Local delivery of antimicrobials in the treatment of bone infections

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Abstract

Treatment of chronic osteomyelitis and infected non-unions revolves around four core principles: adequate debridement of infected bone and soft tissue, appropriate sampling for infection and targeted antibiotics, bony stabilization and soft-tissue coverage. Despite a specialist multidisciplinary approach to diagnosis and treatment, the management of chronic infection remains challenging. One of the central tenets of the surgical treatment of osteomyelitis is to ensure that the dead space left at the end of the surgery is appropriately managed. Whilst the key factor is undoubtedly the filling of the defect with healthy vascularized tissue, an attractive option to augment dead space management and maximize local antibiotic delivery is to use an antibiotic carrier that can fill the void and deliver high concentrations of local antibiotics. In this article, we will discuss the importance of local delivery of antibiotics as part of the debridement and dead space management, and we will describe the Oxford protocol.

Keywords ceramic antibiotic carrier; Cierny–Mader; dead space; infected non-union; local antibiotics; osteomyelitis; Oxford protocol; weber cech

Introduction

Long bone osteomyelitis describes infection, typically bacterial, and the associated inflammatory response of bone to the infection. Despite the overall decrease in incidence of osteomyelitis and infected non-unions since the introduction of antibiotics in the 1940s, the incidence of chronic osteomyelitis is on the increase, especially in developed countries, and this is likely due to a combination of factors including ageing of the population, the increased prevalence of trauma, the rising prevalence of diabetic foot infections and improvements in the diagnosis of the disease. Osteomyelitis following trauma remains the most common cause, with infection rates in open long bone fractures ranging between 4% and 64%, whereas recurrence rates following bony infection have been reported to be as high as 20–30%.

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Treatment of chronic osteomyelitis and infected non-unions requires delivery of four core principles:

1) adequate debridement of infected bone and soft tissue
2) appropriate sampling for microbiological diagnosis
3) targeted antibiotics (empiric followed by culture-specific)
4) bony stabilization and soft-tissue coverage.

Despite a specialist multidisciplinary approach to diagnosis and treatment, the management of chronic osteomyelitis remains challenging.

In chronic osteomyelitis, infected metalwork and dead sequestered bone become a nidus for infection with the formation of a bacterial colony biofilm. The presence of this biofilm significantly undermines the body's ability to mount an effective immune response. Adequate debridement of infected and dead bone must include removal of all metalwork and adequate excision of this dead bone and biofilm. At the end of adequate debridement, the whole operative field will be contaminated with bacteria disseminated during the procedure. Bone is an unyielding tissue so any defect left at the end of the surgery will remain and will fill with haematoma. This poorly perfused, low oxygen and low pH environment provides an ideal medium for the persistence of planktonic bacteria, allowing early biofilm development. Poor soft tissue cover, together with chronic scarring in the tissues, reduces penetration of systemic antibiotics and host immune system. It has been shown in several animal studies that tissue around a chronically infected bone defects reduces levels of antibiotic given systemically to values which are below the minimum inhibitory concentration for most common bacteria. This will result in failure to eradicate the infection and increase the likelihood of microbial resistance.

The current standard of care in most UK centres includes a prolonged course (4–6 weeks) of intravenous antibiotics supported, if available, by an outpatient parenteral antibiotic therapy service. Intravenous therapy carries with it substantial risks and inconvenience to patients, and the antibiotic-related costs are approximately ten times that of oral therapy. A Cochrane review of antibiotics for treating chronic osteomyelitis reported that the remission rates at 12 months were not found to be different comparing oral and parenteral antibiotics, suggesting that oral therapy does not result in inferior outcomes. This has now been confirmed in the large OVIVA (oral versus intra-venous antibiotics) trial, in which patients had only 7 days of intravenous antibiotics, followed by either continued IV therapy or oral therapy.

One of the main tenets of the surgical treatment of osteomyelitis is to ensure that the dead space left at the end of the surgery is appropriately managed.[1,2] Whilst the key factor is undoubtedly filling of the defect with healthy vascularized tissue, an attractive option that augments dead space management and maximizes local antibiotic delivery, is to use an antibiotic carrier that can fill the void and deliver high concentrations of local antibiotics.

In this article we will discuss the importance of the local delivery of antibiotics as part of the debridement and dead space management step in treatment, and we will describe the Oxford protocol.

Local versus systemic antibiotics

Systemic antibiotics are expensive and are associated with considerable morbidity in patients. Over 30% of patients stop

antimicrobial therapy earlier than planned due to side-effects. Renal and hepatic toxicity are common, together with allergic reactions and gastrointestinal intolerance.

Local antibiotic carriers elute the drug gradually, often over weeks to months, providing sustained local antibacterial activity. They often exceed the minimum inhibitory concentration for the organisms present and potentially above the mean biofilm eradication concentration.[3] Biofilm eradication is paramount, as biofilm can confer organism resistance to antibiotics in the order of a thousand times higher than normal therapeutic concentrations.[3] Following adequate debridement, there will be very little biofilm present with static bacteria and thus the use of local antibiotics ensures that residual planktonic bacteria are killed before new biofilm and resistant colonies can be established. Local antibiotic carriers may be effective at eradicating even moderately resistant organisms in situations where systemic antibiotics would not, due to the limitations posed by systemic toxicity. Despite these high local levels, the systemic serum concentrations of antibiotic observed with the use of local carriers remain low.[4]

Local antibiotics have been used for many years and there is now convincing evidence that they are effective in preventing infection in open fractures and in treating established bone infections.

The issue of defect filling and local antibiotics is not a new one and several methods are described.

Probably the most widely used method is that of using gentamicin-loaded polymethyl methacrylate (PMMA) bone cement, which has been in widespread in clinical practice for over 40 years. A clinical example is illustrated in Figure 1. This method relies on surface diffusion of the antibiotics and the rate of antibiotic release is influenced by the surface area of the cement spacer and the concentration gradient between its surface and that of the surrounding soft tissues.[3] However, there are several drawbacks with PMMA cement. Firstly, the dose of antibiotic will be limited, as adding a high volume of drug to cement will affect its mechanical strength. Secondly, the drug must be water soluble to allow diffusion out of the cement. Thirdly, it must be thermodynamically stable at the high temperatures that occur during the exothermic curing process of the PMMA cement. Finally, because PMMA is not biodegradable, a second surgical procedure is required in order to remove the implants after the infection has been treated and the residual defect filled with viable and structural tissue. The antibiotic release seen with PMMA is initially high, during the first 48–72 hours postoperatively, but quickly falls to lower levels. This long release profile is a major drawback in osteomyelitis treatment because prolonged low-level release of antibiotics below the minimum inhibitory concentration needed to eradicate organisms may cause multi-drug-resistant organisms to predominate. Furthermore, once the antibiotic levels are too low to kill organisms the PMMA itself can become colonized and organisms are able to form a biofilm upon its surface, thereby necessitating the need for a second removal surgery which is not always ideal with a tenuous soft tissue envelope.

The need to fill the residual defect with structural graft is the basis of the Masquelet technique.[6] Originally described in 1986 for the reconstruction of extensive diaphyseal bone loss up to 25 cm in length, the reconstruction requires a two-staged approach. At the first operation, radical soft tissue and bone debridement is undertaken and a PMMA cement spacer is implanted at the site of the bone defect and the limb is stabilized with an external fixator. Any definitive soft tissue reconstruction or flap is carried out at this first stage. The cement spacer has two roles; firstly, it fills the defect and limits the invasion of fibrous tissue into the defect. Its second role is that of the biological induction of a surrounding membrane that will eventually revascularize the bone graft and prevent its resorption. At the second stage, typically about 6–8 weeks later, the cement spacer is removed ensuring that the induced membrane is minimally disturbed and the defect is filled with morcellized cancellous autologous bone graft. The bone is then stabilized with a plate or other means of fixation. This method has produced good results in terms of eradication of infection, but bone consolidation can be very slow or inadequate, resulting in multiple reoperations to secure union.

Probably the most efficient method of delivery of local antibiotics currently is the use of a combination of antibiotics with a dissolving ceramic carrier. Several authors have published significant series with good results in osteomyelitis and fracture-related infections.[7] Ceramic carriers are bioabsorbable, which negates the need for further surgery to remove implanted antibiotic spacers once they have served their purpose, and makes single-stage surgery for osteomyelitis a viable option. Furthermore, antibiotic-containing ceramic carriers have the advantage

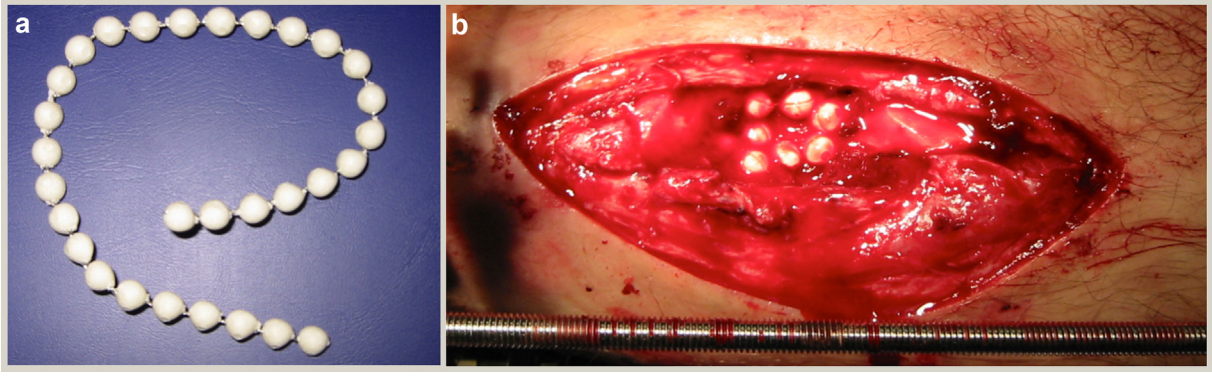

Figure 1 (**a**) A string of 30 preformed polymethyl methacrylate (PMMA) beads with gentamicin. (**b**) Osteomyelitis of the tibia, excised and defect filled with PMMA cement beads with gentamicin. The soft tissue defect will be covered with a free muscle flap. The beads must be removed at 3–4 weeks after insertion.

of producing high local antibiotic elution for a finite release time without a prolonged low-level release of antibiotics afterwards, as seen with PMMA, and the problems associated with this as described earlier. This is the basis of the Oxford protocol, which will be described below.

Ceramic antibiotic carriers

There is a wide range of inorganic ceramics available in orthopaedic surgery. Some simple molecules (calcium sulphate) can deliver drugs but will dissolve quickly, giving little mechanical support and no scaffold for osteoconduction. Other composite materials can deliver antibiotics and provide structure for bone formation.

The gold standard against which all bone graft substitutes must be compared remains autologous bone graft. Any ceramic antibiotic carrier used as bone graft in void filling must be biocompatible, bioabsorbable to avoid the need for removal surgery, able to elute high levels of local antibiotics, able to provide mechanical strength to support bone, and be at least osteoconductive to encourage new bone ingrowth and remodelling. Whilst autologous bone graft is osteoconductive, osteoinductive and osteogenic, the use of a ceramic antibiotic graft negates the need to harvest autologous bone graft with the incumbent morbidity.

The principle types of biodegradable ceramics available for antibiotic delivery are based on either calcium sulphate or calcium phosphate, with the two principle types in the latter group being tricalcium phosphate and hydroxyapatite. Preparations combining ceramics from the two groups also exist.[8] The mechanical properties, resorption time and compressive strength of the different types vary and are illustrated in Table 1.[8]

Polyphasic ceramics possess the key advantage of a bimodal distribution to their phases of resorption, and therefore their antibiotic elution and structural properties. The faster resorbing component, such as calcium sulphate, dissolves quickly allowing high early release of antibiotic, and leaves behind a porous scaffold offering more prolonged structural stability and encouraging bone ingrowth.[9] However, in order to optimize new bone formation, a balance between the rate of resorption and bone formation must be reached. If resorption of the ceramic is too slow, this will delay bone healing; conversely, if resorption is too fast the gap in the bony defect will persist and the resultant high-strain environment will mean that bony ingrowth will not occur.

The optimal resorption rate is best achieved using combinations of calcium sulphate with calcium phosphates. For example, by combining calcium sulphate and amorphous hydroxyapatite in a ceramic cement, a more porous hydroxyapatite scaffold is left behind after the calcium sulphate undergoes early dissolution. This higher porosity provides a greater available surface area for breakdown by osteoclastic activity, accelerating the resorption rate.

The antibiotic elution profiles of various ceramic antibiotic carriers have been studied extensively in vitro and in animal studies. Many have also been subject to study as part of the surgical management of chronic osteomyelitis. The reported antibiotic elution profiles of different bioceramics remain fairly similar, with the majority of carriers delivering antibiotics above the minimum inhibitory concentrations for between 3 and 4 weeks, as discussed earlier, and this is often dependent on when the antibiotic is added to the ceramic. If the antibiotic is added to the ceramic once it is in solid form, then its release is governed by diffusion alone. If, on the other hand, the antibiotic is added before the ceramic has set, then a proportion of the antibiotic may be trapped within the ceramic and only become available for release on the dissolution of the carrier.

Some of the commercially available antibiotic carriers include the following[8]

- Osteoset T, α-hemihydrate calcium sulphate pellets, with tobramycin
- Herafill G, calcium sulphate and carbonate pellets, with gentamicin
- Cerament G and Cerament V, a biphasic paste mix of calcium sulphate and nanocrystalline hydroxyapatite with gentamicin (G) or vancomycin (V)

Other unlicensed, biodegradable ceramics include Stimulan, which is a calcium sulphate injectable paste or can be provided in pellet form, to which antibiotics can be added. However, as discussed previously, this means the elution of the antibiotic is reliant entirely on diffusion and may be variable due to inadequate hand mixing.

Figures 2 and 3 illustrate clinical cases in which some of the commercially available antibiotic carriers were used.

The mechanical properties of resorption time and compressive strength of different antibiotic carriers

Material	Resorption time	Compressive strength
Calcium sulphate	6–12 weeks in bone (less in soft tissues)	Poor
Tricalcium phosphate	6–18 months	Intermediate
Calcium phosphate	Up to 10 years	Excellent
Hydroxyapatite (in one of two forms):		
• Amorphous precipitated, low-temperature form	6–12 months	Excellent
• Sintered, high-temperature form	More than 10 years	Excellent

Table 1

Outcomes of various ceramic antibiotic carriers

The different ceramic antibiotic carriers have been investigated extensively and reported in the literature, particularly Osteoset T[7] and Cerament G.[10] Ferguson et al.[8] looked at the outcomes of chronic long bone osteomyelitis in humans treated with commercially available antibiotic carriers. The infection recurrence rate ranged between 4% and 20% for most of the studies, with one small series of 6 patients claiming a 0% infection recurrence rate. Of these, the only study investigating a commercially available biphasic cement (Cerament G)[10] showed the lowest infection recurrence rate of 4%. Eighty of the 100 cases in this large study were patients with poor Cierny–Mader host status, and Type 3 and 4 chronic osteomyelitis, infected nonunion and concomitant septic arthritis. Despite the significant comorbidities that would normally predict a high recurrence rate, the recurrence rate was one of the lowest.

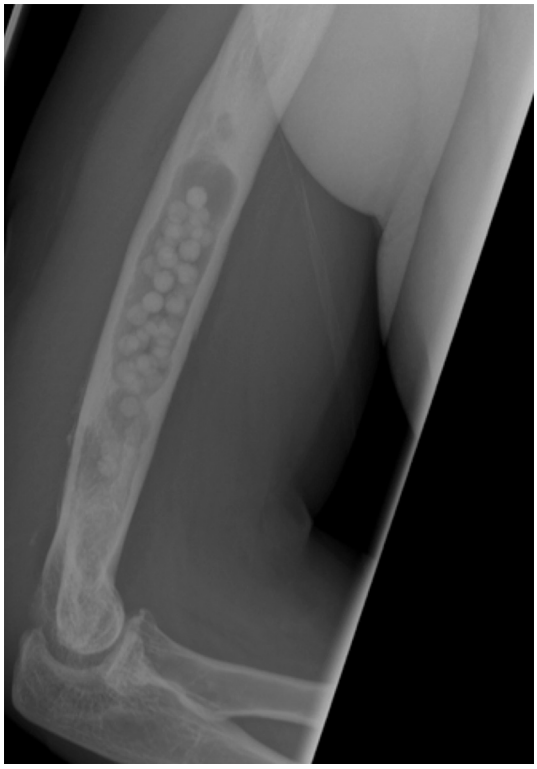

Figure 2 Calcium sulphate pellets with gentamicin used to fill the medullary canal of a Cierny–Mader Type 1 infection of a distal humerus.

Apart from adequate debridement and appropriate antibiotics, bony stability is essential for infection healing.[11–14] There is a greater risk of fracture if there is a larger defect, particularly if it involves the cortex and thus, when planning the debridement of the dead or sequestered bone, it is important to identify and preserve any involucrum or healthy bone to augment the bony stability and continuity. Any local antibiotic carrier should offer as much mechanical support as possible and thus calcium phosphate and hydroxyapatite ceramics are the most desirable, with fracture rates as low as 3% in some series.[10] Calcium sulphate alone, has been associated with a post-surgical fracture rate of between 5% and 14%.[7]

Delayed wound healing is another concern with some of the ceramic antibiotic carriers. The rapid resorption of calcium sulphate releases a calcium-rich fluid which can cause inflammation, as described by some authors with an incidence of up to 20%. However, McNally et al.[10] had a wound leakage rate of 6% with the use of the biphasic cement carrier Cerament G and this may be due to the fact that 40% by weight of Cerament G is hydroxyapatite, meaning there is relatively less of the more soluble calcium sulphate.

The safety profile of ceramic antibiotic carriers is not of concern. None of the published series investigating ceramic antibiotic carriers have thus far demonstrated systemic toxicity, and various animal models and human tests on serum and urine levels have consistently shown levels well beneath the threshold for toxicity.[5,15] Rarely, hypercalcaemia has been described, but is not usually clinically relevant.

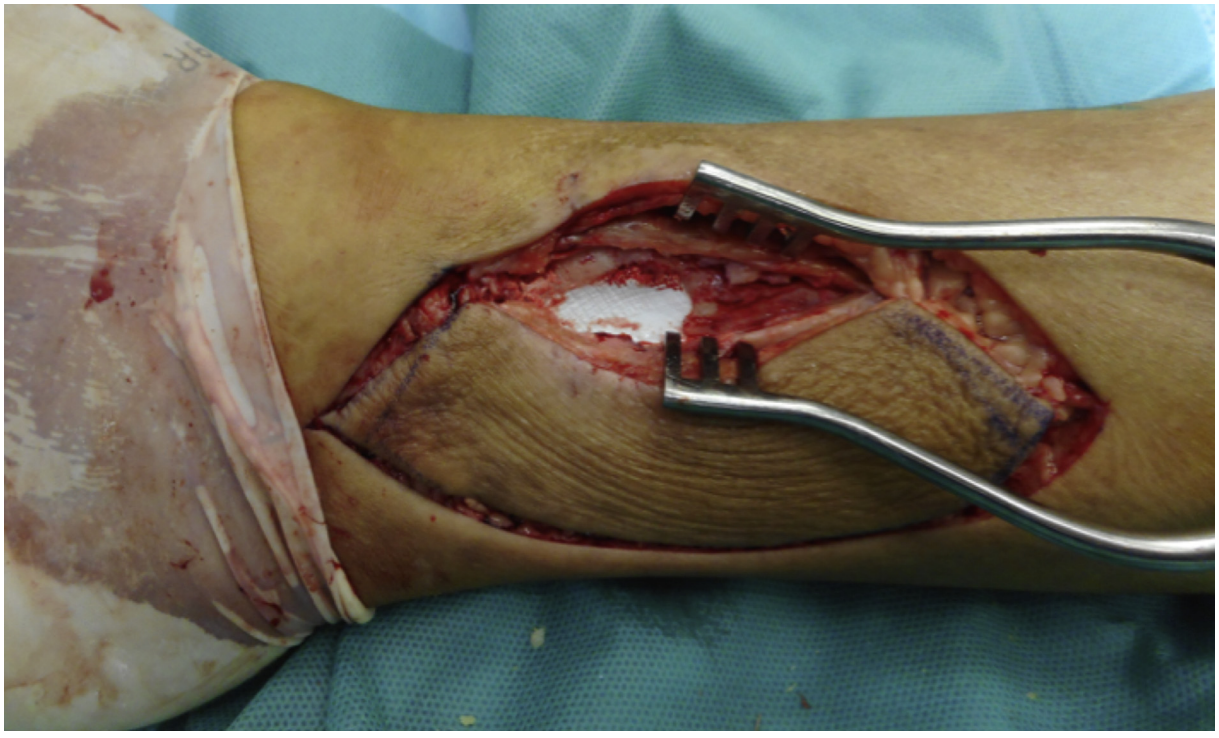

Figure 3 Cierny–Mader Type 3 (cortico-medullary) osteomyelitis of the distal tibia treated with excision and defect filling using Cerament G and a local keystone soft tissue flap.

The Oxford protocol

The Oxford protocol is based on the principles of a multidisciplinary approach to infection with specialist input from infectious diseases medical specialists, limb reconstruction surgeons, microvascular plastic surgeons, anaesthetists familiar with poor host patients, and Ilizarov and outpatient antibiotic nurse specialists. The principles of surgical treatment deliver a single-stage surgery in which there is appropriate sampling of dead and sequestered bone, sending five specimens for microbiology and at least one for histology, adequate debridement, local antibiotics, bony stabilization typically with an external fixator, and skin closure. Simultaneous free flap transfer is performed if required.

The protocol uses the Cierny–Mader classification to divide cavitary defects into medullary (Type 1), cortical (Type 2) or cortico-medullary (Type 3). Each defect type requires a different dead space management, facilitated by local antibiotic delivery.

In Type 1 (medullary defects), a fast-dissolving carrier with high levels of local antibiotic is used. No structural support or bone ingrowth is needed in medullary infections.

In Type 2 defects, the cortical bone is resected and the defect covered with healthy soft tissue. Usually, there is no remaining bone defect, so no local antibiotic carrier is needed. The restored soft tissue cover will deliver adequate antimicrobial levels.

In Type 3 defects, there is a need for high-level antibiotic release, together with bone ingrowth to restore bony integrity and prevent fracture. In these cases, a biphasic ceramic carrier will deliver both roles.

The protocol has been evaluated in over 700 patients with cavitary infected defects (Cierny–Mader Type 1, 2 and 3) in the long bones. Surgery was possible in 98.2% of cases and eradication of infection was achieved in 95.6% of patients at a minimum of 1 year after surgery (mean follow-up 21 months: range 12–61 months). A recent analysis of 56 consecutive cases treated with simultaneous free flaps in this protocol, together with Ilizarov reconstruction showed excellent results with bony union rates at 97.7%, infection recurrence rates of 8.9%, and flap failure rates of 3.6%.

Table 2 summarizes the Oxford protocol for cases of cavitary bone infection categorized according to the Cierny–Mader

The Oxford protocol for cases of cavitary bone infection categorized according to the Cierny–Mader classification

Cierny–Mader type	Method of bone excision	Local antibiotic type used	Method of stabilization	Rationale
1 (Medullary)	Medullary sequestrum debrided using combination of curettes and intramedullary reamers under image intensifier guidance	Calcium sulphate pellets with aminoglycoside antibiotic (Herafill G or Osteoset T)	Often not required. Monolateral fixator. In severe osteoporotic bones, intramedullary nail covered in antibiotic-loaded ceramic	Often the bone has enough cortical continuity that the debridement of the medullary osteomyelitis does not compromise the integrity of the bone. Infection eradication requires high-dose antibiotic in the canal.
2 (Cortical)	Debridement of dead cortex using chisels and gouges under direct vision	Not usually needed. Good soft tissue cover provides adequate perfusion from systemic therapy	No fixation, or monolateral frame	The resultant defect is often localized and superficial. Bony stabilization is not often required. The key is adequate soft tissue coverage (if needs be with muscle flap) to ensure adequate perfusion of affected area.
3 (Cortico-medullary)	Debridement of cortical component using drills, chisels and gouges and medullary component using combination of curettes and intramedullary reamers under image intensifier guidance	Calcium sulphate and hydroxyapatite paste with gentamicin (such as Cerament G)	Often require stabilization with external fixation. In the femur, internal fixation may be preferred and combined with local antibiotics around the fixation	Dead space management is key and thus bioceramic pastes ensure the defect is adequately filled and a high concentration of antibiotics is eluted into the lesion. The biphasic composite enhances bone formation and reduces fracture risk.
Combined defects	Combinations of above	Calcium sulphate pellets to medullary defect. Cerament G to cortical and subarticular defects. Soft tissue cover over exposed superficial cortex	External or internal fixation as needed	The different components of the defect can be addressed with multiple approaches, using the principles of delivering high levels of antibiotic in poorly perfused areas

Table 2

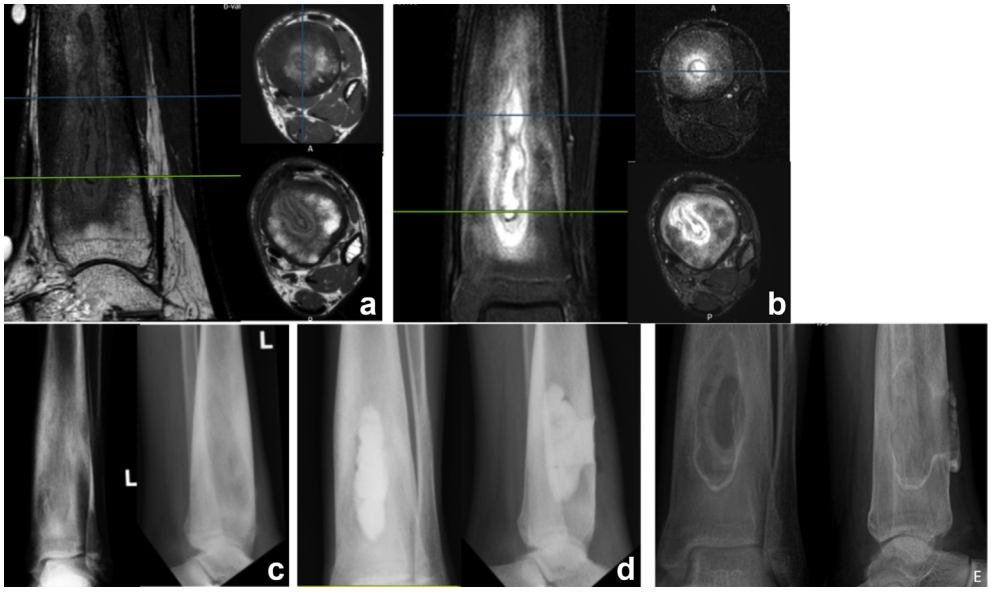

Figure 4 Preoperative T1 (**a**) and STIR (**b**) MRI images and plain radiograph (**c**) of patient with Brodie's abscess distal tibial (Cierny–Mader Type 1). Radiographs of immediate postoperative period showing anterior cortical window used to access abscess and the use of bioceramic to fill void (**d**). Radiographs at 6 months postoperative (**e**) showing complete resorption of bioceramic, good void filling of bone, and early cortication of the anterior window.

classification of osteomyelitis.[1] Figure 4(A-E) illustrates a case treated using the Oxford protocol.

Conclusion

With adherence to the principles of adequate debridement, proper sampling for infection, good use of local antibiotics and bony stabilization, chronic osteomyelitis can be successfully treated with greater satisfaction to patients and surgeons.

Concerns over the delivery of adequate antibiotic levels from systemic therapy can be addressed by insertion of local carriers. These have been shown to be highly effective and safe, in both prevention and treatment of infection in bones. The benefits of local antibiotic carriers in the treatment of these complex cases cannot be overstated and may, in future, obviate the need for systemic antibiotics. In particular, they facilitate single-stage surgery, reducing costs and morbidity for patients. ◆

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