Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite

A PROSPECTIVE SERIES OF 100 CASES

Aims
Chronic osteomyelitis may recur if dead space management, after excision of infected bone, is inadequate. This study describes the results of a strategy for the management of deep bone infection and evaluates a new antibiotic-loaded biocomposite in the eradication of infection from bone defects.

Patients and Methods
We report a prospective study of 100 patients with chronic osteomyelitis, in 105 bones. Osteomyelitis followed injury or surgery in 81 patients. Nine had concomitant septic arthritis. 80 patients had comorbidities (Cierny-Mader (C-M) Class B hosts). Ten had infected nonunions.

All patients were treated by a multidisciplinary team with a single-stage protocol including debridement, multiple sampling, culture-specific systemic antibiotics, stabilisation, dead space filling with the biocomposite and primary skin closure.

Results
Patients were followed up for a mean of 19.5 months (12 to 34). Infection was eradicated in 96 patients with a single procedure and all four recurrences were successfully managed with repeat surgery. Adverse events were uncommon, with three fractures, six wound leaks and three unrelated deaths. Outcome was not dependant on C-M host class, microbial culture, wound leakage or presence of nonunion.

Conclusion
This single-stage protocol, facilitated by the absorbable local antibiotic, is effective in the treatment of chronic osteomyelitis. It offers a more patient-friendly treatment compared with other published treatment options.

Cite this article: Bone Joint J 2016;98-B:1289–96.

Chronic osteomyelitis is a devastating complication after trauma or orthopaedic surgery. Patients may present with multiple comorbidities, poor soft tissues and multi-resistant organisms, having endured prolonged unsuccessful treatment over many years.

Staged surgical treatment is common, with repeated debridement and delayed skin closure. Further operations may be required to remove polymethylmethacrylate (PMMA) antibiotic-loaded beads or to reconstruct bone defects. Recently, negative pressure wound therapy (NPWT), has been combined with multiple debridement, increasing the number of revision procedures but not improving the rate of resolution of osteomyelitis.

There is now increasing interest in developing a one-stage approach, which might be more patient friendly. This requires effective dead space management, to eradicate the infection and prevent the need for secondary bone grafting.

In animal studies, Branstetter et al showed that local antibiotics in calcium sulphate eradicated bacteria better after debridement when compared with calcium sulphate alone. Rand, Penn-Barwell and Wencke confirmed that local delivery of antibiotics into an infected bone defect, with or without an implant, was superior to systemic antibiotics alone at 14 days after surgery. Xie et al compared debridement alone with bioglass, antibiotic-loaded calcium sulphate (CS) and antibiotic-loaded bioglass in a rabbit methicillin resistant staphylococcus aureus (MRSA) osteomyelitis model. Bioglass alone was no better than
debridement, but both antibiotic-loaded materials were highly effective. CS-based materials are effective for eradicating infection in humans, but bone formation in the defects caused after excision of infected bone is unreliable, with pathological fractures occurring in 5% to 8% of patients.

The combination of CS and hydroxyapatite (HA) in a synthetic, injectable composite is, however, more promising. The biphasic resorption of CS/HA forms an osteoconductive scaffold and leads to an early biological response. This combination may be both osteoinductive and osteoconductive and is now available loaded with gentamicin (175 mg gentamicin in 10 mls CS/HA: CERAMENT G; Bonesupport, Lund, Sweden). It has been shown that CERAMENT G injected into osteomyelitic bone voids, decreased the rate of infection and increased bone formation in a rat osteomyelitis model.

We present the first series of patients with chronic osteomyelitis treated with a one-stage surgical protocol, using CERAMENT G in dead space management.

**Patients and Methods**

**Inclusion criteria.** All patients presenting with possible Cierny-Mader (C-M) Type III (Localised) and Type IV (Diffuse) chronic osteomyelitis were recruited into this study. The patients were assessed by both orthopaedic and plastic surgeons specialising in bone infections, as well as by a microbiologist/infectious disease physician.

Chronic osteomyelitis was defined as having symptoms for a minimum of six months with clinical and radiological features accompanied by at least one of the following: the presence of a sinus, an abscess or intra-operative pus, supportive histology, or two or more microbiological cultures with indistinguishable organisms. When cultures were negative, a patient was only included in the study when there was positive histology, with the presence of a draining sinus or intra-operative pus. Infected nonunions were included if the bone loss was < 1 cm at presentation. Exclusion criteria included diabetic foot infections, patients with calcium metabolism disorders or a known allergy to CS, HA or aminoglycosides and patients with renal failure.

A total of 106 consecutive patients were recruited between March 2013 and February 2015. However, six patients were excluded because intra-operative microbiological and histological samples did not meet the diagnostic criteria. The remaining 100 patients (65 male, 35 female) with infection involving 105 bones, were included. No patient was excluded due to known gentamicin allergy or renal compromise. Their mean age was 51.6 years (23 to 88). All patients were reviewed at a mean of 19.5 months (12 to 34), except one patient who died of a drug overdose five months into the study.

**Data collection.** Demographics, comorbidities, aetiology of infection, clinical features, diagnostic tests, antibiotic treatment choice and duration, were collected prospectively.

The extent of bony involvement (C-M anatomical type) was determined at operation. The host’s physiological status was recorded at presentation as either Class A (no comorbidities), Class B (local compromise in the affected limb), Class B (systemic compromise) or Class B (local and systemic comorbidities). Radiological and microbiological outcomes were confirmed by two assessors who were not involved in the management of the patients.

**Surgical management.** All patients were treated according to a single-stage protocol for chronic osteomyelitis. Where possible, a tourniquet was used. Multiple deep intra-
operative samples were taken, using an established protocol. Sinus tracts were excised and infected implants removed with excision continuing until healthy, bleeding bone was exposed. After excision, the area was irrigated with 0.05% aqueous chlorhexidine solution and the cavity dried by packing with gauze. If instability was present, stabilisation was provided by external or internal fixation.

After changing of drapes and gloves, the dry dead space was filled with CERAMENT G (Fig. 1). No additional material or antibiotic was added and primary skin closure was achieved either directly or by local or free microvascular muscle flaps.

**Antibiotic management.** Antibiotic therapy was stopped in all patients at least two weeks prior to surgery, provided it was safe to do so. During surgery, patients were given intravenous vancomycin (continued as 1 g every 12 hours initially) and meropenem (500 mg every eight hours initially) after samples had been taken. This empirical antibiotic regime (a glycopeptide and a carbapenem) has been shown to be effective against 96% of the isolated organisms in a similar heterogeneous cohort of patients with osteomyelitis.

**Outcomes.** The primary outcome was eradication of infection at a minimum of one year after surgery. Failure of treatment was defined as recurrent infection with positive cultures from further radiologically guided aspiration or biopsy; recurrent sinus formation; further surgery performed for infection; or any patient requiring antibiotic treatment for persisting symptoms.

Secondary outcomes were death, need for re-operation, pathological fracture at the site of surgery and disturbance of wound healing.

**Statistical analysis.** Data were collated using Microsoft Excel (Redmond, Washington) and analysed with SPSS v20 (SPSS Inc., Chicago, Illinois). Patient data were regarded as non-parametric and groups were compared using the chi-squared test for low frequency variables. A p-value < 0.05 was considered significant.

**Results.**

**Patients.** The C-M classification defined 78 patients as Type III and 22 as Type IV. A total of 80 patients (80%) were Class B hosts (Table I). Nine patients had septic arthritis of an adjacent joint (three shoulders, two elbows, three ankles, one wrist) and ten had infected nonunion (four tibiae, three femurs, three humeri). Chronic osteomyelitis most commonly followed a history of an open fracture or following fixation of closed fractures (71 patients). A total of 19 patients had haematogenous infection, six had infection after elective surgery (osteotomy, ligament repair, arthroscopy or fusion) and four followed a soft-tissue injury without a fracture.

The tibia, femur and humerus were the most commonly involved bones, with five patients having two bones involved (Table I).

**Microbiology.** Staphylococci were the most common organism (41 cultures; 41.8%), with MRSA in six patients (Table II). *Proteus mirabilis* and *Pseudomonas spp* were more common in polymicrobial infection, often with a gram-positive organism, usually *Staphylococcus aureus*. A total of 16 patients cultured organisms which were shown to be gentamicin resistant using EUCAST breakpoints. Of these,
some organisms exhibited intrinsic (*Salmonella enteriditis*, streptococci) and high level resistance (*enterococci*). Gentamicin resistance was just as likely to be present in patients with haematogenous infections (3/19; 15.8%) as in patients following trauma (13/81; 16%) (chi-squared test, \( p = 0.978 \)). Gentamicin resistant organisms were more likely to be in polymicrobial infections (9/21; 42.8%) than in single isolates (7/79; 8.9%) (chi-squared test, \( p < 0.001 \)).

**Recurrence of infection.** Infection was eradicated in 96 out of 100 patients by a single-stage operation. Recurrence occurred in four patients (Table III). Recurrence was no more likely with a resistant organism (1/16; 6.25%) than after fully sensitive cultures (3/84; 3.6%; chi-squared test, \( p = 0.62 \)). Physiological host class did not predict the likelihood of recurrence (1/20 Class A; 5% vs 3/80 Class B; 3.75%; chi-squared test, \( p = 0.799 \)). At final follow-up, all four patients remained infection-free at 13, 16, 17 and 20 months after revision surgery. All ten infected nonunions were infection-free at final follow-up; eight were united with planned primary surgery alone (Table IV).

### Table II. Microbiological results by aetiology of infection

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Total</th>
<th>Post-fracture</th>
<th>Haematogenous</th>
<th>Infection after soft-tissue injury</th>
<th>Infection following elective surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>30</td>
<td>18 (1)</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>MRSA</td>
<td>6</td>
<td>3 (1)</td>
<td>1</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>CoNS</td>
<td>5</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas spp</em></td>
<td>7</td>
<td>5 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>5</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter spp</em></td>
<td>5</td>
<td>3 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacteria spp</em></td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Achromobacter spp</em></td>
<td>3</td>
<td>(1)</td>
<td></td>
<td>1</td>
<td>(1)</td>
</tr>
<tr>
<td><em>Proteus spp</em></td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bacillus spp</em></td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus spp</em></td>
<td>5</td>
<td>(6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides spp</em></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus spp</em></td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td><em>Klebsiella spp</em></td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
<td>(1)</td>
</tr>
<tr>
<td><em>Morganella spp</em></td>
<td>3</td>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Citrobacter</em></td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Propionobacteria spp</em></td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Serratia spp</em></td>
<td>1</td>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella spp</em></td>
<td>1</td>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Clostridia spp</em></td>
<td>1</td>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>21</td>
<td>10(7)</td>
<td></td>
<td>1</td>
<td>1(1)</td>
</tr>
</tbody>
</table>

MSSA, methicillin sensitive *Staphylococcus aureus*; CoNS, coagulase negative *Staphylococcus*; MRSA, methicillin resistant *Staphylococcus aureus*

Numbers in parentheses are organisms which exhibit gentamicin resistance

### Table III. Details of recurrent infections

<table>
<thead>
<tr>
<th>Case</th>
<th>Site</th>
<th>Aetiology</th>
<th>Cierny-Mader stage</th>
<th>Initial surgery</th>
<th>Days to recurrence</th>
<th>Initial microbiology</th>
<th>Recurrent microbiology</th>
<th>Revision treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Distal Radius</td>
<td>Fracture with ORIF</td>
<td>III A</td>
<td>Excision 4 mls CG</td>
<td>156</td>
<td>No growth</td>
<td>MSSA Serratia marcescens</td>
<td>Drainage of abscess only</td>
</tr>
<tr>
<td>2</td>
<td>Tibial diaphysis</td>
<td>Gunshot wound to tibia</td>
<td>III B</td>
<td>Excision 30 mls CG Latissimus dorsi free flap</td>
<td>214</td>
<td>MSSA</td>
<td>MSSA Streptococcus agalactiae</td>
<td>Revision excision 20mls CG</td>
</tr>
<tr>
<td>3</td>
<td>Femur diaphysis</td>
<td>Open femoral fracture with ORIF</td>
<td>III B</td>
<td>Excision 20 ml CG Monolateral external fixator</td>
<td>563</td>
<td>Resistant <em>Pseudomonas spp.</em></td>
<td>Resistant <em>Pseudomonas spp.</em></td>
<td>Revision excision with Amikacin in Calcium Sulphate</td>
</tr>
<tr>
<td>4</td>
<td>Calcaneum</td>
<td>Heel shift Osteotomy</td>
<td>III B</td>
<td>Excision 6 mls CG Direct closure of previous ALT Flap</td>
<td>145</td>
<td>MSSA</td>
<td>MSSA</td>
<td>Revision excision 8mls CG Gracilis Muscle Flap</td>
</tr>
</tbody>
</table>

CG, CERAMENT G; MSSA, methicillin-sensitive *Staphylococcus aureus*; ALT, anterolateral fasciocutaneous thigh flap; ORIF, open reduction and internal fixation
All five joint fusions healed with no recurrence of infection at final follow-up.

Complications. Three patients died of causes unrelated to the osteomyelitis or surgery. Table IV summarises the main complications and unplanned re-operations.

A total of 94 patients had normal wound healing. Six patients had white wound drainage which had the appearance of liquefied CS residue. It was managed expectantly with dressings and required no other intervention. Leakage was most common in distal tibial cases (4/6) when no muscle flap was used. No patient with early wound drainage developed a recurrence of infection.

A total of 11 patients had signs of minor extraosseous leakage of CERAMENT G into the surrounding soft tissues which was visible on the radiograph. This was not related to the volume of the material used, the site of infection or the soft-tissue cover. It was managed expectantly with dressings and required no other intervention. Leakage was most common in distal tibial cases (4/6) when no muscle flap was used. No patient with early wound drainage developed a recurrence of infection.

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Of note, there was no statistically significant difference in recurrence rate, fracture rate, wound leak or extraosseous collection between those with a history of a fracture and the remaining patients. Nor was there any difference between patients treated with flaps and those treated with direct wound closure, or with those with differing C-M stage, although the numbers with complications were small.

Discussion

In 1931, Kulowski, showed that Orr’s method, (radical excision, immobilisation and open wound dressings), was successful in 74% of 130 patients with chronic osteomyelitis, at one year after surgery. This was without antibiotics or skin closure.

Since then, principles of treatment have evolved which have confirmed the place of adequate excision and stabilisation but have also added careful diagnostic sampling, antimicrobial therapy, dead space management and soft-tissue closure. Despite these advances, there remains a significant risk of recurrence.

In recent years, staged surgery, involving repeated excisions, placement of PMMA-gentamicin loaded beads or rods, or irrigation systems and delayed skin closure, has been used to improve outcomes. However, PMMA carriers have to be removed, as they prevent bone ingrowth and can lead to antibiotic resistance. Multi-stage surgery often requires prolonged hospital stay with high costs. Also outcomes have been variable, with infection recurrence rates commonly reported to be above 10%. Despite these advances, there remains a significant risk of recurrence.

On the other hand, bioabsorbable antibiotic-impregnated materials offer the possibility of single-stage surgery, with reduced hospital stay and a more patient friendly approach to treatment. In this study, we were able to treat chronic osteomyelitis in all patients with a single operation. The low recurrence rate of 4% at a minimum of one year.
follow-up, is encouraging as the series included many patients with medical comorbidities, polymicrobial cultures and segmental involvement. In previous studies, these features were associated with higher recurrence rates of up to 27%. In this study, we found no correlation between C-M physiological grade or polymicrobial infection and recurrence. This suggests that the single-stage approach with high bioavailability local antibiotics is a robust management strategy, applicable across a wide range of patients.

Recent papers describing similar cohorts using various methods of dead space management (CS, bioglass, PMMA rods, biocomposite granules, antibiotic-loaded demineralised bone matrix), have reported recurrence rates of 9% to 37.5% at a similar follow-up period. Our lower rate with CERAMENT G may reflect the increased ability of an injectable delivery system to coat the bone over areas which may harbour residual bacteria, or small fragments of biofilm. The high level of a bacteriocidal antibiotic from CERAMENT G acts at an important time, when most...
residual bacteria will be in planktonic form, following adequate debridement.

The use of implanted local antibiotics removes concerns about compliance with antibiotic therapy and systemic toxicity. CERAMENT G delivers a burst of gentamicin with high local concentrations, around 100 times above the minimal inhibitory concentration (MIC) for gentamicin sensitive Staphylococcus aureus or Pseudomonas species in in vitro testing. Rapid dissolution prevents a prolonged period of low-level antibiotic release, thus reducing the risk of gentamicin resistance.

In this study we successfully treated bacteria which were gentamicin resistant on laboratory testing. Resistance reporting is based on exposing bacteria to levels of antibiotic, which can be given systemically without toxicity. The survivability of bacteria when exposed to very high levels of antibiotics, up to 100 times above serum concentrations, is unknown.

Previous studies on antibiotic-loaded CS, have reported prolonged wound drainage affecting 15% to 32% of patients. In our series, wound leakage was infrequent and was mainly related to poor skin cover around the distal tibia. In all patients, we managed wound or extraosseous leaks expectantly, providing the patient was well. We do not believe that these leaks are an indication for re-operation and we found that it had no relationship with later recurrence of infection. This has also been described for other absorbable antibiotic carriers.

The low fracture rate in our study may reflect the higher stability achieved with an injectable in situ hardening material. The compressive strength of CERAMENT G is similar to that of cancellous bone in in vitro biomechanical testing. The inclusion of HA, which is not passively dissolved, may provide a longer-lasting scaffold for bone formation. Serial radiographs over the follow-up period demonstrated bone remodelling in the majority of patients. Bone formation appears to progress from the periphery of the material (Fig. 2). Progressive remodelling is governed by Wolff's law and will stop once sufficient bone has been formed to cope with daily load bearing. It is unlikely that large central medullary zones will fill with new bone after cortical integrity has been restored.

This study is limited by the relatively short follow-up and by patient selection. We have not investigated this material in large segmental defects and would not recommend its use for this indication without further study. Our limited clinical experience suggests that CERAMENT G would not have adequate mechanical strength to support a segmental defect without supplementary fixation.

There are many important principles of treating chronic osteomyelitis, including: obtaining multiple bacteriological samples, performing a thorough debridement with metalwork removal, ensuring adequate osseous stabilisation, eliminating the dead space and providing sufficiently vascularised soft-tissue cover. We accept that the low recurrence rate of this study is not solely due to the CERAMENT G. In our Institution, we have previously used different types of biodegradable antibiotic carriers as adjuncts in the treatment of chronic osteomyelitis in the same surgical protocol.

We have previously described our experience of using calcium sulphate pellets with tobramycin in 195 patients, with an infection recurrence rate of 9.3% and an associated wound leak rate of 15.4%, which is higher than the recurrence rate and wound leak rate in this series.

In conclusion, we report a large series of patients, managed with a single-stage protocol, facilitated by the use of CERAMENT G as a bioabsorbable dead space filler. This protocol delivered low recurrence rates with few re-operations or complications over a one- to three-year follow-up period. Our initial experience shows that this offers a patient-friendly treatment which merits further study.

Take home message:
This single-stage protocol, facilitated by the absorbable local antibiotic, is effective in the treatment of chronic osteomyelitis. It offers a more patient-friendly treatment compared with other published treatment options.

References