1.8. PREVENTION: ANTIMICROBIALS (LOCAL)

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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 TKA. 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 prior to 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 prior to injection, the antibiotic distribution is restricted "regionally" to the lower limb, similar to the manner of a "Bier's block" used in anaesthesia [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 (IVRA) of prophylactic antibiotics via cannulation of a foot vein [4–7] and demonstrated tissue concentrations two to ten 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 IVRA.

Vancomycin in particular may be suited for use with IORA. It covers resistant organisms commonly causing PJIs, such as coagulase-negative staphylococci and methicillin-resistant S*taphylococcus aureus* (MRSA) [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 gm systemic cefazolin vs. 1 gm IORA cefazolin in 22 patients, reporting tissue concertation ten 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 gm of vancomycin systemically [12]. Tissue concentrations were four to ten 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 gm 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 intraosseous (IO) injection, and the tourniquet is often deflated during prolonged revision procedures. The study found tissue concentrations of vancomycin 5 to 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 (body mass index (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 to 52) in the two groups. Tissue concentrations were five to nine times higher in the IORA versus 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 (AUC) divided by the minimum inhibitory concentration (MIC) (AUC/MIC ratio) [9], thus greater tissue concentrations may be expected to increase efficacy. An animal study comparing six prophylaxis regimes in a murine model of TKA found IORA of both cefazolin and vancomycin to be more effective than systemic prophylaxis [13], but clinical data is 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.

TABLE 1. Studies investigating the use of IVRA prophylaxis in TKA via foot vein cannulation

Study	Study Design	Patients	Findings
Hoddinott (1990) [4]	Comparative Cohort	5 patients, 1,000 mg IV cefamandole vs.750 mg IVRA cefuroxime via a foot vein in same 5 patients	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); $p < 0.001$
de Lalla (1993) [5]	RCT	24 patients comparing 800 mg IV teicoplanin 2.5 hours preoperatively vs.400 mg IVRA teicoplanin via foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2–10 times higher through the regional route

de Lalla (2000) [6]	Cohort	Clinical study of 160 patients (205 TKAs), 400 mg IVRA teicoplanin via foot vein	One superficial infection; no deep infections at 2-year follow-up
Lazzarini (2003) [7]	Comparative Cohort	5 patients 800 mg IV teicoplanin 2.5 hours preoperatively vs.15 patients 200 mg IVRA teicoplanin via a foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2 times higher through the regional route

IV, intravenous; IVRA, intravenous regional administration; RCT, randomized control trial; TKA, total knee arthroplasty

TABLE 2. Studies investigating the use of IORA prophylaxis in TKA

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

BMI, body mass index; IORA, intraosseous regional administration; TKA, total knee arthroplasty; RCT, randomized controlled trial

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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 orthopaedic infections. Other adjunctive treatment modalities need to be combined with local delivery of antibiotics.

LEVEL OF EVIDENCE: Limited

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 [1–7], the development of certain phenotypical variants, such as small colony variants and intracellular persisters [7–16], and leucocyte dysfunction in the close vicinity of the surface of implants [17], are among the most important causes of identified microbial resistance.

Systemic antibiotic treatment with duration of 6 to 12 weeks is usually recommended for non-tuberculous bone and implant-related infections [18–20], 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 [21,22]. 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 [23,24].

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 [6]. It is known that biofilm is a complex structure that matures over time [1,6]. It is also known that mature biofilm is much more difficult to eradicate than biofilm of 24 hours age or less [25–28]. Considering the time course of musculoskeletal infections, only experiments studying 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 [6,29–32]. The exact conditions in vivo are, however, not fully measurable nor understood and probably have important variability [6], but there are nonetheless physicochemical stresses acting on biofilm formation such as the host immune system. Thus, publications describing dynamic conditions are probably more valuable than those describing static conditions only. Prolonged exposure to antibiotics increases susceptibility of biofilm bacteria to antibiotics [33]. Studies examining short exposure to antibiotics with time-dependent killing effect overestimate resistance of biofilm.

A thorough search of the literature using both PubMed and Google Scholar for prolonged exposure to antibiotics (> 72 hours) of matured biofilm (> 48 hours), complemented by cross-referencing, identified the studies listed in Table 1 [34–38]. While thousands of biofilm eradication have been published, only a very small number tested 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 matured biofilm can be potentially eradicated solely by prolonged exposure to antibiotics.

Required concentrations, however, are higher and exposure times longer than those obtained from carrier materials currently available [39–41]. For many antibiotics, stability in aqueous solution and at body temperature also is limiting for local application [42]. 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 [43–45] or by the addition of antibacterial peptides [46–48], quorum-sensing inhibitors [49], biofilm-dispersing drugs [50–52] or nitric oxide [46]. Of note, the addition of ethylenediaminetetraacetic acid (EDTA) already is applied in antibiotic lock solutions for treatment of catheter-associated infection [53]. Also, n-acetylcysteine is utilized in the treatment of pulmonary infection in cystic fibrosis, a biofilm-associated disease without implant, to disperse biofilm and enhance the effect of co-administered antibiotics [52,54]. 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 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 biofilm could be eradicated within a port system by the sole action of local antibiotics combined with additives such as EDTA or L-arginine [50,55]. 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 five-day-old staphylococcal biofilm, with a potential regrowth phase of up to seven days followed by sonication [56].

TABLE 1. List of publications identified studying the effect of prolonged exposure (> 72 hours) to antibiotics on matured biofilm (> 48 hours old)

Microorganism	Biofilm Age and Substrate	Antibiotics	Test Conditions	Conclusions	Reference
Staphylococcus aureus UAMS-1	7 days old Titanium-aluminium-niobium discs	Vancomycin up to 2,000 mg/l	Static and shaking Sonication	Vancomycin ≥ 200 mg/l eradicated biofilm within 28 days under static conditions. No eradication could be obtained within 28 days under shaking conditions.	Post et al. *J Orthop Res* 2017[34]
Staphylococcus aureus ATCC 6538 and ATCC 43300 *Staphylococcus epidermidis* ATCC 35983 and ATCC 12228	4 days old Polycarbonate discs	Ceftobiprole, vancomycin, daptomycin, rifampin, and combinations of ceftobiprole + rifampin and vancomycin + rifampin, at various clinical concentrations	Static Vortexing	No more biofilm could be detected after 7 days exposure in certain combinations of strains and antibiotics. As only vortexing was performed for recovery cultures, sensitivity of the study is suboptimal and this limits interpretation of results.	Abbanat et al. *Int J Antimicrob Agents* 2014[38]
Staphylococcus aureus methicillin-resistant, clinical strain *Staphylococcus epidermidis*, methicillin-resistant, clinical strain *Enterococcus faecalis* clinical strain *Enterococcus faecium* clinical strain	7 days old Silicon tube	Vancomycin 50 mg/l or linezolid 5 mg/l 14 days exposure	Continuous flow Regrowth phase of 7 days	Both MRSA and MRSE biofilms could be eradicated by both antibiotics within < 5 days treatment. Enterococcal biofilm could not be eradicated under the conditions of the experiment.	Bayston et al. *Antimicrob Agents Chemother* 2012[37]
Cutibacterium. acnes clinical strain	6 days Titanium discs	Penicillin G 12 mg/l, linezolid 20 mg/l with or without rifampin 8 mg/l	Rolling Regrowth phase of 9 days	After 14 days treatment with penicillin G or with a combination of linezolid with rifampin, biofilm was eradicated, without late relapse.	Bayston et al. *J Antimicrob Chemother* 2007[36]

Pseudomonas aeruginosa, 23 clinical strains	12 days old Polystyrene pegs	Tobramycin 4 mg/l and/or clarithromycin 200 mg/l 28 days exposure	Static Sonication	6/23 *P. aeruginosa* biofilm eradicated after 28 days treatment by tobramycin with or without addition of clarithromycin. Synergistic effect of tobramycin with clarithromycin in 9/23 strains. No eradication by clarithromycin alone.	Tré-Hardy et al. *Int J Antimicrob Agents* 2009[35]

MRSA, methicillin-resistant *S. aureus*; MRSE, methicillin-resistant *S. aureus*

The focus of orthopaedic research has been mainly related to development and application of carrier materials that resorb in situ, in order to circumvent the known insufficiencies and disadvantages of bone cement that is currently the most preferred method of delivery of local antibiotics. Particularly, bone cement can act as a foreign body recolonized by biofilm after the initial peak release of added antibiotics [57,58]. Antibiotics have been applied locally without any carrier material or with collagen, calcium sulphate based materials in combination with calcium phosphate/calcium carbonate/hydroxyapatite, hyaluronic hydrogels, or with polymers as carrier. Bone allograft can also be used successfully as carrier for antibiotics.

Local administration of powdered antibiotics on a large scale was explored during World War II, in the very beginning of the era of antibiotics [59,60]. There is only one randomized clinical trial, which included 907 patients who underwent both instrumented and non-instrumented spinal surgery in India [61]. All patients received systemic prophylaxis with intravenous cefuroxime, the intervention group also receiving 1 gm of topical vancomycin. No significant difference in the rate of surgical site infection (SSI) 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 [42]. Reported success rates vary from 18 to 85% [62–65]. Only one study examined isolated local antibiotic administration without debridement [62]. In the only modern study, primary implants thus treated did not experience relapse and recurrence of infection was seen in all but one megaprosthesis patients [65]. This study, however, included only 12 subjects [65]. Successful eradication was observed in patients with a short duration of symptoms, susceptible gram-positive organisms, absence of a sinus tract and no prosthetic loosening [63].

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 or after sternotomy [66], when applying collagen fleece with gentamicin [67]. The benefit of the 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 ($p = 0.024$) [68]. In two very recent randomized trials, antibiotic-loaded hydrogel showed a significant reduction of SSI in 380 cases of primary or aseptic revision arthroplasty ($p = 0.003$) [69], as well as in 253 cases of internal fixation of closed fractures ($p < 0.03$) [70]. Also, calcium sulphate/calcium carbonate loaded with gentamicin, implanted at the second stage of septic revision total knee arthroplasty, showed a reduction in reinfection rate, comparing two groups of 28 patients in a retrospective study [71]. But, as discussed above, this favorable effect might be lost in treatment of 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 sulphate with bone cement as antibiotic carrier and filler material, cure rates for chronic osteomyelitis were similar, but the resorbable material did not require a second operation for removal [72]. A retrospective study of 65 cases of chronic osteomyelitis, comparing calcium sulphate loaded with tobramycin to debridement without filler material, identified a significantly better healing rate in the local antibiotic treatment group [73]. Interestingly, management of dead space around the bone in chronic osteomyelitis 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 [74,75]. In a large study investigating an absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite in chronic osteomyelitis in 100 patients with poor Cierny & Mader hosts and Type III and IV chronic osteomyelitis, infected non-union 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 [76].

Local application of antibiotics carries some adverse effects. Calcium-containing carrier materials can induce life-threatening hypercalcaemia [76–78]. 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 [39,79-81], hypercalcaemia is reported only in isolated cases. Antibiotic release can also be rapid and reaching toxic serums levels [82]. This can also be the case with calcium sulphate, depending on the quantity used, the total dose of antibiotics and the renal function of the patient [83].

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 [18–20] with adverse effects associated with administration of antibiotics [84], large-scale studies are needed to examine the role of local antibiotics as sole treatment modality in biofilm-associated musculoskeletal infections.

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QUESTION 3: Does the local administration of vancomycin powder to a wound during surgery reduce the risk of subsequent surgical site infection/periprosthetic joint infection (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 published randomized control trial (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 antibiosis to the wound site without risk for systemic effects. This method has been used with some success in other surgical fields, in particular abdominal surgery prior to the existence of safe and effective systemic antibiotics for prophylaxis [1]. However, vancomycin powder has gained widespread acceptance for prevention of SSIs in spinal surgery.

The use of powdered intra-wound vancomycin became routine practice in spinal surgery based on evidence from more than 20 retrospective studies, which demonstrated its efficacy (Table 1) [2–3]. However, many of these retrospective studies were performed with a pre- and post-intervention study design, in which the current practice of administering topical vancomycin powder was compared to an historical control [4–5]. Furthermore, 8 retrospective studies reported SSI rates above 11% for the control group [4,8–10,17,19–21]. 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 surgical site infection with vancomycin powder [6].

TABLE 1. Spine literature on vancomycin powder

Author	Year	Category	Procedure	Study Design	Sample size	Infection Outcome	Infection Rate*	OR
Tubaki	2013	Spinal Surgery	Spinal fusion, all levels	Prospective; RCT	907	Superficial and deep	1.6% vs. 1.7%	0.96
Dennis	2016	Spinal Surgery	Instrumented spinal fusion	Retrospective; Consecutive	389	Superficial and deep	0.8% vs. 6.3%	0.13
Gaviola	2016	Spinal Surgery	Multilevel spinal fusion	Retrospective; Consecutive	326	Superficial and deep	5.2% vs. 11%	0.26
Ross	2016	Spinal Surgery	Lumbar fusion	Retrospective; Consecutive	210	Deep	0% vs. 5%	0.13
Martin	2015	Spinal Surgery	Posterior cervical fusion	Retrospective; Consecutive	289	Deep	5.2% vs. 6.9%	0.74
Theologis	2014	Spinal Surgery	Multilevel spinal fusion for deformity	Retrospective; Consecutive	215	Superficial and deep	2.6% vs. 10.9%	0.22
Hill	2014	Spinal Surgery	Posterior spinal fusion, all levels	Retrospective; Consecutive	300	Superficial and deep	1.5% vs.5.5%	0.44
Emohare	2014	Spinal Surgery	Posterior thoracolumbar fusion	Retrospective; Consecutive	303	Superficial and deep	5.2% vs. 5.8%	0.89
Godil	2013	Spinal Surgery	Posterior spinal fusion for trauma	Retrospective; Consecutive	110	Superficial and deep	0% vs. 13%	0.06

Schroeder	2016	Spinal Surgery	Spinal fusion, all levels	Retrospective; Pre-post	3477	Deep	0.4% vs. 1.3%	0.30
Heller	2015	Spinal Surgery	Posterior instrumented fusion	Retrospective; Pre-post	683	Superficial and deep	2.6% vs. 5.3%	0.48
Tomov	2015	Spinal Surgery	Spinal fusion, all levels	Retrospective; Pre-post	3598	Superficial and deep	1.3% vs. 2.4	0.53
Martin	2014	Spinal Surgery	Thoracolumbar fusion for deformity	Retrospective; Pre-post	306	Deep	5.1% vs. 5.2%	0.96
Strom	2013	Spinal Surgery	Posterior cervical fusion	Retrospective; Pre-post	171	Superficial and deep	2.5% vs 10.9%	0.21
Kim	2013	Spinal Surgery	Spinal fusion, all levels	Retrospective; Pre-post	74	Superficial and deep	0% vs. 12.5%	0.09
Strom	2013	Spinal Surgery	Lumbar fusion	Retrospective; Pre-post	253	Superficial and deep	0% vs. 11%	0.02
Caroom	2013	Spinal Surgery	Posterior cervical instrumented fusion	Retrospective; Pre-post	112	Superficial and deep	0% vs. 15%	0.07
Pahys	2013	Spinal Surgery	Posterior cervical procedures	Retrospective; Pre-post	2001	Deep	0% vs. 1.9%	0.13
Rahman	2011	Spinal Surgery	Multilevel spinal fusion for deformity	Retrospective; Pre-post	920	Deep	0.7% vs. 5%	0.14
Sweet	2011	Spinal Surgery	Posterior thoracolumbar instrumented fusion	Retrospective; Pre-post	1732	Deep	0.2% vs. 2.6%	0.08
Singh	2015	Trauma	Tibial plateau and pilon fracture ORIF	Retrospective; Consecutive	93	Deep	10% vs. 16.7%	0.55
Yan	2014	Shoulder and elbow	Open release of traumatic stiff elbow	Retrospective; Consecutive	272	Superficial and deep	0% vs. 6.5%	0.04

Wukich	2015	Foot and ankle	Foot and ankle surgery in diabetics	Retrospective; Pre-post	162	Superficial and deep	4.9% vs. 18.5%	0.27
Omrani	2015	Adult reconstruction	Total hip arthroplasty	Retrospective; Consecutive	125	Superficial and deep	NA	NA

OR, odds ratio; ORIF, open reduction and internal fixation
*Intervention vs. control infection rate

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 intra-wound and intravenous vancomycin compared to patients receiving only systemic prophylaxis [7]. Small studies on tibial plateau or pilon fractures and reconstructive foot and ankle surgery have demonstrated a modest improvement with topical antibiotics [8].

While the efficacy of topical vancomycin remains in question, it appears that there have been few adverse effects from its use in spinal surgery. A systematic review reported only 23 complications in 6,700 patients, most commonly seromas [9]. However, there have been case reports of renal insufficiency, circulatory collapse and hearing loss that were attributed to topical vancomycin [10–11]. 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.

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QUESTION 4: Is there a role for the use of antibiotic-loaded carriers (calcium sulfate/calcium phosphate (CaS/CaP) in the treatment of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The use of antibiotic-loaded carriers, specifically CaS and 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 SSIs and PJIs 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 PJIs [1].

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 (ALAC) [2]. Numerous other antibiotics carriers have been developed. A potentially useful group are the synthetic resorbable CaS and CaP compounds. There are currently four 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 pre-set beads and two carriers are injectable. The injectable carriers are biphasic composites where hydroxyapatite particles are surrounded by an in situ setting calcium sulfate.

In vitro studies have shown that the very high local concentrations achieved with local antibiotic carriers can have an effect on biofilm, which is a major issue in PJIs [3,4]. A single recommended daily antibiotic dose incorporated into a biphasic resorbable carrier has been reported to result in local antibiotic levels of 100 to 1,000 times of the minimum inhibitory concentration (MIC) for the first few days and is sustained above the MIC for up to four weeks [5]. The elution occurs from the resorbing calcium sulphate material, from both bulk and surface which makes the elution complete and no antibiotics are trapped, nor is the release maintained over time at sub-inhibitory levels as with polymethyl methacrylate (PMMA), which may induce antibiotic resistance [6], ototoxicity and nephrotoxicity [7], if patients already are suffering from renal insufficiency.

Surgical Site Infection

In regard to SSI, this systematic review resulted in nine studies **(**Table 1**)**. Most of these were retrospective studies with low levels of evidence. McNally et al. [8] 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 longstanding chronic osteomyelitis with an infection eradication in 96% of the patients at a mean follow-up of 19.5 months.

In a long-term retrospective study of 65 patients using plain preset calcium sulphate 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 calcium sulphate beads (80% healing) and debridement alone (60% healing), at a mean follow-up time of 75 months [9]. However, in a subgroup of 39 patients with medullary osteomyelitis and a normal immune system (Cierny-Mader classification IA), 17 patients with debridement and calcium sulphate beads and 22 patients with debridement alone, the difference in healing rates was statistically significant in favor of using calcium sulphate beads and debridement ($p < 0.05$) [9]. In a larger retrospective series of 193 patients using calcium sulphate beads in chronic osteomyelitis the eradication rate was 90.8% at a mean follow-up of 44 months [10].

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 [11].

In a prospective study using Herafill (Heraeus Medical, Hanau, Germany), a preset carbonate sulphate composite in the treatment of osteomyelitis reported on infection eradication in 16 out of 20 patients at a mean follow-up of six months [12]. Smaller series of patients show consistently higher success rates [13–15].

Clinical studies consistently reported that approximately 5 to 15% of the patients treated with calcium sulfate carriers developed a seroma and fluid drainage, but as much as 32% was reported by McKee et al. [16]. A composite carrier consisting of calcium sulfate/hydroxyapatite has reduced the occurrence of sterile drainage to 6% [8].

There is one randomized controlled trial on the use of antibiotic-loaded ceramic carrier, where calcium sulfate (CS) beads were used in the treatment of chronic osteomyelitis and infected nonunion with standard antibiotic-impregnated PMMA beads as control [16]. In addition to demonstrating an equivalent rate of infection eradication (86% at 24 months mean follow-up), the ceramic beads decreased the rate of secondary surgical procedures significantly (7 CS vs. 15 PMMA, $p = 0.04$) required for PMMA bead removal and bone grafting.

Ferguson et al. [10] described tobramycin-loaded calcium sulfate 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 calcium sulphate beads does produce a seromatous reaction.

TABLE 1. Included studies for SSI

Author	Year	Study Design	Number of Patients	Mean Follow-Up (Months)
McNally [8]	2016	Prospective case series	100	19
Fleiter [21]	2014	Prospective open label phase 2	20	6
Von Stechow [22]	2009	Prospective case series	20	12
Drampalos [23]	2017	Retrospective	12	4
Ferguson [10]	2014	Retrospective	195	42

Humm [15]	2014	Retrospective	21	15
Romano [11]	2014	Retrospective	27	22
Chang [9]	2007	Retrospective	65	75
McKee [16]	2010	Prospective RCT	30	38

RCT, randomized clinical trial; SSI, surgical site infection

TABLE 2. Included studies for PJI

Author	Year	Study Design	Number of Patients	Mean Follow-Up (Months)
Logoluso [18]	2016	Prospective case series	20	12
McPherson 19]	2013	Prospective trial	250	12
Flierl [21]	2017	Retrospective	32	12.7
Kallala [20]	2015	Retrospective	15	16
Sakellariou [17]	2015	Prospective trial	46	36

PJI, periprosthetic joint infection

Perirprosthetic Joint Infection

Focussing on PJIs, there is a paucity of robust data in the literature (Table 2). Combinations of cement spacer and calcium sulfate/phosphate carrier of antibiotics showed significantly lower recurrence rate ($p < 0.05$) in the group receiving the carrier (6.6%) compared to the group with cement spacer alone (16.1%) [17].

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 a mean follow-up of 12 months [18].

The largest retrospective cohort study was performed by McPherson et al. This described the use of calcium sulfate beads loaded with antibiotics in 250 cases after two-stage prosthetic revision with the use of PMMA. The rate of wound drainage in this series was 3.2% [19].

Flierl et al. described the use of plain calcium sulfate 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 [12].

Kallala et al. reported on 15 patients who had undergone revision procedures for PJIs incorporating antibiotic-loaded calcium sulfate beads. They noted postoperative hypercalcemia in three patients (18%) and in one case this required treatment. This metabolic disorder was attributed to the rapid dissolution and absorption of the plain calcium sulfate beads typically seen with this product. They alerted surgeons to this potentially dangerous side effect [20].

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 PJIs. 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 (pre-set or injectable), the variation in antibiotics used as well as the dosage, makes comparison between the materials difficult and not possible to draw conclusions.

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QUESTION 5: Can fresh-frozen allograft (FFA) 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 FFA 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 they are not suitable for use alone during the management of periprosthetic joint infections (PJIs). The addition of antibiotics to bone cement is one method to potentially reduce the risk of PJIs and surgical site infections (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 bacteriae to evade the host immune system, as well as to attenuate the effectiveness of antibodies. Biofilm-embedded bacteria, therefore, require higher concentrations of antibiotics for elimination, in comparison to their planktonic counterparts [1,2].

The antibiotic-carrying capability of allograft far exceeds that of bone cement [3–5]. A number of studies have reported on the use of FFAs mixed with antibiotics during revision surgery for PJIs [5–7]. These studies support the use of FFAs as an antibiotic carrier in aseptic revision arthroplasty and in the second stage of two-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. While some antibiotics (e.g., vancomycin

or tobramycin) are tolerated very well, others show a deleterious effects on osteoblasts (e.g., ciprofloxacin) [8–10]. Nevertheless, FFAs with antibiotic powder mixed have been used clinically in sites without evident florid infection as a more prophylactic tool [5]. 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 [11,12].

This has led to the development of specially-prepared allografts that are more suitable for one-stage revisions, due to their ability to provide the necessary high antibiotic concentrations for prolonged durations [13,14]. The use of these antibiotic-loaded allografts may be considered safe and incorporation of allografts into the host bone seems to not be impaired [5,7,15]. 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 [16,17]. However, published literature on the clinical use of such allograft preparations is limited and further studies are necessary to determine their long-term effectiveness [18].

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