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General

Utilization of Antibiotic Bone Cement in Spine Surgery: Pearls, Techniques, and Case Review

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Vertebral osteomyelitis (VO) encompasses a spectrum of spinal infections ranging from isolated mild vertebral osteomyelitis to severe diffuse infection with associated epidural abscess and fracture. Although patients can often be treated with an initial course of intravenous antibiotics, surgery is sometimes required in patients with sepsis, spinal instability, neurological compromise, or failed medical treatment. Antibiotic bone cement (ABC) has been widely used in orthopedic extremity surgery for more than 150 years, both for prophylaxis and treatment of bacterial infection. However, relatively little literature exists regarding its utilization in spine surgery. This article describes ABC utilization in orthopedic surgery and explains the technique of ABC utilization in spine surgery. Surgeons can choose from multiple premixed ABCs with variable viscosities, setting times, and antibiotics or can mix in antibiotics to bone cements themselves. ABC can be used to fill large defects in the vertebral body or disc space or in some cases to coat instrumentation. Surgeons should be wary of complications such as ABC extravasation as well as an increased difficulty with revision. With a thorough understanding of the properties of the cement and the methods of delivery, ABC is a powerful adjunct in the treatment of spinal infections.

1. INTRODUCTION

Vertebral osteomyelitis (VO), also known as spondylodiscitis, refers to a spectrum of spinal infections ranging from isolated vertebral osteomyelitis and/or discitis to diffuse infection with associated epidural abscess.[1] It can present in a number of ways, from an isolated lesion in a neurologically intact patient to a critically ill patient in septic shock with spinal instability and/or neurological compromise.[2,3]

Treatment is often guided by the status of the patient at the time of clinical presentation. Patients with a known organism who are clinically stable without evidence of spinal instability can often be treated with an initial course of antimicrobial therapy. Surgery is often required in patients with sepsis, spinal instability, neurological compromise, (such as weakness, paralysis, or bowel/bladder dysfunction), or in chronic cases where medical treatment has previously failed.[4,5]

The appropriate surgical treatment varies based on the nature of the infection and the condition of the patient. Lesions that are otherwise stable may sometimes require procedural biopsy of the inflammatory tissue in question to help guide antibiotic therapy. Patients without instability who have failed medical treatment and require debridement or decompression of the neural elements may be treated with isolated decompression and/or debridement alone.[6] If the infection has progressed to the point at which it disrupts the mechanical stability of the spine, or if obtaining adequate decompression warrants a degree of bony resection that destabilizes the spine, spinal fusion may be required.[7,8]

While the role of systemic antibiotic therapy is well established in the treatment of VO, there is not a standardized method of local antibiotic delivery. A variety of techniques are utilized in orthopaedic surgery for local antibiotic delivery, including application of local antibiotic powder to the wound, use of antibiotic beads, and the use of antibiotic bone cement.[9]

Although antibiotic bone cement (ABC) is commonly utilized in other orthopedic subspecialties such as adult reconstruction/joint arthroplasty, the routine use of ABC in spine surgery is not well established. The purpose of this manuscript is to review the principles and techniques associated with the use of ABC in orthopaedic surgery and to broaden its applications to spine surgery. This will be illustrated with several case examples.

2. ESTABLISHED CLINICAL USES OF ANTIBIOTIC CEMENT IN ORTHOPAEDIC SURGERY

Bone cement has been routinely used in orthopaedic surgery since 1870, when Themistocles Gluck, a German surgeon, pioneered its use for the fixation of a total knee prosthesis.[10] Early bone cement consisted primarily of

plaster and colophony. In 1960, Sir John Charnley introduced polymethyl methacrylate (PMMA), which has become the gold standard for cemented fixation in total joint arthroplasty.[11] PMMA acts as a space-filler to ensure a close mechanical interlock between the bone and the prosthesis.[10] Buchholz et al. further expanded the use of bone cement by demonstrating that it was capable of releasing substances like antibiotics and copper ions from its surface.[12] Since this discovery, PMMA cement impregnated with antibiotics has been a key component in the treatment of prosthetic joint infections through local antibiotic delivery. Over the years, the use of ABC has expanded, and many surgeons utilize antibiotic cement for infection prophylaxis in both primary and revision joint replacements.

Bone cement can also address segmental bone defects in orthopedic trauma surgery. Masquelet et al. describe a technique that combines induced membrane formation technology with bone grafting for the management of long (> 5 cm) diaphyseal defects in poorly vascularized, infected, and/or irradiated sites (Figure 1). The induced membrane's unique biological and structural properties act as an envelope that preserves and protects the bone graft and aids in the revascularization process. The Masquelet technique is a two-stage process which may also be applicable to spine surgery. The first stage involves extensive debridement of devitalized tissue with osseous stabilization across the bone graft. The osseous void is filled with a PMMA cement spacer, often loaded with antibiotics, which prevents soft tissue invasion of the defect. The second stage is performed after 6-8 weeks or when the tissue is healthy. At this point, the biomembrane around the spacer is incised and the spacer is removed and replaced with bone graft around the induced membrane to allow for osseous integration across the bone defect.[13,14]

Antibiotic cement has also been used in the form of antibiotic cement beads. After setting, antibiotic beads can be introduced to a surgical site where they provide local wound control through antibiotic elution. Recent studies have demonstrated this technique to be effective in treating spinal surgical site infections.[15,16]

3. EFFICACY & SAFETY

Antibiotic-loaded cement spacers play a role in both the prevention and treatment of extremity infections. A systemic review revealed that prophylactic use of ABC in hip and knee replacements led to a 20 to 84% risk reduction of prosthetic joint infections (PJI).[17] Leong et al. utilized the National Joint Registry for England to reveal that patients undergoing primary total hip arthroplasty with ABC had lower rates of revision for PJI.[18] Wang et al. performed a meta-analysis and discovered that prophylactic utilization of ABC reduced deep infection rates but not superficial infection rates after primary arthroplasty.[19]

In a study of 27 patients with open fractures and long segmental defects, the Masquelet technique with antibiotic cement led to zero long term residual infections.[20]

Additionally, Masquelet retrospectively reviewed 18 of his patients that underwent his induced membrane technique with a follow-up of 10-22 years. There were no cases of recurrent infection in the reconstruction zone in any of the patients.[21]

Safety concerns have been raised regarding the use of ABC. These concerns include local toxicity, monomethyl methacrylate (MMA) vapor exposure, allergic response, structural compromise, inhibition of bone formation, and the development of drug-resistant bacteria.[22-32] However, numerous studies confirm that ABC is safe and effective in the majority of patients.[19,33-36]

4. CEMENT PROPERTIES AND TECHNIQUE IN SPINE SURGERY

Cement utilized in extremity surgery primarily consists of PMMA. PMMA is an acrylic polymer formed by mixing liquid MMA monomer and a powdered MMA-styrene co-polymer.[37] The liquid monomer polymerizes around the powdered particles to form the hardened cement through an exothermic reaction.[10] (Figure 2) PMMA often contains a radio-opacifier such as barium sulfate which allows for radiographic visualization of the cement.[37]

Several different commercial PMMA products are available that have distinct qualities. (Table 1)

During the polymerization process, surgeons can add antibiotic powder, which allows for local antibiotic delivery.[38]

Bone cement has been used widely in spine surgery to augment fixation in osteoporotic bone.[39,40] Mechanically, bone cement increases pedicle screw fixation pullout strength.[41] Previous studies have shown some decrease in structural integrity of bone cement when augmented with antibiotics.[28-30] Although these structural concerns are valid, ABC is not primarily used in the spine for structural support–rather it is a vehicle for antibiotic delivery. In this light, the addition of cement, irrespective of antibiotic impregnation, would result in a net improvement in structural support. The relatively diminished integrity of antibiotic-treated cement compared to cement without antibiotics is more of a concern in cases in which cement is primarily used for structural stability, such as in a load-bearing joint like the hip or knee.

Choice of antibiotic is based on the identified or suspected organism. (Table 1)

5. TECHNIQUE FOR UTILIZATION

Different PMMA products and antibiotic concentrations can affect cure time and often require surgeon familiarity with the different cement products and antibiotics to accurately predict curing.

5.1. CURING

The curing of ABC is divided in to 4 phases: 1) mixing; 2) handling (sticky); 3) working (doughy); 4) hardening.

During the mixing period, which generally takes about one minute, the liquid monomer is mixed with the powder and antibiotics. This can be done either by hand or with the

Table 1. Antibiotic choice, mix, spectrum, elution, resistant organisms, and complications[25,37-55]

Antibiotic Family	Antibiotic	AB cement mix	Spectrum	Elution duration	Resistant organism	Complications	References
Carbapenems	Meropenem	Simplex P bone cement with 5 % meropenem	Staphylococcus aureus P. aeruginosa, E. coli and K. pneumoniae	> least 3 weeks	Enterococcus Faecalis and Staphylococcus aureus MRSA were resistant to 5-10% after 7 days.	Not reported	Samuel, 2012[37] Galvez-Lopez, 2014[38]
		Simplex P bone cement with 10 % meropenem		27 days			
Glycopeptides	Vancomycin	1 g AB in 40g PMMA	antibacterial effects did not last more than 2 days, regardless of the test organism or the antibiotic loaded	2 days	MSSA, MRSA and VISA after 2 days	possible Acute Kidney Injury at high doses	Galvez-Lopez, 2014[38] Chang, 2011[39] Edelstein, 2018[40]
		3g AB in 40g	Not reported	Not reported	Not reported		
		4 g AB in 40g PMMA	MSSA & MRSA 21d/ VISA 5d	5-21 days	VISA after day 5		
		8 g AB in 40g PMMA	MSSA, MRSA, and VISA	60 days	none		
	Teicoplanin	1 g AB in 40g PMMA	antibacterial effects did not last more than 2 days, regardless of the test organism or the antibiotic loaded	2 days	MSSA, MRSA and VISA after 2 days	Not reported	
		4 g AB in 40g PMMA	MSSA & MRSA (40d) VISA 21d	21-40 days	VISA after day 21		
		8 g AB in 40g PMMA	MSSA, MRSA, and VISA	60 days	none		
Licopeptides	Daptomycin	1 g AB in 40g PMMA	antibacterial effects didn't last more than 2 days, regardless of the test organism or the antibiotic loaded	2 days	MSSA, MRSA and VISA after 2 days	Not reported	
		4 g AB in 40g PMMA	MSSA & MRSA (40d)/ VISA 14d	14-40 days	VISA after day 14		
		8 g AB in 40g PMMA	MSSA, MRSA, and VISA	60 days	none		

Antibiotic Family	Antibiotic	AB cement mix	Spectrum	Elution duration	Resistant organism	Complications	References
Aminoglycosides	Amikacin	1g AB in 40g PMMA	Gram negative bacilli	2 days	P. aeruginosa, K. pneumoniae, E. coli, Serratia marcescens, Proteus vulgaris	nephrotoxicity	Kuechle, 1991[41] Tai, 2021[42] Phillips, 2007[43]
		4.8g AB in 40g in PMMA		Not reported			
		5g AB in 40 g PMMA		>30 days			
	Tobramycin	1g AB in 40g in Simplex P	Gram negative bacilli, MSSA, mycobacteria	detected concentration: 2.8 mg/L at 118 days	P. aeruginosa	in vitro concentrations of 10,000 µg/mL caused death of osteoblast like cells, possible Acute Kidney Injury at high doses	Edelstein, 2018[40] Jiranek, 2006[44] Shahpari, 2020[45] Slane, 2018[46] Meeker, 2019[47]
		1.2g AB in PMMA		2 days			
		3g AB in 40g		Not reported			
		4.8g AB in 40g		detected concentration: 9.12 mg/L at 118 days			
		9.6g AB in 40g PMMA		Not reported			
	Gentamicin	0.5g AB in 40 g PMMA	Gram negative bacilli	>6 weeks	Enterobacteriaceae, P. Aeruginosa	possible Acute Kidney Injury at high doses	Galvez-Lopez, 2014[38] Edelstein, 2018[40] Nagy, 2021[48] Liawrungrueang, 2021[49]
		2g AB in 40 g PMMA		6 weeks			
		4g AB in 40g PMMA		detected concentration: 4mg/L at 30 days			
		4.8g AB in 40g PMMA		Not reported			
		8g in 40g PMMA		detected concentration: 6mg/L at 30 days			
		12.5g AB in 40g PMMA					

Antibiotic Family	Antibiotic	AB cement mix	Spectrum	Elution duration	Resistant organism	Complications	References
Cephalosporins	Cefazolin	1g AB in 40g	Gram-positive cocci, Gram negative cocci, Proteus, E. coli, K. pneumoniae	>30 days	Mycoplasma, Chlamydia	neurotoxicity	Galvez-Lopez, 2014[38] Phillips, 2007[43] Paz, 2015[50]
		4g AB in 40g		>30 days			
		7g AB in 40g PMMA		>30 days			
		8g AB in 40g		>30 days			
	Cefotaxime	1g AB in 40g	Gram negative bacilli, Enterobacteriaceae, Neisseria spp., H. influenzae, MSSA, Streptococcus pneumoniae,	Not reported	Pseudomonas aeruginosa. Escherichia coli and Enterobacter spp	rare neurotoxicity	Galvez-Lopez, 2014[38]
		4g AB in 40g		28 days			
		8g AB in 40g		1mg/L at 30 days			
	Cefuroxime	1.5g AB in 40g	Haemophilus influenzae, Moraxella catarrhalis, and Bacteroides spp	Not reported	Serratia, Proteus, Bacteroides fragilis	neurotoxicity	Galvez-Lopez, 2014[38]
		3g AB in 40g					
Antipseudomonal	Piperacillin/ Tazobactam	1g AB in 40g	Pseudomonas	detected concentration: .4 mg/L at 2 days	Escherichia coli and Klebsiella pneumoniae	possible drug fever	Park, 2011[25] Chang, 2011[39] Abdelraouf, 2019[51]
Polymyxins	Colistin	0.24g AB in 40g	Gram-negative multi drug resistant organisms	Not reported	Escherichia coli, Salmonella, Klebsiella	neurotoxicity and nephrotoxicity	Loho, 2015[52] Aghapour, 2019[53]
Macrolides	Erythromycin	2.2 AB in 40 g PMMA	Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Listeria monocytogenes, Corynebacterium minutissum, Corynebacterium diphtheria, Legionella pneumophila, Neisseria gonorrhoeae, Haemophilus influenzae, Bordetella pertussis, Chlamydia trachomatis, Entamoeba histolytica, Mycoplasma pneumoniae, Treponema pallidum, Ureaplasma urealyticum	42 days	Group A and Group B Streptococcus	Not reported	Oungeun, 2019[54] Desjardins, 2004[55]

PMMA: polymethyl methacrylate, MSSA: methicillin-susceptible Staphylococcus aureus, MRSA: Methicillin-resistant Staphylococcus aureus, VISA: Vancomycin-intermediate Staphylococcus aureus

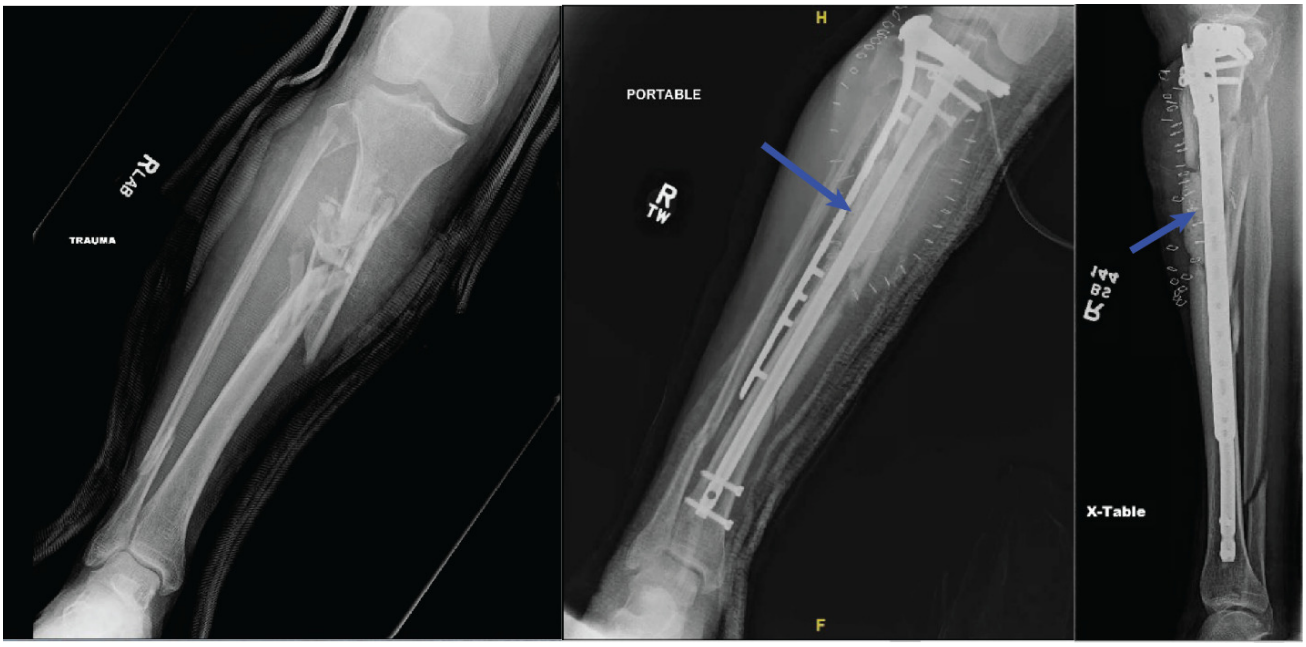

Figure 1. Anterior posterior and lateral radiographs of comminuted right tibia shaft fracture and fibula shaft fracture, status post open reduction and internal fixation and intramedullary nailing with a large osseous defect filled with antibiotic cement using the Masquelet Technique.

Arrows indicate placement of antibiotic cement.

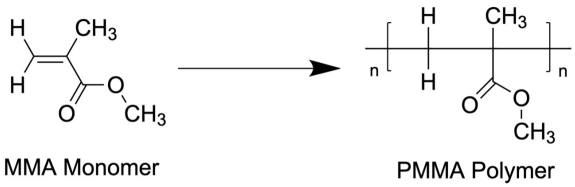

Figure 2. PMMA Chemical Structure and Polymerization

assistance of vacuum suction devices.[38] The handling period is the time it takes for the compound to reach a consistency state where it is doughy enough to be delivered to the tissues for its intended state, known as the working state. The hardening period is the time it takes for the cement to fully harden after delivery, or until it can no longer be delivered.[10]

Bone cement is heat sensitive, and variations in room or tissue temperature or humidity can affect the characteristics and setting time of the cement.[56,57] Lower temperatures can increase the handling, working, and hardening periods, while higher temperatures can conversely decrease these phases.[58] Manual handling of the cement can also accelerate the curing process.[38] Although exact requirements vary from product to product, in general, ABC should be utilized at a temperature of 73 degrees F (23 degrees C).[59]

5.2. APPLICATION OF CEMENT

Cement can be delivered to the spine in various ways depending on the intended usage. It can be delivered manually to the spine to fill large defects in the vertebral body or disc space.[60,61] Some surgeons have also described coating the instrumentation constructs with cement to minimize the risk of local infection and biofilm formation.[62,63]

Multiple delivery methods exist to allow for direct delivery to the vertebral body. For instance, the following case examples describe treatment of VO by augmenting pedicle screws with ABC in the local environment. One method to do this is to inject cement directly into the vertebral body after cannulating the pedicle screw tracts, in a manner similar to vertebroplasty or kyphoplasty. This is immediately followed by placement of the pedicle screws into the cemented path before the cement fully hardens. Several manufacturers also make fenestrated pedicle screws that allow for direct delivery of cement to the vertebral body through the cannulated screw. (Figure 3) This can allow for efficient cement augmentation across multiple vertebral bodies. Surgeons should closely scrutinize imaging during this process to watch for cement extravasation.

5.3. COMPLICATIONS OF CEMENT DELIVERY

Although antibiotic cement may be a powerful resource in the treatment of spine infections, usage of ABC may be associated with several complications and should be carefully planned and closely scrutinized. Surgeons should be mindful of the potential for cement extravasation, especially when the bone is weakened secondary to infection, tumor, or fracture. Cement can extravasate posteriorly into the canal, which can cause emergent neurological deficits (Figure 4), can extravasate anteriorly to the vertebral body and damage visceral structures, and in some cases has the

Figure 3. Fenestrated screw with poly-axial head. Stryker. Kalamazoo, MI.

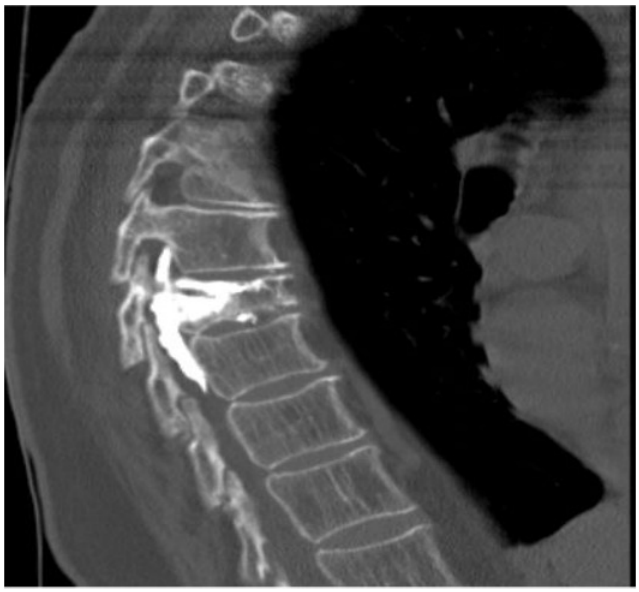

Figure 4. Sagittal plane view of cement extravasation into spinal canal

propensity to enter the vasculature, which can lead to cement embolization (Figure 5).

Given the heat generated during the exothermic curing process, damage to neural structures can occur due to thermal injury.[64,65] This is of particular concern in cases of extravasation where cement could come into direct contact with sensitive neurovascular structures

Of note, cement can make revision cases more difficult. Cemented screws that have failed can compromise bone stock and make it difficult to achieve revision transpedicular fixation, often warranting an extension of prior surgical constructs. Moreover, if an infected vertebral body is treated with ABC and then progresses to the point of requiring further surgery, the subsequent case could be substantially more challenging. An example of this is in the setting of a cemented vertebral body, which might require corpectomy.

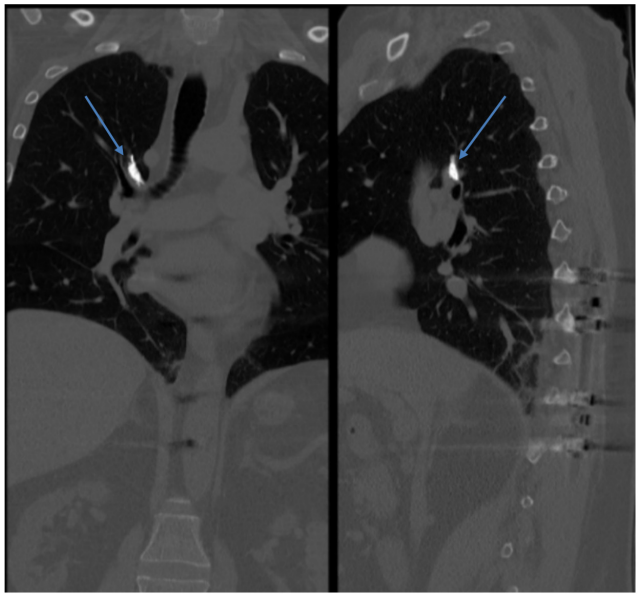

Figure 5. Sagittal & coronal plane views from a patient suffering a pulmonary embolism secondary to Cement extravasation

5.4. CASE EXAMPLE

A 57-year-old female was initially admitted to an outside facility and found to have L5-S1 osteodiscitis with a ventral epidural phlegmon and blood cultures positive for Methicillin-Sensitive Staph Aureus. She was treated for 6 weeks with Oxacillin with persistent low back pain, as well as persistently elevated inflammatory markers. Repeat imaging revealed progression of her osteodiscitis at the lumbosacral junction with development of spondylolisthesis (Figure 6). Given her failure to respond to medical treatment, she was treated with surgical decompression, debridement of osteodiscitis, and stabilization from L5 to the pelvis with ABC augmentation of her pedicle screw fixation. Postoperatively, she remained on antibiotics for 6 weeks with gradual improvement in her back pain and normalization of her inflammatory markers.

6. CONCLUSION

Antibiotic-loaded bone cement has been widely used in orthopedic surgery for more than 150 years, both for prophylaxis and treatment of bacterial infection. Efficacious results have been observed in both settings.[66] However, little literature exists regarding the use of ABC in the field of spine surgery. With a thorough understanding of the prop-

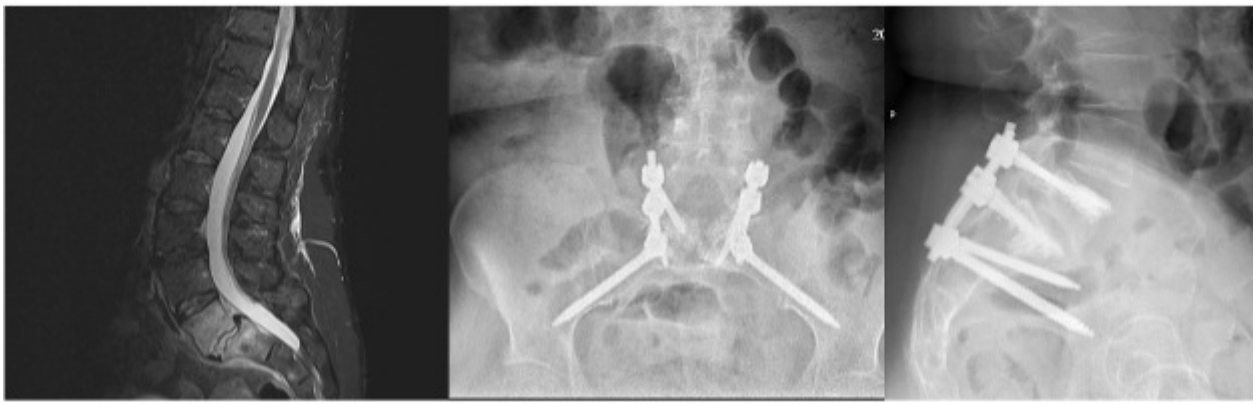

Figure 6. Sagittal T2 sequence MRI, and AP, and Lateral radiographs of Lumbar spine, demonstrating successful debridement and stabilization of lumbosacral osteodiscitis supplemented with ABC.

erties of the cement and the methods of delivery, ABC is a useful adjunct in the treatment of spinal infections.

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Conceptualization, EO, CO, GA, AD; methodology, EO, CO, GA; software, CO, GA; validation, EO, JAY, AD; formal analysis, CM; investigation, CO, GA, CM; resources, CM, JAY; data curation, GA, CM; writing—original draft preparation, EO, CO, GA, CM writing—review and editing, EO, CO, GA, CM, JAY, AD; visualization, CO, CM, JAY; supervision, EO, AD; project administration, AD; funding acquisition, AD. All authors have read and agreed to the published version of the manuscript

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