Successful Treatment of Osteomyelitis and Soft Tissue Infections in Ischemic Diabetic Legs by Local Antibiotic Injections and the End-diastolic Pneumatic Compression Boot

RICHARD S. DILLON, M.D., F.A.C.P.*

Thirty-four legs at risk of amputation due to peripheral arterial insufficiency associated with ischemic necrosis, soft tissue infections, osteomyelitis, and variable degrees of peripheral neuropathy were reported in 28 diabetic patients. Amputation had been considered in 27 legs for which standard therapies had failed for the current illness and in two legs in which standard therapy had failed for previous illnesses. Local therapy was the initial form of therapy for five legs in which standard therapy appeared likely to fail. Infection was controlled in all patients with the use of local antibiotics and compression boot therapy. Early leg amputation was avoided in all but one patient. Late leg amputation occurred in two patients who were lost to follow-up care. Osteomyelitis, ischemic necrosis, and advanced soft tissue infection were shown not to be clear-cut indications for amputation in the ischemic diabetic foot.

From the Department of Medicine Section of Endocrinology, Bryn Mawr Hospital, Bryn Mawr, and Jefferson Medical School, Philadelphia, Pennsylvania

EFFECTIVE LEVELS OF ANTIBIOTICS in tissue may not be achieved in foot lesions of patients with ischemic peripheral arterial disease or osteomyelitis when administered by conventional oral or intravenous (I.V.) routes. In this study, antibiotics were injected into infected tissue to ensure effective local antibiotic concentrations.

The literature on local antibiotic usage in soft tissue infections or in osteomyelitis is scant. Many topical antibiotic creams and ointments are available. Antibiotics have been used locally in peritoneal dialysis fluids, in chest aerosols,[1] in irrigation fluids for an infected arterial graft[2] and joint infections,[3] and in bone cement after total hip arthroplasty.[4] In these cases, blood supply was adequate, the distance between the infection and the antibiotic solution was small, and surgical debridement and drainage procedures were performed. In contrast, in the 28 patients reported here, diabetes was present, osteomyelitis was common, the blood supply was marginal, the infected tissue was intact, and debridements or drainage incisions were rarely used. Little and Kobayashi[5] concluded that amputation is almost inevitable in such patients.

The injection of high concentrations of antibiotics into partially devitalized ischemic foot tissue can be ineffective, hazardous, and painful. Simple injection may not disseminate antibiotic throughout the infected tissue, and high concentrations of antibiotic could be harmful to the tissue. Finally, even in the presence of adequate antibiotic levels, ischemic lesions will not heal without adequate blood flow. The Circulator Boot™ Systems (the Circulator full-leg boot and the Circulator Miniboot) (Circulator Boot Corporation, Ardmore, PA) were used to solve these problems. The full-leg Circulator Boot encloses the leg from the groin to the toes. It is an end-diastolic pneumatic compression boot that is purported to increase peripheral blood flow by improving cardiac output, increasing venous and lymphatic return, stimulating fibrinolysins, and promoting arterial rechannelization and the development of collateral arterial flow.[6–9] The Circulator Miniboot encloses the foot and as much of the lower leg as necessary to include 4–6 inches of well-vascularized tissue. It is used in the sitting position to treat the distal leg only if the distal arterial circulation is abnormal. In the current cases, the boots were used both to increase blood flow and to disseminate locally injected antibiotics throughout the infected area of the foot. Patients with normal sensation in their feet tolerated the injections of antibiotics because their pain was relieved within a few minutes by the boot therapy.

* Clinical Assistant Professor of Medicine, Jefferson Medical School.
Reprint requests: Richard S. Dillon, 212 Bryn Mawr Medical Building, Lindsey Avenue and County Line Road, Bryn Mawr, PA 19010.
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TABLE 1. *Patient Characteristics*

	No. of Patients N = 28
Treatment of diabetes	
Insulin	27
Sulfonylureas	1
Smoking habits	
Active	9
Previous	13
Nonsmokers	6
Sex (age)	
Male	17 (68 ± 7.62 yrs)*
Female	11 (70.3 ± 9.8 yrs)*
Associated previous conditions	
Blood pressure > 160/90 despite medication	14
Angina of previous myocardial infarction	14
Congestive heart failure	7
Cerebrovascular disease (stroke or TIA)	7
Chronic renal failure	4
Calf claudication limiting activity	6

* Mean ± SD.

TABLE 2. *Thirty-four Legs Treated in 28 Patients*

	No. of Patients
One leg treated	22
Both legs treated	3
Same leg treated for separate illnesses	3

Methods

Patients

Consecutive patients who had no palpable pedal pulses, had abnormal noninvasive vascular tests, and were candidates for local antibiotic therapy are reported. Such patients were considered candidates because of failure of their previous therapy or because of the presence of ischemia or osteomyelitis, which was believed to make a successful outcome for conventional therapy unlikely. Their baseline characteristics are summarized in Tables 1–6.

Neuropathic Feet

The prognosis of the patients was diminished to some extent by the presence of variable degrees of neuropathy. Patients with obviously well-vascularized neuropathic ulcers were treated with the same techniques and did well but are excluded from this report. Eight patients, however, had one or more of the following features, which suggested an important neuropathic element to their disease: misshapen feet, ulcerated plantar callus, small muscle atrophy, calcified pedal arteries,[10] or a marked decrease in sensation. Reasons for claiming ischemia as a more important factor in their disease, however, was the normal shape and sensation of the other foot, the documentation of abnormal vascular tests, the failure of previous therapies and, as discussed later, their response to therapy.

Control Studies

These patients had already served as their own controls and could not, with good conscience, be divided into new treatment and conventional treatment groups: initial conventional treatment had failed for 27 of the 34 legs. Because of this history of failure, local treatment was started for second illnesses in two of the 27 legs. In five legs for which it appeared that conventional therapy was likely to fail, local antibiotics and boot therapy were the initial therapy. Because of the combination of ischemia and infection across either toe or transmetatarsal amputation sites, likely alternate therapy was leg amputation for 30 legs, toe amputation for one leg, transmetatarsal amputation for one leg, and resection of the fifth toe and metatarsal for one leg. The possibility of arterial bypass surgery and toe amputation had not been ruled out in one patient. All but four of the patients had been offered leg amputation before referral for boot therapy or had been advised that amputation would likely be necessary if boot therapy failed.

Antibiotics

Antibiotics were chosen according to sensitivities of cultured bacteria. Only preparations claimed by the manufacturer to be safe for intramuscular use were used. When no culture report was available, therapy was begun with gentamicin. Gentamicin and tobramycin are supplied in vials containing 80 mg of antibiotic in 2-ml solution. Ampicillin, cefazolin, carbenicillin, and nafcillin are supplied in powder form and were diluted with sterile water (free

TABLE 3. *Combinations of Major Lesions*

	Type of Lesion						
	Abscess	Cellulitis	Osteomyelitis	Gangrene	Ulcer	Paronychia	Neuropathy
34 legs at start	11	15	20	13	8	3	8
31 legs saved	10	13	18	11	7	3	7
3 BK amputations	1	2	2	2	1	—	1

TABLE 4. *Noninvasive Vascular Testing**

	No. of Legs N = 34
Ankle:arm blood pressure ratios	
≤50% in 1 tibial artery	20
≤50% in anterior and posterior tibial arteries	11
>100% (medial calcinosis)	6
>50% and absent to faint Doppler in foot	12

* Ankle Doppler Ultrasound tracings abnormal in all patients.

TABLE 5. *Previous Antibiotic Therapies*

	No. of Legs N = 34
Previous history of unsuccessful antibiotic therapy	29
Previous unsuccessful courses of 1 or more antibiotics given intravenously in hospital	20
Local initial treatment by author	5

of benzyl alcohol) to make solutions containing 100–200 mg of antibiotic per milliliter. Areas of cellulitis less than 7.5 cm in diameter usually were injected at one or two sites with 1 ml of antibiotic solution. Larger areas were injected at 2–5 sites with a total of 2 ml of antibiotic solution. Areas adjacent to known osteomyelitis were especially targeted. The bone itself was not purposely injected. The antibiotics were injected with disposable insulin syringes. Immediately after the antibiotic injection, the patient received a 40-minute treatment with either the full-leg Circulator Boot or the lower-leg Circulator Miniboot to disseminate the antibiotic around the foot and to increase the arterial circulation to the foot. The feet of nine patients with superficial necrotic ulcers were also placed in plastic bags containing 200-ml multielectrolyte solution (Sea Soaks™) and appropriate antibiotics; the bagged feet were then placed within the Miniboot and thus pumped within the antibiotic solution. The full-leg boot was generally timed to deliver a 40-msec compression of 56 mmHg (30 inches of water pressure) 30–60 msec after every other QRS complex of the EKG. The Miniboot was generally timed to deliver a 32-msec compression of 76 mmHg (40 inches of water pressure) 40–60 msec after every other QRS complex. Injections were administered once a day and from 3–7 times a week depending on the response of the infection and the tolerance of the tissues to the injections.

Results

Overall therapeutic results are summarized in Table 7. Immediate amputation was avoided in 32 of 34 legs (94%) and was not performed after the first 6 months.

Osteomyelitis

Of the 18 patients with definite osteomyelitis and two with probable osteomyelitis, 16 were cured. Small sequestra were removed with forceps from the ulcers of three patients who went on to heal. The initial 24-day hospitalization of another patient was terminated by our Utilization Committee because he appeared to be almost healed. He experienced a relapse at home and returned for a successful amputation of his fifth toe and metatarsal head. Two women, whose care was shared with a general surgeon, had below-the-knee (BK) amputations. One had been lost to boot follow-up therapy after a successful transmetatarsal amputation and the other had a sterilized but unstable foot after open amputation of the first metatarsal bone and toe. Serial x-rays illustrating the healing of osteomyelitis are shown in Figures 1A–D.

Soft Tissue Infections and Gangrene Without Associated Osteomyelitis

One transmetatarsal and one BK amputation were performed in this group of 14 legs. One patient had gangrene of all five toes and cellulitis in the midfoot. His leukocytosis and fever were normalized and he was discharged pain-free and ambulatory to our rehabilitation home where he remained 1 day. It was hoped that additional boot therapy in the home might improve his plantar flap and allow a successful transmetatarsal amputation. His family doctor placed him in another hospital for an immediate BK amputation. The foot of another patient was sterilized and a transmetatarsal amputation was performed to remove extensive distal tissue necrosis. Four patients had successful autoamputation of portions of their toes. Finally, areas of superficial gangrene sloughed off and the skin healed in the legs of two patients. An example of difficult soft tissue infection cured with the described techniques is shown in Figure 2.

Overall, of the 34 legs, 31 were spared amputation. Pain was lessened or relieved in all lesions within a few days of the local injection of antibiotics in spite of persisting ischemia. The walking capacity in the six patients with calf claudication after two or three steps, 25 feet, ½ block, ½ block, ½ block, and one block, respectively, improved to 2–3 blocks, unlimited, unlimited, one block dyspnea,

TABLE 6. *Risks for Leg Amputation*

Risk	No. of Legs N = 34
Infection	34
Severe ischemia without gangrene	19
Gangrene	10
Severe pain	4
Failure of conventional therapy	29

TABLE 7. *Results of Boot Therapy and Local Antibiotic Administration in Treatment of 34 Legs at Risk of Amputation*

Months from Presentation	Patients (Legs) at Risk	Original Lesion Being Treated	Original Lesion Stable at Death	Legs Removed	Relapse of Original Lesion and OPD Rx	New Lesion Same Leg	New Lesion Other Leg	Deaths with Intact Legs
0–1	28 (30)	28 (30)	0	2	0	0	0	0
1–6	24 (26)*	14	0	1	2	0	1	1
7–12	22 (24)	3	1	0	3	1	1	2
13–18	16	1	0	0	2	1	0	0
19–24	13	1	0	0	1	1**	0	3**
25–30	8	0	0	0	0	1	0	0
31–36	5	0	0	0	0	0	0	0
37–48	4	0	0	0	0	0	0	1
49–60	2	0	0	0	0	0	0	0
60+	1	0	0	0	0	0	0	0

* One patient with 2 legs lost to follow-up.

** One patient sought operative care elsewhere and died after operation.

2 blocks dyspnea, and 2–3 blocks dyspnea and fatigue, respectively.

Neuropathic Feet

In those diabetic patients with neuropathic feet, sensation improved as the infection and swelling of their feet were controlled. Early in their course they commonly did not sense the needle injections; however, they did sense the last few injections. In these patients it appeared that the infection, ischemia, and swelling of the feet were causes rather than results of their decreased sensation.

Follow-up

Seven patients died after a mean ± SD of 22.6 ± 24 months after presentation. All but one died without additional leg surgery. The latter patient transferred to another hospital after having a stroke; 11 months after his course of boot therapy he underwent a successful distal bypass but died in the postoperative period. Among the living patients, the lesions of two patients relapsed after 4.5 ± 2 months; they were treated again, and have done well for 22 ± 3 months. Three patients have gone 51 ± 17 months without relapse of their original lesions but have had other lesions that were successfully treated. One uncooperative and immobile patients with Alzheimer's disease required intermittent maintenance treatments. Eleven patients have gone 21.9 ± 16 months without relapse or new lesions. The three amputations and one patient lost to follow-up complete the list of 28 patients.

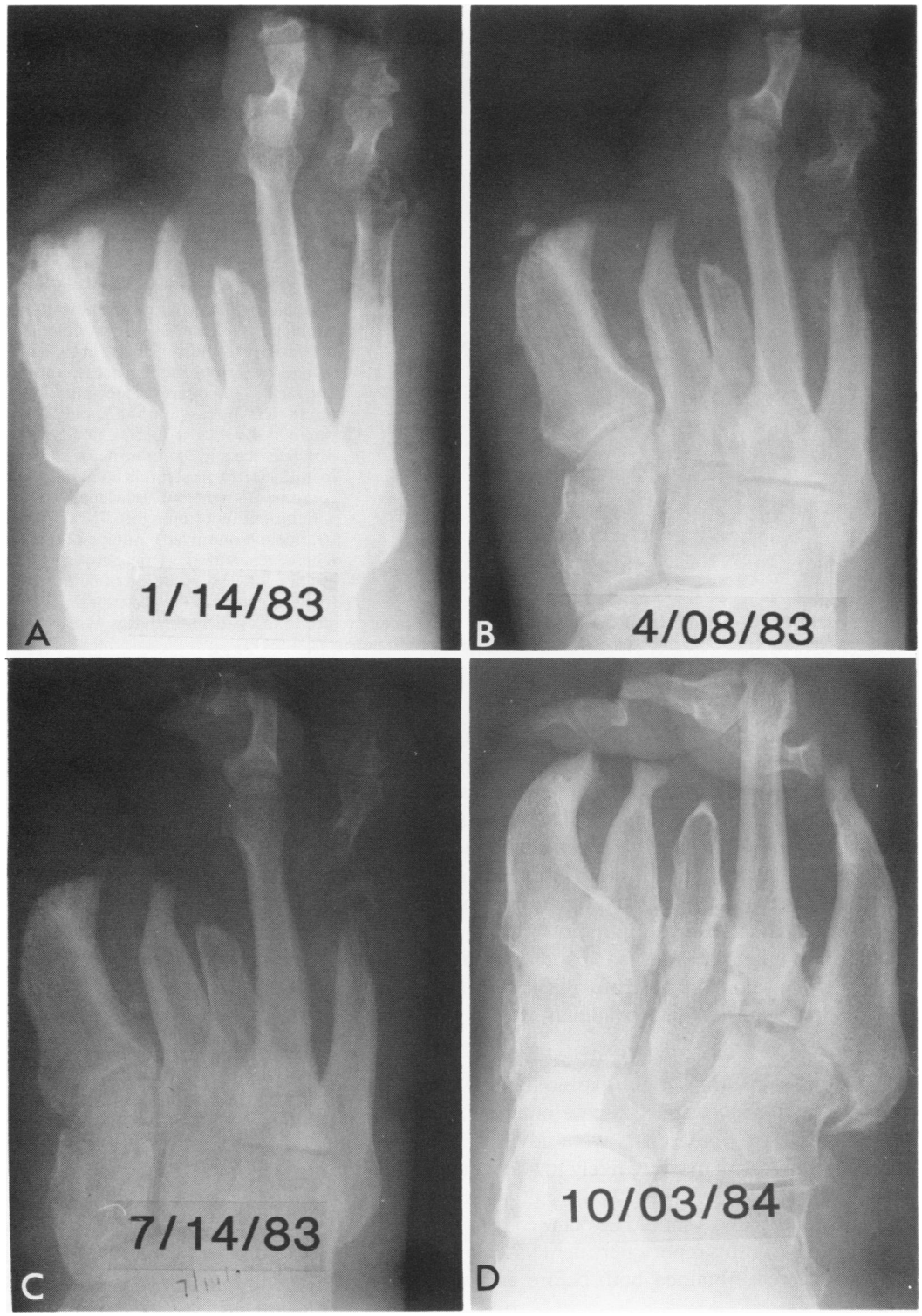
Discussion

Alternate suction and pressure treatment of ischemic feet was practiced with moderate success in several centers in the 1930s before the discovery of antibiotics.[11–13] The presence of cellulitis or osteomyelitis was considered a contraindication to therapy.[11] Infection was a common cause of treatment failure. Infection and its associated pain likewise have made treatment with the Circulator Boot intolerable for some patients. For such patients, the pain relief associated with local antibiotic usage has made boot therapy possible.

This report does not separate the effects of boot therapy from that of the use of local antibiotics. However, before the use of local antibiotics, boot therapy and systemic antibiotics were unsuccessful in sterilizing infected bone so that some amputations became necessary. The use of local antibiotics without boot therapy may prove hazardous. Some tissue necrosis was occasionally seen at the injection site even with boot therapy. In these patients the devitalized areas healed and the patient was benefited by both pain relief and sterilization of his lesion, which made the risk of the injections worthwhile.

Currently, the author commonly uses both local and systemic antibiotics in patients referred for boot therapy if infected lesions are present. Infected calluses, blisters, and soft tissue infections may respond rapidly, and hospitalization is commonly avoided. The drainage from infected bone is also quickly sterilized, but x-ray changes in the bone are seen over 1 or more weeks. On occasion, infection may be cured by the "wrong" antibiotic; the high concentration of antibiotic achieved by local injection may effectively eradicate infection when the antibiotic sensitivity studies report that the usual concentrations achieved in serum would be ineffective.

The administration of local antibiotics appears to be especially advantageous in diabetic patients in whom vascular disease and renal failure are commonly found, making nephrotoxic drugs less effective and more dangerous. In the few patients in whom it was measured, little or no gentamicin was found in the serum after the administration of 80 mg in divided doses in various areas of the foot. Again, neuropathy commonly makes diabetic patients relatively insensitive to the pain of the injection.



FIGS. 1A–D. Osteomyelitis treated successfully twice. This patient had three gangrenous toes amputated and a femoral–tibial bypass performed from May–December 1982. He then received an unsuccessful 3-week course of intravenous tobramycin for osteomyelitis of the fifth metatarsal head and cellulitis of the midfoot. On 1/14/83 he was referred for boot therapy (*A*). *Staphylococcus aureus* was cultured from an ulcer under the fifth metatarsal head and from drainage from other amputation sites. The drainage from the osteomyelitis was sterilized and the ulcers healed after 25 injections of gentamicin on different days, all delivered as an outpatient. Doppler arterial sounds were restored in his lateral foot. On 4/08/83 the amputation site and planar ulcer had been healed and his fifth toe appeared solid for 1 month (*B*). He returned 7/2/83 with a 1-day history of shaking chills, nausea, and a red, swollen foot. About 60 ml of pus under pressure gushed from an 18-gauge needle introduced into a tense swelling over the fifth metatarsal head. *S. aureus* (with new antibiotic sensitivities), Streptococcus, and *Bacteroides fragilis* were cultured. Gentamicin and cefazolin were injected into the abscess and fifth metatarsal head and disseminated by Miniboot therapy. Intravenous tobramycin was discontined when antibiotic sensitivity studies showed his organisms were resistant. By day 2 his fever and foot swelling were gone. By day 3 antibiotic solutions could not readily be injected into the abscess cavity which appeared to have closed. In all, the local injections into his foot included five of gentamicin, five of cefazolin, and one of clindamycin (*C*). Over the next year his fourth and fifth toes were dislocated medially (*D*). His ½-block claudication improved with the therapy and he has had unlimited walking capacity for more than 2 years.

Most of the patients reported were unlikely to have avoided amputation without the described treatments for the reasons summarized in Table 6. The arm:ankle blood pressure ratios summarized in Table 4 did not accurately reflect the risk of amputation. Indeed, the three leg amputations were performed in patients who had arm:ankle

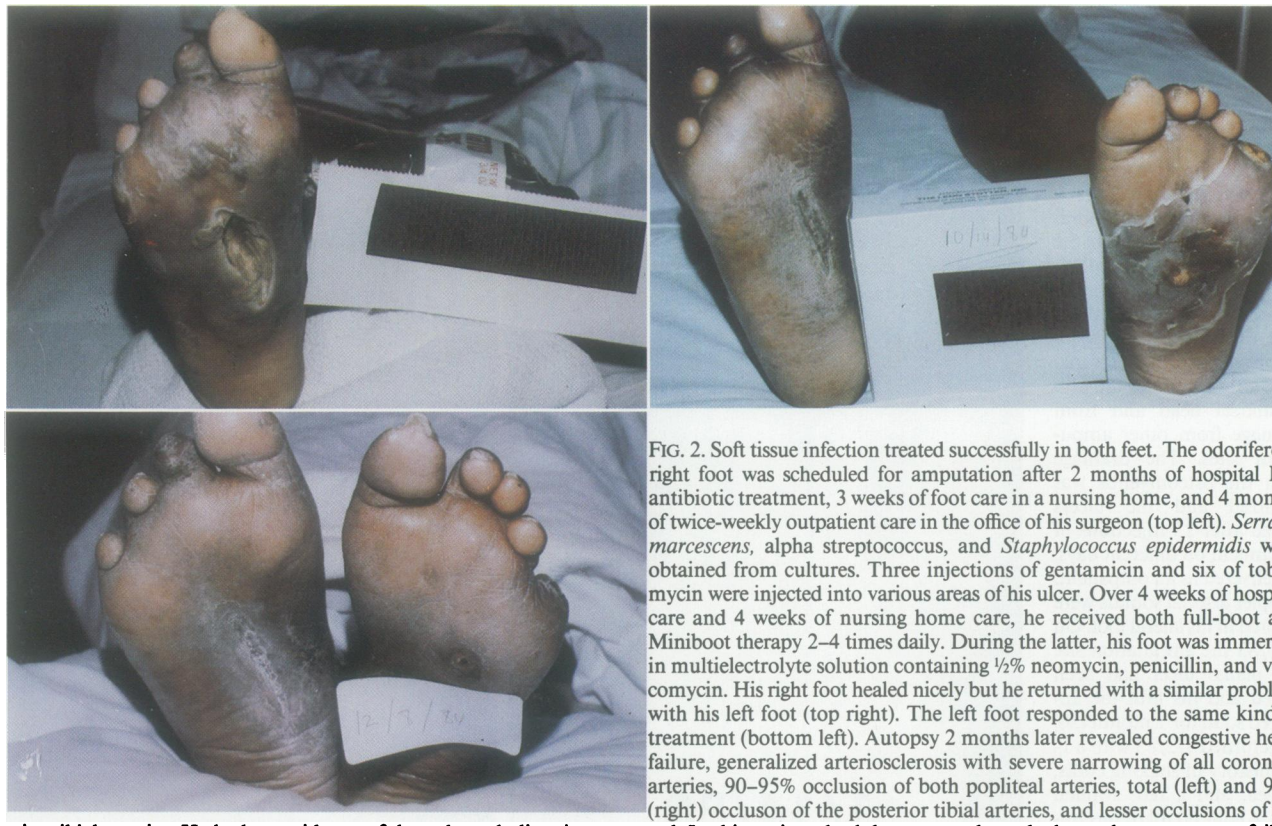


FIG. 2. Soft tissue infection treated successfully in both feet. The odoriferous right foot was scheduled for amputation after 2 months of hospital I.V. antibiotic treatment, 3 weeks of foot care in a nursing home, and 4 months of twice-weekly outpatient care in the office of his surgeon (top left). *Serratia marcescens,* alpha streptococcus, and *Staphylococcus epidermidis* were obtained from cultures. Three injections of gentamicin and six of tobramycin were injected into various areas of his ulcer. Over 4 weeks of hospital care and 4 weeks of nursing home care, he received both full-boot and Miniboot therapy 2–4 times daily. During the latter, his foot was immersed in multielectrolyte solution containing ½% neomycin, penicillin, and vancomycin. His right foot healed nicely but he returned with a similar problem with his left foot (top right). The left foot responded to the same kind of treatment (bottom left). Autopsy 2 months later revealed congestive heart failure, generalized arteriosclerosis with severe narrowing of all coronary arteries, 90–95% occlusion of both popliteal arteries, total (left) and 95% (right) occluson of the posterior tibial arteries, and lesser occlusions of the anterior tibial arteries. He had no evidence of thromboembolism in any vessel. In this patient, both legs were salvaged when other treatments failed. His cardiac status likely would not have allowed surgery had it been possible.

ratios of greater than 50%, and two of the patients had ankle blood pressures of greater than 100 mmHg in at least one tibial vessel. Gibbons et al. reported similar results. They found that segmental pressure measurements and pulse volume recordings, which included the forefoot, were misleading in many of their amputation cases in diabetic patients and emphasized the importance of clinical judgment in choosing amputation sites.[14]

Although studies such as this in patients with end-stage disease may be said to suffer from a lack of internal controls, the five features listed by Bailar et al.[15] are found here:

(1) The investigator should express before the study that the treatment will affect disease outcome. Both patients and referring physicians were advised before the study that the treatments were likely to affect patient outcome.

(2) The data analysis should be planned before the data are generated. For this report, pertinent vascular data and photographs were obtained both before and after treatment.

(3) The investigator should articulate a plausible hypothesis before the results are observed. The means whereby boot therapy benefits peripheral blood flow have been previously published[7] and the means whereby local administration of antibiotics achieves effective local levels of antibiotics needed no explanation even for patients who accepted it as obvious.

(4) The study results should be of some interest even if "negative" or "opposite" findings are achieved. This report would still have been of some interest had negative results been found: either boot therapy might have proved useless or the local injection of antibiotics ineffective or hazardous.

(5) Lastly, there should be reasonable grounds for generalizing the results of the study to a broader group of patients. The results of this study extend the limited observations of others on the effectiveness of local therapy.[1–4] Further experience may justify the recommendation that local therapy be used in the care of other tissues and organs.

The economic benefits of the described methods might be emphasized. Hospitalization was avoided in the nine patients who were treated as outpatients. The administration of local antibiotics required the presence of the physician but required less antibiotic and no I.V. apparatus, no I.V. team, and no serum determinations of antibiotic levels. The local approach was faster; sterilization of the

ulcers was commonly seen within a few days when conventional treatment had failed over several days to weeks. The avoidance of leg amputation also obviously spared the patient and society major expenses. The prolonged hospital stays for diabetic patients after major amputations have changed little over the years. Cameron et al.[16] reported in 1964 that their patients required 77 postoperative days after above-the-knee (AK) amputation and 55 days after BK amputation. Ecker and Jacobs[17] found their patients required 5.9 postoperative hospital months after AK amputation and 6.7 months after BK amputation if no further surgery was performed. Hayes and Middleton[18] reported in 1981 that the mean postoperative stay for their diabetic and nondiabetic patients was 65 days. The mean ± SD length of hospital stay for my boot patients, who were spared amputation at discharge, was 25.3 ± 14.0 days. The length of hospitalization was in part decreased by our outpatient program and by transfer of chronic patients to a nearby nursing facility that is equippped with a compression boot service. For patients who were referred from a distance, overall costs would have been further reduced if our treatment methods had been available at their local hospitals.

Diabetic patients with nonhealing foot ulcers and peripheral ischemia are commonly urged to undergo arterial bypass surgery.[19,20] There are no controlled studies to justify such surgery. This report involving patients with advanced ischemia not amenable to vascular surgery shows that: (1) bypass surgery is not indicated in all such patients; (2) osteomyelitis in the foot of a patient with ischemic diabetes is not an absolute indication for surgery or amputation; and (3) advanced soft tissue suppuration need not spell amputation. Both osteomyelitis and soft tissue infections can be successfully treated without any surgical interventions, in some cases even in an outpatient setting. The techniques described saved legs for which amputations had been advised elsewhere.

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