

# Role of Systemic and Local Antibiotics in the Treatment of Open Fractures



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## KEYWORDS

- Open fractures • Systemic antibiotics • Infection • Local antibiotics • PMMA • Chitosan sponge
- Calcium sulfate

## KEY POINTS

- Systemic antibiotics have been shown to decrease infection rates after open fracture.
- Controversy continues to exist over the ideal systemic antibiotic prophylaxis, particularly for type III open fractures.
- Local antibiotic delivery, although not new, is an area of renewed interest.
- Local antibiotics allow delivery of high concentrations of antibiotic without systemic toxicity.
- Many modes of local antibiotic delivery currently exist.

## INTRODUCTION

Open fractures can be problematic for the patient, orthopedic surgeon, and society in general. An open fracture occurs when communication exists between fracture or fracture hematoma and the outside environment. This communication potentially allows bacteria from the environment to colonize the fracture site. Colonization of the fracture site with pathogenic bacteria may result in infection, which is known to be one of the more common causes of fracture nonunion.<sup>1</sup> Infection and nonunion result in significant cost to the patient and society.<sup>2,3</sup>

Antibiotics work in many different ways to disrupt the life cycle of bacteria. Antibiotics can be administered systemically or locally to a fracture site. Both methods of administration have been used in attempts to reduce infection after open fracture. This article reviews the data supporting both systemic and local antibiotics.

## SYSTEMIC ANTIBIOTICS

### History, Incidence of Infection, and Infecting Organisms

Patzakis and colleagues<sup>4</sup> in 1974 were the first to demonstrate in a prospective randomized trial the efficacy of systemic antibiotics in decreasing infection rates after open fractures. Patients (310 open fractures) were randomized to 3 groups: no antibiotics, penicillin/streptomycin, or cephalothin. Patients receiving cephalothin had a lower incidence of infection (2.4%) than those receiving penicillin/streptomycin (9.8%) and patients not receiving antibiotics at all (13.9%).

Gustilo and Anderson<sup>5</sup> in 1976 reported antibiotic sensitivity data as part of analysis of more than 1000 open fractures; 50.7% of open fractures were colonized on admission and an additional 20.0% of patients had a positive culture at wound closure. Sensitivity analysis of cultured organisms led to the investigators' recommendation that a first-generation cephalosporin was the antibiotic of choice for open fractures. All *Staphylococcus* species, both coagulation

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positive and negative, were sensitive to cephalothin. Fifty-seven of 143 isolates reported were gram negative. Of these 57 gram-negative isolates, 23 were either *Pseudomonas* or *Enterobacter* and were not sensitive to cephalothin. Interestingly, the investigators cautioned about the nephrotoxic effects of adding aminoglycosides and advocated doing so only when “the anticipated beneficial effects are deemed essential after careful weighing of the potential benefits and dangers.”<sup>5</sup>

Gustilo and colleagues<sup>6</sup> in 1984 further classified type III open fractures (Table 1).<sup>6</sup> Subclassifications of type III open fractures were found to be predictive of infection and need for amputation. The infection rate was found to be 4%, 52%, and 42% for type IIIA, type IIIB (Fig. 1), and type IIIC open fractures, respectively. Of the infections reported after type III open fractures, 77% (24/31) were caused by gram-negative bacteria. Ten of 24 gram-negative infections were secondary to *Enterobacter* or *Pseudomonas* species, 2 organisms previously shown not to be sensitive to cephalothin.<sup>5</sup> The investigators did recommend a change in antibiotic prophylaxis for type III open fractures. They recommended adding an aminoglycoside to a first-generation cephalosporin or using a

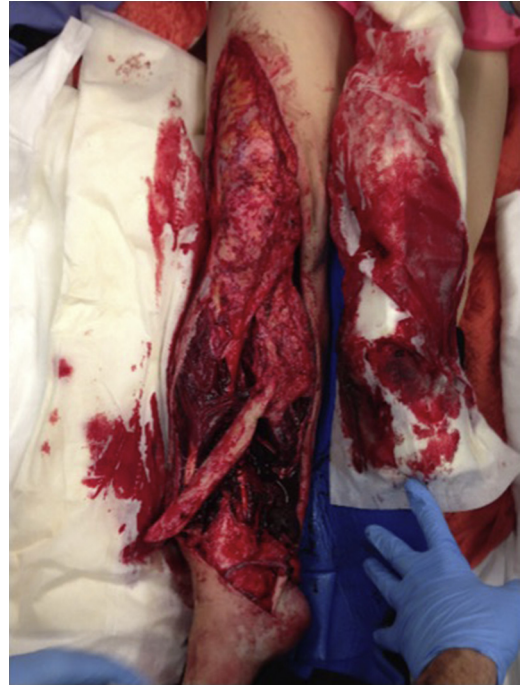


Fig. 1. Clinical photo of patient with type IIIB open tibia fracture.

Table 1  
Gustilo and Anderson classification of open fractures

Type	Description
I	Wound <1 cm; clean; simple fracture pattern; minimal comminution; minimal soft tissue injury.
II	Wound 1–10 cm; simple fracture pattern; moderate soft tissue injury.
IIIA	Extensive soft tissue injury but with adequate soft tissue coverage over bone; high-energy, comminuted, or segmental injuries.
IIIB	Extensive soft tissue injury with soft tissue loss and periosteal stripping; inadequate soft tissue coverage over bone.
IIIC	Open fracture with associated vascular injury requiring repair.

From Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Joint Surg Am* 1976;58A:453–8; and Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *J Trauma* 1984;24:742–6.

third-generation cephalosporin with the goal of “avoiding potential aminoglycoside toxicity.”<sup>6</sup>

Templeman and colleagues<sup>7</sup> retrospectively evaluated infection rate based on the Gustilo and Anderson<sup>5</sup> classification; 11.3% of open tibia shaft fractures were complicated by infection with infection rates of 0%, 3%, and 21% for type I, II, and III open tibial shaft fractures, respectively. Patzakis and Wilkins<sup>8</sup> reported similar infection rates based on the Gustilo and Anderson<sup>5</sup> classification. They reported infection rates of 1.4%, 3.6%, and 22.7% for type I, II, and III open fractures, respectively, with an overall incidence of 10.5%. They also reported that the rate of infection is dependent on anatomic site, with the tibia having a 10% infection rate versus a 5.3% infection rate for other sites combined.

In a more contemporary study, Chen and colleagues<sup>9</sup> reported the most common infecting organisms after open fracture. Overall, the investigators reported a 10% infection rate after 202 open fractures. *Staphylococcus* was the most common organism cultured (55% of infections), with coagulase-negative *Staphylococcus* and methicillin-resistant *Staphylococcus aureus* (MRSA) representing 30% and 25% of infections, respectively. Interestingly, 67% (4/6) of coagulase-negative *Staphylococcus* infections

included a second organism. Overall, 55% of infections included at least 1 gram-negative organism. Thirty-two percent of type IIIB open fractures were complicated by infection. Overall, 2.5% of open fractures were complicated by infection with MRSA.

Another contemporary study reported the most common infecting organisms after treatment of both open and closed fractures. A total of 214 infections were analyzed, of which 103 involved the tibia. *S aureus* was responsible for 56% of infections, with MRSA being responsible for 32% of infections. In type III open fractures, *S aureus* was responsible 21% of the time with gram-negative rods (GNR) and anaerobes being responsible 14% and 7%, respectively. Of the GNR infections found after open fracture, 35% were found in type III open fractures compared with 18% in type II open fractures and 0% in type I open fractures. However, there was no statistically significant difference in comparing rates of GNR infection between type III open fractures and types I and II combined. Interestingly, 32% of open fractures and 33% of closed fracture infections involved GNR. Although "barnyard-type" injuries did receive penicillin, type III open fractures did not routinely receive aminoglycosides for prophylaxis.<sup>10</sup>

### Timing of Antibiotic Administration

Time to antibiotic administration was first shown to be predictive of infection by Patzakis and Wilkins<sup>8</sup> in 1989. These investigators reported a 4.7% infection rate when antibiotics were administered within 3 hours of injury and a 7.4% infection rate when antibiotics were administered after 3 hours. This series included all types of open fractures and only 35.5% of open fractures received antibiotics within 3 hours. Several different antibiotic regimens were used during the course of the study. The investigators concluded that "the single most important factor in reducing the infection rate was the early administration of antibiotics that provide antibacterial activity against both gram-positive and gram-negative microorganisms." This conclusion appears at least partly based on the fact that patients who received cefamandole and tobramycin did have the lowest infection rates after open fractures and more specifically open tibia fractures (4.5%).<sup>11</sup> A confounding variable is that wound care differed throughout the study among groups.

Lack and colleagues<sup>12</sup> also reported that time to antibiotic administration is predictive of infection. The investigators reported on 137 type III open tibia fractures, of which 94.9% received

antibiotics within 3 hours of injury. Cefazolin was the only agent given in 93.4% of cases. The overall deep infection rate was 17.5%. Patients who received antibiotics within 1 hour of injury had a 6.8% infection rate compared with 27.9% in those receiving antibiotics after 90 minutes. The organisms responsible for deep infection were not reported.

One of the shortcomings of the Gustilo and Anderson<sup>5</sup> classification includes lack of interobserver reliability. Brumback and Jones<sup>13</sup> recommended delaying fracture classification until the first operative debridement. With fractures not classified until the first debridement, appropriate antibiotic treatment could be delayed. As more and more data suggest that time to debridement is not predictive of infection,<sup>14–18</sup> the average time to debridement is likely to increase. If time to debridement increases, then time to classification and appropriate antibiotic treatment could be delayed. An example would be an open tibia fracture that was thought on initial physical examination to be a type II open fracture. Based on many protocols, this patient would prophylactically receive a first-generation cephalosporin. If at surgery, the patient's fracture was classified as a type IIIB open fracture, he or she would have had a delay in administration of an antibiotic with effective gram-negative coverage. The importance of the time to administration of an antibiotic with effective gram-negative coverage is not well established in the literature.

### Established Guidelines (Agent and Duration)

Eastern Association for the Surgery of Trauma (EAST) Practice Management Guidelines strongly advocate for gram-positive coverage in type I and II open fracture wounds with the addition of gram-negative coverage for type III open wounds. Guidelines also advocate for the addition of penicillin with open fracture wounds at risk for fecal or clostridial contamination, discontinuation of antibiotics by 24 hours after wound closure in type I and II open fractures, and discontinuation of antibiotics in type III wounds by 72 hours after injury or by 24 hours after closure or coverage, whichever occurs first.<sup>19,20</sup>

The Surgical Infection Society Guidelines differed from the EAST Practice Management Guidelines concluding that insufficient evidence existed to advocate using gram-negative antibiotics and antibiotics with clostridial coverage. These guidelines advocated using a first-generation cephalosporin in conjunction with modern wound care techniques.<sup>21</sup>

Additional guidelines published in 2011 regarding combat-related injuries, endorsed by both the Surgical Infection Society and the Infectious Diseases Society of America, recommended cefazolin (clindamycin in patients with allergy to  $\beta$  lactams) for extremity wounds. The guidelines did not advocate for addition of gram-negative coverage nor did they advocate for addition of penicillin. These guidelines call for duration of antibiotic therapy of 1 to 3 days.<sup>22</sup>

Dellinger and colleagues<sup>23</sup> in a randomized trial reported no differences in infection rates comparing 1 day of antibiotic coverage with 5 days of antibiotic coverage. Patients were randomized to 1 of 3 groups: cefonicid  $\times$  1 day, cefonicid  $\times$  5 days, cefamandole  $\times$  5 days. There also was no significant difference in infection rates for type III open fractures treated with 1 day versus 5 days. Although *S aureus* was the most common infecting organism identified (58%), GNRs were identified in 33% of infections. Patzakis and colleagues<sup>11</sup> also concluded that antibiotic duration is not a significant predictor of infection and have not advocated routinely extending duration beyond 3 days.

Clindamycin has been supported as an alternative to first-generation cephalosporin in patients with  $\beta$  lactam allergy. Benson and colleagues<sup>24</sup> reported no difference in infection rates in a prospective study of open fractures comparing clindamycin with cefazolin. In a separate prospective study of open fractures, patients treated with prophylactic clindamycin had a lower incidence of infection than those treated with cloxacillin (9.3% infection in clindamycin group; 20.0% infection in cloxacillin group). All infections in type I and II open fractures were secondary to gram-positive organisms. Both antibiotics were associated with high infection rates in type III open fractures, with the investigators recommending additional gram-negative coverage for type III open fractures.<sup>25</sup>

### Nephrotoxicity with Aminoglycosides?

Although Gustilo and colleagues, in 1976<sup>5</sup> and 1984,<sup>6</sup> warned about the potential systemic toxicity associated with gentamicin, the EAST Practice Management Guidelines have given some support for the safety of once-daily aminoglycoside administration.<sup>19,20</sup> This guideline was based on data published by Sorger and colleagues<sup>26</sup> in 1999 and Russell and colleagues<sup>27</sup> in 2001. Sorger and colleagues<sup>26</sup> compared once-daily dosing of gentamicin with twice-a-

day dosing of gentamicin in 71 patients with type II and III open fractures. In addition to gentamicin, patients received cefazolin. Antibiotics were continued for 48 hours after each operation and until wound closure or coverage. Incidence of infection was 6.4% in the once-daily dosing of gentamicin compared with 13.6% in the twice-a-day dosing; however, this difference was not statistically significant. No patients in either group treated with prophylactic gentamicin experienced renal complications. Two patients receiving extended therapeutic treatment with gentamicin for diagnosis of infection did have an increase in serum blood urea nitrogen (BUN)/creatinine ratio and both patients were receiving twice-daily therapeutic treatment with gentamicin. Of note is that patients with renal insufficiency were excluded from the trial.<sup>26</sup> Russell and colleagues<sup>27</sup> reported a very small series of patients ( $n = 16$ ) treated with cefazolin and once-daily dosing of gentamicin for types II and III open tibia fractures. BUN and creatinine were followed and no patients in this series showed evidence of nephrotoxicity.

Recently, Bell and colleagues<sup>28</sup> reported an increased rate of acute kidney injury (AKI) in orthopedic patients in Scotland after surgical prophylaxis was changed from cefuroxime to flucloxacillin and gentamicin. Gentamicin was administered as a single dose, 4 mg/kg. This study included 12,482 patients; of those patients, 7666 underwent orthopedic procedures. The mean age of orthopedic patients was 71. Patients undergoing surgery for femoral neck fracture were excluded because of concern of administering gentamicin to this patient population. The incidence of AKI in orthopedic patients increased from 6.2% to 10.8% after protocol change.

Risk factors associated with nephrotoxicity after once-daily dosing of aminoglycoside usage have recently been reported. Oliveira and colleagues<sup>29</sup> reported an increased rate of AKI with aminoglycoside usage in the intensive care unit in patients with a history of diabetes mellitus, hypotension, iodinated contrast, and administration of other nephrotoxins. Unfortunately, the mortality rate of patients who experienced AKI was 44.5% (vs 29.1% in the group without AKI). The average duration of usage of aminoglycoside between patients who developed AKI (9.4 days) was similar to patients not developing AKI (9.9 days).

Usage of aminoglycosides among orthopedic trauma surgeons remains high, with 76.3% of respondents in a recent survey using aminoglycosides in contaminated type IIIB open fractures.

Interestingly, aminoglycosides also are being used in lower-grade open fractures, with 29.8% of respondents using aminoglycosides in contaminated type I open wounds and 15% of respondents using aminoglycosides in noncontaminated type II open wounds.<sup>30</sup> Patient and fracture characteristics and AKI have to be considered in the care of patients with open fracture, as AKI has been shown to be an independent risk factor for mortality<sup>31</sup> and even uncomplicated AKI is associated with a 10% risk of mortality.<sup>32,33</sup>

### Contemporary Antibiotic Options

Recently, studies have challenged the traditional antibiotic regimen for type III open fractures and fractures with potential fecal or clostridial contamination. Rodriguez and colleagues<sup>34</sup> reported no statistically significant difference in infection rates for type III open fractures primarily treated with ceftriaxone compared with a traditional antibiotic regimen including a first-generation cephalosporin and aminoglycoside. Gram-negative organisms comprised 33.3% of cultured organisms with the traditional antibiotic regimen and 40.0% of cultured organisms with the ceftriaxone regimen. The investigators effectively reduced the use aminoglycosides, vancomycin, and penicillin (53.5% usage in the traditional antibiotic group vs 16.4% usage in the ceftriaxone group).

Similarly, Redfern and colleagues<sup>35</sup> reported on 72 type III open fractures treated with piperacillin/tazobactam versus cefazolin/gentamicin. Patients treated with piperacillin/tazobactam did have a lower infection rate at 30 days compared with cefazolin/gentamicin (11.4% vs 21.6); however, this difference was not statistically significant. There was no statistically significant difference in infection at 1 year.

Johnson and colleagues<sup>36</sup> in an earlier study also provided some support for usage of a third-generation cephalosporin in higher-grade open tibia fractures. The investigators compared cefazolin with cefotaxime in a prospective randomized trial. Forty-six open tibia fractures (type II, IIIA, IIIB) were randomized to treatment with either cefazolin or cefotaxime. Patients treated with cefotaxime had a lower infection rate (19% vs 25%); however, this difference was not statistically significant. Interestingly, only 1 of 4 infections in the cefotaxime group involved a gram-negative organism compared with 4 of 6 in the cefazolin group.

Recently, the results of a large retrospective study of 1539 open fractures comparing

traditional antibiotic prophylaxis of cefazolin and a gentamicin (CG) with a new regimen of vancomycin and cefepime (VC) were presented. No differences were found in overall infection. However, the vancomycin/cefepime group demonstrated a significantly lower infection rate (3.1% vs 6.8%) in the type III open fractures; 22% of infections were secondary to MRSA with 8 infections in each group. Overall, 1% of open fractures were complicated by infection with MRSA. Significantly fewer infections secondary to *Enterococcus* (0 VC, 6 CG) and *Pseudomonas* (2 VC, 9 CG) occurred in the VC group. The investigators reported a zero incidence of AKI in patients presenting with normal renal function.<sup>37</sup> Saveli and colleagues<sup>38</sup> reported the results of a randomized trial comparing cefazolin with cefazolin plus vancomycin for the treatment of open fractures. Overall, the investigators reported a 16.8% infection rate with no difference between treatment groups. The rate of infection in type III open fractures was 29%. MRSA was responsible for 1 infection in each group (overall, 18% of infections); 27% of infections involved gram-negative bacilli. *Enterococcus* was involved in 18% of infections (1 vancomycin-susceptible *Enterococcus*; 1 vancomycin-resistant *Enterococcus*). Although appearing safe, neither study appears to show a significant benefit of vancomycin in the prophylaxis of open fractures. Cefepime and potentially other fourth-generation cephalosporins show promise and deserve further investigation.

### Importance of Body Weight on Dosing

Previous recommendations and doses of cefazolin frequently appearing in the literature include 1 g in patients weighing 80 kg or less and 2 g in patients weighing more than 80 kg. Recent guidelines for routine surgical antibiotic prophylaxis developed jointly by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America recommend 2 g of cefazolin in adult patients weighing less than 120 kg and 3 g of cefazolin in adult patients weighing 120 kg or more.<sup>39</sup> Underdosing of antibiotics has been found to be relatively common, as 21% of patients in a study by Collinge and colleagues<sup>40</sup> did not receive appropriate weight-based dosing of antibiotic before implementation of a performance-improvement initiative. The clinical implications of underdosing weight-based antibiotics are not yet clear.

### Potential Implications of Changing Wound Care on Infecting Organisms

Most early studies from which our antibiotic recommendations have largely been derived treated open fractures by initially leaving wounds open or partially open.<sup>11,24</sup> At the very least, most type III wounds were left open after initial debridement.<sup>6,7</sup> Early studies supported the concept that infections were most likely due to nosocomial organisms. Of 21 infections associated with type IIIB open tibia fractures, 57% were due to organisms not cultured within the first 2 weeks.<sup>41</sup> Similarly, Lee<sup>42</sup> reported that the organism responsible for infection after open fracture was not present in 78% of predebridement and 58% of postdebridement cultures. Current treatment of open fractures is more aggressive with regard to early wound closure and negative pressure wound therapy (NPWT) is more frequently used in wounds that are not closed. These 2 changes in wound management may lead to decreased nosocomial infection. Jenkinson and colleagues<sup>43</sup> recently reported a lower incidence of infection when open fractures (types I, II, and IIIA) were closed primarily (4.1%) versus delayed (17.8%). Although 3 of 73 patients closed primarily developed infection, none of the 3 was infected by a clostridial or gram-negative organism.

Unfortunately, a prospective randomized trial illustrating the benefit of NPWT in high-energy open fractures failed to describe any differences in identity of infecting organisms between groups. Nine infections occurred overall in this series with an infection rate of 28% in the gauze-dressing group and 5.4% in the NPWT group. Ten organisms were identified, including 7 gram-positive and 3 gram-negative organisms. Clostridium was not cultured in this study.<sup>44</sup> Blum and colleagues<sup>45</sup> reported similar findings in a retrospective study of open tibia fractures. The investigators reported an 8.4% infection rate with NPWT versus 28% with conventional dressings. The incidence of polymicrobial infection was decreased with NPWT (17% vs 47%). Dedmond and colleagues<sup>46</sup> reported results of using NPWT in the treatment of 50 type III open tibia fractures; 29.2% of type III open tibia fractures required debridement for deep infection. Ten deep infections occurred, with at least 6 involving MRSA (3 MRSA alone; 3 polymicrobial including MRSA). The identity of the other organisms identified in the polymicrobial infections was not reported.

Moues and colleagues<sup>47</sup> investigated bacterial counts after treatment with NPWT versus gauze

dressings. Although the total bacterial load did not differ between groups, gram-negative bacilli load was decreased with NPWT. The basic science indicates that NPWT does reduce levels of *Pseudomonas* compared with wet to dry dressing changes in a goat wound model. This same reduction was not observed with NPWT and *Staphylococcus aureus*.<sup>48</sup> Whether NPWT decreases the level of contamination of gram-negative organisms in open fracture wound or serves as a barrier to colonization with nosocomial gram-negative organisms is not completely clear in clinical practice.

### Systemic Antibiotic Recommendations in 2017

Choice of antibiotic is guided by the Gustilo and Anderson classification.<sup>5,6</sup> Patients with type I and II open fractures should be given a first-generation cephalosporin (cefazolin). In patients with serious  $\beta$  lactam allergy, clindamycin is an appropriate alternative.<sup>24,25</sup> Patients with type III open fractures also should be given an agent with gram-positive coverage but consideration should be given to adding an agent with effective gram-negative coverage or using an agent with both effective gram-positive and gram-negative coverage (Table 2). Traditionally,

**Table 2**  
Recommended systemic antibiotic prophylaxis (2017)

Open Fracture Type	Recommended Systemic Antibiotic Prophylaxis
Gustilo and Anderson Type I	First-generation cephalosporin (cefazolin) Alternative: clindamycin with $\beta$ lactam allergy
Gustilo and Anderson Type II	First-generation cephalosporin (cefazolin) Alternative: clindamycin with $\beta$ lactam allergy
Gustilo and Anderson Type III	First-generation cephalosporin (or clindamycin with $\beta$ lactam allergy) plus aminoglycoside (gentamicin) Alternatives: Third-generation cephalosporin (ceftriaxone or piperacillin/tazobactam)
Fecal or potential clostridial contamination	Consider addition of penicillin to above regimen (cefazolin/gentamicin)

patients with type III open fractures have been given cefazolin and gentamicin. Penicillin or an agent with anaerobic coverage should be considered for fractures associated with fecal or clostridial contamination.<sup>19,20</sup> If gentamicin is administered, patient and injury characteristics need to be considered. Duration and dosing schedule should be monitored, as a short course of once-daily dosing of gentamicin in a patient without risk factors for AKI appears relatively safe. Other agents with potential promise for treatment of type III open fractures include ceftriaxone,<sup>34</sup> piperacillin/tazobactam,<sup>35</sup> and cefepime.<sup>37</sup> All 3 agents deserve further study.

## LOCAL ANTIBIOTICS

### History and Potential Advantages

The use of locally applied antibiotics is not a novel concept. Locally applied antiseptics date back to the mid-1800s when Joseph Lister began using carbolic acid as an antiseptic on surgical wounds.<sup>49</sup> In 1939, Jenson and colleagues<sup>50</sup> were able to reduce their infection rate for open fractures from 30% to 5% by placing sulfanilamide powder directly into wounds before wound closure. The modern use of local antibiotics in orthopedics began in Europe with the use of polymethylmethacrylate (PMMA) cement impregnated with antibiotics to treat infected joint prostheses.<sup>51,52</sup> The use of locally applied antibiotics allows delivery of high concentrations of antibiotics without significant risk of systemic toxicity. High concentrations of antibiotics have been shown to be effective against biofilms<sup>53</sup> and therefore local antibiotics may have a significant role in reducing infections from biofilm-producing bacteria.

Various methods and techniques have been developed that allow for the direct placement of antibiotics into open wounds. Although PMMA cement is the “gold standard,” it is not the ideal delivery system. PMMA beads and cement spacers can be bulky, which can prove difficult in open fractures without significant bone loss. Additionally, PMMA cement requires a second procedure for removal. The optimal antibiotic delivery system provides high concentrations of antibiotics over an extended period, without causing systemic toxicity or adverse effects to the local host environment, and does not require subsequent surgical removal. Avoidance of surgical removal has motivated the development of several different bioabsorbable delivery systems that are reviewed in the following sections.

### Polymethylmethacrylate

PMMA has been used for antibiotic delivery for more than 40 years and is still considered the gold standard of local delivery.<sup>54</sup> PMMA is a synthetic polymer that is nonbiodegradable by nature with favorable biocompatibility and high mechanical strength.<sup>55</sup> In orthopedics, it has been used extensively as an anchoring platform in arthroplasty components and as a local antibiotic delivery agent in orthopedic trauma and osteomyelitis treatment.

In the trauma literature, PMMA has been used in many applications. Broadly, it is used as a treatment for soft tissue infection or osteomyelitis and in infection prevention of open fractures (Fig. 2). PMMA antibiotic administration has many different forms. Specifically, it is used in the form of beads,<sup>56</sup> spacers, and antibiotic nails or antibiotic-coated nails.<sup>57</sup> The membranes formed in reaction to PMMA spacers have been found to be biologically active and usage of spacers with the goal of membrane formation is called the Masquelet technique.<sup>58,59</sup>

Advantages of PMMA include its structural properties and space-filling capacity. These advantages are lacking in other forms of local antibiotic administration, such as antibiotic powder, aqueous solutions, gels, and collagen or chitosan sponges. Like many other forms of local



**Fig. 2.** Radiograph of patient with type IIIA open femur fracture treated initially with debridement and irrigation, placement of vancomycin/tobramycin-impregnated PMMA beads, and placement of external fixator.

antibiotic delivery, PMMA beads provide a method of delivery of high local antibiotic concentrations without associated high systemic levels.<sup>60,61</sup> Disadvantages include its nonbiodegradable nature and need for subsequent surgical removal. PMMA beads, spacers, or nails, if left in place, may act as a foreign body actually harboring biofilm and antibiotic-resistant bacteria.<sup>62</sup>

Antibiotics mixed with the PMMA must have certain qualities. They must be available in powder form, have broad antibiotic coverage with little resistance, and be thermally stable due to the exothermic polymerization process of PMMA formation. Commonly used antibiotics include vancomycin, tobramycin, gentamycin, erythromycin, and cefuroxime.<sup>63</sup>

The elution profile of antibiotic PMMA has been well delineated in multiple studies. There appears to be a rapid release of a high concentration of antibiotic during the first several days after implantation, the amount of which is quite variable among different subjects.<sup>61</sup> This rapid release is followed by a sustained release of antibiotic below a therapeutic concentration allowing biofilm formation in *in vitro* studies.<sup>64</sup> Additionally, this low-level release may also contribute to antibiotic resistance.<sup>63</sup> The type and combination of antibiotics used along with the type of PMMA used also has an effect on the elution profile of the antibiotic.<sup>65</sup>

Recent literature has focused on improving the consistency and duration of antibiotic elution from PMMA. In one study, addition of a hydrophilic additive, Pluronic F68, showed sustained release of vancomycin for approximately 11 weeks and allowed almost 100% release of the antibiotic without affecting the mechanical properties of the cement.<sup>63</sup> In another study, low-frequency ultrasound was used to increase both short-term and long-term antibiotic elution without compromising mechanical strength.<sup>66</sup> These newer additions to PMMA and mixing techniques may make PMMA antibiotic delivery more efficacious and possibly expand indications.

Literature supports the efficacy of PMMA delivery of local antibiotic in the treatment of open fractures. The adjunctive use of local antibiotics in addition to systemic antibiotics for open tibia fractures undergoing intramedullary nailing was recently analyzed with a systematic review and meta-analysis. In that study, all Gustilo and Anderson<sup>5</sup> types of tibia fracture had lower infection rates when local antibiotics were used in addition to systemic antibiotics. For type III open fractures, patients receiving only systemic antibiotics had an infection rate of 14.4%,

compared with an infection rate of 2.4% when local antibiotics were used. For type IIIB and IIIC fractures, the risk of infection was 31.2% for those receiving only systemic antibiotics, but was lowered to 8.8% with the addition of local antibiotics. The studies that used local antibiotics, almost exclusively used PMMA beads impregnated with vancomycin or tobramycin. A gentamicin-coated intramedullary nail was used in a very small number of patients.<sup>67</sup>

Ostermann and colleagues<sup>68</sup> reported the results of 1085 open fractures treated with an antibiotic bead pouch and systemic antibiotics versus systemic antibiotics alone. The investigators reported a 3.7% incidence of acute infection and/or chronic osteomyelitis in the group treated with the addition of the bead pouch versus a 12% incidence in the group treated without the bead pouch. Higher-grade open fractures (type IIIB) obtained the greatest benefit from the addition of the tobramycin-impregnated beads.<sup>68</sup>

Polymethylmethacrylate will likely continue to have a role in the management of high-grade open fractures, infections, bone defects, and arthroplasty. Its unique advantages include its ability to fill dead space and confer certain mechanical properties not available in other antibiotic delivery methods. The recent additions and modifications to the PMMA mixing process may improve its antibiotic elution profile and increase its effectiveness and potential uses.

### Antibiotics Without Carrier

In the simplest form, antibiotics can be directly placed into wounds without the use of a carrier substrate. The use of topical vancomycin in powder form is well described in the orthopedic literature, with most applications describing its use in spinal surgery for the prevention of surgical site infection, but with mixed results.<sup>69–71</sup> However, little has been described for the use of open fractures. Recent animal studies have evaluated the use of vancomycin powder in a contaminated fracture model in rats. Tennent and colleagues<sup>72</sup> found that vancomycin powder was effective at reducing bacterial counts when applied within 6 hours of contamination; however, when the powder was applied 24 hours after contamination, there was no significant reduction in the bacterial counts. Similar results were found when vancomycin-impregnated PMMA beads were placed into the wounds. However, vancomycin was detectable in the blood of all animals at 6 and 24 hours postapplication when vancomycin powder was used. These levels declined over time, with fewer than 30%



of the animals having detectable quantities of vancomycin in their serum by day 14. In contrast, those animals that received vancomycin-impregnated PMMA beads had negligible levels of serum vancomycin at 6 and 24 hours postapplication.

Other investigators have evaluated the use of injected aqueous antibiotic solutions for infection prophylaxis. Lawing and colleagues<sup>73</sup> in a retrospective review studied 351 open fractures that were treated with systemic antibiotics alone (183 fractures) or a combination of systemic antibiotics plus locally injected aminoglycosides at the time of index surgical procedure (168 fractures). For the local antibiotic group, an aqueous solution of either gentamicin or tobramycin was injected into the wound cavity after wound closure. For select high-grade fractures, a catheter was placed into the wound and irrigated with the antibiotic aqueous solution every 6 hours for 3 to 5 days postoperatively. The aqueous aminoglycoside group had a significantly lower infection rate (9.5%) compared with the control group (19.7%). After adjusting for potential confounding variables, the administration of aqueous aminoglycoside was found to be an independent predictor of lower infection rates in both deep and superficial infections. There was no impact, however, on the rate of nonunion between the 2 groups. Interestingly, there was no apparent benefit in the group of select high-grade fractures that received postoperative irrigations of the antibiotic solution.

Aqueous antibiotic solutions have been used in other orthopedic specialties. Lovullo and colleagues<sup>74</sup> studied the use of aqueous gentamicin in shoulder arthroplasty. They compared 164 patients treated with systemic antibiotics alone with 343 patients treated with systemic antibiotics plus an intra-articular injection of gentamicin at the conclusion of the procedure. The patients with systemic antibiotics alone had a 3.0% infection rate, compared with an infection rate of 0.29% in those who received intra-articular gentamicin.

Similar results have been reported in animal studies. Cavanaugh and colleagues<sup>75</sup> evaluated the use of injected antibiotics in a contaminated surgical site infection model. They found that the use of systemic cefazolin plus locally injected gentamicin lowered the rate of postoperative infection approximately sevenfold. The use of systemic cefazolin alone lowered the rate of postoperative infection only approximately twofold. Another animal model of contaminated surgical sites previously showed that aqueous gentamicin injected after wound closure was

significantly better at reducing bacterial counts than systemic gentamicin alone.<sup>76</sup> Similar results have been found using animal models for total knee arthroplasty in which local cefazolin and local vancomycin were more effective at lowering bacterial counts than the same dose of antibiotic given systemically.<sup>77</sup> More studies are needed to evaluate the possible systemic effects of locally applied antibiotics, but it appears as though antibiotics applied to contaminated wounds can lower bacterial counts more than systemic antibiotics alone.

### Gels

A novel approach to local antibiotic delivery is the recent development of bioabsorbable gels. Few studies have been published, but a recent animal study suggests that further clinical investigations are warranted. Penn-Barwell and colleagues<sup>78</sup> investigated the use of a bioabsorbable phospholipid gel (DFA-02; Dr Reddy's Laboratories Inc, Bridgewater, NJ) that delivers vancomycin and gentamicin and compared this gel with the traditional use of PMMA cement beads. This study used a segmental defect rat model contaminated with *S aureus*. In the gel group, 1 mL of gel containing vancomycin and gentamicin was spread throughout the wound. In the bead group, four 3-mm beads containing vancomycin and tobramycin were placed within the wound. After 2 weeks, 19 of the 20 specimens that used only antibiotic-laden PMMA beads had detectable bacteria. In the gel group, only 8 of the 20 specimens had detectable bacteria. All 20 of the control specimen (no local antibiotics placed) had detectable bacteria. Additionally, quantitative cultures demonstrated significantly less bacteria in the wounds treated with the gel than in the control or bead group.<sup>78</sup> However, in a separate study by the same group using fewer subjects per study group, they found that there was no difference in bacterial eradication when using PMMA beads or bioabsorbable gel.<sup>79</sup> Regardless, the combination of systemic antibiotics plus either antibiotic-impregnated PMMA beads or gel was superior to the use of systemic antibiotics alone at eradicating infection. Although not yet approved by the Food and Drug Administration for use, bioabsorbable gels do provide certain advantages to traditional PMMA beads and do warrant additional research.

### Collagen Sponge

Collagen sponges have been used in clinical practice for more than 3 decades,<sup>80</sup> having first been used for wound dressings and

hemostasis.<sup>81</sup> The collagen sponge is unique when compared with PMMA in that it is characterized by complete dissolution by phagocytosis and enzymatic degradation,<sup>82</sup> thus eliminating the need for a second procedure for PMMA removal. This process takes, on average, approximately 8 weeks for full absorption of the sponge.<sup>83</sup> The collagen sponge also is characterized by rapid release of antibiotic from the sponge. In vitro studies have compared the release of gentamicin from collagen sheets with PMMA beads. With the collagen sheet, 95% of the gentamicin was released within 1.5 hours, whereas only 8% had been released from the PMMA beads.<sup>84</sup> However, in vivo studies suggest that the release appears to be dependent on the fluid supply of the surrounding tissues. Effective local concentrations of antibiotics can be maintained in bony sites for approximately 1 week, but for less than 24 hours in well-perfused areas.<sup>85</sup>

Studies evaluating the use of gentamicin-collagen sponges in orthopedic trauma are encouraging.<sup>86,87</sup> Chaudhary and colleagues<sup>88</sup> recently reviewed a series of 35 patients presenting acutely with open fractures. These patients underwent irrigation and debridement, immediate open reduction and plate fixation, along with placement of an antibiotic-eluting collagen sponge around the plate just before wound closure. Deep infection subsequently developed in 6.5% of patients (2 of 31 available for follow-up). No patient required implant removal and no patient developed nonunion.

Gentamicin-collagen sponges have been used extensively for the treatment of osteomyelitis. Leung and colleagues<sup>89</sup> report on a cohort of 50 patients treated for chronic osteomyelitis. All patients underwent surgical debridement, intravenous (IV) antibiotics, and placement of a collagen sponge infused with gentamicin. They reported a 12% recurrence rate of infection, compared with a recurrence rate of 20% to 30% often reported in the literature. A prospective randomized study of 20 patients with long-bone osteomyelitis directly compared collagen sponges with PMMA beads, both infused with gentamicin. Complete resolution of the infection was noted in 80% of the patients with collagen sponge and in 90% of the patients with PMMA. As expected, gentamicin was rapidly released from the collagen sponge, leading to high levels of antibiotic in the wound exudate and in the urine within the first 48 hours, whereas gentamicin was more slowly released from the PMMA beads.<sup>90</sup> Ipsen and colleagues<sup>91</sup> previously reported on a series of 10 patients

treated with gentamicin-collagen sponge, in which no recurrence of infection was observed in any of the patients. Similar studies have previously been reported, in which gentamicin-collagen sponges show good results in eradicating osteomyelitis.<sup>92</sup>

Studies evaluating the use of gentamicin-collagen sponges in clean surgical wounds are mixed. In a multicenter randomized controlled trial of nearly 700 patients receiving hemiarthroplasty for femoral neck fracture, the addition of gentamicin-eluting collagen sponge had no impact on deep or superficial infection rates.<sup>93</sup> However, in a meta-analysis of randomized trials evaluating the nonorthopedic use of gentamicin-containing collagen sponges, there was a significant decrease in surgical site infection in both clean and clean-contaminated surgeries.<sup>94</sup>

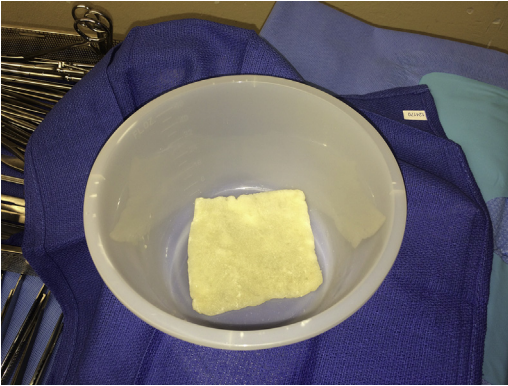
Adverse effects also have been reported with the use of gentamicin-collagen sponges. In a series of 12 patients being treated for infected total hip arthroplasty with gentamicin-impregnated collagen sponges, 7 of the 12 patients were found to have toxic serum levels of gentamicin (>2 mg/L). In 3 cases, there was a significant drop in renal clearance that persisted, and in 3 other patients there was a temporary decrease in renal clearance that resolved. Each patient in that study received between 4 and 6 sponges implanted, with each sponge containing 130 mg gentamicin.<sup>95</sup>

Other studies have shown a possible increased risk of infection with collagen sponges. In a large prospective trial evaluating the use of gentamicin-collagen sponge for infection prophylaxis in colorectal surgery, investigators found that patients treated with the collagen sponge actually had a higher infection rate, presumably because the antibiotics eluted quicker than the sponge degraded, leaving foreign material within the wound.<sup>96</sup>

Additionally, collagen sponges have been available commercially only as sponges infused with gentamicin. Gentamicin has previously been shown to have detrimental effects on fracture healing,<sup>97–100</sup> making them less desirable for use in open fractures.

### Chitosan Sponge

Another type of sponge that has recently come into use is the chitosan sponge (Fig. 3). Similar to the collagen sponge, it is an antibiotic-impregnated sponge that is absorbed by the host tissue if left in place. Chitosan is the second-most abundant polysaccharide after cellulose and is made from shellfish sources, such as shrimp and crab.<sup>101</sup> Chitosan is a deacetylated



**Fig. 3.** Clinical photo of chitosan sponge.

derivative of chitin,<sup>102</sup> both of which are well known to have positive effects on wound healing.<sup>103–105</sup> Animal studies have shown that chitosan accelerates infiltration of polymorphonuclear cells into wounds at the early stages of wound healing, followed by the increased production of collagen by fibroblasts within granulation tissue as compared with control materials.<sup>106</sup>

Studies evaluating the elution of antibiotic from chitosan sponges show quick delivery of antibiotic. In one study, *in vitro* elution of amikacin was 85% complete after 1 hour and 96% complete after 72 hours. For daptomycin, 31% was released by 1 hour and 88% was released at 72 hours. For both agents tested, the eluted antibiotic was able to inhibit the growth of *S aureus*, indicating that the eluted antibiotic retained its antimicrobial activity.<sup>107</sup> A follow-up *in vitro* study from the same group showed similar results. In that study, the release of vancomycin from the chitosan sponge remained above the minimum inhibitory concentration (MIC) for *S aureus* for 72 hours and the release of amikacin remained above the MIC for *Pseudomonas aeruginosa* for 48 hours.<sup>108</sup>

Few clinical studies are available to demonstrate the *in vivo* effectiveness of antibiotic-eluting chitosan sponges for orthopedic applications. In a recent animal study, chitosan sponges eluting either vancomycin or amikacin were effective in decreasing bacterial counts in contaminated wounds. Serum antibiotic concentrations remained less than 15% of the target serum level for systemic treatment. Additionally, by 42 hours, the sponges were, on average, 85% dissolved.<sup>101</sup> Additional studies are needed to evaluate the chitosan sponge as a potential alternative to traditional PMMA beads. Furthermore, the chitosan sponge is available without antibiotics already infused. The surgeon can thus select which antibiotics they want to

incorporate, unlike the gentamicin-collagen sponge. The surgeon also has more antibiotic options available than with PMMA beads, as antibiotic thermal stability is not a concern.

### Calcium Sulfate

Another potential drug-delivery device is calcium sulfate. Calcium sulfate impregnated with antibiotics (Fig. 4) has been used for decades in the treatment and prevention of orthopedic infections.<sup>109,110</sup> Calcium sulfate is an osteoconductive material that is resorbed at a rate similar to that of bone formation.<sup>111</sup>

Animal studies have evaluated the local and systemic levels of tobramycin after impregnated calcium sulfate beads are implanted into tissues. Local tobramycin levels have been found to rapidly rise over the first 24 hours, and then rapidly decline. Levels of tobramycin were found to still be therapeutic at 14 days after implantation. Some animal subjects, however, had elevated local tobramycin levels for at least 28 days. Serum levels, however, rose quickly and peaked during the first hour after implantation. Serum levels became undetectable after 24 hours.<sup>112</sup> *In vitro* testing has compared the elution of daptomycin and tobramycin from calcium sulfate beads. Similar to other studies, both antibiotics are rapidly released from the beads over the first 24 hours, followed by a rapid decline in the following days. However, after a 28-day period, the daptomycin-containing beads released only 35% of the total antibiotic incorporated into the beads, whereas 68% of the total tobramycin had been released.<sup>113</sup> Other *in vitro* studies have shown that the peak local concentration of vancomycin when eluted from calcium sulfate beads occurs 48 hours after implantation.<sup>114</sup> Other variations of calcium sulfate beads have been developed that elute



**Fig. 4.** Clinical photo of vancomycin/tobramycin-impregnated calcium sulfate beads.

antibiotics quicker and dissolve over only a few days,<sup>115</sup> which may pose a clinical advantage in certain situations.

Few clinical studies are available to document the effectiveness of calcium sulfate in preventing and treating infection. One study evaluated the use of calcium sulfate beads in open long-bone fractures treated with internal fixation. That study of 28 patients had 15 type II open fractures, 11 type IIIA open fractures, and 2 type IIIC open fractures as classified by Gustilo and Anderson.<sup>5</sup> All fractures were treated with vancomycin-impregnated calcium sulfate beads and internal fixation. At an average follow-up of 10.5 months, no infection was present in the 26 patients available for follow-up. Two patients were found to have exudation from the wound or drain incision, but both were treated with local wound care only. The calcium sulfate beads were no longer visible on plain radiographs at 1 month (15 cases) and 2 months (11 cases).<sup>116</sup> Other case series have documented the beneficial use of antibiotic-impregnated calcium sulfate in combat-related fractures.<sup>117</sup>

Several studies have evaluated the use of tobramycin-impregnated calcium sulfate beads in osteomyelitis. A prospective randomized clinical trial evaluated the effectiveness of traditional PMMA beads with tobramycin-impregnated calcium sulfate beads in patients with chronic osteomyelitis and/or infected nonunions. At 24 months, both groups had eradication of infection in 86% of patients (12 of 14 patients in each group). As expected, the PMMA group required more repeat surgical procedures for removal of the PMMA beads.<sup>118</sup> One study evaluated the addition of tobramycin-impregnated calcium sulfate to the standard treatment of surgical debridement and IV antibiotics. In that study, infection was eradicated in 23 (92%) of the 25 study participants. The calcium sulfate pellets were no longer visible on plain radiographs at 1 month (1 case), 2 months (12 cases), 3 months (10 cases), and 6 months (2 cases), with the average time to resorption being 2.7 months. Eight patients developed a sterile draining sinus, which closed on average at 2 to 3 months postoperatively, around the same time that the calcium sulfate was no longer visible on plain radiographs.<sup>119</sup>

One retrospective review evaluated the use of commercially available tobramycin-impregnated calcium sulfate beads as adjunctive treatment for chronic osteomyelitis. The addition of local antibiotics to the standard treatment of surgical debridement plus IV antibiotics resulted in eradication of infection in 20 of 21 patients at an

average follow-up of 16 months. Seven of the 21 cases were complicated by wound drainage. Three-quarters of these cases went on to have wound-healing problems as compared with one-third of the cases without wound drainage. Accordingly, serous drainage appears to double the relative risk of wound-healing problems ( $P = .06$ ). Additionally, 1 patient developed transient AKI.<sup>120</sup> A similar study evaluated 65 patients also receiving surgical debridement, IV antibiotics, and implantation of tobramycin-impregnated calcium sulfate beads for chronic osteomyelitis. That study showed that the addition of tobramycin-impregnated calcium sulfate pellets did not have a significant impact on infection eradication, except in a small subset of patients who had normal immune systems.<sup>121</sup>

Several animal studies are available evaluating the use of calcium sulfate. Animal studies show that tobramycin-impregnated calcium sulfate beads are equally as effective as traditional tobramycin-impregnated PMMA beads in preventing infections in a contaminated open fracture model.<sup>122</sup> Similar efficacy also was shown when the tobramycin-impregnated calcium sulfate was combined with demineralized bone matrix, resulting in similar reduced bacterial counts compared with tobramycin PMMA beads.<sup>123</sup> Additionally, there appears to be equal effectiveness between "hand-made" tobramycin PMMA beads, commercially available tobramycin PMMA beads, and commercially available tobramycin calcium sulfate beads.<sup>124</sup>

The most common complication associated with the use of calcium sulfate is serous drainage from the wound, which occurs in from 4% to 51% of cases<sup>125,126</sup>; however, as shown previously, this tends to resolve as the calcium sulfate is resorbed. Regardless, calcium sulfate has been shown effective for use in acute open fractures as well as for the treatment of established osteomyelitis.

## SUMMARY

The orthopedic community has learned much about the treatment of open fractures from the tremendous work of Ramon Gustilo, Michael Patzakis, and others. However, open fractures continue to be very difficult challenges. Type III open fractures continue to be associated with high infection rates. Some combination of systemic and local antibiotics may be most appropriate in these high-grade open fractures. Further research is still necessary in determining optimal systemic antibiotic regimens, as well as the role of local antibiotics. Any new discoveries

related to novel systemic antibiotics or local antibiotic carriers also will need to be evaluated related to cost.

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