

## 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)?

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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)

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### 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

### Periprosthetic 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 PJI 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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