Advances in Skin & Wound Care

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[FEATURES: ORIGINAL INVESTIGATION]
Managing Lower-Extremity Osteomyelitis Locally with Surgical Debridement and Synthetic Calcium Sulphate Antibiotic Tablets

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Author Information

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The author discloses that he discusses the off-label usage of calcium sulphate tablets, which are approved for use as a bone void filler in orthopaedic, oncologic, and infection surgical cases.
The use of the antimicrobial is physician choice and off-label.

ABSTRACT

OBJECTIVE: The objective of the study was to determine if the use of locally implanted, synthetic calcium sulphate tablets, impregnated with antibiotics, can heal lower-extremity osteomyelitis, without the use of oral and/or intravenous antibiotics or wound complications associated with similarly used mined or refined calcium sulphate.

PATIENTS: Over a 5-year period, 354 patients with clinically confirmed osteomyelitis of the lower extremity were evaluated, and 337 met the inclusion criteria; 14 were lost to follow-up.

METHODS: Devitalized or infected bone was debrided to the level of healthy cancellous and cortical bone. Compromised soft tissue was resected. At the onset of each operative encounter, the synthetic calcium sulphate tablets were mixed with a standard antibiotic mixture: 500 mg of powdered vancomycin mixed into 240 mg of gentamicin (normally supplied as a liquid in a concentration of 80 mg/2 mL). Vancomycin and gentamicin were chosen because they cover a broad spectrum of both gram-positive and gram-negative bacteria.

RESULTS: A total of 279 of 323 patents (86.4%) clinically healed without the use of intravenous antibiotics following surgical debridement and tablet implantation. In addition, 24/323 (7.4%) required the use of intravenous antibiotics, but still healed; 20/323 (6.2%) required amputation, of which, 12 (3.7%) were digital amputations, 2 (0.6%) were ray amputations, and 6 (1.9%) were below-knee amputations.

CONCLUSIONS: The use of locally implanted antibiotic-impregnated, synthetic calcium sulphate tablets in the surgical debridement site for bone infections of the lower extremity, without the concurrent use of intravenous antibiotics, has shown encouraging results.

INTRODUCTION

The standard treatment of osteomyelitis in the lower extremity often includes the use of intravenous antibiotics. The effectiveness of an antimicrobial agent is dependent on its concentration in the affected tissue. Concentration is dependent on a number of factors, primarily vascular supply. Being a distal organ, the foot is often affected by vascular insufficiency. Among the many comorbidities contributing to vascular impairment and poor perfusion are diabetes, age, hepatic/renal disease, peripheral vascular disease, and a variety of metabolic diseases.[1]

The infusion of intravenous agents can lead to adverse affects, such as complications at the infusion site, lack of patient adherence, systemic drug toxicity, and dead space formation. This can also increase costs.[2] When the treatment is for superficial/periosteal osteomyelitis, the lack of soft tissue covering on the exposed bone further decreases the surface area needed for optimal absorption of the antibiotics.

The most common pathogens in diabetic osteomyelitis are gram-positive cocci; however, a variety of infectious organisms is often cultured.[3] Deep, soft tissue infections and osteomyelitis are often polymicrobial including aerobic gram-positive organisms, gram-negative bacilli, and anaerobes (anaerobic streptococci, Bacteroides fragilis group, Clostridium species). Staphylococcus aureus is also common as a single organism.[4] Infections of surgically implanted devices have been reported to occur up to 5% of the time, with the major pathogens being coagulase-negative staphylococci, S aureus, and other staphylococcal species.[5]

Although oral antibiotics are used successfully to treat soft tissue infections in the lower extremity, they often fail to achieve sufficient and consistent therapeutic levels, which then require the use of intravenous agents. They are selected by culture results and/or empiric choice, and serum levels are maintained. It is commonly accepted that 4 to 6 weeks of intravenous antibiotics be used in the treatment of osteomyelitis. Even after this prolonged treatment, recurrence of infection is not uncommon.[6]

Increasingly, biofilm formation within a wound and/or upon osseous structures has led to actual or apparent bacterial resistance to antimicrobials. According to Hadju et al,[7] a biofilm consists of a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to a surface Figure 1. Biofilm-associated infections are frequently resistant to conventional antimicrobial therapy, because the bacterial biofilm on the surface serves as a reservoir where bacteria are quasi-inaccessible to antibiotics and the host defenses.[7]

Figure 1. YELLOW FIBRIN AND SLOUGH BIOFILM COVERS FIRST METATARSAL HEAD

There is a debate about biofilm's role in drug resistance. Does biofilm create drug resistance, or does it merely establish a barrier between the antibiotics and the infectious organisms? Evidence has shown that high local levels of antibiotics can penetrate biofilm and successfully treat it.[8] The testing of tissue levels reveals that oral antibiotics are not strong enough to penetrate biofilm. Increasingly, it appears that intravenous agents also cannot penetrate biofilm [7]; however, this may be a result of inaccessibility to the bacteria.

Local delivery systems have been explored to minimize systemic toxicity and eliminate concerns about antibiotic penetration, while also achieving high local doses of antibiotics.[9] Jackson et al [10] reported that initial attempts at local implantation were not successful because of uncontrolled and rapid release of the antimicrobial agent at the target site.

Gentamicin-loaded polymethylmethacrylate tablets have been widely accepted as a local delivery system of antibiotics into infected tissue; however, Nuet et al [11] retrieved implanted polymethylmethacrylate beads (with gentamicin), and the cultures of the beads themselves revealed bacterial growth on 18 of 20 of them. Of the 28 strains cultured, 19 were gentamicin-resistant organisms. This finding suggests that the resistance may occur because the beads act as a biomaterial surface to which bacteria preferentially adhere.[11,12]

The use of silver-impregnated packing strips has been reported but has not been thoroughly investigated.[13] Antibiotics have been incorporated into absorbable internal fixation devices. These include polylactic acid and poly(dl-lactide)-coglycolide in varying ratios combined with vancomycin, clindamycin, and tobramycin. They have been shown to provide sustained antibiotic release for at least 68 days; however, they have a complete dissolution rate up to 180 days. This raises concerns of the foreign material being in the wound for 6 months, as well as the possibility of bacterial resistance from low-grade levels of the antibiotic after initial surge and release.[14]

Calcium sulphate has been used as a bone graft substitute since the late 1800s. In 1977, a medical-grade calcium

sulphate impregnated with tobramycin was introduced commercially overseas.[15] The advantages of calcium sulphate over other antibiotic delivery systems include its biodegradability, its predicable elution characteristics, its osteoconductivity, and its ability to fill dead space.[15,16] It has been reported that elution levels of antibiotic from calcium sulphate have surpassed 200 times the minimal inhibitory concentration for specific organisms over a minimum of 14 days. Even when large doses of calcium sulphate have been implanted (50 mL calcium sulphate, 5 g vancomycin, and 2.4 g tobramycin), serum levels of calcium sulphate and antibiotics were not detected throughout the treatment process.[17]

Synthetic calcium sulphate was introduced in 2000 as a 100% pure, synthetic, biocompatible bone graft material with the absence of any traces of toxic impurities. Such impurities have been associated with the complications of mined and refined calcium sulfate.[18]

Elution of antibiotics from implanted synthetic calcium sulphate tablets has been shown to be predictable. The studied antibiotics include vancomycin, amikacin, moxifloxacin, gentamicin, fusidic acid, and daptomycin.[2,10,17-19] Detectable amounts of antibiotic in the wound serum have been seen in as little as 6 hours. During in vitro testing, elution has been shown to last 28 days.[19] Clinical experience has revealed a longer time frame if the tablets are not completely covered by soft tissue.

When stored under normal room temperature and ambient humidity, antibiotic-impregnated calcium sulphate tablets appear to maintain their antimicrobial characteristics for at least 120 days.[20]

Initial success with the use of implanted calcium sulphate tablets, with and without antibiotic impregnation, has been met with reports of significant effusion leading to wound complications. Several theories exist as to why there is excessive effusion from mined and refined calcium sulphate tablets. They include (1) the presence of regular, prism-shaped crystals; (2) the formation of a calcium-rich fluid upon degradation; (3) osmotic effects; and (4) the presence of impurities in the calcium sulphate itself.[21-24] Lee et al [21] have described this type of effusion as a white, foamy fluid seeping out of the wound. When cultured, the Gram stain was negative for bacteria but did show inflammatory cells.[21] A microstructure analysis report revealed that contaminants found in mined and refined calcium sulphate bone void filler products include potassium sulphate, cristobalite, gypsum, and quartz as well as detectible levels of calcium sulphate anhydrite (the preferred form being hemihydrate). It may be that the wound complications associated with mined and refined calcium sulphate decrease when using synthetic calcium sulphate without these impurities.

CLINICAL INVESTIGATION

The objective of the author's study was to determine the safety, clinical outcomes, and systemic antibiotic requirements associated with managing lower-extremity osteomyelitis using antibiotic-impregnated synthetic calcium sulphate tablets implanted locally after surgical resection of devitalized tissue and to determine if the use of systemic antibiotics can be reduced.

PATIENT AND METHODS

This retrospective study included patients with intact local perfusion and osteomyelitis that was not responding to

previous or ongoing treatment. These treatments included oral and/or intravenous antibiotics, local wound care, offloading where indicated, appropriate dressings, negative-pressure wound therapy (NPWT), and/or management of comorbidities. A majority of these patients were referred from outside sources; therefore, pre-evaluation treatment could not be standardized.

Osteomyelitis was diagnosed by plain film, magnetic resonance imaging, computed tomography, and/or direct bone biopsy. In each case, resected bone was shown to have changes consistent with osteomyelitis upon microscopic examination.

Patients who met inclusion to this study had (1) intact vascular status. This was determined by either palpable pulses with evidence of intact local perfusion, ankle-brachial indices greater than 0.7, or transcutaneous oxygen measurement readings of greater than 40 mm Hg within 1 cm of the wound/surgical site(s); (2) confirmation of osteomyelitis by microscopic examination of resected bone; (3) ability to give informed consent; and (4) able to have affected the area offloaded.

Patients who were excluded from the study were those who had active peripheral vascular disease, had active Charcot foot, were unable to be offloaded as instructed, and exhibited sepsis or other infected site not on the lower extremity.

SURGICAL TECHNIQUE

Following induction of general anesthesia or conscious sedation,a local block of 1% lidocaine (plain) was administered either proximal to the involved area(s) or by regional (popliteal or ankle) block. The author prefers to prepare only the periwound area with an antimicrobial scrub and not the wound itself. This is to ensure accurate identification and antimicrobial sensitivities of infecting organism(s). The use of a tourniquet (ankle or thigh) is the choice of the surgeon, taking into account the type of anesthesia, level of perfusion, patient use of anticoagulants, and pertinent medical history, for example, sickle cell disease or history of previous deep vein thrombosis or phlebitis.

Devitalized or infected bone was debrided to the level of healthy cancellous and cortical bone. Compromised soft tissue was resected. Wide resection of bone with an extra 2- to 3-mm resection to expose healthy bone was performed even if some of the normal bone was lost.[25] Edges were sent for histological examination to verify that enough bone had been resected. Power irrigation and debridement systems were used to remove as much devitalized tissue as possible.[2]

At the onset of each operative encounter, the synthetic calcium sulphate tablets were mixed with a standard antibiotic mixture: 500 mg of powdered vancomycin mixed into 240 mg of gentamicin (normally supplied as a liquid in a concentration of 80 mg/2 mL). Vancomycin and gentamicin were chosen because they cover a broad spectrum of both gram-positive and gram-negative bacteria. After pouring the vancomycin into a sterile cup, the liquid gentamicin was added and thoroughly mixed until all of the vancomycin dissolved. Next, 10 mL of synthetic calcium sulphate powder was added and mixed to a uniform paste consistency acceptable for spreading onto the tablet template provided. This mixing procedure enabled the tablets to set in less than 10 minutes, depending on ambient

temperature and humidity. Generally, anywhere from 5 to 20 mL of synthetic calcium sulphate is needed for a foot or ankle procedure; however, the use of 60 mL has been reported for larger orthopaedic procedures such as in the femur.[17,26]

The author believes that tablets of uniform shape are not necessary and that tablets of different shapes and sizes, as well as wafer-like pieces formed by using the flat portion of the mold, allow for easier packing into the wound and better elution characteristics.

In cases where vancomycin and/or gentamicin were not clinically indicated, or the patient had a known allergy/sensitivity, other antibiotics were used as listed in Table 1.

Single Antimicrobial Agents	Combined Antimicrobial Agents
Amikacin	Gentamicin/cefazolin[a]
Amphotericin B	Vancomycin/amikacin
Cefazolin[a]	Vancomycin/amphotericin B
Cefotaxime	Vancomycin/fluconazole
Ciprofloxacin	Vancomycin/gentamicin[a]
Clarithromycin	Vancomycin/gentamicin/amphotericin B
Fluconazole	Vancomycin/piperacillin-tazobactam
Gentamicin[a]	Vancomycin/tobramycin
Meropenem	Vancomycin/tobramycin/amphotericin B
Rifampin	
Tobramycin	
Vancomycin[a]	

[a]Used in the present cohort.

Table 1. SINGLE AND COMBINED ANTIMICROBIAL AGENTS THAT READILY SET WHEN MIXED WITH SYNTHETIC CALCIUM SULFATE

Following the resection of devitalized bone and/or soft tissue, the wound was flushed with sterile saline solution (with or without antimicrobial agent added) and suctioned. The tablets were released from the mold into a sterile basin and inserted, usually one at a time, into the wound. Starting at the deepest aspect of the wound, the tablets were gently packed to above the skin surface using a hemostat, a spatula, a trephine, and an osteotome. This created a visible trail from the exterior of the wound (Figure 2A and B), carefully minimizing dead space, particularly deep in the wound. Although the amount of material used may be more than previously reported, the synthetic calcium sulphate will help stabilize the local wound environment, and fluid egress is easily managed, to the point that a majority of postoperative secondary dressings used are normally a hydrogel to hydrate the wound and not one that absorbs wound drainage, such as a silver alginate.

Figure 2. VISIBLE TRAIL OF TABLETS FROM (A) FIFTH DIGIT AND (B) FIFTH METATARSAL HEAD

The wounds were not primarily closed to allow for minor drainage expected with the synthetic calcium sulphate. Retention sutures (3-0 or 4-0 nylon) were used when possible to approximate wound edges. Primary dressings were selected to accommodate for egress of drainage, permit regular changing of the secondary dressing(s), keep the tablets in place, and allow the clinician to examine the wound (Figure 3A and B). The author applied an antimicrobial barrier dressing containing silver as a primary dressing sutured in place with a secondary silver alginate to manage moderate to severe drainage, and a primary soft silicone wound contact layer 3 covered with a hydrogel-impregnated gauze secondary dressing to manage mild to moderate drainage. All primary and secondary dressings were changed weekly or as indicated.

Figure 3. PRIMARY DRESSING HOLDS TABLETS IN PLACE (A) AND PERMITS EXAMINATION OF THE WOUND (B)

Successful treatment was considered achieved for osteomyelitis when the wound/ulceration had completely resurfaced, no clinical signs of infection were noted, and radiographic and/or monitored laboratory values (sedimentation rate, C-reactive protein, white blood count) returned to normal (Figure 4A, B, and C).

Figure 4. (A) INITIAL PRESENTATION OF WOUND WITH EXPOSED BONE AND NECROTIC TISSUE (B) 5 WEEKS AFTER TABLET IMPLANTATION (C) 7 WEEKS AFTER TABLET IMPLANTATION

RESULTS

Over a 5-year period, 354 patients with clinically confirmed osteomyelitis of the lower extremity were evaluated, and 337 met the inclusion criteria; 14 were lost to follow-up. A total of 279 of 323 patients (86.4%) clinically healed without the use of intravenous antibiotics following surgical debridement and tablet implantation. In addition, 24 of 323 (7.4%) required the use of intravenous antibiotics, but still healed; 20 of 323 (6.2%) required amputation, of which, 12 (3.7%) were digital amputations, 2 (0.6%) were ray amputations, and 6 (1.9%) were below-knee amputations (Figures 5-9. The author found no clinically evident difference in the amount of wound drainage between any of the individual or combination mixtures of antimicrobial agent and the synthetic calcium sulphate tablets and did not experience the complications previously described using mined and refined calcium sulphate sources. A wide range of antimicrobial agents have been successfully mixed with this synthetic calcium sulphate delivery system to form fully hardened tablets ready for implantation Table 1. This tablet form was exclusively used in this study. Prior to 2005, the author had attempted to use mined and refined calcium sulphate products but discontinued use because of excessive effusion leading to wound complications.
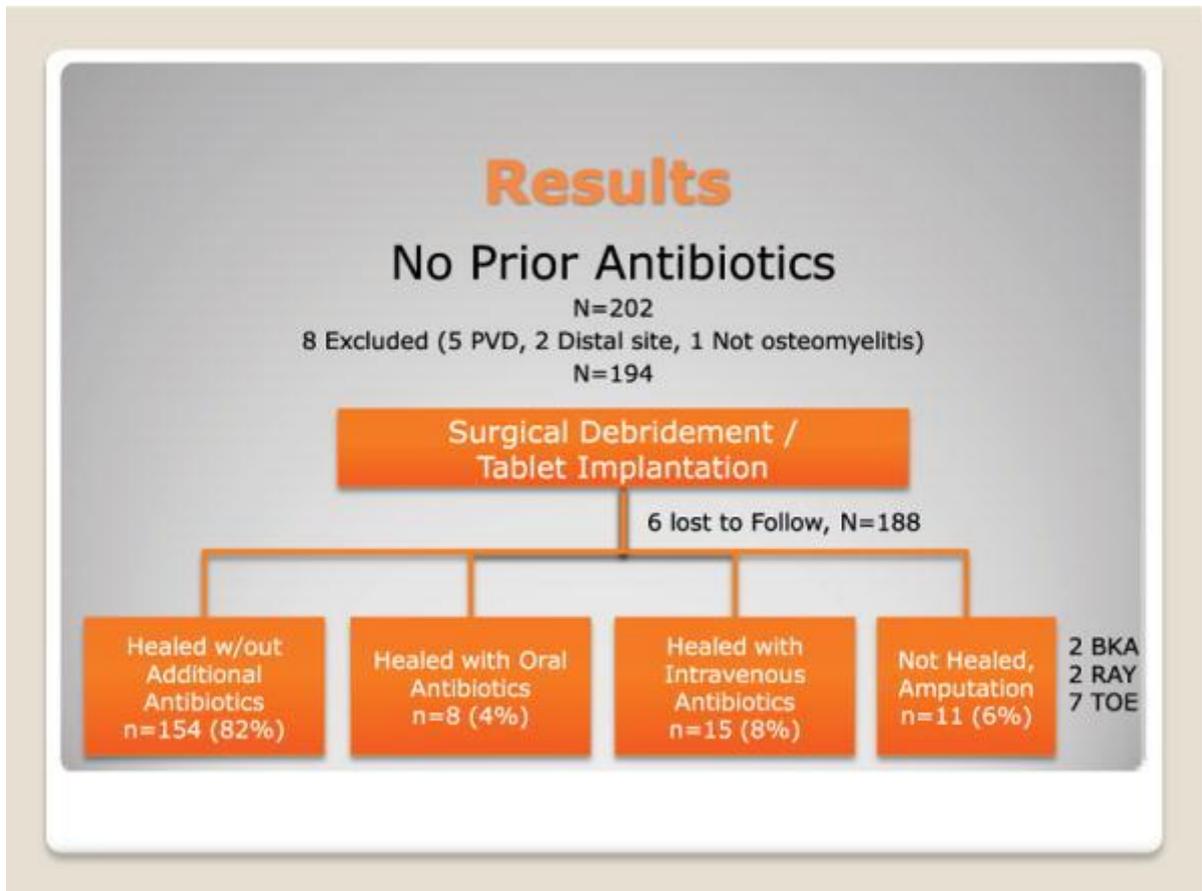
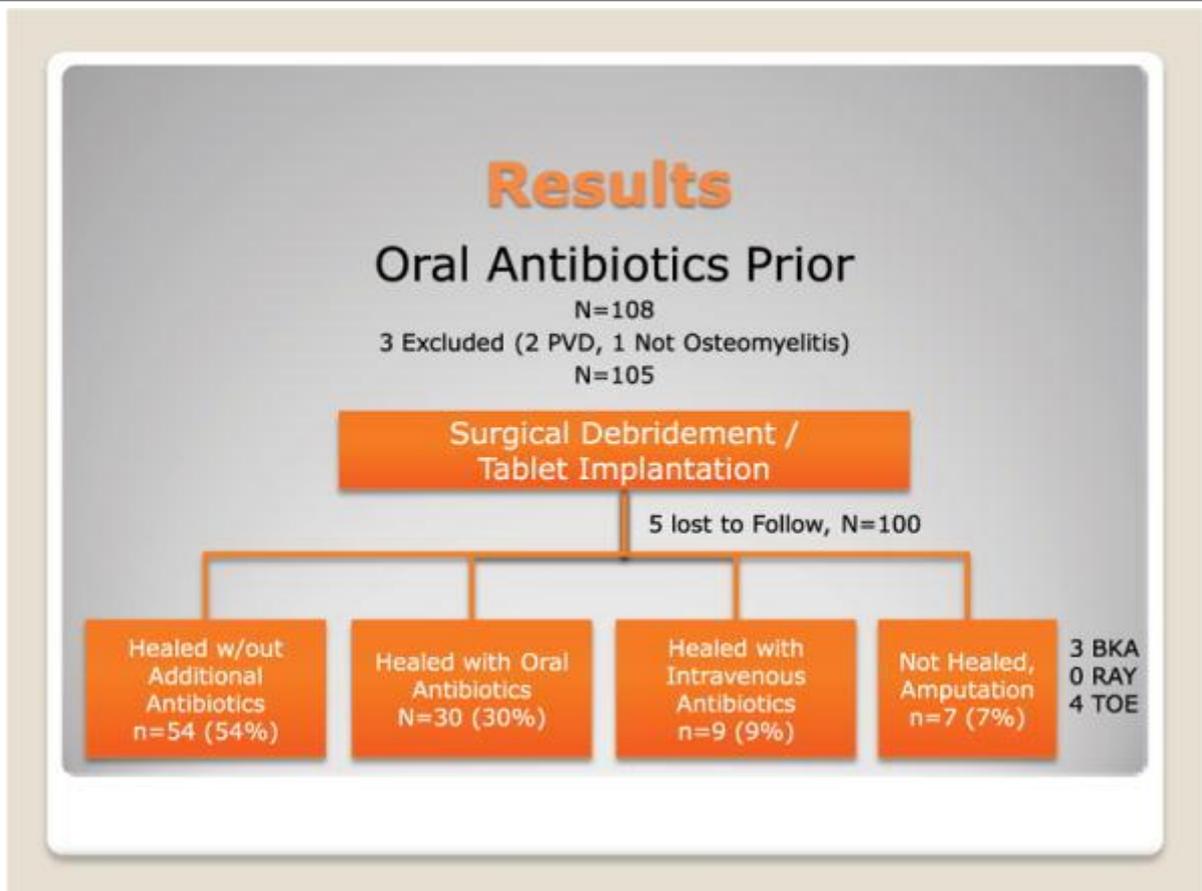Figure 5. CLINICAL OUTCOMES FOR PATIENTS WITH NO PRIOR ORAL OR INTRAVENOUS SYSTEMIC ANTIBIOTICS

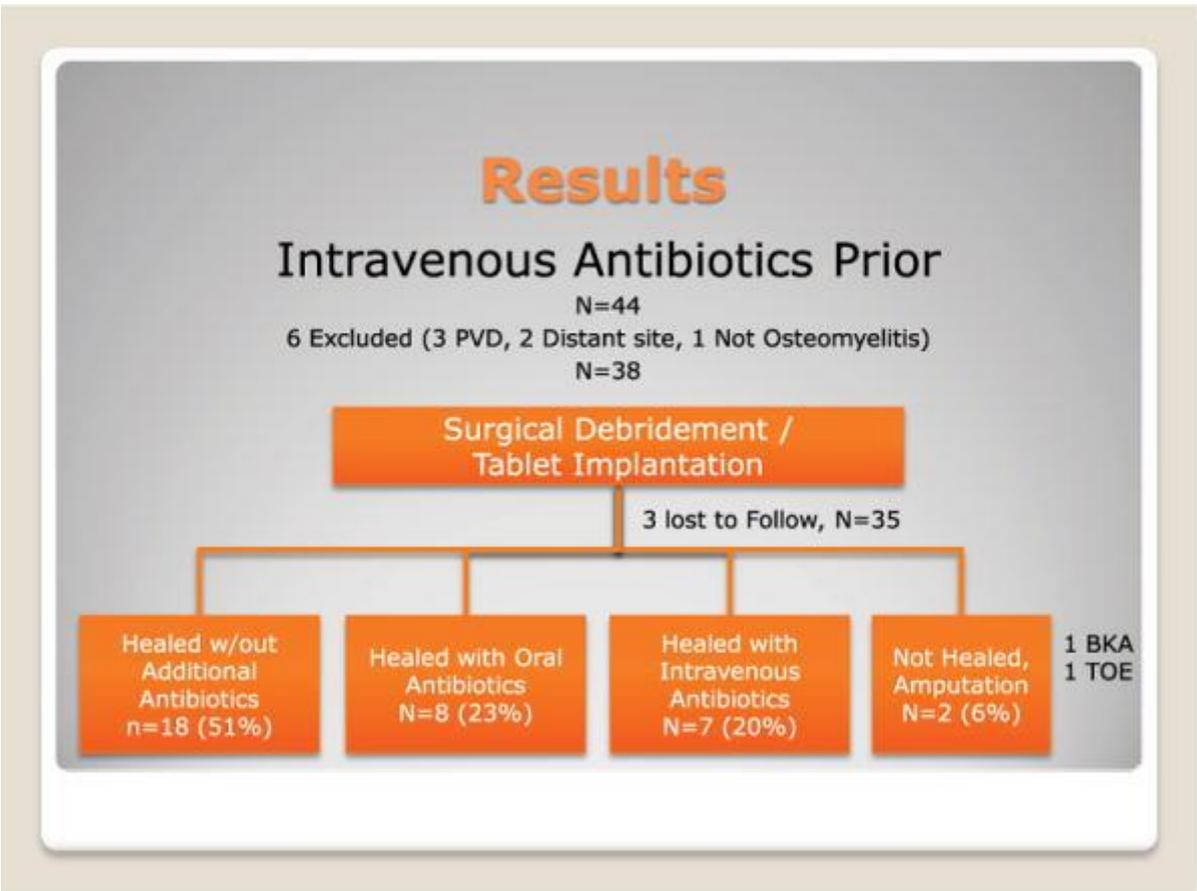Figure 6. CLINICAL OUTCOMES FOR PATIENTS WITH PRIOR INTRAVENOUS SYSTEMIC ANTIBIOTICS

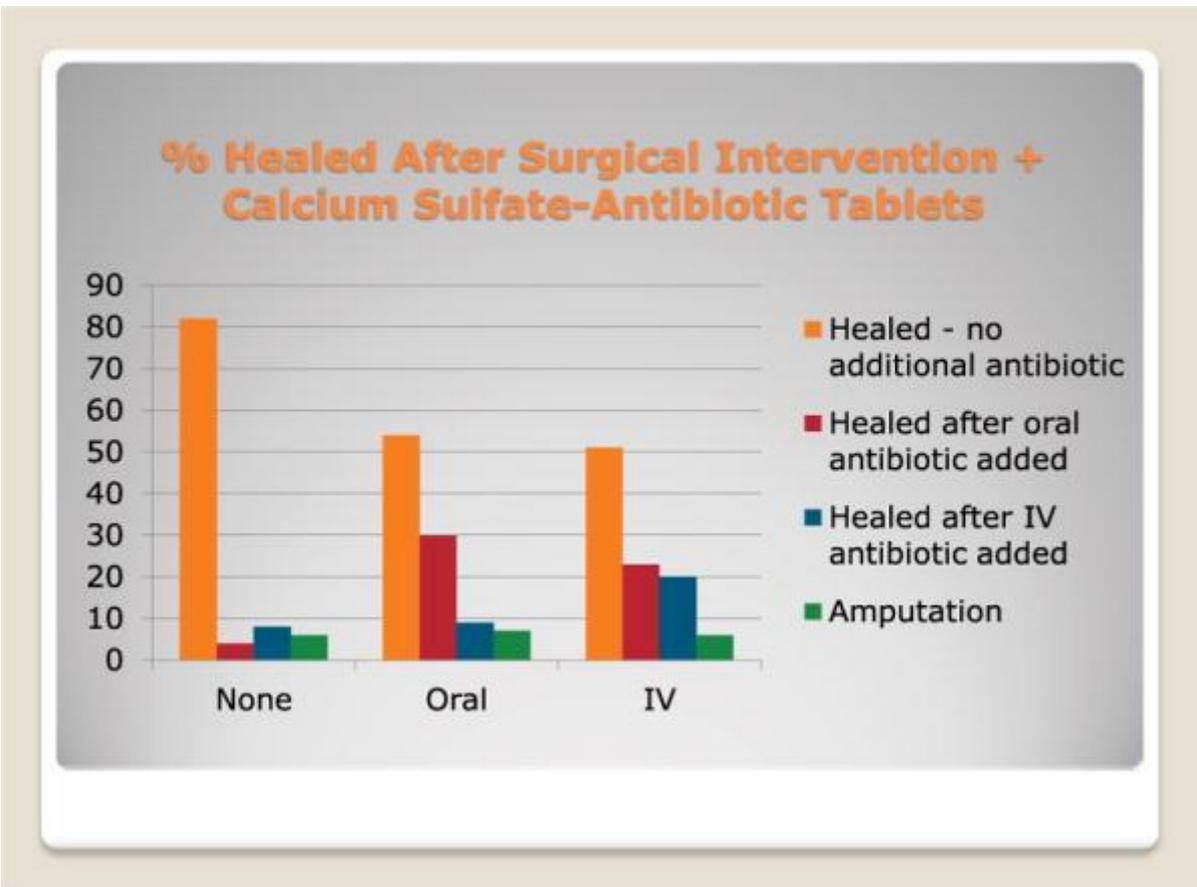Figure 7. CLINICAL OUTCOMES FOR PATIENTS WITH PRIOR INTRAVENOUS SYSTEMIC ANTIBIOTICS

Figure 8. PERCENTAGE OF ALL 323 PATIENTS WITH LOWER-EXTREMITY OSTEOMYELITIS WHO HEALED AFTER SURGICAL INTERVENTION FOLLOWED BY IMPLANTED CALCIUM SULFATE TABLETS IMPREGNATED WITH APPROPRIATE
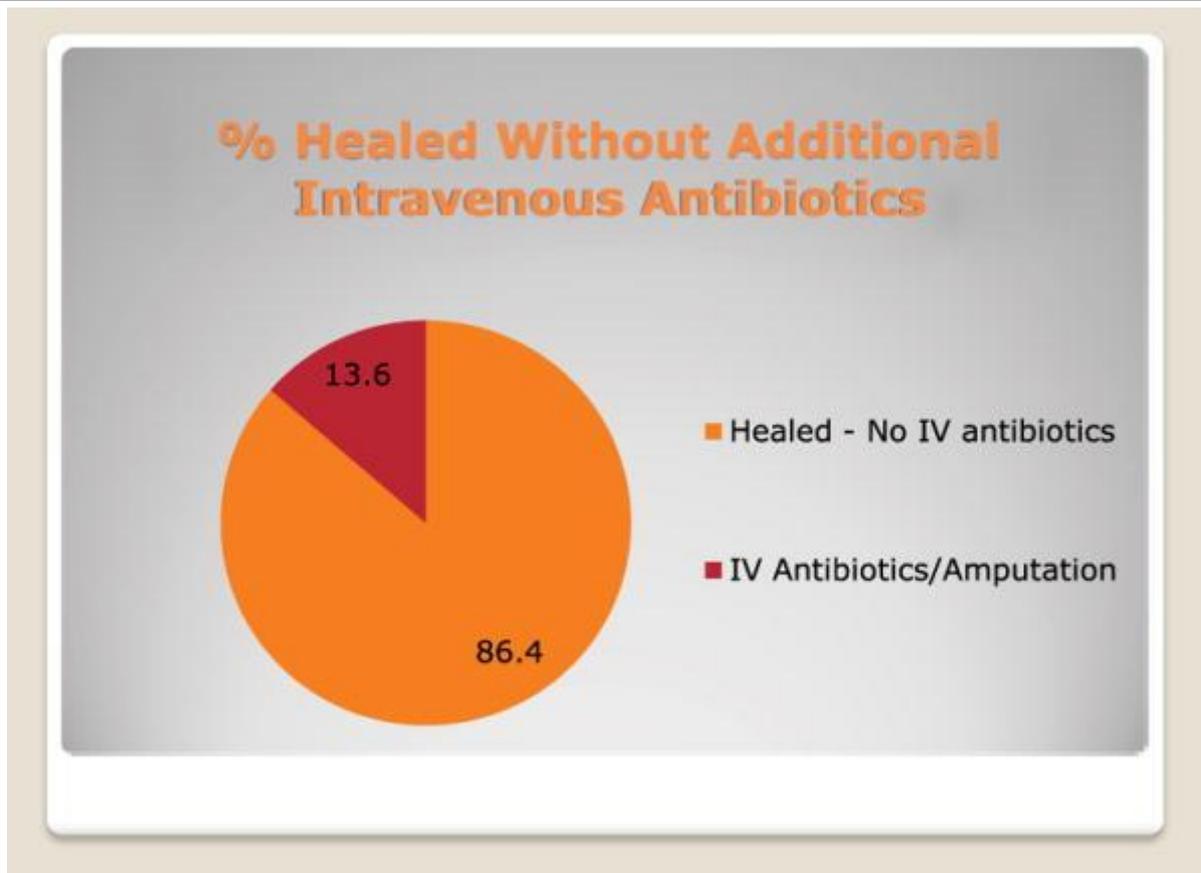
ANTIBIOTICS

Figure 9. PROPORTION OF ALL 323 PATIENTS WHO HEALED WITH NO INTRAVENOUS ANTIBIOTICS AND NO AMPUTATION OR WHO REQUIRED INTRAVENOUS ANTIBIOTICS AND/OR AMPUTATION

DISCUSSION

The goals of this treatment protocol are to eradicate infection, heal the ulceration/wound, and reduce or eliminate the need for intravenous antibiotics in the treatment of osteomyelitis in the lower extremity. Over the past 5 years, this treatment algorithm has proven successful for a majority of patients with this condition. It is also important to note that although not included in the outcomes provided in this article, the author's clinical team has also noted success in 26 patients with poor perfusion, those with ankle-brachial index less than 0.7, and/or those with transcutaneous oxygen readings less than 40 mm Hg. This is attributed to the high concentration of local antibiotic delivery (not possible by systemic means of delivery) and possibly the local effects of the synthetic calcium sulphate itself. These local effects include maintaining physiologic pH, filling in dead space, and less drainage from the wound compared with mined and refined calcium sulphate product. These results merit further study ([Figures 10A and B](#)).
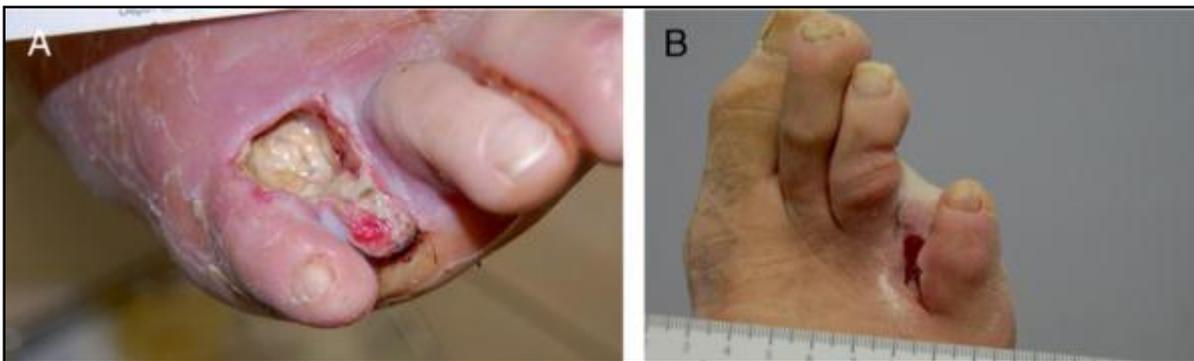

Figure 10. (A) 10 WEEKS AFTER AMPUTATION OF FOURTH DIGIT, NONHEALING WOUND WITH EXPOSED METATARSAL HEAD, BIOFILM, AND SLOUGH (B) 5 WEEKS AFTER TABLET IMPLANTATION

A concern when treating osteomyelitis is whether the infection has been completely eliminated, or it has just been placed in remission or slowed to the point where clinical symptoms are not experienced. Although in 8% of the cases reported, a second debridement and tablet implantation was performed (all within 30 days of initial debridement and implantation), the author has not seen any recurrence of osteomyelitis to any specific anatomical location to date, with the longest patient follow-up period recorded being 5.5 years.

The mixing of the synthetic calcium sulphate and antibiotics is straightforward. The choice of vancomycin and gentamicin as a standard preparation allows for empiric coverage of both gram-positive and gram-negative bacteria. This formula mixes easily and sets quickly, and its elution characteristics are predictable. When this treatment protocol was initially proposed and implemented, gentamicin was chosen because of its long record of use in polymethylmethacrylate beads. Vancomycin was then added to empirically treat gram-positive bacteria and methicillin-resistant S aureus in particular.

A question encountered was that if there were bone cultures available before the tablet implantation procedure-either by a previous surgical encounter or direct biopsy of bone-should the antibiotics mixed follow the sensitivity report provided? Initially, this was attempted. This led to the mixing of a variety of antibiotics with the synthetic calcium sulphate either alone or in combination. To be considered successful, the mixture needed to set in approximately 45 minutes or less. Several antifungal agents have also been successfully mixed and used in the

surgical setting. In most cases, vancomycin and gentamicin were indicated for antibiotic treatment.

Even with numerous and varied antimicrobial choices for mixture and implantation, a high rate of clinical success was seen with the vancomycin-gentamicin mixture. For a majority of the procedures performed (both in the initial stages of the algorithm and at the time of print), there were no bone biopsy microbiological sensitivities available prior to the procedure. Once bone biopsies were obtained, clinical healing was noted to have occurred even at times when the sensitivities may have shown that vancomycin and/or gentamicin were not ideal candidates for treatment. It is the author's belief that the high local levels of antibiotic provided better in vivo results than expected by empiric choice and/or microbiological sensitivities. As discussed earlier, some patients clinically worsened after 1 or more surgical debridements and tablet implantation. Before considering use of systemic antibiotics or amputation, if clinically acceptable improvement did not occur within 2 to 3 weeks after the implantation, it was assumed that unappreciated devitalized bone and/or soft tissue was still present and/or resistance of the infecting organisms was present. Any patient requiring a subsequent procedure had his/her antibiotic sensitivities obtained from the initial debridement more closely scrutinized and appropriate antibiotics chosen.

At this time, the author does not recommend the use of NPWT immediately after tablet implantation. It is believed that NPWT would remove too much of the antimicrobial agent from the wound. Perhaps a study comparing the drainage obtained from a NPWT system with that of wounds without its use would be beneficial to confirm this. If wound effusion indicates NPWT be considered, an oral or intravenous antibiotic and/or a subsequent surgical debridement (with close evaluation of microbiology sensitivities) may be warranted. There is no known contraindication for concurrent use of impregnated tablet therapy and hyperbaric oxygen therapy. It is the author's preference to initiate hyperbaric oxygen therapy only if the wound/osteomyelitis does not appear to be responding to current treatment.

CONCLUSION

The use of locally implanted antibiotic-impregnated, synthetic calcium sulphate tablets in the surgical debridement site for bone infections of the lower extremity, without the concurrent use of intravenous antibiotics, has shown encouraging results. Seventy percent of patients healed without needing systemic oral or intravenous antibiotics. Elution of antibiotic is predicable, and drainage is easily managed. Commonly available antibiotics are conveniently mixed with the calcium sulphate immediately prior to the procedure. The technique adds minimal additional operating/anesthesia time and risk and establishes a benchmark for clinical outcomes using locally applied antibiotics as an intervention to manage lower-extremity antibiotics.

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