Clinical Practice Guidelines for Antimicrobial-Loaded Cements and Beads in Orthopedic Trauma and Arthroplasty

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INTRODUCTION:

The utilization of hardware and implants within orthopedic trauma and arthroplasty 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 antimicrobial-loaded bone cements (ABCs). Over the past several years, bone cement and beads impregnated with antibiotics have become popular in the treatment of infected orthopedic implants; however, the growing incidence of antimicrobial resistance has necessitated the exploration of alternative antibiotic medications, both as targeted and as broad-spectrum ABCs. When selecting the optimal antibiotic to incorporate into the spacer, many surgeons focus on gram-positive organisms as they predominate in skin flora and are notoriously pathogenic, thus rendering them a logical target for preventing infection in orthopedic procedures. However, some surgeons utilize a broad-spectrum treatment regimen to achieve theoretically superior treatment of infection with any combination of resident gram-positive, gram-negative, anaerobic, and fungal organisms that may have colonized a wound.

The following review will summarize antimicrobial choice and dosage for ABCs and beads in orthopedic trauma and arthroplasty. 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).

This review has the following objectives concerning structure and content: 1) to provide practical instructions for the dosing administration of antimicrobials in the cement/beads, 2) to give options for the combination of two or more antibiotics/antifungals, and 3) to demonstrate clinical decision-making guidance for orthopedic surgeons in approaching the management of these complex infections.

METHODS:

Relevant dosing, efficacy, and elution profiles were reviewed and compiled from 74 articles published between 1976 and 2019. First-line and targeted therapies were identified against rare and resistant bacteria. Drug therapies not recommended due to excessive cytotoxicity or poor delivery kinetics were also elucidated.

RESULTS:

This reviewed covers thirty-seven antibiotic and eight antifungal medications.

The compilation describes thirty-two antibiotics and three antifungals that have been successful in managing orthopedic surgery-related infections, including infections with numerous recalcitrant and multidrug-resistant species. Optimized ratios of carrier to antimicrobial are provided for each delivery method. When available, the elution and efficacy profiles of the various antibiotics are described.

Vancomycin is perhaps the most commonly relied upon antibiotics both as monotherapy and in conjunction with other antibiotics. It is widely used to prevent and treat gram-positive intrawound infections due to its activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus* spp. (CoNS), the most prevalent causes of FRI and PJI.

There are five antibiotics, ampicillin, amoxicillin/clavulanate, cefepime, oritavancin, and piperacillin/tazobactam, with poor elution characteristics or excessive cytotoxicity that are not recommended for treating bacterial FRI and PJI.

There are five antifungals, ampicillin, amoxicillin/clavulanate, cefepime, oritavancin, and piperacillin/tazobactam, with poor elution characteristics or excessive cytotoxicity that are not recommended for treating fungal FRI and PJI.

DISCUSSION AND CONCLUSION: This review highlights the salience of antibiotic utilization in treating FRIs and PJIs. While first-line treatment modalities for use in targeted therapy against gram-positives and broad-spectrum empiric therapy are described, this paper also supports the necessity for a regimen tailored to the specific pathogens and sensitivities and provides a single compiled source for dosages of most available antimicrobials. Lastly, the delivery methods compatible with each drug were outlined.

These results encapsulate a useful set of clinical practice guidelines for antibiotic- and antifungal-loaded bone cements and beads to treat musculoskeletal infections. 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; the state of the antibiotic profile limits some at the time of elucidation. Collaboration with medicine, infectious disease, and/or pharmacology teams is recommended in creating institutional protocols for antibiotic-eluting implants and close co-management of particular infections as needed to ensure patient safety and efficacy.

Antibiotics in Bone Cement	Stimulan™ (dissolvable calcium sulfate) **Amount per 20 gm** **10 ml = 20 gm** Dissolves over 2 weeks	Cerament G™ (dissolvable calcium sulfate & calcium phosphate) Dissolves over 4 months	Simplex™ HV (PMMA) **Amount per 40 gm** Non-dissolvable	Simplex™ P (PMMA with Tobramycin 1gm) **Amount per 40 gm** Non-dissolvable
Amikacin	1000 mg: 4 ml (do 5gm powder in luture)		4 ml liquid (1000 mg) showed good elution only up to 7 days (1:1) 15000 mg powder in lumen)	
Amoxicillin	570 mg (72 hr study)		1450 mg (72 hr study)	
Azlreonam			Yes up to 4000 mg **(up to 31 days)**	
Cefazolin			Yes up to 4500 mg	Yes up to 1000 mg
Cefotaxime			Yes up to 8000 mg	
Ceftazidime Fosamil			Yes up to 1800 mg	
Ceftazidime			Yes up to 4000 mg	Yes up to 4000 mg
Ceftriaxone	1000 mg		Yes up to 4000 mg	
Cefuroxime	1500 mg		Yes up to 4000 mg	Yes up to 4500 mg (doses above 1500 mg had no structural strength)
Cephalexin			Yes up to 4000 mg	
Ciprofloxacin	1000 mg		Yes up to 4000 mg (powder)	
Clindamycin	Does not set with liquid		Yes up to 4000 mg powder	
Colistin	400 mg		2.4% [1,000,000 IU] (960 mg)] showed good elution only up to 7 days (11) [8,000,000 IU] (40 mg elution for 72 hr)	[(24,000,000 IU) (1020 mg)] showed good elution to 30 days (70)
Daptomycin	Yes up to 1000 mg (28 days)		Yes up to 4000 mg	Yes up to 2000 mg
Doxycycline			196 mg	
Gentamicin	Yes up to 1000 mg. QC [45 mg (4 ml of 40 mg/ml)	175 mg premix Cerament G	Yes up to 4000 mg	
Ertapenem			Yes up to 3000 mg	Yes up to 4000 mg
Erythromycin			720 mg gluceleptonate (360 mg base)	
Imipenem / Cilastatin	500 mg (elutes **up to 48 hrs not for monotherapy**)		4000 mg (elutes **up 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	Yes up to 1500 mg
Meropenem	1000 mg		Yes up to 8000 mg	Yes up to 5000 mg
Moxifloxacin	Yes up to 1000 mg (31 days)		Yes up to 8000 mg	
Nafcillin	1000 mg			
Oxacillin			Yes up to 2000 mg	
Piperacillin			Yes up to 8000 mg	
Quinupristin Dalfopristin [1, 2] (Synercid)			Yes up to 3000 mg	
Rifampin	Yes up to 600 mg		4800 mg minimum for detectible 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	(Dose 5ml liquid in lumen)		400-80 mg liquid	
Teicoplanin	400 mg		Yes up to 4000 mg	Yes up to 280 mg
Ticarcillin			12,000 mg	
Tobramycin	Yes up to 500 mg powder or 6 ml (40mg/ml)		Yes up to 8000 mg	
Vancomycin	Yes up to 5000 mg		Yes up to 10,000 mg	Yes up to 2000 mg
Tobramycin/Vancomycin	1000 mg vancomycin with tobramycin (340 mg liquid (40) or (600 mg powder (60))		4800 mg vancomycin with 4800 mg tobramycin	1000 mg vancomycin with tobramycin (400 mg powder (40))