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# Evidence-Based Recommendations for Local Antimicrobial Strategies and Dead Space Management in Fracture-Related Infection

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**Summary:** Fracture-related infection (FRI) remains a challenging complication that imposes a heavy burden on orthopaedic trauma patients. The surgical management eradicates the local infectious focus and if necessary facilitates bone healing. Treatment success is associated with debridement of all dead and poorly vascularized tissue. However, debridement is often associated with the formation of a dead space, which provides an ideal environment for bacteria and is a potential site for recurrent infection. Dead space management is therefore of critical importance. For this reason, the use of locally delivered antimicrobials has gained attention not only for local antimicrobial activity but also for dead space management. Local antimicrobial therapy has been widely studied in periprosthetic joint infection, without addressing the specific problems of FRI. Furthermore, the literature presents a wide array of methods and guidelines with respect to the use of

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local antimicrobials. The present review describes the scientific evidence related to dead space management with a focus on the currently available local antimicrobial strategies in the management of FRI.

**Key Words:** local antimicrobials, local antibiotics, fracture-related infection, dead space management, debridement, irrigation, PMMA, osteomyelitis, ceramics, carriers, fracture, infection

**Level of Evidence:** Therapeutic Level V. See Instructions for Authors for a complete description of levels of evidence.

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## INTRODUCTION

Fracture-related infection (FRI) remains a challenging complication. Surgical management is often unavoidable, particularly for chronic/late onset infections where osteolysis and biofilm formation are generally present. Successful eradication of infection requires debridement of affected tissues, removal of loose implants or foreign bodies, creation of a stable fracture environment, dead space management, and systemic antimicrobial therapy. Administration of local antimicrobials, in addition to systemic therapy, may be beneficial.<sup>1,2</sup>

The adjunctive application of local antimicrobial agents in FRI offers the prospect of improved therapeutic efficacy over that achievable by systemic delivery alone.<sup>3–7</sup> This is expected because the antimicrobial agent is placed directly within the surgical field and any vascular compromise at the fracture site or surrounding soft tissues does not limit local concentrations as it may do for systemically administered antimicrobials. In addition, with local delivery, the total drug amount may be reduced, yet the local concentrations exceed systemic administration. This improves the impact of antimicrobial agents, while reducing the risk of systemic toxicity.

Many related studies primarily focused on periprosthetic joint infection (PJI), and few investigations have addressed the specific problem of FRI with different opinions and practices on the use of local antimicrobials. Indications, application techniques, dosages, types of antibiotics, elution properties, and pharmacokinetics are poorly defined in the clinical setting, leading to a variation in clinical practice.<sup>8</sup>

Inappropriate and overuse of antibiotics is becoming an important issue in orthopaedic trauma surgery.<sup>8,9</sup>

This review describes the scientific evidence for currently available local antimicrobial strategies in the management of FRI.

## DEBRIDEMENT, IRRIGATION, AND DEAD SPACE MANAGEMENT

Debridement remains critical in the treatment of FRI, and it should include the excision of necrotic and poorly vascularized (ie, nonbleeding) bone/soft tissue and removal of loose implants or foreign bodies. Furthermore, multiple tissue samples should be taken for diagnostic purposes.<sup>1,2,10</sup>

Debridement is followed by irrigation to further decrease the bacterial load. Open fracture studies showed that irrigation should be performed using normal saline at low pressure to avoid bacterial seeding.<sup>11–13</sup> Antimicrobial additives are not advised.<sup>14,15</sup> The optimal amount of irrigation fluid is unknown, and irrigation should be continued until the wound is macroscopically clean.

Debridement in FRI often creates a dead space, which is a poorly perfused defect allowing bacterial proliferation. Furthermore, this environment of low oxygen and pH is ideal for the development of biofilm and bacterial persistence. Therefore, local antimicrobial delivery systems are often used as temporary or definitive strategies for dead space management.<sup>16</sup>

## LOCAL ANTIMICROBIAL STRATEGIES BASED ON ANTIBIOTICS

### Antibiotics Available for Local Use

The chosen antibiotic must provide coverage against a wide range of pathogens (ie, broad-spectrum antibiotic) or against a specific pathogen identified by culture<sup>17,18</sup>; it must be compatible with and achieve an adequate release from the chosen carrier, and it must have a good toxicity and hypersensitivity profile, and a low rate of resistance.<sup>19</sup> In clinical orthopaedic practice, gentamicin, tobramycin, vancomycin, and clindamycin are the most common commercially available formulations for local antibiotic delivery. They are industrially incorporated into bone cement, collagen, and other bone void fillers that are available for clinical use.<sup>8</sup> Aside from commercially available preparations, the off-label addition of antibiotics to polymethyl methacrylate (PMMA) is an option. The mechanical needs of the construct may have to be considered because an antibiotic can compromise the strength and setting characteristics of PMMA. In most FRI cases, antibiotic-impregnated PMMA beads and spacers are used for dead space management, and any deterioration of their mechanical properties is not an issue. However, in large segmental defects of the lower extremity, the structural integrity of the spacer (in combination with the osteosynthesis/external fixator) may facilitate weight bearing.

Although local administration of antibiotics is generally considered safe,<sup>20</sup> the potential for systemic toxicity should not be neglected.<sup>21</sup> Also, due consideration should be given to the effect that antibiotics have on cell viability and osteogenic activity in the immediate vicinity of the applied material.<sup>22,23</sup>

Local antibiotics in very high concentrations produce cellular toxicity and may lead to attenuated fracture healing. This is a concern given that most local delivery systems release a very high dose of antibiotics, in some cases, more than 1000 times the minimal inhibitory concentration (MIC).<sup>23,24</sup> However, no specific cutoff values for local skeletal toxicity exist. Data from in vitro studies indicate increased toxicity—decreased proliferative capacity of osteoblasts and chondrocytes<sup>23</sup>—with increased antibiotic concentration and exposure time, which suggests that although higher doses of antibiotic may be better at controlling infection, they are not benign.

Rathbone et al<sup>22</sup> showed in vitro that the antibiotics that caused the greatest destruction of cell viability and suppression of osteoblast activity included rifampin, minocycline, doxycycline, nafcillin, penicillin, ciprofloxacin, colistin methanesulfonate, and gentamicin. More recent, in vivo studies have demonstrated that the local application of gentamicin, in standard available doses, does not interfere with fracture/bone healing.<sup>25,26</sup> Amikacin, tobramycin, and vancomycin were the least cytotoxic until very high concentrations were used.<sup>22</sup> Chu et al<sup>27</sup> evaluated the effect of topical vancomycin on mesenchymal stem cells in vitro. The authors concluded that there was a dose-dependent cell death with vancomycin use. These data suggested that more vancomycin is harmful in vitro, and surgeons should restrict local vancomycin use to the doses currently reported in the available published studies (ie, 1–2 g). Also, Naal et al<sup>28</sup> demonstrated that clindamycin levels higher than 500 mg/mL had cytotoxic effects on osteoblasts. The authors suggested that the observed effects could lead to a potential alteration of bone metabolism in vivo. Fluoroquinolones have been shown to inhibit growth and extracellular matrix mineralization in osteoblastic cell culture<sup>29</sup> and found to inhibit bone growth in an experimental fracture model.<sup>30</sup> Fluoroquinolones may therefore compromise the clinical course of fracture healing. A review by Kallala et al<sup>31</sup> confirmed the negative in vitro and in vivo effects of high doses of local antibiotics on bone cell metabolism and fracture healing. With this in mind, treating physicians should be careful not to induce local and/or systemic toxicity. Table 1 gives an overview of local antimicrobials and the doses that have been reported in the literature.

Discrepancy exists between in vitro and in vivo antibiotic release, and these data are not interchangeable. A typical in vitro experiment will allow antibiotics to diffuse into a large volume of a solution that may be regularly refreshed. In contrast, in vivo antibiotic release may differ because the properties of the fluid medium (amount of fluid, exchange rate) in the vicinity of the material may vary from the in vitro situation. In vitro data should be considered an indicator of potential antibiotic release rather than a real measure of in vivo release.

For PMMA, where the exothermic polymerization process can result in temperatures exceeding 100°C, thermal stability is a key factor in determining the suitability of an antibiotic for incorporation.<sup>19</sup> Moreover, any antimicrobial or carrier should be thermally stable at body temperature for the duration of release.<sup>19</sup> A recent study found that beta-lactam antibiotics degrade quite rapidly at 37°C, whereas excellent

**TABLE 1.** Overview of Local Antimicrobials and Recommended Local Dosages

Local Antimicrobial	Minimum (Reported) Dose	Maximum (Reported) Dose	Ref.	Examples of Commercially Available Brands	Toxicity*
PMMA (40 g)					Vancomycin: Allergic reactions
Commercially available					Nephrotoxicity
Gentamicin	0.5 g	1 g		Palacos R + G	Ototoxicity
Gentamicin + vancomycin	0.5 g + 2 g			Copal G + V	Neutropenia
Gentamicin + clindamycin	1 g + 1 g			Copal G + C	Gentamicin:
Tobramycin	1 g			Simplex P	Nephrotoxicity
Erythromycin + colistin	0.73 g + 0.24 g			Simplex	Ototoxicity
Customized†‡					Tobramycin:
Gentamicin	0.4 g	4.8 g	32		Neurotoxicity
Vancomycin	2 g	6 g	32–36		Nephrotoxicity
Tobramycin	1.2 g	4.8 g	32,33,37		Erythromycin:
Gentamicin + vancomycin	0.5 g + 2 g	4.8 g + 4 g†	20,38,39		Allergic reactions
Tobramycin + vancomycin	1.2 g + 1 g	3.6 g + 4 g	40,41		Ototoxicity
Gentamicin + tobramycin + vancomycin	0.5 g + 2.4 g + 2 g		42		QT-interval elongation
Gentamicin + clindamycin	0.5–1 g + 1 g		43		Reversible disturbance of liver function tests
Gentamicin + linezolid	0.5 g + 1 g				Colistin:
Gentamicin + daptomycin	0.5 g + 2 g				Allergic reactions
Gentamicin + fosfomycin	0.5 g + 1–2 g				Neurotoxicity
Gentamicin + amphotericin B (liposomal)	0.5 g + 0.2–0.3 g				Nephrotoxicity
Gentamicin + amphotericin B (not liposomal)	0.5 g + 0.2 g–0.8 g				Clindamycin:
Gentamicin + voriconazol	0.5 g + 0.3–0.6 g				Gastrointestinal side effects
Ceramics					Ampicillin:
Commercially available					Not to be used in patients with penicillin allergy
Tobramycin	262 mg	4 pellets/kg§		Osteoset T (calcium sulfate)	Rash
Vancomycin + gentamicin	1 g + 240 mg			Stimulan 10cc (calcium sulfate)	
Vancomycin + tobramycin	1 g + 240 mg				
Vancomycin	1 g				
Tobramycin	1.2 g				
Gentamicin	240 mg				
Tobramycin	240 mg				
Gentamicin	175 mg	350 mg		Cerament 10 mL (calcium sulfate/hydroxyapatite)	
Vancomycin	660 mg	1.32 g			
Customized†‡					
Vancomycin	250 mg	6 g	44	Osteoset (calcium sulfate) (variable number of batches (25 g) was used)	
Vancomycin	1 g		45	Allomatrix 10 cc (deminerallized bone matrix and calcium sulfate)	
Vancomycin + gentamicin	2 g + 240 mg		46	Stimulan 10 cc (calcium sulfate)	
Vancomycin + tobramycin + cefazolin	1 g + 1.2 g + 1 g		47	Stimulan (calcium sulfate)	
Naked antibiotics					
Vancomycin (powder)	0.5 g	6 g¶	48–50		
Tobramycin (liquid)	80 mg/40 mL saline		51,52		
Vancomycin + tobramycin (powder)	1 g + 1.2 g		53		
Ampicillin (powder)	1 g		54		

\*General toxicities associated with the use of these antibiotics are reported because reports on side effects of local antibiotic therapy are scarce. All customized dosages reported in this table could not be associated with systemic toxicity. However, studies on the local management of PJI have reported cases of acute renal failure secondary to the use of antibiotic impregnated cement spacers.<sup>21,55–57</sup> Furthermore, the effect of the antibiotic's concentration on cell viability and osteogenic activity should be considered.<sup>22</sup>

†The American Academy of Orthopaedic Surgeons (AAOS) published guidelines for the treatment of PJI using antibiotic-loaded cement spacers. They recommend dosages between 3 and 8 g of antibiotic per batch of cement. Vacuum mixing is contraindicated because it reduces the elution of the antibiotic.<sup>58</sup> However, for the cement to remain stable and to keep its structural integrity, we recommend to add up to 10% of its weight to the cement batch. Therefore, we would recommend a maximum dose of 4 g per batch (40 g) of PMMA. The integration of β-lactam antibiotics and carbapenems (ie, meropenem) in PMMA was excluded from this table because these antibiotics show poor thermal stability and degrade rapidly at a physiologic temperature of 37°C.<sup>19</sup> Also, fluoroquinolones (ie, ciprofloxacin, levofloxacin), rifampin, tetracyclines (ie, doxycycline, minocycline, tigecycline), and macrolides (ie, azithromycin) were excluded due to their potential local detrimental effects on cell viability and osteogenic activity, as described *in vitro*.<sup>19,22,29</sup>

‡The use of more than 1 batch of local antibiotic carrier has been reported, resulting in a higher local dose, without side effects.<sup>20,59</sup>

§The package insert of Osteoset T calcium sulfate pellets with tobramycin recommends not to exceed the maximum dosage of 4 pellets/kg for adults with normal renal function. An excess usage may cause serum levels of tobramycin to be elevated above the recommended maximum. In these cases, neurotoxicity and nephrotoxicity may manifest. If the bone defect size requires a higher number of pellets to be administered, it is recommended to mix the antibiotic-loaded pellets with standard Osteoset bone graft pellets.

¶Caution should be taken when applying such high doses of vancomycin because clinical evidence on safety is scarce. Only one retrospective study of 981 patients who received topical vancomycin during spinal surgery reported the use of 6 g vancomycin in rare cases. The average dose of vancomycin was 1.16 g in this study.<sup>49</sup> In general, most reported vancomycin dosages range between 0.5 g and 2 g.<sup>48,50,60</sup> Depending on the extent of the surgical site that is to be covered, we would recommend to adhere to the upper limit of 2 g.

||Maximum and minimum doses were not always mentioned in the literature.

long-term stability was observed for aminoglycosides, glycopeptides, tetracyclines, and quinolones.<sup>19</sup>

## Delivery of Antibiotics Without Carrier

In daily clinical practice, this is represented by antibiotics in aqueous solution or powder form. A systematic review demonstrated that local administration of antibiotic (ie, vancomycin) powder significantly decreased infection rates in spine surgery.<sup>48</sup> However, the only randomized controlled trial (RCT) on this topic found no difference in infection rate when vancomycin powder was used in addition to systemic prophylaxis compared with systemic prophylaxis alone.<sup>61</sup> Other studies reported an increased rate of Gram-negative infections following the introduction of vancomycin powder in the operative bed in spine surgery.<sup>49,62</sup> The use of intrawound antibiotic powder has not been studied extensively in orthopaedic trauma. Few preclinical and clinical studies report the technique and even a positive outcome, but comparative studies are lacking.<sup>53,63–66</sup> An ongoing multicenter prospective RCT run by the Major Extremity Trauma Research Consortium is assessing whether local vancomycin therapy can reduce infection rates after operative treatment of fractures at high risk of infection.<sup>67</sup>

Antibiotics can also be administered in aqueous solution (eg, tobramycin). These antibiotic solutions have already been used for many years, and experimental and clinical data suggest that this method of delivery is effective.<sup>51,68</sup> In a case series, the local injection of aminoglycosides was found to reduce the infection rate in open fractures.<sup>52</sup>

Delivering “naked” antibiotics does not require a specialized carrier, and therefore, the cost is lower. However, an important drawback to this method is the fact that high local antibiotic levels cannot be sustained.

To date, the application of antibiotics without any carrier has not been documented in human clinical trials focused on the treatment of FRI, and further research is required to make recommendations.

## Delivery of Antibiotics by Carrier

### Autograft

Autograft provides a combination of scaffolding and biologically active cells to enhance healing at fracture nonunion sites. Methods for obtaining autograft and potential sites for harvest are numerous.<sup>69,70</sup> Autograft has been well studied in its natural state,<sup>71</sup> complimenting an induced membrane approach,<sup>72–76</sup> or combined with antibiotics.<sup>77,78</sup> Autograft exhibits some natural resistance to infection, as evidenced by the Papineau technique,<sup>79,80</sup> where the graft is applied into open wounds that are left to heal for months through neoepithelialization. However, an experimental study revealed that when bone marrow aspirate was injected into active sites of osteomyelitis, the resulting inflammation created significantly more bony destruction.<sup>81</sup> This supports the importance of debridement of all infected, poorly vascularized tissue before grafting.<sup>82</sup>

Autograft can also be used as a carrier for local antibiotics. In theory, mixing antimicrobials with autograft

provides the optimal solution of dead space management, enhanced biology, and infection control and has been used successfully for second-stage grafting of bone defects.<sup>73</sup> As mentioned earlier, part of the resistance to using antibiotics with fresh autograft is concern regarding cytotoxic effects on osteocytes/osteoblasts.

A number of clinical studies have been performed on antibiotic-loaded autograft. Lindsey et al<sup>83</sup> showed that tobramycin could be mixed with autograft without negative effects on healing. A study by Chan et al<sup>84</sup> reported the effects of antibiotic-impregnated cancellous bone grafting on infection elimination and bone incorporation in patients with infected tibial nonunions. The authors used different antibiotics targeted to the infecting organisms that were found during the initial debridement (ie, first stage). The results suggested that impregnated antibiotics have no adverse effects on autogenous cancellous bone graft incorporation. Furthermore, recurrence rates were lower in the group that received local antibiotics. In a study on infected tibial nonunions, vancomycin-impregnated cancellous bone graft was a safe method, with no recurrence of infection.<sup>85</sup> However, the study had a reoperation rate of 28% for “healing disturbances.”

Because scientific evidence from large clinical series is lacking and optimal antibiotic doses are currently not available, the routine combination of local antimicrobials with autogenous cancellous bone graft is not recommended as the standard of care.

### Allograft

The use of human allograft bone avoids the morbidity of harvesting autologous bone graft but poses a potential risk for infection when used in a contaminated site both by introducing bacteria<sup>86</sup> and by serving as a sequestrum for bacteria in the previously infected site.<sup>87</sup> Also, allograft bone lacks the osteoinductive properties of autograft. For these reasons, allograft has not found wide application in FRIs associated with bone defects.

Modification of allograft tissue has allowed it to become a carrier for antibiotics.<sup>88</sup> These modifications include porphyrin adsorption,<sup>89</sup> antibiotic impregnation,<sup>90–92</sup> antibiotic tethering,<sup>93</sup> and chitosan-heparin coating.<sup>94</sup> Studies show that when mixing bone allografts with antibiotics, their storage capacity and release profile vastly exceeds that of PMMA.<sup>88</sup>

In a series of 45 patients undergoing revision of infected hip and knee prosthetic replacement with impaction grafting, femoral head allografts were soaked in an antibiotic solution and revision surgery was done in one stage, eradicating infection in 96% of the patients.<sup>95</sup> Although positive results have been published, surgeons should be aware that after release of the antimicrobial substance, allograft still functions as a foreign body.

Although the incorporation of antimicrobials in bone graft (ie, autograft and allograft) has been studied for decades with promising results, there is currently insufficient information available with respect to the optimal carrier (ie, allograft or autograft), optimal antibiotic, and preferred doses (ie, local and systemic toxicity profiles).

## Polymethyl Methacrylate

PMMA is a commonly used delivery vehicle for antibiotic therapy. The most popular drugs used are aminoglycosides (ie, gentamicin—tobramycin) and vancomycin.<sup>96,97</sup> These antibiotics exert a synergistic effect with superior elution properties when used together.<sup>98</sup> Other antimicrobials can also be used, including daptomycin,<sup>99</sup> amikacin,<sup>100</sup> and voriconazole.<sup>101</sup> The amount of antimicrobials mixed into PMMA significantly varies between studies, specifically with respect to off-label mixing procedures, yet it is unclear if the success rate depends on the quantity of drug used. Table 1 gives an overview of standard available and recommended doses of antimicrobials mixed with PMMA.

PMMA has been used as an antibiotic carrier for decades.<sup>102</sup> It delivers a high dose of antibiotic and may be used in spacer or bead form for both prevention and treatment of FRI.<sup>103</sup> PMMA can be used as a spacer (eg, Masquelet technique), or it can be applied in the shape of beads at the site of infection.<sup>104</sup> The local application of antibiotics to the intramedullary (IM) canal can be achieved by coating ball-tipped guide wires or flexible rods with antibiotic cement. Such coating can be achieved by pumping PMMA into a large chest tube or using a “hand rolling technique” (Fig. 1). This IM spacer technique is often used for the 2-stage treatment of infected long bone nonunions and has shown good results.<sup>105,106</sup>

The off-label coating of definitive internal implants, including plates<sup>107</sup> and locked IM nails,<sup>96,97,108–110</sup> with PMMA has also been a treatment option for FRI. These self-made coated implants can provide an alternative to staged treatment with external fixation followed by definitive internal fixation.<sup>111</sup> Antibiotic-coated implants must often be custom molded (handmade) in the operating room using PMMA and a combination of antibiotics (Fig. 1). The antibiotic-coated locked IM nail has been used with increasing frequency for internal fixation of long bone fractures<sup>40</sup> and in complex knee and ankle fusion cases.<sup>112</sup> Disadvantages to the use of these implants include controlling the heterogeneity of the antibiotic distribution in the cement, undulations in the diameter of the nail coating, and the release profile of the antibiotics from the PMMA.

The type of PMMA used will also affect the elution characteristics. When PMMA is more porous, it allows antibiotics to escape from the cement matrix, more readily improving antibiotic concentrations.<sup>113</sup> Furthermore, the addition of vancomycin or amphotericin B antibiotic powder in distilled water before mixing with bone cement improves antibiotic release.<sup>114</sup> Porosity will improve the elution for bone void PMMA spacers and beads but is not ideal for coating implants or cement rods where fragmentation complicates cement removal.

The variable antibiotic elution rates of PMMA and the requirement for removal has led to the investigation of alternative carriers. A systematic review showed that, despite the long experience with its use and the theoretical advantages, there are no well-executed, prospective studies investigating the efficacy of antibiotic-loaded PMMA beads in treating orthopaedic infections.<sup>115</sup> However, studies with

respect to the prevention of FRI describe an improved clinical outcome when using PMMA beads, especially in open fractures.<sup>103</sup>

In addition, van de Belt et al<sup>116</sup> evaluated the release profiles of 6 types of bone cements in vitro and found that the released antibiotic fell below the detection limit after 1 week and only 4%–17% of the incorporated antibiotic was released. In a clinical study by Neut et al,<sup>117</sup> the authors retrieved gentamicin-loaded PMMA beads after revision surgery for PJs. Cultures were positive for bacteria on gentamicin-loaded beads in 90% of the patients. A significant amount of these strains proved to be gentamicin resistant, which raises concerns over the development of antibiotic resistance due to prolonged release at subtherapeutic levels.

Local delivery of antibiotics is not a substitute for thorough debridement. In the presence of remaining avascular tissue and foreign bodies, bacteria may remain viable despite initial high doses of antibiotics. Also, PMMA spacers/beads are not intended for permanent implantation but are temporarily used for dead space management and local antibiotic delivery. During the second-stage procedure, they are removed, and the dead space is addressed with a reconstructive procedure (eg, bone grafting).

## Ceramics

This review describes 2 types of ceramics that are used in FRI patients: biodegradable ceramics and bioactive glasses. Both are biodegradable substances, which raise the possibility of single-stage surgery with definitive soft tissue closure, avoiding the need for subsequent surgery for spacer (eg, PMMA) removal.<sup>16</sup>

### Biodegradable Ceramics

The principle types of biodegradable ceramics available for antibiotic delivery are based on either calcium sulfate or calcium phosphate.<sup>16</sup> The reported antibiotic elution profiles of both remain fairly similar, with the delivery of antibiotics above the MIC for between 3 and 4 weeks.<sup>16,118</sup> This elution profile is superior to that of PMMA. For example, Howlin et al<sup>119</sup> showed that calcium sulfate beads maintained antibiotic concentrations above MIC for 39 days compared with PMMA, which was only effective for 12 days.

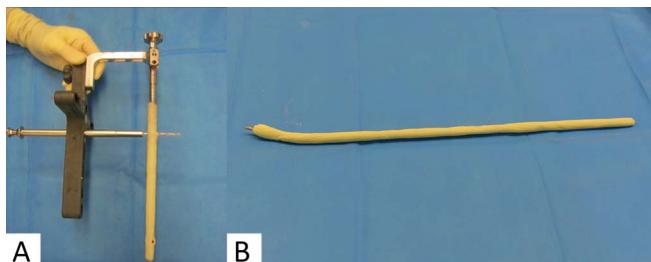
The most extensively investigated biodegradable ceramic in the surgical management of FRI and chronic osteomyelitis is Osteoset T [Wright Medical, Memphis, TN; Food and Drug Administration (FDA) approved].<sup>120–123</sup> In an RCT, 30 patients with infected long bones received either Osteoset T or antibiotic-loaded PMMA beads with no difference in infection eradication or union.<sup>120</sup> However, significantly more surgical procedures were needed in the cement group (15 vs. 7;  $P = 0.04$ ). In a randomized trial, debridement alone was statistically less effective than debridement with implanted calcium sulfate with tobramycin (60% vs. 80%) in medullary infections.<sup>122</sup> In a series of 195 cases of long-bone infection, including 110 infected fractures, Osteoset T was an effective antibiotic carrier, with 91% infection eradication in single-stage surgery.<sup>124</sup> However, bone formation was poor, and posttreatment fractures occurred through the defect in 4.6% of cases.

In an attempt to improve the performance of inorganic ceramics, Cerament (Bonesupport, Lund, Sweden; FDA approval for an investigational device exemption study) with gentamicin or vancomycin has been developed. It is a flowable, cold curing, biphasic composite containing 60% calcium sulfate and 40% hydroxyapatite. It forms a paste that can be injected into bone defects.<sup>59</sup> In a series of 100 cases, including 71 FRIs, Cerament G eradicated infection in 96%.<sup>59</sup> A comparison of the outcomes for Osteoset T and Cerament G in the surgical treatment of chronic osteomyelitis showed fewer wound healing problems in the Cerament G group, with infection recurrence and refractures being 2 times less likely compared with those in the Osteoset T group.<sup>125</sup>

Cerament G can be injected into the IM canal in a fluid state before nail insertion. The carrier coats the surface of the nail, potentially protecting it from colonization and delivering a high local dose of antibiotic. Cerament G has been evaluated in a series of 12 infected nonunions with single-stage revision fixation. All 12 were infection free at a minimum of 1 year, and 11 healed with single-stage surgery.<sup>126</sup>

### Bioactive Glass

Bioactive glass, a synthetic silicate material, has been shown to have antibacterial properties that can allow osteoconduction and possibly osteostimulation.<sup>127</sup> Most data in FRI is available for the bioactive glass S53P4 (Bioglass; BonAlive Biomaterials Ltd, Turku, Finland; not FDA approved). Upon implantation, bioactive glass S53P4 undergoes chemical degradation, thereby releasing sodium and calcium ions. Eventually, together with an increase in pH, this leads to the conversion of the glass into a carbonate-substituted hydroxyapatite-like layer similar to bone.<sup>127,128</sup> The intrinsic antibacterial property of bioactive glass S53P4 is due to the ion dissolution process that starts immediately after the bone substitute has been implanted into the body.<sup>129</sup> The ion release at the bioactive glass surface induces an increase in pH and also an osmotic pressure around the bioactive glass. These phenomena have shown to kill both planktonic bacteria and bacteria in biofilm in vitro.<sup>130</sup> In an *in vitro* study, bioactive glass S53P4 was compared to antibiotic-loaded PMMA, with both showing comparable antibacterial properties against multidrug-resistant bacteria.<sup>131</sup>



**FIGURE 1.** A, Polymethyl methacrylate (PMMA)-coated humeral nail. The nail was custom molded (handmade) in the operating room using PMMA and a combination of antibiotics. B, PMMA spacer for application in the IM canal of the tibia. The application of PMMA on a rod was achieved using a hand rolling technique.

Clinical studies showed a success rate of approximately 90% in the treatment of chronic osteomyelitis, using bioactive glass S53P4.<sup>129,132</sup> However, Geurts et al<sup>133</sup> treated 18 patients in a low-income country with a success rate of only 38%.

### Poly(D,L-Lactide) (PDLLA)

The clinical application of antibiotics through a biodegradable implant [Poly(D,L-Lactide) (PDLLA)] coating is a relatively new development.<sup>134</sup> Antibiotic-coated implants do not necessitate additional removal surgeries or delay wound closure. The only PDLLA-coated fracture-related implant that is currently commercially available is the PRO-Tect tibia nail (DepuySynthes; Johnson/Johnson Company, Inc, New Brunswick, NJ; not FDA approved). It is coated with a layer of PDLLA impregnated with gentamicin. The coating releases gentamicin over a period of 2 weeks, with a burst release in the first days.

Two clinical studies evaluated these gentamicin-coated tibia nails in acute complex fractures and revision cases. In both studies, no postoperative infectious complications were documented.<sup>135,136</sup> Antibiotic-PDLLA-coated implants may be a promising option for the prevention of FRI in open fracture or revision cases.

### Collagen Sponges

Collagen is a natural polymer that can be used for drug delivery.<sup>137</sup> Antibiotic impregnated collagen sponges are not a new development,<sup>138</sup> but clinical studies in the field of FRI are scarce.<sup>139</sup> Initially, these sponges were developed to prevent infections by providing high local gentamicin concentrations, but more recently, authors also suggested their use in the treatment of infection.<sup>140</sup> Although previous studies suggested promising results with respect to infection prevention in open fractures,<sup>139</sup> a recent RCT showed that the use of 2 gentamicin-collagen sponges compared with no intervention did not reduce the 90-day sternal wound infection rate.<sup>141</sup> Treatment-related studies are all retrospective and published at least 2 decades ago, with variable results.<sup>138,142,143</sup>

### Hydrogels

Hydrogels are a newer option for the local delivery of antibiotic agents. Hydrogels in general consist of a polymerized macromolecule that is hydrated with water (and antibiotics) to form easily manageable materials with gel-like properties. Hydrogels can be injectable, allow for minimally invasive application, can sustain antibiotic release,<sup>144</sup> are biodegradable, and thus do not require removal surgery. Hydrogels have been studied in more detail in preclinical studies, showing prophylactic efficacy in rabbit FRI and PJI models.<sup>25,145</sup> Furthermore, these gels have shown to allow normal bone apposition and fracture healing.<sup>25,146</sup>

Clinical studies focusing on FRI are scarce. In a recent RCT, 256 patients who were scheduled to receive osteosynthesis for a closed fracture were randomly assigned to an antibiotic-loaded hydrogel or a control group.<sup>147</sup> The authors concluded that there was a reduced infection rate in the hydrogel group, without any detectable adverse events or side effects.

**TABLE 2.** Key Recommendations

- The critical element for success is the removal of all dead or poorly vascularized tissue before the use of any type of local antimicrobial strategy.
- Irrigation should be performed using normal saline at low pressure to avoid bacterial seeding deeper into soft tissue and bone. The use of antimicrobial additives is currently not advised because they may add toxicity, although clinical data within this field are scarce.
- The use of naked antibiotics (eg, vancomycin powder) has not been well documented in treatment of FRI and further research is required.
- Although the incorporation of antimicrobials in bone graft (ie, autograft and allograft) has been studied for decades with promising results, information with respect to the optimal carrier (ie, allograft or autograft), optimal antibiotic, and preferred doses (ie, local and systemic toxicity profiles) are currently not well defined.
- PMMA remains the best understood carrier for antibiotics. The surgeon must select the correct antimicrobial(s), the state (ie, liquid or powder), and dosage; the cement type, the use of a porogen, and the mixing method, in combination with the final form and function of the PMMA (spacer, bead, or coating).
- The off-label use of IM PMMA-coated rods or nails, loaded with antibiotics, currently remains a good treatment option in cases of FRI in long bones.
- Biodegradable ceramics offer advantages over PMMA, including no need for additional removal surgery and an improved release profile (when carrying antimicrobials).
- Although higher doses of antimicrobials may be better for infection control, they may not be benign.
- Although local antimicrobials are mostly safe, certain patients are at risk of local and systemic toxicity (eg, nephrotoxicity). The total dose of antibiotic used and anticipated local concentration should be considered and preoperative patient comorbidities.
- Multicenter prospective studies comparing the best current practices with a uniform product and standard antibiotic concentrations would provide better data for informed surgical planning.

FRI, fracture-related infection; PMMA, polymethyl methacrylate; IM, intramedullary.

Overall, although hydrogels have the disadvantage of lacking structural strength and release antimicrobials for a shorter period compared with biodegradable ceramics, the advantage is a rapid resorption, thereby leaving no foreign body for biofilm formation.

## NONANTIBIOTIC ANTIMICROBIAL STRATEGIES

### Silver

Silver has been used as a disinfectant for many centuries.<sup>148,149</sup> Silver is used in its metallic form as a nanoparticle or in silver-containing polymers and composites.<sup>150</sup> For orthopaedic applications, silver has been introduced into hydroxyapatite and bone cement and as a coating for trauma devices.<sup>151</sup>

The toxicity of silver to eukaryotic cells has been one of the major concerns with respect to its use as an implant coating or as antimicrobial in a bone void filler.<sup>149,152</sup> Despite this, there are numerous silver-functionalized implants and wound dressings available clinically,<sup>153–156</sup> with few reports of induced toxicity.<sup>157</sup> The development and spread of silver resistance in FRI pathogens is another concern that could limit silver-based interventions. In general, resistance to silver is rare, and to date, there are no reports in Gram-positive species, which account for a majority of FRI pathogens.

Overall clinical studies demonstrate a trend in reducing infection with silver-coated central venous catheters, urinary catheters, and ventilator endotracheal tubes.<sup>154–156</sup> Similar positive results were achieved with a silver-coated megaprosthesis, which has been used in revision arthroplasty due to infection or in tumor resection.<sup>158</sup> Silver-coated external fixation pins have also been tested in patients, although a lack of efficacy and elevated serum silver levels have limited the use of these pins.<sup>159</sup>

### Bacteriophages

Bacteriophages (phages) are viruses that selectively infect, multiply within, and subsequently lyse bacteria. The

use of phages for the treatment of bacterial infections is not a novel concept, but it has been applied since the start of the 20th century. With the advent of antibiotics, however, phage therapy lost ground. Although phages have been applied for almost a century in eastern Europe, clinical studies are limited.<sup>160–162</sup> Currently, with the increase in multidrug-resistant strains, phage therapy is regaining interest.<sup>163</sup> Clinical and experimental studies on orthopaedic implant-related infections have shown promising results.<sup>164,165</sup> Future research on this topic, with well-conducted clinical trials, is important.<sup>166,167</sup>

## CONCLUSIONS

In addition to bony stability and soft tissue cover, the treatment pathway for FRI is founded on successful debridement and irrigation of bone and soft tissue, in combination with systemic and local antibiotic administration. This review described the scientific evidence for dead space management with a focus on currently available local antimicrobial strategies in the management of FRI. Key recommendations are summarized in Table 2.

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