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# A Randomized Controlled Trial to Examine the Efficacy and Safety of a New Super-Oxidized Solution for the Management of Wide Postsurgical Lesions of the Diabetic Foot

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## Abstract

This randomized trial was done to test the effectiveness and safety of using a novel antiseptic solution (Dermacyn® Wound Care [DWC], Oculus Innovative Sciences, Petaluma, CA) in the management of the postoperative lesions on the infected diabetic foot. 40 patients with postsurgical lesions wider than 5 cm<sup>2</sup> left open to heal by secondary intention were randomized into 2 groups. Group A was locally treated with DWC, whereas group B received povidone iodine as local medication, both in adjunct to systemic antibiotic therapy and surgical debridement if needed. Ischemia, renal failure, bilateral lesions, or immunodepression were considered as exclusion criteria. Patients were followed up weekly for 6 months. The primary endpoint was healing rate at 6 months, while secondary endpoints were healing time, time to achieve negative cultures, duration of antibiotic therapy, number of reinterventions, and adverse events. Healing rates at 6 months were significantly shorter in group A (90%) than in group B (55%;  $P < .01$ ). The time taken for cultures to become negative and duration of antibiotic therapy were also significantly ( $P < .05$ ) shorter in group A than in group B, whereas the number of reinterventions was significantly higher in group B ( $P < .05$ ). No difference was noted in the adverse events except that for reinfections, which were more frequent in group B than in group A ( $P < .01$ ). DWC is as safe as and more effective than standard local antiseptics in the management of wide postsurgical lesions in the infected diabetic foot.

## Keywords

Diabetic Foot, Ulceration, Infection, Antiseptic solutions, Local care.

Diabetic foot (DF) represents probably the most challenging complications of diabetes mellitus (DM), because its multifactorial pathogenesis may lead to different and complex clinical presentations, which encompass both medical and surgical issues.<sup>1</sup> Offloading the foot, revascularization, and control of infection should all to be addressed to adequately manage the ulcerated DF in order to avoid therapeutic failures, recurrences, and major amputations.<sup>2</sup> The management of the infected DF often requires a prompt and aggressive debridement and drainage alongside systemic antibiotic therapy, especially in case of lesions involving deep structures such as tendons, bones, or joints, which frequently end in a wide open postsurgical lesion, left to heal by secondary intention and which may last for several months.<sup>3</sup> The management of these lesions is complex and there is yet no robust evidence, especially concerning the role of local antiseptic solutions.<sup>4</sup>

Recently Dermacyn® Wound Care (DWC; Oculus Innovative Sciences, Petaluma, CA), a stable super-oxidized solution (SOS) with a neutral pH, produced by the electrolysis of water and sodium chloride to generate reactive species of chlorine and oxygen has been proposed as an antiseptic solution for a number of conditions, including chronic wounds.<sup>5-7</sup> Following a pilot

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observational study in which we retrospectively compared the clinical outcomes of DWC in postsurgical lesions with those of another group of patients treated with povidone iodine, with encouraging results, we elected to do a randomized trial to evaluate the effectiveness and safety of SOS in the management of infected lesions of the diabetic foot after surgical debridement.<sup>8</sup>

## Patients, Materials, and Methods

All the patients undergoing DF surgery for infection, as documented by local and systemic clinical signs and confirmed by cultural examinations in accordance with the International guidelines,<sup>4</sup> between January and December 2006 were screened. The inclusion criteria were as follows: A surgical lesion resulting from drainage or minor amputation, including trans-metatarsal amputations to treat an infected lesion distal to the ankle. The lesion should be grade 2B/3B Texas University (TU) grading score for diabetic foot ulcers, wider than 5 cm<sup>2</sup> and left open to heal by secondary intention; we also required a transcutaneous oxygen tension (TcPO<sub>2</sub>) value >50 mm Hg distal to the ankle. Exclusion criteria were as follows: bilateral lesions, having had a lesion in the same foot of duration longer than 6 months, HIV positive and any cause of immunodepression other than DM, local or systemic documented intolerance to povidone iodine, serum creatinine >2 mg/dL, and life expectancy shorter than 1 year. Successful revascularization for critical limb ischemia, both endovascular or surgical, was not considered as an exclusion criterion.

The study received the approval by the ethical committee of our hospital (Authorization No. 2117-14/09/05). All patients gave prior informed written consent. Patients lesions were evaluated with TU score, photographed, and measured with Visitrak (Smith & Nephew, Hull, UK). The patients were randomized into 2 groups: group A and group B by means of a computer-generated randomization code.

## Microbiological Evaluations

A sample for quantitative microbiology was obtained from each patient using a 6-mm punch from the base of the ulcer. The biopsy sample was weighed and immediately delivered to the microbiological laboratory.<sup>8</sup> Qualitative sampling for the identification of bacterial strains and antibiotic sensitivity was carried out as well using the Kirby–Bauer technique.<sup>9</sup> Sampling for this evaluation was performed at baseline in the same way as the ones taken for quantization and all the specimens were processed within 1 hour from the collection in the laboratory facilities, always by the same biologist (AL) who was blinded to the clinical trial.

## Patient Management

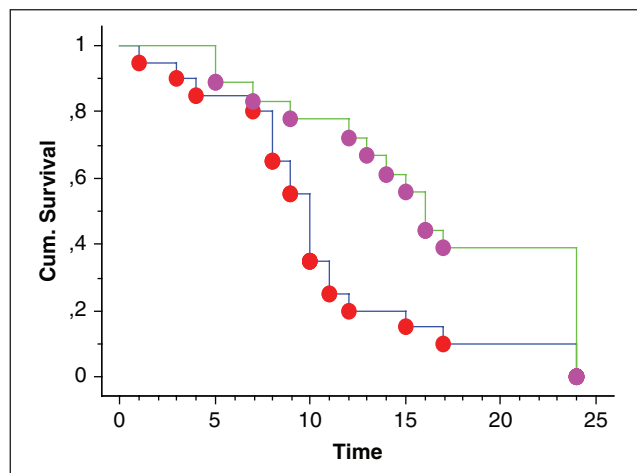
Both groups were treated with a standardized clinical approach, comprising empiric systemic antibiotic therapy according to our Infectious Diseases Department's policy (piperacillin/tazobactam and metronidazole with the adjunct of teicoplanin when methicillin-resistant *Staphylococcus aureus* was present), prompt and aggressive surgical debridement, metabolic control, and stabilization of the systemic conditions of the patient.

As local management of the ulceration, group A was treated with daily instillation of DWC solution via a catheter positioned in the sterile gauzes used as wound dressing: once a day an amount of DWC varying between 5 and 20 mL according to the size of the lesion, was instilled with a disposable syringe, to keep the gauze wet, as previously described.<sup>10</sup> Patients in group B received the same medication with povidone iodine diluted 50% with saline, as the standard local dressing for this type of patients in our department. Instillation of antiseptics was performed by nurses for inpatients. Once discharged, patients or their relatives were instructed to carry out the same procedure at home, without removing the bandages.

All the medical therapies were registered at each visit and continued unless different prescription by the patient's doctor. All the patients were on insulin therapy and they monitored blood glucose; the adjustment of antidiabetic therapy was part of the weekly control visit. Offloading was achieved using irremovable offloading devices and crutches, or alternatively, wheelchairs.<sup>11</sup>

Patients were then followed up weekly for 6 months or up to complete re-epithelization of the lesion; at each visit the bandages were removed, lesions were measured, photographed, and sampled for qualitative microbiology, adverse events were registered and new debridement procedures were performed if needed. One month from the beginning of the study, a new quantitative sampling of the lesion was performed using the same technique as previously. A new dressing was then applied to the wound, and medications were prescribed according to the systemic and local conditions. Antibiotic therapy was adjusted according to the outcomes of cultural exams and prolonged until both clinical signs of infection and cultures from 2 consecutive microbiological screens became negative. In any case, the decision of continuation/discontinuation of the antibiotic therapy was based on clinical evaluation made by an expert physician.

All the clinical procedures were done by a team that included a podiatrist and a diabetologist. Cultures were done in an external laboratory in the Infectious Diseases Department, and the measurements and evaluations were performed by another diabetologist (CG). Both CG and the ID personnel were unaware of the allocation of the patients to the different groups. Clinical management of the patients was performed in a different setting compared with the study evaluations.



**Figure 1.** Kaplan–Meier analysis for ulcers' survival: group A (blue line) versus group B (green line;  $P < .01$ ; time axis is in weeks)

At the end of the study, a retrospective calculation of global expenditures for each case was carried out on the databases of our hospital, including in-hospital stay costs, antibiotic therapy duration, and number of surgical procedures as monitors.

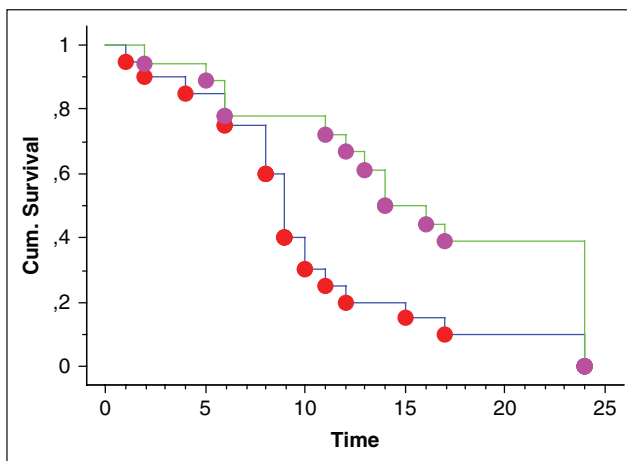
Primary endpoint of the study was healing rate at 6 months. Secondary endpoints were healing time; time for cultures to become negative; duration of antibiotic therapy; and number of reinterventions, defined as any procedure carried out in the operating theatre; adverse events, including reinfections, which were defined as the presence of local or systemic clinical signs of infection confirmed by cultural examination.

### Data Analysis

Data, expressed as mean  $\pm$  standard deviation were analyzed with Student's *t*-test, Kaplan–Meier survival analysis (Figures 1 and 2), and  $\chi^2$  test for dichotomous variables with Fisher's exact test, by means of a commercial software (Statview, SAS Institute, Cary, NC) on a personal computer.

### Results

A total of 170 diabetic foot patients underwent surgery in our department, of whom 68 had wide postsurgical lesions left to heal for secondary intent because of infection. Overall, 51 of these 68 patients fulfilled the inclusion criteria. Only 40 were actually randomized and participated in the study. Of the 11 patients excluded by the study, 7 did not meet the exclusion criteria, whereas 4 refused to give their informed consent. The clinical characteristics of patients are presented in Table 1. No differences were observed in terms of demographics and clinical features for the groups.



**Figure 2.** Kaplan–Meier analysis for cultures' negativization: group A (black line) versus group B (grey line;  $P < .05$ )

**Table 1.** Characteristics of Patients in Groups A and B

	Group A	Group B	P
No. of patients (DM2/DM1)	20 (18/2)	20 (17/3)	NS
Age in years, mean (SD)	62.8 (9.3)	61.3 (7.5)	NS
Duration of diabetes in years, mean (SD)	14.7 (8.2)	13.6 (7.4)	NS
HbA1c in %, mean (SD)	8.9 (1.1)	8.7 (1.4)	NS

NOTES: DMI = diabetes mellitus type 1; DM2 = diabetes mellitus type 2; SD = standard deviation; NS = nonsignificant.

The mean areas of lesions at baseline were similar in both groups:  $32.7 \pm 19.8$  cm<sup>2</sup> in group A compared with  $31.3 \pm 22.4$  cm<sup>2</sup> in group B ( $P > .05$ , nonsignificant [NS]). No differences were found between the groups for the prevalence of lesions involving bone or joints (3B—60% in group A vs 55% in group B,  $P > .05$ , NS) and for the minor amputations (65% in group A vs 60% in group B,  $P > .05$ , NS).

Qualitative analysis of the microbiological sampling did not reveal differences between the 2 groups: polymicrobial flora with a predominance of Gram-positive cocci and a high prevalence of Gram-negative rods; methicillin-resistant *Staphylococcus aureus* were present in one third of the cases (see Table 2). Quantitative microbiological sampling showed no statistically significant differences between the 2 groups ( $30.56 \pm 11.02 \times 10^6$  colony-forming units [CFU]/g in group A vs  $30.88 \pm 9.94 \times 10^6$  CFU/g in group B).

All the enrolled patients completed the clinical protocol and attended all the visits at the time scheduled except 2 patients, one in each group. In both cases the reason of delay was related to the impossibility for the patients to respect the appointment, so the visits were re-scheduled for the day after.

**Table 2.** Microbiological Characteristics at Baseline

	Group A	Group B	P
No. of bacteria strains/patient	2.5 (1-3)	2.7 (1-3)	NS
Gram positive (%)	66	71	NS
MRSA (%)	34	32	NS
Gram negative (%)	44	40	NS
Anaerobes (%)	8	6	NS
Fungi (%)	5	6	NS

NOTES: MRSA = methicillin-resistant *Staphylococcus aureus*;  
NS = nonsignificant.

**Table 3.** Adverse Events in Groups A and B

Event	Group A	Group B	P
Reinfection	1	9	<.01
Maceration	7	6	Nonsignificant
Peri-wound sensitization	—	1	—
Systemic	2	2	Nonsignificant

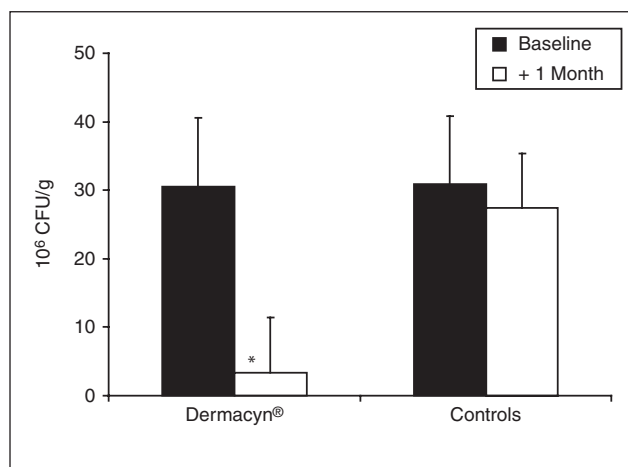
Adverse events, both systemic and local, did not show any difference in the 2 groups, as reported in Table 2, except for reinfections, which were significantly ( $P < .01$ ) more frequent in group B compared with group A (Table 3). Local adverse events were related to the application of local antiseptics. The systemic adverse events related to increase in blood pressure values (1 patient) and 3 episodes of metabolic decompensation were not related to the topical therapy. All the three cases were in the control group. In no case did these lead to the discontinuation of the study with all the patients recovering in 1 week with medical therapy.

Healing rate at 6 months was 90% in group A versus 55% in group B ( $\chi^2 = 9.9$ ,  $P = .002$ ), whereas healing time was  $10.5 \pm 5.9$  weeks in group A versus  $16.5 \pm 7.1$  weeks in group B ( $P = .007$ ). After 1 month of treatment, the number of bacteria present in the lesions showed a reduction of 88% in group A as against a decrease of 11% in group B (Figure 3). Duration of antibiotic therapy was  $10.1 \pm 6.1$  weeks in group A compared with  $15.8 \pm 7.8$  weeks in group B ( $P = .016$ ).

Four patients in group A needed a reintervention during the follow-up, compared with 11 in Group B ( $\chi^2 = 5.23$ ,  $P = .022$ ). All patients in both groups completed the study. None of the patients in either group required a major amputation.

## Discussion

This study shows that DWC is as safe as and more effective than povidone iodine in the management of wide surgical lesions of the DF. The group treated with DWC demonstrated a higher healing rate at 24 weeks (Figure 4).

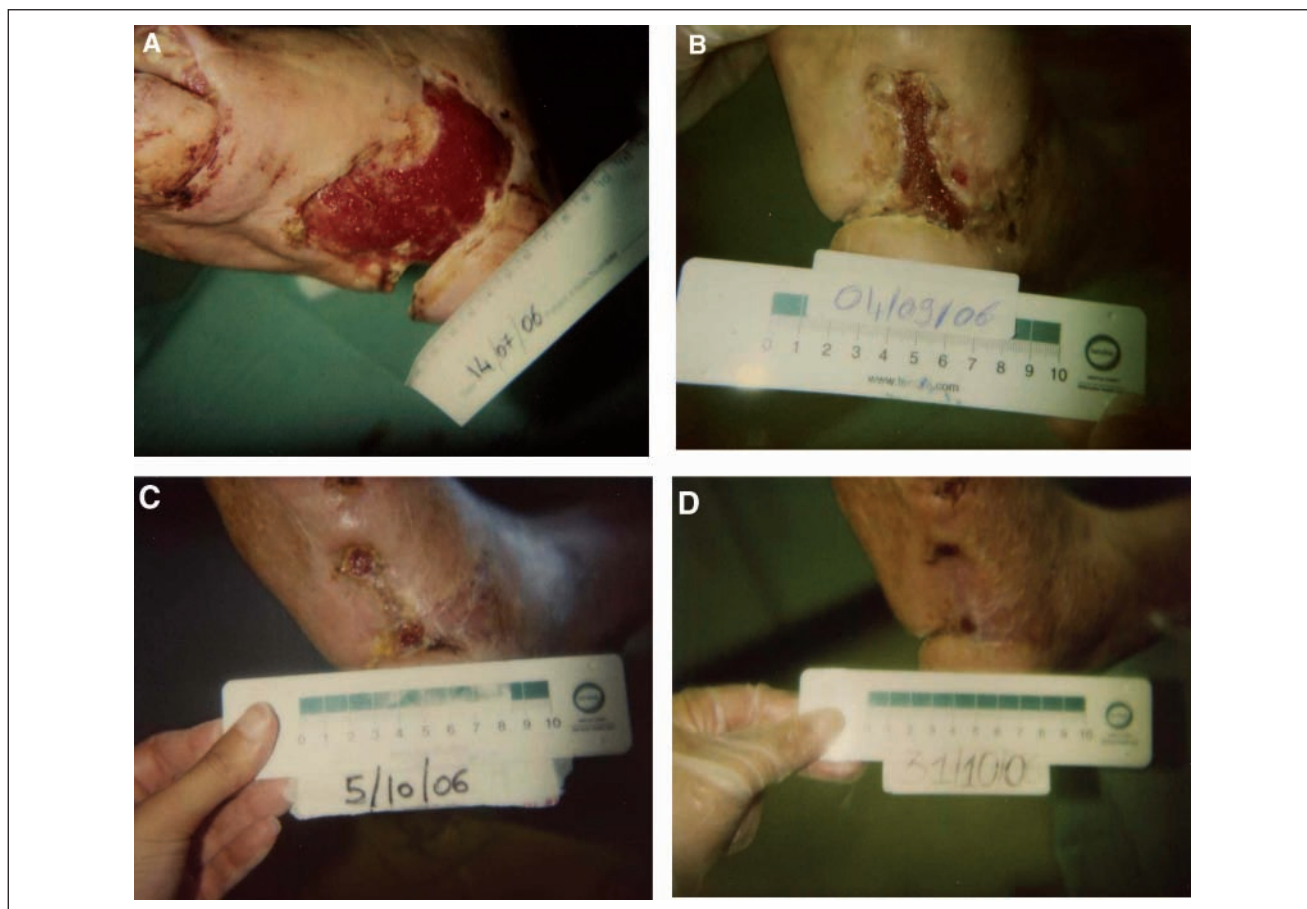


**Figure 3.** Quantitative microbiology at baseline and after 1 month of treatment in both groups. Dermacyn group showed a significant ( $p < .05$ ) reduction in the number of bacteria after 1 month of treatment. Y axis is in  $10^6$  CFU/g (CFU, colony-forming units).

The use of local antiseptics in the management of infected DF ulcers is the subject of debate because the evidence of an effective antibacterial activity is scarce, whereas for some formulations reports exist of suspected tissue damage.<sup>12,13</sup>

The finding that SOS were effective against bacteria, but not against the eukaryotic cells, because of their action on the bacterial wall, yielded a new class of antiseptic agents for clinical purposes.<sup>5-7</sup> However, SOS were unstable, their activity significantly decreased in a relatively short time after their preparation, making it difficult to use them for clinical purposes.<sup>14</sup> DWC is the first SOS that is stable at room temperature up to one year. Reports of its use exist in a variety of pathologies ranging from abdominal infection, gynaecology, and venous ulcers.<sup>15,16</sup> The results of our study support similar findings in other fields and also for DF. This is not surprising when one considers that infections are the main determinants of nonhealing in DF ulceration, especially when ischemia is present.<sup>17</sup>

Diabetes has been associated with a reduced ability to react to infections, due both to a genetic impairment of the immune system and to the effects of chronic hyperglycemia on different steps of the immune response pathways.<sup>18-21</sup> As a result of these disturbances, infections in diabetic patients, and in DF especially, are more frequently polymicrobial, with a higher prevalence of Gram-negative microorganisms, and have a faster and sometimes tumultuous clinical course, compared with those occurring in nondiabetic subjects.<sup>22,23</sup> The problems are more complex when deeper structures such as tendons, joints, and bones are infected, because they both act as a culture medium for bacterial growth and contribute to the proximal diffusion of the infection.<sup>24,25</sup> In all these cases, the key factor for the clinical success is represented



**Figure 4.** (A-D) A case treated with Dermacyn® Wound Care

by the reduction of the bacterial load, which actually constitute the main determinant of the severity of the infection.<sup>26,27</sup>

Surgery is essential in cases where the infection is localized to deep structures or where abscesses are created or tend to infiltrate deep spaces and diffuse proximally: Its role is to eliminate all the infected tissue and pus, thus reducing the infective burden.<sup>28,29</sup>

Though essential, surgical debridement is not always sufficient to eradicate infection, and lesions are left open for a long time to drain and systemic antibiotic therapy is given until both clinical signs and cultural exams are negative.<sup>30</sup> The use of antiseptics in this phase is aimed at minimizing the chance of reinfection and furthermore, at reducing the bacterial activity, creating a unfavorable environment for bacteria. This study demonstrates that DWC is safe and effective compared with povidone iodine both reducing healing time and the needing of antibiotic therapy.

As a side result of DWC use, the costs related to the management of the cases, including the costs of DWC were lower than those of the group treated with standard treatment with a spare of 40% on the expenditures,

mainly related to the shorter systemic antibiotic therapy and fewer surgical procedures.<sup>31</sup> As a recent multicenter prospective trial on a large cohort of patients in 14 centers of excellence for DF across Europe demonstrated, these are among the most important items for expenditures in the management of DF ulceration.<sup>32</sup>

The data from this study permit the observation that DWC should be considered as part of the integrated therapeutic approach in all the cases of infected DF ulceration, alongside surgery, systemic antibiotics, and revascularization when needed.

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The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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## References

1. Boulton AJ. Clinical presentation and management of diabetic neuropathy and foot ulceration. *Diabet Med.* 1991;8:S52-S57.
2. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. *N Engl J Med.* 1994;331:854-860.
3. Aragon-Sanchez FJ, Cabrera-Galvan JJ, Quintana-Marrero Y, et al. Outcomes of a surgical treatment of diabetic foot osteomyelitis: a series of 185 patients with histopathological confirmation of bone involvement. *Diabetologia.* 2008;51:1962-1970.
4. Lipsky BA, Pecoraro RE, Wheat LJ. The diabetic foot. Soft tissue and bone infection. *Infect Dis Clin North Am.* 1990;4:409-432.
5. Tanaka H, Hirakata Y, Kaku M, et al. Antimicrobial activity of superoxidized water. *J Hosp Infect.* 1996;34:43-49.
6. Venkitanarayanan KS, Ezeike GO, Hung YC, Doyle MP. Efficacy of electrolyzed oxidizing water for inactivating *Escherichia coli* O157:H7, *Salmonella enteritidis*, and *Listeria monocytogenes*. *Appl Environ Microbiol.* 1999;65:4276-4279.
7. Yahagi N, Kono M, Kitahara M, et al. Effect of electrolyzed water on wound healing. *Artif Organs.* 2000;24:984-987.
8. Bill TJ, Ratliff CR, Donovan AM, Knox LK, Morgan RF, Rodeheaver GT. Quantitative swab culture versus tissue biopsy: a comparison in chronic wounds. *Ostomy Wound Manage.* 2001;47:34-37.
9. Ratliff C, Rodeheaver G. Correlation of semi-quantitative swab cultures to quantitative swab cultures from chronic wounds. *Wounds.* 2002;14:329-333.
10. Goretti C, Mazzurco S, Ambrosini Nobili L, et al. Clinical outcomes of wide postsurgical lesions in the infected diabetic foot managed with 2 different local treatment regimes compared using a quasi-experimental study design: a preliminary communication. *Int J Low Extrem Wounds.* 2007;6:22-27.
11. Piaggese A, Macchiarini S, Rizzo L, et al. An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast. *Diabetes Care.* 2007;30:586-590.
12. Eckman MH, Greenfield S, Mackey WC, et al. Foot infections in diabetic patients. Decision and cost-effectiveness analyses. *JAMA.* 1995;273:712-720.
13. Lipsky BA. Evidence-based antibiotic therapy of diabetic foot infections. *FEMS Immunol Med Microbiol.* 1999;26:267-276.
14. Sampson MN, Muir AV. Not all the super-oxidized waters are the same. *J Hosp Infect.* 2002;52:228-229.
15. Landa-Solis M, Gonzalez-Espinosa D, Guzman B, et al. Microcyn™, a novel super-oxidized water with neutral pH and disinfectant activity. *J Hosp Infect.* 2005;61:291-299.
16. Ohno H, Higashidate M, Yokosuka T. Mediastinal irrigation with superoxidized water after open-heart surgery: the safety and pitfalls of cardiovascular surgical application. *Surg Today.* 2000;30:1055-1056.
17. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia.* 2008;51:747-755.
18. Joseph WS, LeFrock JL. The pathogenesis of diabetic foot infections—immunopathy, angiopathy, and neuropathy. *J Foot Surg.* 1987;26(1 suppl):S7-S11.
19. Bagdade JD, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. *Diabetes.* 1974;23:9-16.
20. Repine JE, Clawson CC, Goetz FE. Bactericidal function of neutrophils from patients with acute bacterial infections and from diabetes. *J Infect Dis.* 1980;142:869-872.
21. Katz S, Klein B, Elian I, et al. Phagocyte activity of monocytes from diabetic patients. *Diabetes Care.* 1983;6:479-485.
22. Wheat LJ, Allen SD, Henry M, et al. Diabetic foot infections. Bacteriological analysis. *Arch Intern Med.* 1986;146:1935-1939.
23. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *N Engl J Med.* 1999;34:1906-1912.
24. LeFrock JL, Joseph WS. Bone and soft-tissue infections of the lower extremity in diabetics. *Clin Podiatr Med Surg.* 1995;12:87-103.
25. Lew DP, Waldvogel FA. Osteomyelitis. *N Engl J Med.* 1997;336:999-1007.
26. Panuncialman J, Falanga V. The science of wound bed preparation. *Clin Plast Surg.* 2007;34:621-632.
27. Jeffcoate WJ, Price P, Harding KG; International Working Group on Wound Healing and Treatments for People with Diabetic Foot Ulcers. Wound healing and treatments for people with diabetic foot ulcers. *Diabetes Metab Res Rev.* 2004;20(suppl 1):S78-S89.
28. Piaggese A, Schipani E, Campi F, et al. Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial. *Diabet Med.* 1998;15:412-417.
29. Aragon-Sanchez FJ, Lazaro-Martinez JL, Quintana-Marrero Y, et al. Are diabetic foot ulcers complicated by MRSA osteomyelitis associated with a worse prognosis? Outcome of a surgical series. *Diabet Med.* 2009;26:552-555.
30. Lewis SB, Biondo CF, Page JC. Medical management of the diabetic patient during podiatric surgery. *J Am Podiatr Med Assoc.* 1994;84:432-438.
31. Eckman MH, Greenfield S, Mackey WC, et al. Foot infections in diabetic patients. Decision and cost-effectiveness analyses. *JAMA.* 1995;273:712-720.
32. Prompers L, Huijberts M, Schper N, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. *Diabetologia.* 2008;51:1826-1834.