between renal failure and foot ulcer or lower-extremity amputation in patients with diabetes. *Diabetes Care*. 2008 Jul;31(7):1331-6. doi: 10.2337/dc07-2244.
16. Gau BR, Chen HY, Hung SY, Yang HM, Yeh JT, Huang CH, et al. The impact of nutritional status on treatment outcomes of patients with limb-threatening diabetic foot ulcers. *J Diabetes Complications*. 2016 Jan-Feb;30(1):138-42. doi: 10.1016/j.jdiacomp.2015.09.011.
17. Meloni M, Izzo V, Giurato L, Cervelli V, Gandini R, Uccioli L. Impact of heart failure and dialysis in the prognosis of diabetic patients with ischemic foot ulcers. *J Clin Transl Endocrinol*. 2018 Mar 2;11:31-35. doi: 10.1016/j.jcte.2018.01.002.
18. Sayiner ZA, Can FI, Akarsu E. Patients' clinical characteristics and predictors for diabetic foot amputation. *Prim Care Diabetes*. 2019 Jun;13(3):247-251. doi: 10.1016/j.pcd.2018.12.002.
19. Yamine K, Hayek F, Assi C. A meta-analysis of mortality after minor amputation among patients with diabetes and/or peripheral vascular disease. *J Vasc Surg*. 2020 Dec;72(6):2197-2207. doi: 10.1016/j.jvs.2020.07.086.
20. Lane KL, Abusamaan MS, Voss BF, Thurber EG, Al-Hajri N, Gopakumar S, et al. Glycemic control and diabetic foot ulcer outcomes: A systematic review and meta-analysis of observational studies. *J Diabetes Complications*. 2020 Oct;34(10):107638. doi: 10.1016/j.jdiacomp.2020.107638.
21. Lauwers P, Dirinck E, Van Bouwel S, Verrijken A, Van Dessel K, Van Gils C, et al. Malnutrition and its relation with diabetic foot ulcer severity and outcome: a review. *Acta Clin Belg*. 2022 Feb;77(1):79-85. doi: 10.1080/17843286.2020.1800315.