Adjunctive Therapies for Diabetic Foot Infections

Treatment options that go beyond antibiotics may be needed to treat some diabetic foot infections.

BY BENJAMIN A. LIPSKY, MD

Foot infections in patients with diabetes are complex problems that often fail to respond to antimicrobial therapy and surgical procedures. Thus, several adjunctive therapies for these infections have been investigated over the past few years. These include novel antimicrobial delivery systems, larval biotherapy, granulocyte-colony stimulating factor and hyperbaric oxygen.[1,2]

Long-standing diabetes is associated with accelerated atherosclerosis, especially in the tibial and peroneal arteries between the knee and ankle. Several studies have shown that certain antibiotics have limited penetration to infected diabetic foot tissues. The tissue concentrations of a systemically administered antibiotic may be less than the serum level, sometimes as low as 25%.[3-6] Intra-aterial administration of antibiotics could potentially be a method for needed treatment to enter infected areas in patients with limb ischemia. Antibiotics can be injected directly into lower leg arteries, most commonly the femoral artery. Theoretically, this method should result in drug concentrations that are higher and more rapidly delivered via collateral vessels. Current data on this technique is minimal, however, and there are safety issues associated with the technique.[7]

Another way to provide higher tissue antibiotic levels is to give a pressurized IV injection nearer to the site of infection. One technique is called local transvenous pressure injection in Bier's arrest. While this method deposits antibiotic in the infected tissue 10 to 20 times that of serum concentrations, there are few literature reports on its efficacy.[8,9]

Another potential method of delivering high local levels of antibiotic is by a retrograde venous catheter delivery system. The novel experimental TheraPed Catheter (Figure 1) is designed to be threaded through a foot vein, where antibiotic is delivered from a port between two inflated balloons. Limited but promising results using levofloxacin with the catheter in animal studies were presented at the 2002 European Association for the Study of Diabetes meeting.[10] Investigators have looked at using biodegradable sponges impregnated with antibiotics to treat diabetic foot infections. Compared to polymethyl-methacrylate or PMMA beads, this method can be used with a wider variety of antibiotics. Biodegradable sponges, including those made of collagen, can also deliver higher tissue levels of antibiotics. The therapeutic levels do not last as long as with beads, and no repeat operation is needed to extract the sponge.[11,12]

Figure 1. The novel retrograde venous catheter with the catheter balloon being inflated.

IMPLANTS WITH ANTIBIOTICS

Treating infected bones in the diabetic foot is more of a challenge than soft tissue infections. Investigators have sought methods to deliver higher bone concentrations for prolonged periods to treat osteomyelitis.[13] A calcium hydroxyapatite ceramic implant is one antibiotic delivery method tested. These implants are porous and offer excellent biocompatibility. Unlike with PMMA beads, there is no risk of thermal damage to the antibiotic being delivered, and the implant can resist mechanical forces. Calcium hydroxyapatite

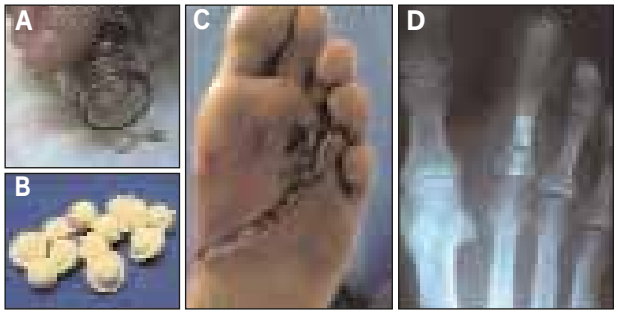

Figure 2. Antibiotic-impregnated calcium sulfate pellets (A,B). Notice the foot 4 days after insertion (C) and the beads on an x-ray (D).

ceramic implants are effective in filling cavity and bone defects. They release antibiotics slowly, fill dead space and encourage bone growth. Unlike PMMA beads, they are not surgically removed.[14]

Another newer method of delivering antibiotics by implant is with antibiotic-impregnated calcium sulfate pellets (Figure 2). These have the advantages of not generating heat and of dissolving over time. Armstrong and colleagues[15] studied these pellets to see if they would release therapeutic levels of antibiotics and tested how long they would retain their effectiveness on the shelf. They found that the pellets released therapeutic levels of antibiotic and saw no significant different in zones of inhibition (ZOI) for any of the tested organisms with the antibiotic pellets stores for 1, 7, 30, 60, 90 or 120 days. ZOIs were similar to those designating antibiotic susceptibility in the Kirby-Bauer test, they reported. These pellets could thus potentially be prepared in advance, stored and implanted when needed for deep diabetic foot infections. Clinical trials with this method have not yet been reported.

TABLE 1. G-CSF FOR TREATING DIABETIC FOOT INFECTIONS: SYSTEMATIC REVIEW AND META-ANALYSIS

Rx Group	Crude Rate #/total in group	Pooled Rate	RR (95% CI)	% RR (95% CI)	NNT (95% CI)
Lower Extremity Amputations					
G-CSF	6/85 (7%)	8.2	0.41	11.6	8.6
Controls	15/82 (18.2%)	13.3			
Overall Invasive Interventions					
G-CSF	11/85 (12.9%)	13.6	0.38	22.3	4.5
Controls	29/82 (35.3%)	32.0			

Source: *Diabetes Care.* 2005;28:454-460

COLONY STIMULATING FACTORS

Several exogenous and endogenous factors that have been discovered serve as stimulators of the inflammatory process.[16,17] Endogenous agents that have been employed therapeutically include cytokines and colony-stimulating factors. Granulocyte colony-stimulating factor (G-CSF) affects mature polymorphonuclear leukocyte neutrophils (PMNs) and activates adherent, not suspended PMNs.

G-CSF also has anti-infective properties. Physiologically, it augments the number of granulocytes that migrate to an infection and activates PMN microbicidal action at the site. G-CSF also inhibits the PMN apoptotic response and down-regulates the proinflammatory response of cytokines.[16] Clinical studies in animals have shown that G-CSF can be beneficial in selected bacterial and fungal infections. Thus, several investigators have studied its effectiveness for diabetic foot infections. Results of these studies have been mixed, making the value of this intervention uncertain.

In a recently published meta-analysis of G-CSF for diabetic foot infections,[18] Cruciani and colleagues reviewed five randomized controlled trials conducted in five countries with a total of 167 patients (Table 1). Filgrastim was given in four trials and lenograstim was given in one; subcutaneous administration was used in four trials and intravenous in one. The meta-analysis revealed that adding G-CSF did not significantly affect the resolution of infection or wound healing, however, it was associated with a significantly reduced likelihood of lower extremity surgical interventions (RR 0.38 [95% CI 0.20-0.69], number of patients who needed to be treated: 4.5), including amputation (0.41 [0.17-0.95], number of patients who needed to be treated: 8.6).

Compared with controls, patients treated with G-CSF had an 11.6% reduced risk for lower extremity amputations and a 22.3% reduced risk of overall invasive interventions. These differences were statistically significant. The small number of patients who needed to be treated to gain these benefits suggested that using G-CSF should be considered, especially in patients with limb-threatening infections.

LARVAL (MAGGOT) THERAPY

Larval or maggot debridement therapy (Figure 3) has been found to be useful in the treatment of some unresponsive diabetic foot infections. One study showed maggot therapy to be more effective in debriding nonhealing ulcers than conventional care.[19] Another study found that surgical maggots spared amputation.[20] It has also been found that presurgical maggot debridement decreases the rate of postoperative infections.[21] In this retrospective review, 10 wounds debrided by maggots 1 to 17 days prior to surgical closure were compared to a matched group. The maggot debridement was effective in all cases, with no postoperative wound infections versus 32% in the matched group ($P<.05$). Results were likely related to the antibacterial effects of maggot debridement therapy. Finally, a recent case-control study of 60 patients found that maggot therapy of lower extremity infections led to shorter healing times, fewer amputations and fewer days of antibiotic therapy. [22]

HYPERBARIC OXYGEN

Hyperbaric oxygen therapy (Figure 4) has anti-infective actions, including supporting tissues rendered hypoxic by infection and activating polymorphonuclear leukocytes (PMNs) while increasing their efficiency.[23] Hyperbaric oxygen also appears to enhance the activity of macrophages,

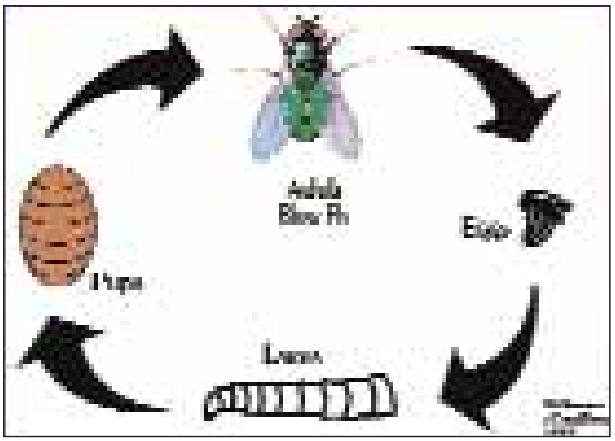

Photo courtesy of the BTER Foundation.

Figure 3. A diagram of larval biotherapy.

Figure 4. A hyperbaric oxygen therapy chamber.

inhibits bacterial growth and the release of some bacterial endotoxins, and it potentates the effects of antibiotics.[24]

While hyperbaric oxygen has been used for years to treat chronic wounds, most supportive data came from retrospective and uncontrolled case series. Several prospective trials have also been published. In a systematic review of hyperbaric oxygen treatment of diabetic foot ulcers, Kranke et al[25] found four randomized controlled trials with 147 total patients that met their inclusion criteria. The outcomes assessed were preventing major and minor amputations and improving healing rate. Pooled data from three trials showed a significant decrease in risk (RR of 0.31) of major amputations, while data from two trials showed no significant difference for minor amputations. Another trial showed that hyperbaric oxygen significantly improved the healing rate after 1 year (RR 2.3). The investigators cautioned that using this expensive technology for patients with diabetic foot infections may be justified where hyperbaric facilities are available, but formal economic evaluations are needed.

When treating a diabetic patient with a foot infection, first think about appropriate foot and wound care, supportive care and whether or not any surgical interventions may be needed. Next, select the appropriate antibiotic regimen and consider modifying therapy based on results of an appropriately obtained wound culture specimen. Most wounds require some debridement. When dealing with a necrotic wound, consider larval biotherapy. Novel antibiotic delivery systems might be considered for treatment of patients with an ischemic limb. Finally, for the treatment of severe or unresponsive infections, consider G-CSF injections and perhaps hyperbaric oxygen therapies. Be aware, however, that the cost effectiveness of such therapies is unclear at this time. ■

Benjamin A. Lipsky, MD, is professor of medicine, University of Washington, and director, General Internal Medicine Clinic and Antibiotic Research Clinic at VA Puget Sound Health Care System. He can be reached at 206-764-2849 (fax), dblipsky@hotmail.com or Benjamin.Lipsky@med.va.gov.

1. Lipsky BA. Adjunctive therapies for diabetic foot infection. Presented at DFCon05 Diabetic Foot Global Conference. March 3-5, 2005. Los Angeles, Calif.
2. Lipsky BA, Berendt A R, Deery H G, 2nd, et al. IDSA Guidelines: Diagnosis and treatment of diabetic foot infections. *Clinical Infectious Diseases.* 2004;39: 885-910.
3. Duckworth C, Fisher JF, Carter SA, et al. Tissue penetration of clindamycin in diabetic foot infections. *J Antimicrob Chemother.* 1993;31:581-584.
4. Seabrook GR, Edmiston CE, Schmitt DD, et al. Comparison of serum and tissue antibiotic levels in diabetes-related foot infections. *Surgery.* 1991;110:671-676.
5. Müller-Bühl U, Diehm C, Gutzler F, et al. Tissue concentrations of ofloxacin in necrotic foot lesions of diabetic and non-diabetic patients with peripheral arterial occlusive disease. *Vasa.* 1991;20:17-21.
6. Raymakers JT, Houben AJ, van der Heyden JJ, et al. The effect of diabetes and severe ischaemia on the penetration of ceftazidime into tissues of the limb. *Diabet Med.* 2001;18:229-234.
7. Dorigo B, Cameli AM, Trapani M, et al. Efficacy of femoral intra-arterial administration of teicoplanin in gram-positive diabetic foot infections. *Angiology.* 1995; 46:1115-1122.
8. Vorbach H, Robibaro B, Armbruster C, et al. Endothelial cell compatibility of clindamycin, gentamicin, ceftriaxone and teicoplanin in Bier's arterial arrest. *J Antimicrob Chemother.* 1999;44:275-277.
9. el-Sarky M el-S. Local intravenous therapy in chronic inflammatory and vascular disorders of the foot. *Int Surg.* 1997; 82:175-181.
10. Lipsky BA et al. Poster 1061. Delivering antibiotics to the lower limb by localized venous perfusion with a novel catheter device. Presented at the annual meeting of the European Association for the Study of Diabetes. Sept. 1-5, 2002. Budapest, Hungary.
11. Becker PL, Smith RA, Williams RS, Dutkowsky JP. Comparison of antibiotic release from polymethylmethacrylate beads and sponge collagen. *J Orthop Res.* 1994;12:737-741.
12. Kollenberg LO. A new topical antibiotic delivery system. World Wide Wounds (online publication) 1998;13:37. Available at www.worldwidewounds.com/1998/july/Topical-Antibiotic-Delivery-System/topical-antibiotic-delivery-system.html.
13. Lipsky BA. Osteomyelitis of the foot in diabetic patients. *Clin Infect Dis.* 1997;25:1318-1326.
14. Yamashita Y, Uchida A, Yamakawa T, et al. Treatment of chronic osteomyelitis using calcium hydroxyapatite ceramic implants impregnated with antibiotic. *Int Orthop.* 1998;22:247-251.
15. Armstrong DG, Stephan KT, Espensen EH, et al. What is the shelf life of physician-mixed antibiotic-impregnated calcium sulfate pellets? *J Foot Ankle Surg.* 2003;42:302-304.
16. Bennett SP, Griffiths GD, SChor AM, Leese GP, Schor SL. Growth factors in the treatment of diabetic foot ulcers. *Br J Surg.* 2003;90:133-146.
17. Deresinski SC, Kemper CA. The potential role of GM-CSF and G-CSF in infectious diseases. *Infect Med.* 1998;15:856-870.
18. Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections? A meta-analysis. *Diabetes Care.* 2005;28:454-460.
19. Sherman RA. Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy. *Diabetes Care.* 2003;26:446-451.
20. Jukema GN, Menon AG, Bernards A et al. Amputation-sparing treatment by nature: "surgical" maggots revisited. *Clin Infect Dis.* 2002;15;35:1566-1571.
21. Sherman RA, Shimoda KJ. Presurgical maggot debridement of soft tissue wounds is associated with decreased rates of postoperative infection. *Clin Infect Dis.* 2004;39:1067-1070.
22. Armstrong D G, Salas P, Short B, et al. Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J Am Podiatr Med Assoc.* 2005;95:254-257.
23. Wunderlich R P, Peters E J and Lavery L A. Systemic hyperbaric oxygen therapy: lower-extremity wound healing and the diabetic foot. *Diabetes Care.* 2000;23:1551-1555.
24. Wang C, Schwaitzberg S, Berliner E, et al. Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg.* 2003;138:272-279.
25. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev.* 2004;2:CD004123. Review.