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Advances in Infections and Wound Healing for the Diabetic Foot: The Die Is Cast

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The diabetic foot remains a considerable health burden worldwide, calling for improvement in diagnosis and management.[1-3] Especially, infections and wound healing pose a challenge for the clinician.[1-3] The present special issue presents advances achieved in these areas.

Management of diabetic foot infections requires appropriate cultures to guide antibiotic treatment.[4] Ideally, tissue cultures should be used,[4] although swabs are generally easier to obtain and are still widely used.[5,6] Demetriou et al[7] have examined the diagnostic performance of swabs versus tissue cultures in 50 diabetic patients (28 with neuropathic and 22 with neuroischemic foot ulcer). All subjects presented with clinically infected foot ulcers.[7] It was found that swabs yielded excellent sensitivity (100%) and negative predictive value (100%), both for confirmation of infection and for identification of true pathogens, whereas their corresponding specificities (14% to 40%) and positive predictive values (54% to 88.5%) were less satisfactory. Thus, negative swab cultures emerged as very reliable in ruling out infection, and similarly, the absence of a microorganism could virtually exclude its role as a pathogen.[7] These diagnostic patterns were seen in neuropathic as well as neuroischemic foot ulcers. The authors have presented a clear and original viewpoint, as well as a novel distinction between neuropathic and neuroischemic ulcers, and so this study appears to have useful clinical implications.[7] However, further experience in larger patient series is desirable.

Patients with diabetic foot osteomyelitis need appropriate diagnosis and follow-up.[3,4,8] Michail et al[9] have looked at the performance of serum inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], white blood cells [WBC], and procalcitonin [PCT]) for the diagnosis and follow-up of such patients. For the diagnosis of osteomyelitis, CRP (cut-off > 14 mg/L) yielded 85% sensitivity and 83% specificity. The corresponding values for ESR (cutoff >67 mm/h) were 84% and 75%, for WBC (cutoff >14 × 10^9/L) were 75% and 79%, and for PCT (cutoff >0.30 ng/mL) were 81% and 71%.[9] All these markers were reduced following initiation of antibiotic treatment. Importantly, WBC, CRP, and PCT soon reverted to near-normal. Conversely, ESR elevation persisted for 3 months in patients with osteomyelitis, distinguishing them from those with simple soft tissue infection.[9] Thus, ESR was identified as the best marker to monitor the response to therapy in patients with osteomyelitis. The strengths of this study include its clear message, the enrolment of an adequate patient series (n = 61), and the 3-month follow-up. Given the clinical conundrum of distinguishing osteomyelitis from soft tissue infection and, worse still, of deciding on the length of optimal antibiotic treatment in the individual patient,[3,4,10,11] the data of Michail et al[9] appear promising for the foot clinic.

A less well-known aspect of diabetic foot infections is the role of local cytokines and proteases in the course of infection and in response to treatment.[12] In a small case series of 8 patients, with methicillin-resistant *Staphylococcus aureus* (MRSA) foot infection, Ambrosch et al[13] have examined the effect of daptomycin therapy (4-6 mg/kg body weight per day) on wound secretion of pro-inflammatory interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9), and metallopeptidase inhibitor-1 (TIMP-1). Daptomycin was administered for a maximum of 14 days. A reduction of IL-6 as early as after 3 treatment days was shown, followed by a reduction of MMP-9 and an increase of TIMP-1 after 14 days, in parallel with a reduction of ulcer dimensions. MRSA was finally eradicated in all patients. Thus, daptomycin led to a cascade of favorable molecular changes, namely reduction of pro-inflammatory IL-6 and MMP-9 with an increase of anti-protease activity. Such actions were reflected in reduction of wound size and microbiolgical eradication. Despite the pilot design, this work opens new perspectives for the study of foot infections at the molecular level, which is becoming an evolving field.[14-16]

Equally interesting is the role of MRSA genetic factors in foot infection with this pathogen.[17] Wang et al[18] have examined risk and genetic factors in 429 patients

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hospitalized with diabetic foot infection. Overall, 57 strains of MRSA were isolated. In these, *pvl* and *lukE-lukD* of the leukocytic toxin superfamily were detected by polymerase chain reaction. Moreover, patient and ulcer characteristics, including prior antibiotic therapy, as well as presence of diabetes complications were recorded.[18] Antibiotic use in the preceding 6 months, long ulcer duration, large ulcer size, osteomyelitis, and reduced serum protein were identified as risk factors for MRSA infection.[18] In the MRSA, *mecA* positive, *lukE-lukD*, and *pvl* positives were 100%, 100%, and 0%, respectively. Overall, 28 strains were SCC*mec* type III and 29 were SCC*mec* type IVa.[18] This work provides useful information on the risk factors for MRSA infection. Importantly, it enriches our knowledge in genetic aspects of this pathogen.

Turning their attention to wound fluid, Löffler et al[19] provide a review on secretions from diabetic foot ulcers. This is a very difficult area, some of the uncertainty arising from the great multitude of (still inadequately standardized) techniques of fluid sampling, the differences between acute and chronic wounds, and the pitfalls in interpreting findings during the various stages of ulceration and wound healing.[19-21] Indeed, the choice of sampling technique depends not only on the type of wound but also on the cytokines and/or other molecules that are being studied. Thus, results obtained with different techniques are difficult to compare.[19] In general, wound fluid may provide information on toxic actions of bacteria (eg, endotoxins), stage of wound healing, any inadequacies of the healing process, and so on. Moreover, IL-1β, vascular endothelial growth factor, MMP-2, and lactate are beginning to be appreciated as markers of inflammation and infection.[19] The authors underline the need to increase our knowledge in the interpretation of wound fluid and to explore its clinical implications. Certainly, their viewpoint is very interesting and the study of wound fluid merits further investigation.

More practically, surgery is frequently used in the management of diabetic foot osteomyelitis: The surgeon resects the infected bone either completely or partially.[22-24] Aragón-Sánchez et al[25] present their preliminary experience on the contribution of postoperative treatment with the superoxidized solution Dermacyn Wound Care (DWC) to promote healing in patients with infected bone remaining after incomplete surgery. They included 14 patients with diabetic foot osteomyelitis and unclean bone margins. Complete healing was accomplished in all patients after a median period of 6.8 weeks.[25] No allergies, dermatitis or other untoward effects were seen. This is the first study on the efficacy of DWC in this setting and its results are very promising, but, as the authors acknowledge, its limitations must not be overlooked. The latter include the small patient series, the relatively short follow-up, and the absence of controls.[25] Additional enquiry is now urgently needed on the role of DWC as adjuvant postoperative treatment for subjects with residual bone infection toward resolution of infection.

As another surgical group, Georgakarakos et al[26] present a very small case series on the utility of negative pressure therapy, or topical negative pressure, in the treatment of challenging ischemic diabetic wounds following major or minor amputation. This type of therapy is being increasingly used in the treatment of the diabetic foot and is thought to act by a variety of mechanisms, such as increased blood flow in the microcirculation, reduction of edema, removal of exudate, reduction of bacterial load, and enhancement of local nutrient and oxygen delivery.[27] The limitations of this work include the very small number of patients, the short follow-up, and the absence of a control group. These caveats notwithstanding, topical negative pressure appears a very useful therapeutic adjunct, facilitating healing in recalcitrant ischemic wounds,[26] thereby further encouraging consideration of this modality by the expert foot care team.

Again, Aragón-Sánchez et al[28] share with us their relatively large retrospective database on revision surgery in the management strategy of the diabetic foot. They have studied factors associated with revision surgery and those associated with major amputation in the event of revision surgery. Out of 417 diabetic patients surgically managed, 167 sustained repeat surgery.[28] Risk factors for revision surgery were ESR >70 mm/h, increased WBC, peripheral arterial disease, and isolation of gram-negative pathogens on tissue culture.[28] Among those undergoing revision surgery, predictors of major amputation included persistent osteomyelitis, coronary artery disease, 2 or more reoperations, isolation of gram-negative pathogens on tissue culture, and peripheral arterial disease.[28] Despite the retrospective design and the potential underrepresentation of anaerobes,[28] these are very useful data that need to be appreciated in the clinical scenario of severe foot infections with surgical treatment and limb loss.[29]

Furthermore, Löndahl[30] discusses the current role of hyperbaric oxygen therapy (HBOT) in the treatment of diabetic foot ulcers. HBOT involves 100% oxygen breathing at a pressure greater than 1 atm, promoting angiogenesis, fibroblast function, and granulation.[30,31] At the same time, it improves leukocyte function and ameliorates tissue edema.[30,31] Its main complication is middle ear barotrauma, whereas less frequent untoward effects are pulmonary barotaruma and oxygen seizures.[30] Despite their serious methodological shortcomings on several occasions, studies in diabetes have consistently shown a beneficial action of HBOT on wound healing.[30] The author's own randomized, double-blinded, placebo-controlled clinical trial has provided more solid evidence that HBOT can facilitate healing of foot ulcers, especially if patients are duly selected.[32] Such selection is mainly based on the severity of ischemia, and the author's group has previously shown that baseline transcutaneous oximetry correlates with repose to

treatment.[33] Of note, health-related quality of life has also been shown to improve with HBOT,[30] prompting further experience with this modality.

Finally, Viswanathan and Rao[34] describe the current management of diabetic foot infections in India where diabetes is fast becoming a major issue. Specific factors predisposing to severe foot infections include barefoot walking, inappropriate footwear, poor knowledge of self-care, inadequate hygiene, along with delayed presentation and referral to foot clinics.[34] Principles of management include regular foot inspection, podiatric screening, evaluation of sensory deficits and arterial supply, elective surgical correction of deformities, and aggressive management of infections.[34] Cephalosporins, penicillin/β-lactamase inhibitor agents, carbapenems, fluoroquinolones, clindamycin, linezolid, daptomycin, and vancomycin have all been used to treat foot infections.[34] Wound debridement, choice of dressings, local herbal formulations,[35] and suitable shoes are additional important aspects of treatment.[34] The authors conclude that improvement is needed in terms of organization of health care services, knowledge of foot pathology, and more widespread implementation of therapeutic principles, coupled with continuing patient and physician education on foot problems.[34] Obviously, this endeavor should be encouraged, so that we can enable a more optimistic prognosis of the diabetic foot across different continents.

All in all, the articles in the present issue testify to the progress that has been accomplished and is still emerging in the field of diabetic foot infections and wound healing. It is anticipated that these achievements will be of some contribution to improved foot health care: The die is cast. Further progress is eagerly awaited in, among others, imaging modalities, revascularization, locally administered antibiotics, systematic management of risk factors, growth factors, and off-loading.[3,4,36-38] Meanwhile, the importance of active engagement by all health care providers involved in the multidisciplinary foot clinic cannot be emphasized enough.[39,40]

References

1. Papanas N, Lazarides MK. Diabetic foot amputations in Greece: where do we go from here? *Int J Low Extrem Wounds*. 2011;10:4-5.
2. Papanas N, Maltezos E, Edmonds M. Salvation of the diabetic foot: still a quest for the Holy Grail? *Vasa*. 2011;40:267-269.
3. Boulton AJ. The diabetic foot: grand overview, epidemiology and pathogenesis. *Diabetes Metab Res Rev*. 2008;24(suppl 1): S3-S6.
4. Lipsky BA, Peters EJ, Berendt AR, et al; International Working Group on Diabetic Foot. Specific guidelines for the treatment of diabetic foot infections 2011. *Diabetes Metab Res Rev*. 2012;28(suppl 1):234-235.
5. Macías Hernández AE, Alvarez JA, Cabeza de Vaca F, et al. Microbiology of the diabetic foot: is the swab culture useful? *Gac Med Mex*. 2011;147:117-124.
6. Tiwari S, Pratyush DD, Dwivedi A, Gupta SK, Rai M, Singh SK. Microbiological and clinical characteristics of diabetic foot infections in northern India. *J Infect Dev Ctries*. 2012;6:329-332.
7. Demetriou M, Papanas N, Panopoulou M, Papatheodorou K, Bounovas A, Maltezos E. Tissue and swab culture in diabetic foot infections: neuropathic vs. neuroischaemic ulcers. *Int J Low Extrem Wounds*. 2013;12:87-93.
8. Byren I, Peters EJ, Hoey C, Berendt A, Lipsky BA. Pharmacotherapy of diabetic foot osteomyelitis. *Expert Opin Pharmacother*. 2009;10:3033-3047.
9. Michail M, Jude E, Liaskos C, et al. The performance of serum inflammatory markers for the diagnosis and follow-up of patients with osteomyelitis. *Int J Low Extrem Wounds*. 2013;12: 94–99.
10. Dinh T, Snyder G, Veves A. Current techniques to detect foot infection in the diabetic patient. *Int J Low Extrem Wounds*. 2010;9:24-30.
11. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clin Infect Dis*. 2008;47:519-527.
12. Lobmann R, Schultz G, Lehnert H. Proteases and diabetic foot syndrome: mechanisms and therapeutic implications. *Diabetes Care*. 2006;28:461-471.
13. Ambrosch A, Halevy D, Fwity B, Brin T, Lobmann R. Effect of daptomycin on local interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) and metallopeptidase inhibitor 1 (TIMP-1) in patients with MRSA-infected diabetic foot. *Int J Low Extrem Wounds*. 2013;12: 100–105.
14. Ambrosch A, Lobmann R, Pott A, Preissler J. IL-6 concentrations rather than serological markers are useful in assessing bacterial triggers of ulcer inflammation. *Int Wound J*. 2008;5:99-106.
15. Dinh T, Tecilazich F, Kafanas A, et al. Mechanisms involved in the development and healing of diabetic foot ulceration. *Diabetes*. 2012;61:2937-2947.
16. Lobmann R, Zemlin C, Motzkau M, Reschke K, Lehnert H. Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with protease absorbent dressing. *J Diabetes Complications*. 2006;20:329-335.
17. Davis SL, Rybak MJ, Amjad M, Kaatz GW, McKinnon PS. Characteristics of patients with healthcare-associated infection due to SCCmec type IV methicillin-resistant *Staphylococcus aureus*. *Infect Control Hosp Epidemiol*. 2006;27:1025-1031.
18. Feng S-H, Chu Y-J, Wang P-H, Jun X, Min D, Li X-M. Risk factors and gene type for infections of MRSA in diabetic foot patients in Tian Jin of China. *Int J Low Extrem Wounds*. 2013;12: 106–112.
19. Löffler MW, Schuster H, Bühler S, Beckert S. Wound fluid in diabetic foot ulcerations—more than just an undefined soup? *Int J Low Extrem Wounds*. 2013;12: 113– 129.
20. Schmohl M, Beckert S, Joos TO, Königsrainer A, Schneiderhan-Marra N, Löffler MW. Superficial wound swabbing: a novel method of sampling and processing wound fluid for subsequent immunoassay analysis in diabetic foot ulcerations. *Diabetes Care*. 2012;35:2113-2120.
21. Löffler M, Zieker D, Weinreich J, et al. Wound fluid lactate concentration: a helpful marker for diagnosing soft-tissue

infection in diabetic foot ulcers? Preliminary findings. *Diabet Med*. 2011;28:175-178.
22. Aragón-Sánchez J. Treatment of diabetic foot osteomyelitis: a surgical critique. *Int J Low Extrem Wounds*. 2010;9:37-59.
23. Aragón-Sánchez J. Seminar review: a review of the basis of surgical treatment of diabetic foot infections. *Int J Low Extrem Wounds*. 2011;10:33-65.
24. Aragón-Sánchez J. Evidences and controversies about recurrence of diabetic foot osteomyelitis: a personal view and an illustrated guide for understanding. *Int J Low Extrem Wounds*. 2012;11:88-106.
25. Aragón-Sánchez J, Lázaro-Martínez JL, Quintana-Marrero Y, et al. Super-oxidized solution (Dermacyn Wound Care) as adjuvant treatment in the postoperative management of complicated diabetic foot osteomyelitis: preliminary experience in a specialized department. *Int J Low Extrem Wounds*. 2013; 12:130–137.
26. Georgakarakos E, Charalampidis D, Kakagia D, Georgiadis GS, Lazarides MK, Papanas N. Current Achievements With Topical Negative Pressure to Improve Wound Healing in Dehiscent Ischemic Stumps of Diabetic Patients: A Case Series. *Int J Low Extrem Wounds*. 2013;12: 138–145.
27. Schintler MV. Negative pressure therapy: theory and practice. *Diabetes Metab Res Rev*. 2012;28(suppl 1):72-77.
28. Aragón-Sánchez J, Lázaro-Martínez JL, Molinés-Barroso R, García Álvarez Y, Quintana-Marrero Y, Hernández-Herrero MJ. Revision surgery for diabetic foot infections: giving another chance to the patient. *Int J Low Extrem Wounds*. 2013;12:146–151.
29. Aragón-Sánchez J, Quintana-Marrero Y, Lázaro-Martínez JL, et al. Necrotizing soft-tissue infections in the feet of patients with diabetes: outcome of surgical treatment and factors associated with limb loss and mortality. *Int J Low Extrem Wounds*. 2009;8:141-146.
30. Löndahl M. Hyperbaric oxygen therapy as adjunctive treatment of diabetic foot ulcers. *Int J Low Extrem Wounds*. 2013; 12:152–157.
31. Tiaka EK, Papanas N, Manolakis AC, Maltezos E. The role of hyperbaric oxygen in the treatment of diabetic foot ulcers. *Angiology*. 2012;63:302-314.
32. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care*. 2010;33:998-1003.
33. Löndahl M, Katzman P, Hammarlund C, Nilsson A, Landin-Olsson M. Relationship between ulcer healing after hyperbaric oxygen therapy and transcutaneous oximetry, toe blood pressure and ankle-brachial index in patients with diabetes and chronic foot ulcers. *Diabetologia*. 2011;54:65-68.
34. Viswanathan V, Rao NV. Managing diabetic foot infection in India. *Int J Low Extrem Wounds*. 2013;12:158–166.
35. Papanas N, Maltezos E. Polyherbal formulation as a therapeutic option to improve wound healing in the diabetic foot. *Indian J Med Res*. 2011;134:146-147.
36. Morona JK, Buckley ES, Jones S, Reddin EA, Merlin TL. Comparison of the clinical effectiveness of different offloading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2013;29:183-193.
37. Antonoglou C, Papanas N, Maltezos E. Lipid-lowering therapy in the diabetic foot: seeing the whole iceberg and not just the tip [published online September 12, 2012]. *Curr Vasc Pharmacol*.
38. Papanas N, Maltezos E. Growth factors in the treatment of diabetic foot ulcers: new technologies, any promises? *Int J Low Extrem Wounds*. 2007;6:37-53.
39. Papanas N, Maltezos E, Edmonds M. The diabetic foot: a plea for the elementary? *Acta Diabetol*. 2006;43:152-153.
40. Edmonds M. Modern treatment of infection and ischaemia to reduce major amputation in the diabetic foot [published online December 26, 2012]. *Curr Pharm Des*.