General Assembly, Prevention, Local Antimicrobials: Proceedings of International Consensus on Orthopedic Infections

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Question 1: Is there a difference in the bioavailability of vancomycin when administered through the intravenous route or intraosseous regional route in total knee arthroplasty (TKA)?

Recommendation:
Yes. Tissue concentrations of vancomycin and other antibiotics are significantly higher when given via intraosseous regional administration for prophylaxis in total knee arthroplasty. Currently, it is unclear whether these higher concentrations will lead to a reduction in prosthetic joint infection (PJI) rates.

Level of Evidence: Strong

Delegate Vote: Agree: 91%, Disagree: 2%, Abstain: 7% (Super Majority, Strong Consensus)

Rationale:
Prophylaxis via intraosseous regional administration (IORA) in TKA involves injection of antibiotics into an intraosseous tibial cannula, after tourniquet inflation and immediately before skin incision [1]. Intraosseous injection is equivalent to intravenous injection [2] but is more rapid than cannulation of a foot vein. As the tourniquet is inflated before injection, the antibiotic distribution is restricted “regionally” to the lower limb, similar to the manner of a “Bier block” used in anesthesia [3]. It allows tissue concentrations of the antibiotic to be maximized during the TKA procedure before decreasing once the tourniquet is deflated.

Earlier studies investigated the use of intravenous regional administration of prophylactic antibiotics via cannulation of a foot vein [4–7] and demonstrated tissue concentrations 2–10 times higher than systemic administration (Table 1). The advantage of IORA is the more rapid and reliable placement of an intraosseous cannula into the proximal tibia compared to the foot vein cannulation required for intravenous regional administration.

Vancomycin in particular may be suited for use with IORA. It covers resistant organisms commonly causing prosthetic joint infections (PJIs), such as coagulase-negative staphylococci and methicillin-resistant Staphylococcus aureus [8,9]. However, when given systemically, it requires a prolonged infusion time [10] and can cause systemic side effects such as nephrotoxicity [10,11]. Vancomycin can be given by IORA as a bolus injection, ensuring optimal timing of prophylaxis. As distribution of the antibiotic is limited by the tourniquet, a lower vancomycin dose can be used, potentially reducing systemic side effects.

Four clinical studies have investigated the use of IORA in TKA (Table 2). One study compared 1 gram systemic ceftazolin vs 1 gram IORA ceftazolin in 22 patients, reporting tissue concentration 10 times higher with IORA [1]. A second study randomized 30 patients to receive either 250 mg or 500 mg of vancomycin by IORA or 1 gram of vancomycin systemically [12]. Tissue concentrations were 4–10 times higher in the IORA groups. As no complications such as red man syndrome were seen on tourniquet deflation in the IORA groups, the authors recommended the use of the higher 500 mg IORA dose.
A third study randomized 22 patients undergoing revision TKA to 500 mg IORA vancomycin or 1 gram systemic prophylaxis [8]. Because revision TKA has a higher PJI rate, it was unclear if IORA prophylaxis would be effective in this setting. The presence of a tibial implant could compromise IO injection, and the tourniquet is often deflated during prolonged revision procedures. The study found tissue concentrations of vancomycin 5-20 times higher in the IORA group, and these were maintained throughout the procedure despite a period of tourniquet deflation. Concentrations from drain samples taken the next morning were similar between the groups.

A fourth study randomized 22 obese patients (BMI > 35) undergoing TKA to 500 mg IORA vancomycin or a weight-adjusted 15 mg/kg systemic vancomycin prophylactic dose. Mean BMI was 41.1 and 40.1 (range, 35-52) in the 2 groups. Tissue concentrations were 5-9 times higher in the IORA vs systemic group.

It is unclear whether the higher tissue concentrations seen with IORA will reduce the incidence of PJIs. Pharmacodynamically, vancomycin’s effect correlates with the area under the concentration-time curve divided by the minimum inhibitory concentration (AUC/minimum inhibitory concentration ratio) [9], thus greater tissue concentrations may be expected to increase efficacy. An animal study comparing 6 prophylaxis regimes in a murine model of TKA found IORA of both cefazolin and vancomycin to be more effective than systemic prophylaxis [14], but clinical data are lacking. As PJIs are rare, a randomized trial of IORA with PJI as the endpoint is unlikely to be feasible; larger cohort studies may offer further insights.

**Question 2: Can local antibiotic delivery alone be effective in the treatment of musculoskeletal infections?**

**Recommendation:**

At the present time and without further refinement of delivery mechanisms and improved pharmacokinetics, local antibiotic alone is not believed to be sufficient for the management of patients with orthopedic infections. Other adjunctive treatment modalities need to be combined with local delivery of antibiotics.

**Level of Evidence:** Limited

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### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazzarini et al. (2003) [7]</td>
<td>Comparative cohort</td>
<td>5 patients 800 mg IV teicoplanin 2.5 h preoperatively vs 15 patients 200 mg IVRA teicoplanin via a foot vein</td>
<td>Tissue samples (skin, subcutaneous tissue, bone, synovium) 2-10 times higher through the regional route</td>
</tr>
<tr>
<td>de Lalla et al. (1993) [5]</td>
<td>RCT</td>
<td>24 Patients comparing 800 mg IV teicoplanin 2.5 h preoperatively vs 400 mg IVRA teicoplanin via foot vein</td>
<td>One superficial infection; no deep infections at a 2-y follow-up</td>
</tr>
<tr>
<td>de Lalla et al. (2000) [6]</td>
<td>Cohort</td>
<td>Clinical study of 160 patients (205 TKAs), 400 mg IVRA teicoplanin via foot vein</td>
<td>Mean concentrations of teicoplanin in bone (133 mg/L) and fat (88 mg/L) were higher than those of teicoplanin in bone (9 mg/L) and fat (10 mg/L); P &lt; .001</td>
</tr>
<tr>
<td>Hodinott et al. (1990) [4]</td>
<td>Comparative Cohort</td>
<td>5 Patients, 1000 mg IV cefamandole vs 750 mg IVRA cefuroxime via a foot vein in the same 5 patients</td>
<td>Mean concentrations of cefuroxime in bone (133 mg/L) and fat (88 mg/L) were higher than those of cefamandole in bone (9 mg/L) and fat (10 mg/L); P &lt; .001</td>
</tr>
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</table>

**RCT**, randomized controlled trial; **TKA**, total knee arthroplasty; **IVRA**, intravenous regional anesthesia.

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young et al. (2013) [11]</td>
<td>RCT</td>
<td>22 Primary TKA patients, 1 g systemic cefazolin vs 1 g IORA</td>
<td>Mean cefazolin subcutaneous fat concentrations: 11 ug/g systemic vs 186 ug/g IORA, mean bone concentrations: 11 ug/g vs 130 ug/g IORA</td>
</tr>
<tr>
<td>Young et al. (2014) [12]</td>
<td>RCT</td>
<td>30 Primary TKA patients, 1 g systemic vancomycin vs 250 mg and 500 mg IORA</td>
<td>Mean vancomycin fat concentrations: 3.2 ug/g systemic group, 14 ug/g 250 mg IORA group, 44 ug/g 500 mg IORA group. Mean bone concentrations: 4.0 ug/g systemic, 16 ug/g 250 mg IORA, 38 ug/g 500 mg IORA</td>
</tr>
<tr>
<td>Young et al. (2017) [8]</td>
<td>RCT</td>
<td>20 Revision TKA patients, 1 g systemic vancomycin vs 500 mg IORA</td>
<td>Mean vancomycin concentrations fat: 3.7 ug/g systemic vs 49.3 ug/g IORA, mean bone concentrations: 6.4 ug/g vs 77 ug/g IORA</td>
</tr>
<tr>
<td>Chin et al. (2018) [13]</td>
<td>RCT</td>
<td>22 Primary TKA patients with BMI &gt;35, 15 mg/kg systemic vancomycin vs 500 mg IORA</td>
<td>Mean vancomycin concentrations fat: 4.4 ug/g systemic vs 39.3 ug/g IORA, mean bone concentrations: 6.1 ug/g vs 34.4 ug/g IORA</td>
</tr>
<tr>
<td>Young et al. (2015) [14]</td>
<td>Animal Model</td>
<td>42 Mice, 6 prophylaxis regimes compared</td>
<td>IORA of vancomycin and cefazolin was more effective than systemic in preventing PJI in murine model of TKA infection</td>
</tr>
</tbody>
</table>

**RCT**, randomized controlled trial; **TKA**, total knee arthroplasty; **IORA**, intravenous regional administration; **PJI**, prosthetic joint infection.

**Delegate Vote: Agree: 91%, Disagree: 6%, Abstain: 3% (Super Majority, Strong Consensus)**

**Rationale:**

Musculoskeletal infections comprise a broad range of conditions with varying presentations and conditions including the presence of implants. Disregarding necrotizing infections of muscles, which are a specific disease, bone and joint infections have in common a well-known difficulty in obtaining eradication, particularly when associated with an implant. Biofilm formation [15–21], the development of certain phenotypical variants, such as small colony variants and intracellular persisters [21–30], and leukocyte dysfunction in the close vicinity of the surface of implants [31], are among the most important causes of identified microbial resistance.

Systemic antibiotic treatment with duration of 6–12 weeks is usually recommended for nontuberculous bone and implant-related infections [32–34], along with surgical debridement, to overcome persistence and potential relapse. There are, however, issues regarding the complexity of pharmacokinetics of antibiotics in bone, with consequences not fully understood yet [35,36]. However, local delivery could provide continuous release in all affected compartments, optimizing the effect of most antibiotics, as time of exposure at adequate concentrations is the most important pharmacodynamic parameter for all antibiotic classes, except aminoglycosides, quinolones, and some newer agents [37,38].

In vitro experiments are ideal to study the effect of a single parameter, such as the effect of antibiotics in isolation. The main difficulty resides in creating realistic conditions that allow...
transposing the observations in vivo [20]. It is known that the biofilm is a complex structure that matures over time [15,20]. It is also known that a mature biofilm is much more difficult to eradicate than a biofilm of 24 hours age or less [39–42]. Considering the time course of musculoskeletal infections, only experiments studying the biofilm matured over more than 48 hours would be of interest. The structure of biofilm also is influenced by the surrounding physicochemical conditions, and its density increases with external stress [20,43–46]. The exact conditions in vivo are, however, not fully measurable or understood, and probably have important variability [20], but there are nonetheless physicochemical stresses acting on biofilm formation, such as the host immune system. Thus, publications describing dynamic conditions thus are probably more valuable than those describing static conditions only. Prolonged exposure to antibiotics increases susceptibility of biofilm bacteria to antibiotics [47]. Studies examining short exposure to antibiotics with a time-dependent killing effect thus overestimate resistance of the biofilm.

A thorough search of the literature using both PubMed and Google Scholar for prolonged exposure to antibiotics (>72 hours) of a matured biofilm (>48 hours), complemented by crossreferencing, identified the studies listed in Table 3 [48–52]. Although thousands of biofilm eradication have been published, only a very small number tested the matured biofilm or antibiotic exposure long enough to obtain not only a reduction of bacterial counts, but complete eradication. Only a limited number of combinations of bacterial strains and antibiotics have been investigated in these studies, but it has been proven that a matured biofilm can be potentially eradicated solely by prolonged exposure to antibiotics.

Required concentrations, however, are higher and exposure times are longer than those obtained from carrier materials currently available [53–55]. For many antibiotics, stability in an environment suitable for biofilm formation is crucial for efficacy and potential antimicrobial resistance. The effects of prolonged exposure to antibiotics on matured biofilm raises the question of how these antibiotics might act on this environment. Antibiotics are substances that are capable of inhibiting or destroying living microorganisms, especially bacteria.
aqueous solution and at body temperature also is limiting for local application [56]. Continuous or repeated exogenous administration of antibiotics would be necessary to reach the required time and concentration profiles. Further studies indicate that the effect of antimicrobial drugs can be enhanced by the use of synergistic combinations of antibiotics [57–59] or by the addition of antibacterial peptides [60–62], quorum-sensing inhibitors [63], biofilm-dispersing drugs [64–66], or nitric oxide [60]. Of note, the addition of ethylenediaminetetraacetic acid already is applied in antibiotic lock solutions for treatment of catheter-associated infection [67]. Also, n-acetylcysteine is used in the treatment of pulmonary infection in cystic fibrosis, a biofilm-associated disease without implant, to disperse biofilm and enhance the effect of coadministered antibiotics [66,68]. But clinical application of these chemicals for treatment of musculoskeletal or implant-associated infections has not been described.

Some studies of catheter-related infections in animal models confirm the in vitro observations, as the biofilm within the catheter could be eradicated by antibiotics in combination with biofilm-dispersing drugs. The main issue, however, is that in some of these studies, systemic antibiotics also had to be administered to prevent sepsis associated with the infected catheter system. In a mouse model, 48- to 72-hour-old S. aureus, E. coli, and P. aeruginosa biofilms could be eradicated within a port system by the sole action of local antibiotics combined with additives such as ethylenediaminetetraacetic acid or L-arginine [64,69]. These observations could be confirmed even in immunosuppressed animals, but microbiological workup was limited to biofluorescence. Eradication could also be obtained with daptomycin in an infected rat model using a 5-day-old staphylococcal biofilm, with a potential regrowth phase of up to 7 days followed by sonication [70].

The focus of orthopedic research has been mainly related to development and application of carrier materials that resorb in situ, to circumvent the known insufficiencies and disadvantages of bone cement, which is currently the most preferred method of delivery of local antibiotics. Particularly, bone cement can act as a foreign body recolonized by the biofilm after the initial peak release of added antibiotics [71,72]. Antibiotics have been applied locally without any carrier material, or with collagen, calcium sulfate–based materials in combination with calcium phosphate/calcium carbonate/hydroxyapatite, hyaluronic hydargols, or with polymers as the carrier. Bone allograft can also be used successfully as the carrier for antibiotics.

Local administration of powdered antibiotics on a large scale was explored during the World War II, the very beginning of the era of antibiotics [73,74]. There is only one randomized clinical trial, which included 907 patients who underwent both instrumented and noninstrumented spinal surgery in India [75]. All patients received systemic prophylaxis with intravenous cefuroxime, the intervention group also receiving 1 g of topical vancomycin. No significant difference in the rate of surgical site infection between the control (1.68%) and treatment (1.61%) groups could be identified. But in the absence of a carrier material delaying absorption, the antibiotics can be expected to be eliminated rather rapidly from the surgical site to be effective.

A different strategy for local antibiotic delivery is continuous irrigation with a catheter, although, it has also been reported in conjunction with surgical debridement. Its main advantage is that the agent can be switched and constant concentrations can be maintained. Only degradation of the drug in the solution to be infused has to be considered [56]. Reported success rates vary from 18% to 85% [76–79]. Only one study examined isolated local antibiotic administration, without debridement [76]. In the only modern study, primary implants thus treated did not experience relapse, recurrence of infection was seen in all but one megaprosthesis patients [79]. This study, however, included only 12 subjects [79]. Successful eradication was observed in patients with short duration of symptoms, susceptible Gram-positive organism, absence of a sinus tract, and no prosthetic loosening [77].

In prophylaxis, there is good evidence supporting local antibiotic administration. A systematic review demonstrated that the local application of antibiotics significantly reduced the infection rates in case of open long bone fractures, regardless of what carrier material was used [80], or after sternotomy, when applying collagen fleece with gentamicin [81]. The benefit of addition of antibiotics to bone cement in primary total knee arthroplasty to prevent postoperative infection has also been shown in a randomized trial, including 340 patients ($P = .024$) [82]. In two very recent randomized trials, antibiotic-loaded hydrogel showed a significant reduction of surgical site infection in 380 cases of primary or aseptic revision arthroplasty ($P = .003$) [83], as well as in 253 cases of internal fixation of closed fractures ($P < .03$) [84]. In addition, calcium sulfate/calcium carbonate loaded with gentamicin, implanted at the second stage of septic revision total knee arthroplasty, showed a reduction in the reinfection rate, comparing 2 groups of 28 patients in a retrospective study [85]. But as discussed previously, this favorable effect might be lost in treatment of the established biofilm.

There is a paucity of data providing comparative evidence regarding the use of local antibiotics in treatment of biofilm-associated musculoskeletal infections. In a randomized trial on 30 patients, comparing calcium sulfate with bone cement as the antibiotic carrier and filler material, cure rates for chronic osteomyelitises were similar, but the resorbable material did not require a second operation for removal [86]. A retrospective study of 65 cases of chronic osteomyelitises, comparing calcium sulfate loaded with tobramycin to debridement without filler material, identified a significantly better healing rate in the local antibiotic treatment group [87]. Interestingly, management of dead space around the bone in chronic osteomyelitises with S53P4 bioglass that has mild intrinsic antimicrobial activity even without antibiotics showed comparable results to calcium-based antibiotic-loaded carriers in 2 retrospective studies with a total of 101 patients [88,89]. In a large study investigating an absorbable, gentamicin-loaded, calcium sulfate/hydroxyapatite biocomposite in chronic osteomyelitises in 100 patients with poor Cierny and Mader hosts and type III and IV chronic osteomyelitises, infected nonunion and concomitant septic arthritis, showed a low infection recurrence rate of 4%, which is much lower than the expected recurrence rate in this group of patients [90].

Local application of antibiotics carries some adverse effects. Calcium-containing carrier materials can induce life-threatening hypercalcemia [90–92]. The exact incidence of this complication is unknown. Despite the frequent use of calcium-based antibiotic carriers, with case series reporting hundreds of patients in total [53,93–95], hypercalcemia is reported only in isolated cases. Antibiotic release can also be rapid and reaching toxic serum levels [96]. This can also be the case with calcium sulfate, depending on the quantity used, the total dose of antibiotics, and the renal function of the patient [97].

In summary, there are no randomized clinical trials or other high-quality studies demonstrating that the use of local antibiotics alone has a role in the management of musculoskeletal infections. Local antibiotics, regardless of the carrier, may have a role in the management of some musculoskeletal infections when combined with surgical intervention and administration of systemic antibiotics. The available local delivery systems in clinical practice are inadequate to allow reaching high enough local concentrations of antibiotics that can eliminate mature biofilms. Further developments are necessary to obtain delivery vehicles that can reach very high local concentrations of antibiotics for a duration long
enough to be effective. Considering the heterogeneity of musculoskeletal infections and the variability of treatment protocols [32–34] with adverse effects associated with administration of antibiotics [98], large-scale studies are needed to examine the role of local antibiotics as the sole treatment modality in biofilm-associated musculoskeletal infections.

**Question 3:** Does the local administration of vancomycin powder to the wound during surgery reduce the risk of subsequent SSI/PJI? If so, what are the risk factors associated with its use?

**Recommendation:**
No. There are no high-quality studies on vancomycin powder for the prevention of PJIs. The abundance of retrospective spine literature suggests that vancomycin powder reduces the incidence of surgical site infections. However, the only RCT suggests that is has no impact.

**Level of Evidence:** Limited

**Delegate Vote:**
- Agree: 90%
- Disagree: 6%
- Abstain: 4% (Super Majority, Strong Consensus)

**Rationale:**
Local delivery of antibiotic powder has been used with the goal of delivering a high concentration of antibiotics to the wound site without the risk for systemic effects. This method has been used with some success in other surgical fields, in particular abdominal surgery before the existence of safe and effective systemic antibiotics [99]. However, vancomycin powder has gained widespread acceptance for prevention of surgical site infections (SSIs) in spinal surgery.

The use of powdered intrawound vancomycin became routine practice in spinal surgery based on evidence from more than 20 retrospective studies, which demonstrated its efficacy (Table 4) [100,101]. However, many of these retrospective studies were performed with a preintervention and postintervention study designs, in which the current practice of administering topical vancomycin powder was compared to an historical control [102,103]. Furthermore, 8 retrospective studies reported SSI rates above 11% for the control group [102,104–106]. It is likely that a publication bias contributed to the consistency of the positive signal of efficacy in retrospective studies. However, the only randomized trial did not demonstrate a reduction in risk for SSI with vancomycin powder [75].

There is not enough evidence to support the use of topical vancomycin powder outside of spine surgery. A single retrospective study on 125 patients undergoing primary total hip arthroplasty demonstrated fewer infections for patients receiving both intrawound and intravenous vancomycin compared to patients receiving only systemic prophylaxis [107]. Small studies on tibial plateau or pilon fractures and reconstructive foot and ankle surgery have demonstrated a modest improvement with topical antibiotics [104].

While the efficacy of topical vancomycin remains in question, it appears there have been few adverse effects from its use in spinal surgery. A systematic review reported only 23 complications in 6700 patients, most commonly seromas [105]. However, there have been case reports of renal insufficiency, circulatory collapse, and hearing loss that were attributed to topical vancomycin [106,108]. It is difficult to assess the contribution of topical vancomycin to bacterial resistance. The short-term exposures from topical vancomycin may be insufficient for the emergence of resistant bacteria, and no cases have yet been reported in the spine literature. However, surgeons must weigh the potential benefits of topical vancomycin against the theoretic risks of overexposure that could increase the prevalence of resistant bacterial strains.

**Question 4:** Is there a role for the use of antibiotic-loaded carriers (calcium sulfate/phosphate) in the treatment of SSI/PJI?

**Recommendation:**
The use of antibiotic-loaded carriers, specifically calcium sulfate (CaS)-based and calcium phosphate (CaP)-based materials, to locally deliver antimicrobials at sites of musculoskeletal infection, specifically SSI and PJI, have not been shown to have any beneficial effect in the management of SSI/PJI.

**Level of Evidence:** Consensus

**Delegate Vote:**
- Agree: 80%
- Disagree: 13%
- Abstain: 7% (Super Majority, Strong Consensus)

**Rationale:**
Patient care for biofilm-based and/or implant-associated infections typical of surgical site infections (SSIs) and prosthetic joint...
infections (PJJIs) presents the need for antimicrobial therapy, dead space management, and bone defect reconstruction. Besides the radical surgical debridement, administration of local and systemic antibiotics is an important part of management of PJJIs [109].

The application of the local antibiotic therapy was championed by Buchholz et al. at the Endo Klinik in 1984 with the development of antibiotic-loaded acrylic cement [110]. Numerous other antibiotics carriers have been developed. A potentially useful group is the synthetic resorbable calcium sulfate (CaS) and calcium phosphate (CaP) compounds. There are currently 4 commercial ceramic bone substitutes with approved (CE-marked) use as carriers of antibiotics. These carriers have different material formulations, degradation profiles, and are loaded with different antibiotics with different dosage. Two of the products are preset beads and two carriers are injectable. The injectable carriers are biphasic composites where hydroxyapatite particles are surrounded by an in situ setting CaS.

In vitro studies have shown that the very high local concentrations achieved with local antibiotic carriers can have an effect on the biofilm, which is a major issue in PJJIs [111,112]. A single recommended daily antibiotic dose incorporated into a biphasic resorbable carrier has been reported to result in local antibiotic levels of 100 to 1000 times the minimum inhibitory concentration for the first few days and is sustained above the MIC for up to 4 weeks [113]. The elution occurs from the resorbing CaS material, from both bulk and surface which makes the elution complete and no antibiotics are trapped nor is the release maintained over time at subinhibitory levels as with polymethyl methacrylate (PMMA), which may induce antibiotic resistance [114], ototoxicity, and nephrotoxicity [115], if patients already are suffering from renal insufficiency.

**Surgical Site Infection**

In regard to SSI, this systematic review resulted in 9 studies (Table 5). Most of these were retrospective studies with low levels of evidence. McNally et al. [94] reported a consecutive prospective series of 100 patients using a biphasic CaS/apatite carrier with gentamicin in a one-stage procedure in the treatment of long-standing chronic osteomyelitis with an infection eradication in 96% of the patients at a mean follow-up of 19.5 months.

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Number of Patients</th>
<th>Mean Follow-up (mo)</th>
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<tr>
<td>McNally et al. [94]</td>
<td>2016</td>
<td>Prospective case series</td>
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<tr>
<td>Fleiter et al. [116]</td>
<td>2014</td>
<td>Prospective open label phase 2</td>
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<td>6</td>
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<tr>
<td>Von Stechow et al. [117]</td>
<td>2009</td>
<td>Prospective case series</td>
<td>20</td>
<td>12</td>
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<tr>
<td>Drampalos et al. [118]</td>
<td>2017</td>
<td>Retrospective</td>
<td>12</td>
<td>4</td>
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<tr>
<td>Ferguson et al. [93]</td>
<td>2014</td>
<td>Retrospective</td>
<td>195</td>
<td>42</td>
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<tr>
<td>Humm et al. [119]</td>
<td>2014</td>
<td>Retrospective</td>
<td>21</td>
<td>15</td>
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<tr>
<td>Romano et al. [120]</td>
<td>2014</td>
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<tr>
<td>Chang W et al. [87]</td>
<td>2007</td>
<td>Retrospective</td>
<td>65</td>
<td>75</td>
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<tr>
<td>McKee et al. [86]</td>
<td>2010</td>
<td>Prospective RCT</td>
<td>30</td>
<td>38</td>
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</tbody>
</table>

RCT, randomized controlled trial.

In a long-term retrospective study of 65 patients using plain preset CaS beads (OsteoSet-T, Wright Medical [now MicroPort], Memphis, Tennessee) in the treatment of adult chronic osteomyelitis, no significant differences were observed in the healing rates between debridement with CaS beads (80% healing) and debridement alone (60% healing), at a mean follow-up time of 75 months [87]. However, in a subgroup of 39 patients with medullary osteomyelitis and a normal immune system (Cierny-Mader classification IA), 17 patients with debridement and CaS beads and 22 patients with debridement alone, the difference in healing rates was statistically significant in favor of using CaS beads and debridement (P < .05) [93]. In a larger retrospective series of 193 patients using CaS beads in chronic osteomyelitis, the eradication rate was 90.8% at a mean follow-up of 44 months [93].

In a retrospective study of 27 patients, the use of bioactive glass S53P4, PerOssal (BonAlive Biomaterials, Turku, Finland), or a mixture of tricalcium phosphate and an antibiotic-loaded demineralized bone matrix in chronic osteomyelitis of the long bones showed no differences between the groups and healing rates surpassing 80% at a mean follow-up time of 21 months [120].

Clinical studies consistently reported that approximately 5-15% of the patients treated with CaS carriers developed a seroma and fluid drainage, but as much as 32% was reported by McKee et al. [86]. A composite carrier consisting of CaS/hydroxyapatite has reduced the occurrence of sterile drainage to 6% [94].

There is one randomized controlled trial on the use of antibiotic-loaded ceramic carrier, where CaS beads were used in the treatment of chronic osteomyelitis and infected nonunion with standard antibiotic-impregnated PMMA beads as control [86]. In addition to demonstrating an equivalent rate of infection eradication (86% at 24 months of mean follow-up), the ceramic beads decreased the rate of secondary surgical procedures significantly (7 CaS vs 15 PMMA, P = .04) required for PMMA bead removal and bone grafting.

Ferguson et al. [93] described tobramycin-loaded CaS in the treatment of 195 cases of chronic osteomyelitis. They demonstrated clinical efficacy but had a clinically relevant wound discharge problem in over 15% of cases. The rapid dissolution of the plain CaS beads does produce a seromatous reaction.

**Periprosthetic Joint Infection**

Focusing on PJJIs, there is a paucity of robust data in the literature (Table 6). Combinations of cement spacer and CaS/phosphate...
carrier of antibiotics showed a significantly lower recurrence rate (P < .05) in the group receiving the carrier (6.6%) compared to the group with a cement spacer alone (16.1%) [124]. The use of CERAMENT G or CERAMENT V (Bonesupport, Lund, Sweden) as a coating on implants in infected revisions has shown initial implant stability in a limited 20-patient study with no signs of radiographic loosening at 12 months of mean follow-up [123]. The largest retrospective cohort study was performed by McPherson et al. This described the use of CaS beads loaded with antibiotics in 250 cases after 2-stage prosthetic revision with the use of PMMA. The rate of wound drainage in this series was 3.2% [116]. Flieler et al. described the use of plain CaS beads in 33 patients undergoing debridement and implant retention of infected total knee and hip arthroplasties. The success rates were not better than the established success rates for this procedure in the literature. The authors concluded that there is currently no indication for their use based on a lack of evidence of their efficacy in the literature and their significant cost [120]. Kallala et al. reported on 15 patients who had undergone revision procedures for PJs incorporating antibiotic-loaded CaS beads. They noted postoperative hypercalcemia in 3 patients (18%), and in one case, this required treatment. This metabolic disorder was attributed to the rapid dissolution and absorption of the plain CaS beads typically seen with this product. They alerted surgeons to this potentially dangerous side effect [90]. There is currently no high level of evidence study that proves that the use of absorbable material containing antibiotics influences the outcome of surgical management of patients with PJs. The low number of studies and low levels of evidence of the included studies are the major limitations. Due to heterogeneous cohorts, large differences in the patients’ conditions, variations in material composition, the form and administration of the materials (preset or injectable), the variation in antibiotics used, as well as the dosage make comparison between the materials difficult and not possible to draw conclusions.

Question 5: Can fresh frozen allograft be used as a carrier to deliver local antibiotics during revision arthroplasty?

Recommendation: Emerging evidence suggests that specialized preparations of antibiotic-impregnated allograft are more effective than fresh frozen allograft mixed with antibiotics.

Level of Evidence: Limited

Delegate Vote: Agree: 63%, Disagree: 14%, Abstain: 23% (Super Majority, Weak Consensus)

Rationale:
Bone allograft is one of the reconstructive options that can be used during revision arthroplasty. However, there are risks of bacterial colonization due to the fact that allografts are non-vascularized and so are not suitable for use alone during the management of periprosthetic joint infections (PJs). The addition of antibiotics to bone cement is one method to potentially reduce the risks of PJs/SSIs. However, another factor that must be taken into account in such situations is the role of the biofilms. Formation of biofilms on implant surfaces enables bacteria to evade the host immune system and to attenuate the effectiveness of antibiotics. Biofilm-embedded bacteria, therefore, require higher concentrations of antibiotics for elimination, in comparison to their planktonic counterparts [15,125].

The antibiotic carrying capability of allograft far exceeds that of bone cement [126–128]. A number of studies have reported on the use of fresh frozen allografts (FFAs) mixed with antibiotics during revision surgery for PJs [128–130]. These studies support the use of FFAs as an antibiotic carrier in aseptic revision arthroplasty, and in the second stage of 2-stage revisions. However, in such situations, only antibiotics in powder form can be added to FFAs, which limits the choice of antibiotics. Another drawback of FFAs applies to the local tissue effect of the high local antibiotic concentrations. Although some antibiotics (e.g. vancomycin or tobramycin) are tolerated very well, others show a deleterious effect on osteoblasts (e.g. ciprofloxacin) [131–133]. Nevertheless, FFAs with antibiotic powder mixed have been used clinically in sites without evident florid infection as a more prophylactic tool [128]. The generated concentrations show a burst release for some days that appear sufficient for avoiding bacterial colonizations. However, the concentrations are not maintained for a prolonged period of time, which is necessary for eliminating chronic infections mediated by biofilms [134,135].

This has led to the development of specially prepared allografts that are more suitable for 1-stage revisions due to their ability to provide the necessary high antibiotic concentrations for prolonged durations [136,137]. The use of these antibiotic-loaded allografts may be considered safe, and incorporation of allografts into the host bone seems to not be impaired [128,130,138]. The removal of bone marrow (i.e. fat and cellular components) in such allograft preparations improves the safety of allograft due to immunological reactions, increases the antibiotic storage capacity of the graft, and aids better incorporation of allograft into the host bone. Other investigators have demonstrated that antibiotics bonded to bone grafts avoid bacterial colonization and biofilm formation, thereby enhancing osteogenesis and integration of the graft and implant [139,140]. However, published literature on the clinical use of such allograft preparations is limited, and further studies are necessary to determine their long-term effectiveness [141].

References


