

## DIABETIC INFECTIONS AND USE OF ANTIBIOTIC BEADS

*Allen Raphael, DPM*

*James L. Bouchard, DPM*

The diabetic infection is an entity encountered by countless health professionals on a daily basis and represents one of the most challenging, as well as costly, endeavors in medicine today.<sup>1</sup> As a disease that requires multidisciplinary involvement, we approach diabetes and its management with a cautious optimism, knowing the ramifications of neglecting this potentially debilitating condition. With the help of primary care physicians, endocrinologists, infectious disease specialists, vascular teams, and a variety of wound care modalities, the diabetic patient should be no stranger to the proverbial white coat. We are obligated to use the full spectrum of pharmacologic agents with this condition. The use of antibiotic impregnated beads in the management of the diabetic infection will be presented (Figures 1, 2).

The use of “bone cement” has roots as early as the 1930s, during which acrylic technology was developed as a dental grout. This method relies on the synthesis of resins derived from acrylic acid, to which a monomeric liquid is added to create a dough-like material that is easily molded. Later this technology evolved into polymethylmethacrylate (PMMA), which was commonly used in dental applications and cranioplasty during World War II. Initially developed in the 1950s by Sir John Charnley, PMMA was used for orthopedic fixation of femoral head prostheses to femoral shafts in the 1960s (Figures 3, 4).<sup>2</sup>

Presently, a variety of commercially available PMMA based beads are manufactured in the US and worldwide. Preparation of antibiotic beads involves a kit containing individually packaged powder and liquid, which are typically sterilized with gamma irradiation and ultrafiltration. Smith and Nephew's Palacos R cement uses ethylene oxide gas for sterilization of these separate components.<sup>2</sup> Packaged powder contains PMMA as its primary constituent, whereas the liquid vial contains the monomer subunit, methylmethacrylate. The powder will generally contain an initiator of polymerization, benzoyl peroxide, and a radio opaque substance, or opacifier, either barium sulfate or zirconium dioxide. The properties of individual bone cement are determined by additional agents that prevent premature polymerization, protect against degradation during the sterilization process, or coloring agents such as chlorophyll or methylene blue.<sup>2</sup>

PMMA has undergone intense scrutiny in regard to its mechanical properties and for its potential adverse effects after implantation. Various studies have been conducted designed to test its static and dynamic material properties, both in situ and using cadaveric specimens via tensiometry readings. Static mechanical properties include compressive, tensile, and shear and involve placing a single, axially oriented load to a cylindrical plug of the material tested. Dynamic material properties are determined using frequent application of submaximal loads, which is

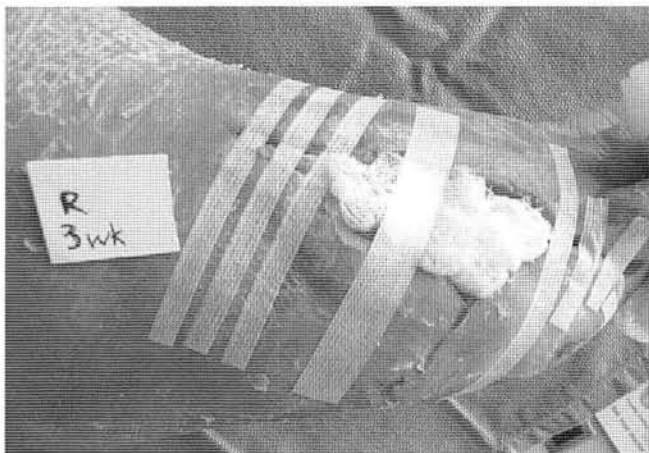


Figure 1. Diabetic foot infection.

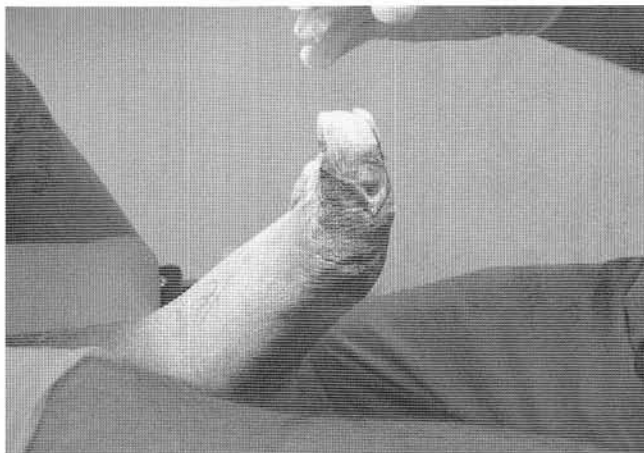


Figure 2. Diabetic foot infection.

thought to more closely correlate to physiologic stresses.<sup>2</sup> Factors such as temperature, aging properties of the material and most importantly, the preparation of PMMA during mixing, will affect the porosity of the cement.

The choice to use antibiotic impregnated beads is ultimately the choice of the treating physician, but certain criteria must be acknowledged before their use. In patients with active osteomyelitis, the ability to provide adequate concentration of antibiotic to the desired site is paramount to successful resolution of infection. Adequate debridement must be performed prior to implantation, and resection of necrotic bone and soft tissue is

recommended to decrease the bacterial load. Ultimately, the dead space created following many of these debridements will provide a scaffold in which beads may deliver their antibiotics. (Figures 5-8)

The patient's vascular, renal, and hepatic status should also be evaluated before choosing the antibiotic delivery system, as peripheral vascular disorders will decrease the ability of any pharmacologic agent to exert its effects. Impaired renal function will require dosing at which adequate antibiotics may not be achieved. Initially, the minimum inhibitory concentration (MIC) of locally delivered antibiotics will far exceed that of traditional

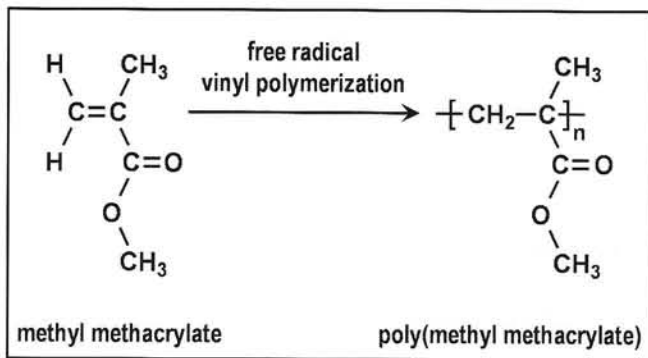


Figure 3. Free radical vinyl polymerization.

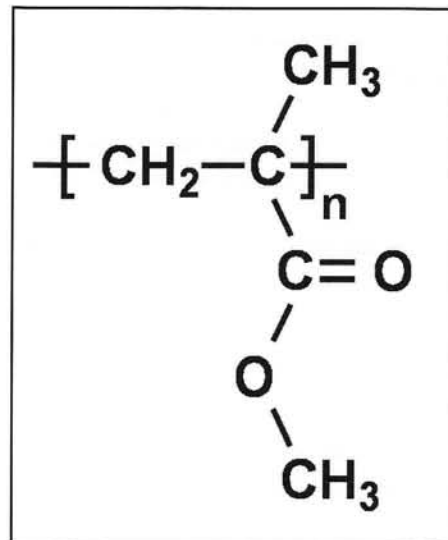


Figure 4. Poly (methyl methacrylate).

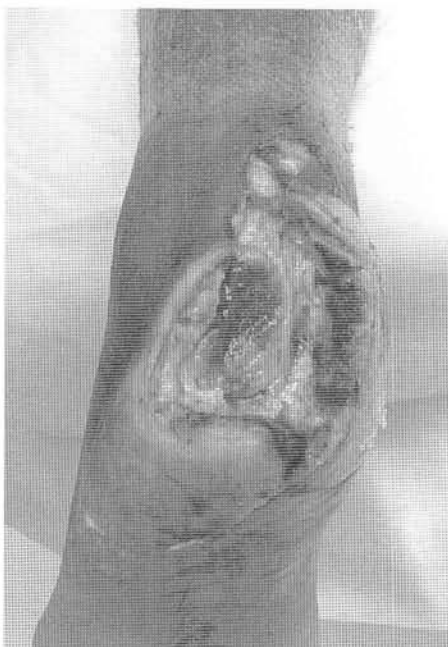


Figure 5. Long standing severe diabetic infection.



Figure 6. Surgical debridement and dead space create a scaffold for antibiotic beads.

intravenous or oral routes, and in the presence of impaired renal or hepatic function, may yield fewer systemic side effects.

The addition of antibiotics to the PMMA compound will ultimately affect the integrity of the material as well, with several studies indicating that voids created by antibiotic particles are to blame. The most commonly used antibiotics used include vancomycin, tobramycin, gentamycin, and metronidazole. Primarily of concern are the elution patterns of various powdered antibiotics from the beads and effects on mechanical properties. Elution characteristics of individual antibiotics have been studied using metronidazole, gentamycin sulfate, and combinations of the two. It was shown that individual elution characteristics are similar in the first day, during which 50% occurred in the first hour, while metronidazole was shown to display dose dependent results and delay polymerization.<sup>3</sup> Combination of the two antibiotics yielded significantly higher rates of elution than of either singular addition.

Choosing the vehicle on which these medicines will be delivered is as vital to successful resolution of infection as the appropriate antibiotic. Authors point out that the exothermic reaction of PMMA polymerization has been shown to denature the molecular structure of antibiotics during loading, sometimes yielding as low as 5% release ratio.<sup>4</sup> Several studies were conducted to investigate other compounds that may provide better elution properties and

avoid the need for bead removal. Typically, traditional PMMA beads require removal after 10-14 days, after which additional cultures are taken to confirm resolution of infection. Studies by Neut et al demonstrated that gentamycin-loaded PMMA beads act as a biomaterial surface to which bacteria preferentially adhere, grow, and develop antibiotic resistance.<sup>5</sup>

Researchers now are studying new compounds that would locally deliver antibiotic therapy while decreasing the incidence of low biocompatibility, low release ratio, and possible thermal damage. Two studies on the effectiveness of calcium hydroxyapatite show that it may be a better alternative than the traditional PMMA bead. Hydroxyapatite (HA) blocks impregnated with antibiotic have shown to have excellent biocompatibility, can resist mechanical forces, have no risk of thermal damage, and are incorporated into the adjacent osseous structures, thus negating the need for a second surgery.<sup>4</sup> Studies using rabbit specimen actually yielded better results with HA vancomycin blocks than with PMMA vancomycin beads (81.8% vs. 70% clearance rate).<sup>6</sup> One author does note that the release of antibiotic from the HA block fell below detectable levels after 28 days, as compared with an apatite-wollastonite glass ceramic (A-W GC) which maintained up to 42 days (Figures 9, 10).<sup>4</sup>

Biodegradable calcium sulfate beads have been used in Britain as early as 1892 and according to Wichelhaus et al, are a viable alternative to PMMA.  $\text{CaSO}_4$  was shown

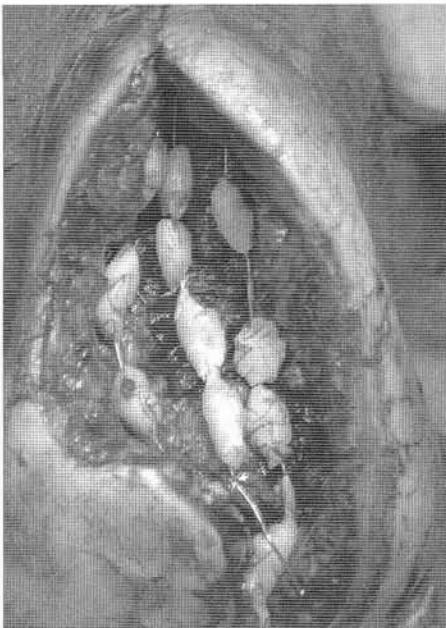


Figure 7. Dead space filled with antibiotic beads.



Figure 8. Final wound.

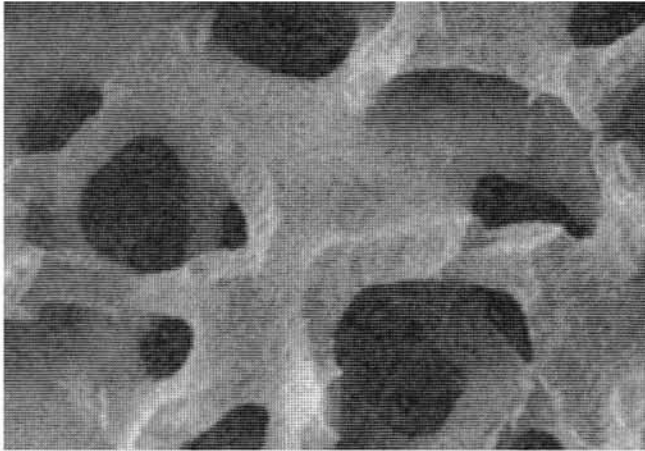


Figure 9. Calcium hydroxapatite is a better alternative to traditional PMMA.

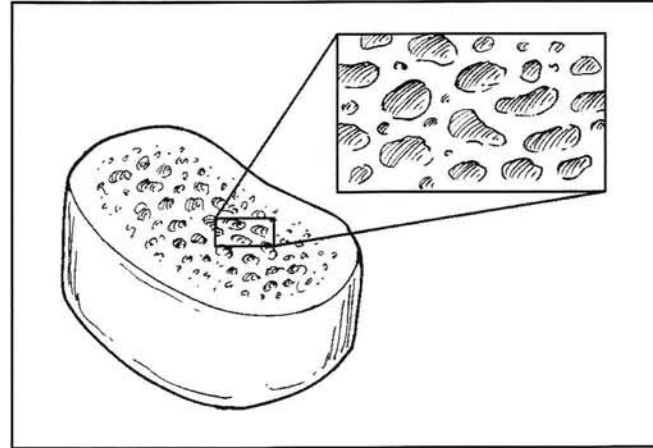


Figure 10. Biodegradable calcium with sulfate is viable alternative to PMMA.

to have a prolonged release time of antibiotic as compared with PMMA, as well as biodegradability and the ability to use a variety of antibiotics including vancomycin, teicoplanin, gentamycin, and clindamycin.<sup>7</sup> Researchers have also explored the use of polycaprolactone tobramycin-impregnated rods, which yielded comparable results to that of PMMA rods.<sup>8</sup> Finally, polylactic acid (PLA) and poly(DL-lactide) coglycolode (PL:CG) have been shown in studies to display better elution properties and biodegradability as compared with PMMA beads.<sup>9</sup>

Management of the diabetic infection is a difficult task, one that requires the physician to call upon all pharmacologic therapies available. At present, companies such as KCI™ are introducing systems named Instill™ that incorporate wound V.A.C. technology coupled with local delivery of liquid antibiotic to the site of infection. An ingress/egress system allows for timed, dose-specific administrations of the antibiotic of choice, again providing the physician with yet another option for local administration of pharmacologic agents. We stand poised to take the next step in management of diabetic infection with ground-breaking technologies from which our patients will ultimately benefit.

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