

Clinical Practice Guidelines for Antimicrobial-Loaded Cements and Beads in the Treatment of Infected Devices in Orthopedic Trauma

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Disclosures: None.

INTRODUCTION: The utilization of implants within orthopedic surgery establishes a milieu conducive to bacterial adherence, biofilm formation, and subsequent infection development. Treatment of these infections often requires stability augmentation and dead-space management with anti-microbial loaded bone cements (ABCs). The growing incidence of antimicrobial resistance has necessitated the exploration of alternative antibiotic medications, both as targeted and as broad-spectrum ABCs. The following will detail the most extensive and all-encompassing summary of antimicrobial choice and dosage for ABCs. It will also include information, when available, regarding the elution kinetics of various drugs discussed when applied with dissolvable calcium sulfate (Stimulan™), dissolvable calcium sulfate *plus* calcium phosphate (Cerament G™), non-dissolvable Simplex™ High Viscosity (HV) (non-medicated Polymethylmethacrylate (PMMA)), or non-dissolvable Simplex™ P (PMMA loaded with Tobramycin 1 gram).¹ The present study has the following objectives with regard to structure and content: 1) to present our institutional protocol for the administration of a wide range of ABCs in the treatment of osteosynthesis-associated infections (OAI), 2) to provide practical instructions for the most efficacious methods for mixing the cement and antimicrobials, 3) give options for the combination of two or more antibiotics, and 4) to demonstrate meaningful clinical decision-making guidance for orthopedic surgeons in approaching the management of these complex infections.

METHODS: In establishing our own institutional protocol, we reviewed and compiled relevant dosing, efficacy, and elution profiles from 74 articles published between 1976 and 2019. Then, we elucidated first-line and targeted therapies against rare and resistant bacteria and drug therapies not recommended due to excessive cytotoxicity or poor delivery kinetics.

RESULTS: We compiled a list of thirty-two antibiotics and three antifungals that have proven successful in managing OAI, including infections with numerous recalcitrant and multidrug-resistant species. Of these antibiotics, twelve are explicitly targeted at eradicating gram-positive bacteria; eighteen are for empiric, broad-spectrum use, and two (isoniazid and streptomycin) are expressly targeted at treating rare *mycobacterium tuberculosis* OAI. The three antifungals (amphotericin B, fluconazole, and voriconazole) target the complication of fungal infection.^{2,3}

We provide optimized ratios of carrier to antimicrobial for each of the delivery methods, including tobramycin-loaded Simplex™ P bone cement, nonmedicated Simplex™ HV, Stimulan™ dissolvable calcium sulfate beads, and Cerament G™ dissolvable calcium sulfate *plus* calcium phosphate beads. When available, the various antibiotics' elution and efficacy profiles are described in our protocol.

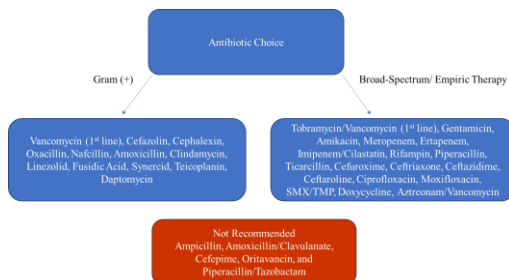
DISCUSSION: The results of this study highlight the salience of antibiotic utilization in treating OAI. While we provide first-line treatment modalities for use in targeted therapy against gram-positives and broad-spectrum empiric therapy, this paper also supports the necessity for a regimen tailored to the specific pathogens and sensitivities and provides a dosage guide for their use. Lastly, we outline the delivery methods compatible with each drug. These results encapsulate what, to our knowledge, are the most comprehensive clinical practice guidelines for antibiotic- and antifungal-loaded bone cements and beads to treat infected implants. These recommendations are based on literature support through *in vitro*, *in vivo*, or case studies. With the ever-evolving propensity of bacteria to develop antibiotic resistance, these recommendations are dynamic; some are limited by the state of the antibiotic profile at the time of elucidation.

SIGNIFICANCE/CLINICAL RELEVANCE: This technique guide will provide meaningful clinical improvement in managing orthopedic implant infections. Clinicians will benefit from a centralized source for dosing and route of administration for both empiric and targeted therapy.

REFERENCES:

- 1) Okike, K. and T. Bhattacharyya. J Bone Joint Surg Am, 2006.
- 2) Masri et al. J Arthroplasty, 1998.
- 3) McPherson et al. Reconstructive Review, 2013.

IMAGES AND TABLES:



Antibiotics in Bone Cement	Stimulan [®] (dissolvable calcium sulfate) Amount per 20 gm 10 ml ~ 20 gm Dissolves over 3 weeks	GaX [®] (dissolvable calcium sulfate & calcium phosphate) Amount per 40 gm Dissolves over 6 months	Simplex HV [®] (PMMA) (Colbalt HV in component) Amount per 40 gm Non-dissolvable	Simplex P [®] (PMMA with Tobramycin 1 gm) Amount per 40 gm Non-dissolvable
Amikacin	1000 mg / 4 ml		4 ml liquid (1000 mg) stored good elution only up to 7 days (31)	
Ampicillin	370 mg (72 hr 300%)		1450 mg (72 hr 300%)	
Aztreonam			Yes up to 4000 mg (up to 31 days)	
Cefazolin			Yes up to 4100 mg	Yes up to 1000 mg
Cefepime			Yes up to 4000 mg	
Ceftriaxone			Yes up to 1800 mg	
Cefuroxime			Yes up to 4000 mg	Yes up to 4000 mg
Ceftazidime	1000 mg 1500 mg		Yes up to 4000 mg	Yes up to 4100 mg (above 1500 mg had no structural strength)
Ciprofloxacin			Yes up to 4000 mg	
Ciprodexacin	1000 mg		Yes up to 4000 mg	
Clindamycin	Does not set with liquid		Yes up to 4000 mg	
Colistin	400 mg		2.4% (12,000,000 IU) (100 mg) stored good elution only up to 30 days (70)	1200 mg (100 mg) stored good elution only up to 30 days (70)
Daptomycin	Yes up to 10000 mg (24 hrs)		Yes up to 4000 mg	Yes up to 2000 mg
Ertapenem	Yes up to 1000 mg (Or 240 mg 6 ml of 40 mg/ml)	171 mg per gram Cement G	100 mg	
Erythromycin			Yes up to 4000 mg	Yes up to 4000 mg
Imipenem + Cilastatin	500 mg (elutes)		Yes up to 4000 mg (300 mg beads)	

	up to 48 hrs not for monotherapy	to 6 days not for monotherapy
Isoniazid		Yes up to 4000 mg
Fusidic Acid	Yes up to 1000 mg (14 days)	
Linezolid		Yes up to 4000 mg
Meropenem	1000 mg	Yes up to 4000 mg
Moxifloxacin	Yes up to 1000 mg (31 days)	Yes up to 4000 mg
Nafcillin	1000 mg	
Oxacillin		Yes up to 2000 mg
Piperacillin		Yes up to 4000 mg
Quinupristin-Dalfopristin (Synercid)		Yes up to 3000 mg
Rifampin	Yes up to 600 mg	4000 mg minimum for detectable elution out to 14-24 days. Up to 8000 mg studied. All doses delays cement hardening to 1 hr
Streptomycin		Yes up to 7000 mg
Sulfamethoxazole/Trimethoprim		400-80 mg liquid
Teicoplanin	400 mg	Yes up to 4000 mg
Ticarcillin		12,000 mg
Tobramycin	Yes up to 500 mg powder or 6 ml (40 mg/ml)	Yes up to 9800 mg
Vancomycin	Yes up to 2000 mg	Yes up to 10,000 mg
Tobramycin/Vancomycin	1000 mg vancomycin with tobramycin (240 mg liquid (30) or (400 mg powder))	4000 mg vancomycin with 4800 mg tobramycin