Applications of Local Antibiotics in Orthopedic Trauma

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KEYWORDS

• Infection • Trauma • Local • Antibiotics • Bead • Prophylaxis

KEY POINTS

- Local antibiotics have the advantage of high local concentrations (thus efficacy at the surgical site), and low systemic concentrations (less risk of systemic side effects).
- Local antibiotics have been proven effective for infection prophylaxis and treatment of established infection, and are typically used in concert with systemic antibiotics.
- Multiple delivery systems are available for antibiotic delivery, with each having unique properties that may be advantageous.
- Antibiotic delivery from PMMA is highly variable and depends upon: surface area (bead size), antibiotic used, number of antibiotics, mixing technique, time since implantation, Fluid characteristics around the beads, and others.
- Aqueous antibiotic solution injected locally after wound closure is a simple delivery method that has demonstrated positive results in animal and clinical models.

INTRODUCTION

Local antibiotic use began more than 100 years ago with Joseph Lister, who pioneered safe, antiseptic surgery. Before Lister's innovations, as many as 80% of all operations were complicated by infection. He was the first to apply local antiseptics, including carbolic acid, to surgical wounds to treat open fractures.[1] This led to further use of local antiseptics by Fleming during World War I, and in 1939 with Jensen instilling sulfanilamide crystals as local antibiotic in open fractures for infection prevention.[2,3] Despite significant advances in the use of prophylactic antibiotics and perioperative protocols, orthopedic surgical site infections still remain a significant source of morbidity and mortality and result in a substantial financial burden to the health care system. Surgical site infections are the second most common cause of nosocomial infections in extra-abdominal surgeries, with an incidence of 2% to 5%,[4,5] and approximately 5% of orthopedic internal fixation implants becoming infected. The rate of infection following internal fixation of closed fractures is generally much lower than that of open fractures, with open fractures approaching 30%. Despite the higher infection rate seen in the treatment of particular fractures compared with arthroplasty, there is much less literature available on the prophylactic use of local antibiotics for infection prevention in open and closed fracture treatment.[6–8]

Local antibiotics provide high local concentrations with lower systemic levels than parenterally administered antibiotics. The delivery of local antibiotics can both supplement and sometimes obviate the need for systemic antibiotics. In certain instances, the target area of treatment may be avascular, preventing systemic antibiotics from reaching the targeted site. In these scenarios, local

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Orthop Clin N Am 46 (2015) 495–510
http://dx.doi.org/10.1016/j.ocl.2015.06.010
0030-5898/15/$ – see front matter

antibiotics may serve as the only effective option in treating the infection. Perhaps the main advantage of local antibiotic therapy is the ability of an antibiotic to reach a high local concentration while simultaneously having a low or undetectable systemic concentration, thereby avoiding certain negative side effects, such as nephrotoxicity and ototoxicity and decreasing the chances of developing pathogenic resistance.[9–11] At this high level of local concentration, many bacteria that might otherwise be normally resistant to an antibiotic fall within its spectrum of activity.[12]

In addition to infection prophylaxis, local antibiotics may have a role for treatment of established infections. This antibiotic therapy is typically coupled with surgical debridement when necessary,[13] which includes wide excision of infected and devascularized tissues, curettage of abscesses and sequestra, restoration of soft tissue coverage, and removal of all foreign bodies.[14] Although these techniques help to eradicate infection, they also contribute to the formation of dead space. Various antibiotic carriers can help fill and manage this potential space caused by bone or soft tissue defects, preventing subsequent development of infection (**Table 1**).

One potential negative implication of a high local concentration of antibiotics is cytotoxicity, which could inhibit new bone formation and delay fracture union at high enough levels.[15–17] We will review commonly used carriers and methods for local antibiotic administration, their indications, and recent clinical trials evaluating the success of these methods.

Biofilm

One aspect of treating infection involves isolating the pathogen from the infected tissue or bone and determining the sensitivity of that pathogen to different antimicrobial agents. This goal is most readily accomplished when treating the unicellular, planktonic bacteria that are present in an infected wound bed. Conversely, biofilms interfere with this strategy. A biofilm is an extracellular matrix produced by bacteria that offers protection and provides an organizing scaffold to facilitate metabolic activity and communication between the bacteria within the matrix (**Fig. 1**).[18] In a biofilm, bacteria may tolerate antibiotic concentrations up to 1000-fold greater than the same bacteria in planktonic form.[19] Biofilm bacteria are not as mobile or virulent within the body as their unicellular phenotypes; however, they are much more protected from host immunity and systemic antibiotics and thus more difficult to eradicate.

Once established, the biofilm can provide a continual source of bacteria that can detach as planktonic cells or biofilm fragments that can then travel to and infect other sites or cause a systemic infection.[20] Even though they are less virulent, biofilms cause damage by invoking a host inflammatory response that generates adjacent tissue destruction, manifesting clinically as pain and implant loosening.[20] Biofilms, and the bacteria that comprise them, have the ability to attach to orthopedic implants through their unique surface structures.[21] The most common biofilm-producing organisms found in orthopedic infections are

Table 1
The author's preferred concentrations for local antibiotic carriers

	Recommended Mixture	Trade Examples	Other Considerations
PMMA	2 g vancomycin and 2.4 g tobramycin in 40 g PMMA cement	Palacos (Zimmer, Warsaw, IN), Simplex (Stryker, Kalamazoo, MI), SmartSet (DePuy, West Chester, PA)	May take longer to set up and may require additional monomer when additional antibiotics are added
Calcium sulfate	1 g vancomycin and 1.2 g tobramycin in 10 mL packet of calcium sulfate	Osteoset (Wright Medical, Memphis, TN), Stimulan (Biocomposites, Wilmington, NC)	FDA approved as a bone void filler, antibiotic delivery is off-label use; adding tobramycin powder only after mixing $CaSO_4$ will help it set up
Aqueous solution	80 mg tobramycin in 40 mL solution	Available as generic tobramycin, prepared in the OR	Inject into wound AFTER wound closure; if a drain is in place, clamp drain while injecting solution

Abbreviations: PMMA, polymethylmethacrylate; OR, operating room.