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GENERAL REVIEW

Clinical practice guidelines for antimicrobial-loaded cements and beads in orthopedic trauma and arthroplasty

Aaron B. Epperson[1] · Mohamed E. Awad[1] · Melissa Gorman[1] · Kristin Loker[1] · Nicholas A. Alfonso[1] · Jason W. Stoneback[1]

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Abstract

Purpose Implants in orthopedic trauma and arthroplasty surgery establish a milieu conducive to biofilm formation. Antimicrobial-loaded cements (ABCs) and beads have become popular in treating acute and chronic orthopedic surgery-related infections. The growing incidence of antimicrobial resistance has necessitated the exploration of alternative antibiotic medications. This review aims to demonstrate meaningful clinical decision-making guidance for orthopedic surgeons in approaching the management of these complex infections.

Methods This study protocol was conducted following the PRISMA checklist and guidelines of the Cochrane Handbook for Systematic Reviews of Interventions. PubMed, Ovid MEDLINE, Web of Science, and other databases were queried using applicable search terms. 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 compilation describes thirty-two antibiotics and three antifungals that have successfully managed 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. The elution and efficacy profiles of the various antibiotics are described when available.

Discussion/conclusion These recommendations offer the most up-to-date and comprehensive practice guidelines for using antimicrobials in cements and beads for treating orthopedic hardware-related infections. With the ever-evolving propensity of bacteria to develop antibiotic resistance, these recommendations are dynamic. Collaboration with medicine, infectious disease, and/or pharmacology teams is recommended to create institutional protocols for antibiotic-eluting implants and close comanagement to ensure efficacy and patient safety.

Keywords Biofilm · Biomaterials · Clinical outcomes research · Antimicrobial cement · Implant materials · Infection · Microbiome

Introduction

The utilization of implants within orthopedic trauma and arthroplasty surgery establishes a milieu conducive to bacterial adherence, biofilm formation, and subsequent infection development. [1] Treatment of these infections often requires stability augmentation and dead-space management with antimicrobial-loaded bone cements (ABCs). In this context, fracture-related infection (FRI) is defined as the clinical or subclinical infection of a fracture site following surgical fixation with an internally placed implant. FRI poses a significant risk of severe disability after fracture care [2]. The incidence of FRI varies between 10 and 50%, contingent upon the fracture type and surrounding soft tissue injury. In turn, this may lead to amputation of the affected limb in 3–5% of cases [3–5].

Arthroplasty data report infection rates lower than those seen in orthopedic trauma, with most national databases reporting rates of around 1–2% of primary hip and knee arthroplasties [6]. Despite this low rate, prosthetic joint

✉ Aaron B. Epperson
aaron.epperson@kansascity.edu

[1] Department of Orthopedics, University of Colorado Anschutz Medical Campus, 12631 E. 17th Avenue, Mail Stop B202, Aurora, CO 80045, USA

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infection (PJI) in arthroplasty is a notable concern as the incidence of these procedures has risen vastly over recent decades, and the demand for arthroplasty is expected to increase by nearly 200% by 2040 and over 650% by 2060[7]; furthermore, the rate of PJI is rising [8], and the risk of revision surgery secondary to PJI in total hip arthroplasty (THA) has increased in recent years [9]. The most common cause of hardware infection is *Staphylococcus aureus*, which almost always necessitates hardware removal [10]. When this complication occurs, placing a cement spacer into the space previously occupied by the implant as a temporary measure to provide local therapeutic concentrations of antibiosis to help eradicate the infection is commonly practiced. [11]

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 [12]. 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 [13].

This systematic review aims to 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 g).

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. This review includes detailed antibiotic/antifungal elution and efficacy data from tobramycin-loaded Simplex™ P bone cement, non-medicated Simplex™ HV, Stimulan™ dissolvable calcium sulfate beads, and Cerament G™ dissolvable calcium sulfate + calcium phosphate beads, supported by a literature review.

The results of this review are organized by coverage, include a brief history and rationale for each drug, and present the respective dosages for each delivery method**.**

Methods

Protocol

This study protocol was conducted following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) checklist [11] and guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [12] [Fig. 1].

Search methodology

A detailed, comprehensive literature search for all relevant studies was performed using several online databases: PubMed, MEDLINE via Ovid, Web of Science, Cochrane database, and Science-Direct. The search strategy was a

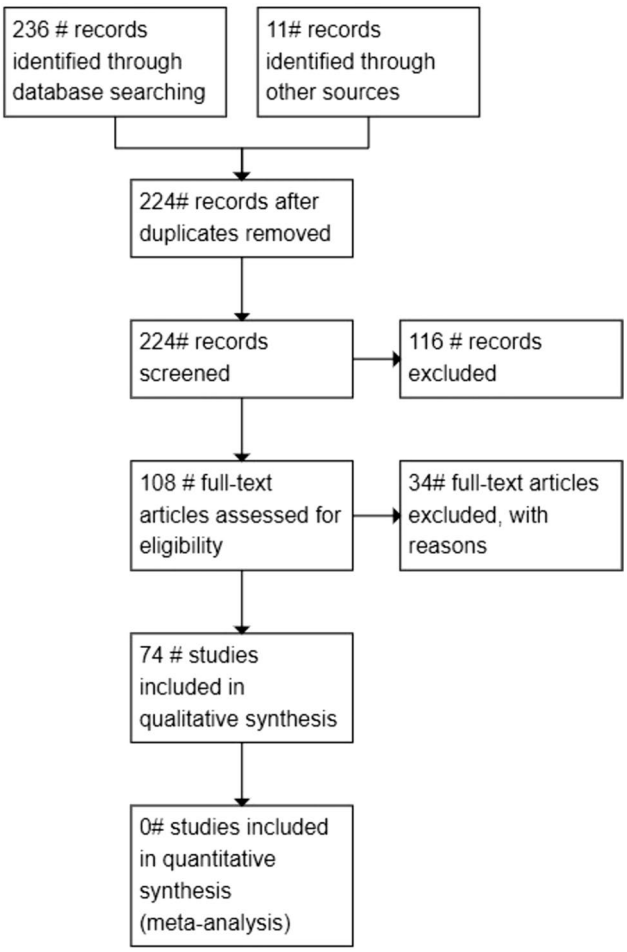

Fig. 1 PRISMA flowchart of study search and inclusion

combination of subject headings and free-text words in Ovid MEDLINE, topic searching in Web of Science, and free-text words in the other databases using the following search terms: ((antibiotic bone cement) OR (antibiotic-loaded cement)) AND (fracture-related infection). The references of available studies were manually examined for any studies that met our inclusion criteria to ensure the inclusion of all available relevant evidence.

Study selection and eligibility criteria

Two independent reviewers assessed the eligibility of the study titles, abstracts, and full-text articles based on the eligibility criteria.

Eligibility criteria

Criteria included randomized controlled trials, non-randomized prospective trials, retrospective observational cohort studies, in vitro studies, in vivo studies, and case series/reports published in the English language investigating the feasibility and efficacy of various antimicrobials for the management of FRI and PJI.

Data Extraction

The authors extracted the required data from all included studies. Data collection tables were designed to sort quantitative and qualitative data for our analysis. The following data variables were extracted: maximum dose for respective antimicrobials in Stimulan™ dissolvable calcium sulfate beads, Cerament G™ dissolvable calcium sulfate + calcium phosphate beads, Simplex HV™ polymethylmethacrylate, and Simplex P™ polymethylmethacrylate loaded with 1 g gentamycin. Specific notes regarding the duration of elution and the form of impregnated antimicrobial (i.e., liquid or powder) were included when applicable. Relevant dosing, efficacy, and elution profiles of antimicrobials obtained from 74 articles published between 1976 and 2019 were reviewed and compiled. Then, first-line and targeted therapies against rare and resistant bacteria and drug therapies not recommended due to excessive cytotoxicity or poor delivery kinetics were described.

Results

Search result and study selection

Using the previously mentioned keywords, 224 relevant citations were obtained from online databases and manual cross-reference retrieval. The selection process yielded 74 studies investigating elution and efficacy profiles for impregnable antimicrobials.

Characteristics of the included studies

Gram (+) coverage

Gram-positive bacteria predominate on the skin and are known to be the predominant cause of FRI and PJI. Therefore, many surgeons opt to target these pathogens specifically. The quality of evidence in the 25 supporting studies is varied with one Level I evidence study, four Level IV studies, one Level V study, and 19 foundational evidence in vitro studies in accordance with the AAOS Levels of Evidence. See Table 1 for dosing recommendations based on carrier and Fig. 2 for supported antibiotic use and coverage.

Vancomycin

Vancomycin is widely used to prevent and treat gram-positive intrawound infections due to its activity against methicillin-resistant *S. aureus* (MRSA) and coagulase-negative *Staphylococcus* spp. (CoNS), the most prevalent causes of FRI and PJI [39]. Despite its widespread use, the literature does not define best practices for administering vancomycin.

Vancomycin has been used for many years as the antibiotic of choice for implantation into PMMA spacers. In Simplex™ P, up to 2 g of vancomycin as therapeutic augmentation is safe [40]. In Simplex™ HV, up to 10 g of vancomycin has demonstrated safety by eliminating all bacteria in subsequent cultures [10]. More recent studies from 2014 and 2015 showed that, using Stimulan™, up to 2 g of vancomycin was safe and effective, with high bioactivity against MRSA and S. epidermidis and the ability to prevent biofilm formation [41, 42]. Additionally, calcium sulfate beads demonstrated equal or greater performance than PMMA beads in inhibiting bacterial growth and elution of vancomycin [43]. A study from 2018 examined the addition of borate glass, which has been shown to aid in osteogenesis, to PMMA constructs and found that adding borate glass significantly increased the elution of vancomycin [44].

Cefazolin ± Vancomycin

Due to the familiarity with its activity as local antibiosis in standard carriers, vancomycin is often the subject of studies involving comparative or synergistic activities with other antibiotics. One such study examined vancomycin with cefazolin to target gram-positive bacteria. Paz et al. reviewed this combination's efficacy and any alteration of elution kinetics when used together in an in vitro comparative study in PMMA. The investigators compared the activity of each

Table 1 List of supported antibiotics for use in the treatment of FRI and PJI and their respective doses in common carriers

Antibiotics in Bone Cement	Stimulan™ (dissolvable calcium sulfate) Amount per 20 gm 10 ml = 20 gm Dissolves over 3 weeks	Cerament G™ (dissolvable calcium sulfate & calcium phosphate) Dissolves over 6 months	Simplex™ HV (PMMA) Amount per 40 gm Non-dissolvable	Simplex™ P (PMMA with tobramycin 1 gm) Amount per 40 gm Non-dissolvable
Amikacin	1000 mg/4 ml (do 5 gm powder in house)		4 ml liquid (1000 mg) showed good elution only up to 7 days (11) (5000 mg powder in house)	
Amoxicillin	570 mg (72 h study)		1450 mg (72 h study)	
Aztreonam			Up to 4000 mg (up to 21 days)	
Cefazolin			Up to 4500 mg	Up to 1000 mg
Cefotaxime			Up to 8000 mg	
Ceftaroline fosamil			Up to 1800 mg	
Ceftazidime			Up to 4000 mg	Up to 4000 mg
Ceftriaxone	1000 mg		Up to 4000 mg	
Cefuroxime	1500 mg		Up to 4000 mg	Up to 4500 mg (doses above 1500 mg had no structural strength)
Cephalexin			Up to 4000 mg	
Ciprofloxacin	1000 mg		Up to 6000 mg (powder)	
Clindamycin	Does not set with liquid		Up to 6000 mg powder	
Colistin	400 mg		2.4% [(12,000,000 IU) (960 mg)] showed good elution only up to 7 days (11) (3,000,000 IU) 240 mg elution for 72 h	[(24,000,000 IU) (1920 mg)] showed good elution to 30 days (70)
Daptomycin	Up to 1000 mg (28 days)		Up to 8000 mg	Up to 2000 mg
Doxycyclin			100 mg	
Gentamicin	Up to 1000 mg Or 240 mg (6 ml of 40 mg/ml)	175 mg premix Cerament G	Up to 8000 mg	
Ertapenem			Up to 8000 mg	Up to 4000 mg
Erythromycin			720 mg glucoheptonate (500 mg base)	
Imipenem/Cilastatin	500 mg (elutes up to 48 h not for monotherapy)		4000 mg (elutes up to 6 days not for monotherapy)	
Isoniazid			Up to 4000 mg	
Fusidic acid	Up to 1000 mg (14 days)			
Linezolid			Up to 4000 mg	Up to 1200 mg
Meropenem	1000 mg		Up to 8000 mg	Up to 5000 mg
Moxifloxacin	Up to 1000 mg (31 days)		Up to 8000 mg	
Nafcillin	1000 mg			
Oxacillin			Up to 2000 mg	
Piperacillin			Up to 8000 mg	
Quinupristin-Dalfopristin (Synercid)			Up to 3000 mg	
Rifampin	Up to 600 mg		4000 mg minimum for detectable elution out to 14–24 days Up to 8000 mg studied All doses delay cement hardening to 1 h	

Table 1 (continued)

Antibiotics in Bone Cement	Stimulan™ (dissolvable calcium sulfate) Amount per 20 gm 10 ml = 20 gm Dissolves over 3 weeks	Cerament G™ (dissolvable calcium sulfate & calcium phosphate) Dissolves over 6 months	Simplex™ HV (PMMA) Amount per 40 gm Non-dissolvable	Simplex™ P (PMMA with tobramycin 1 gm) Amount per 40 gm Non-dissolvable
Streptomycin			Up to 7000 mg	
Sulfamethoxazole/Trimethoprim	(Done 5ml liquid in house)		400:80 mg liquid	
Teicoplanin	400 mg		Up to 4000 mg	Up to 200 mg
Ticarcillin			12,000 mg	
Tobramycin	Up to 500 mg powder or 6 ml (40mg/ml)		Up to 9800 mg	
Vancomycin	Up to 2000 mg		Up to 10,000 mg	Up to 2000 mg
Tobramycin/Vancomycin	1000 mg vancomycin with tobramycin (240 mg liquid (30)) or (600 mg powder (60))		4000 mg vancomycin with 4800 mg tobramycin	1000 mg vancomycin with tobramycin (600 mg powder (60))

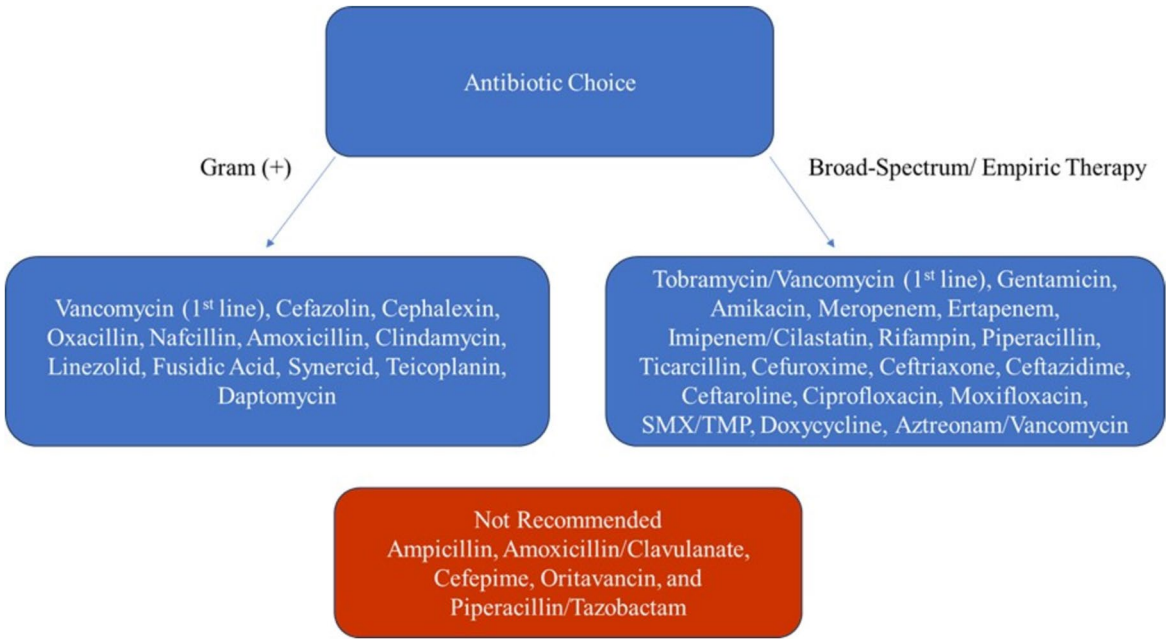

Fig. 2 Chart displaying the supported antibiotics based on the spectrum of coverage and antibiotics not supported for use upon review of available literature

antibiotic individually and the activity of the antibiotics together. Groups with cefazolin showed much higher elution than those containing the same vancomycin concentration, and optimal elution occurred when the two were used concomitantly. The study supports safety and efficacy in concentrations of cefazolin up to 1 g in Simplex™ P bone cement [45].

Cephalexin

Cephalexin is a first-generation cephalosporin that is one of the most utilized treatments for superficial skin infections due to its activity against gram-positive bacteria. Cephalexin is safe and effective at doses of up to 4 g in non-medicated Simplex™ HV [28].

Oxacillin

Oxacillin is a second-generation, penicillinase-resistant penicillin. It is effective against resistant strains of gram-positive bacteria, especially *S. aureus*. To tailor antibiotic therapy to the most likely pathogen, Ueng et al. compared in vivo the activity of two antibiotics with predominately gram-positive activity, oxacillin and vancomycin, against *S. aureus* with a particular interest in eradicating MRSA and found that vancomycin provided superior anti-MRSA activity to oxacillin; however, oxacillin still demonstrated antibacterial activity and is safe at doses up to 2 g in Simplex™ HV [46].

Nafcillin

Nafcillin is another penicillinase-resistant penicillin, making it an attractive option in severe gram-positive infections. It is safe and effective at doses up to 1000 mg in Stimulan™ [29].

Amoxicillin

Amoxicillin is an aminopenicillin with a broader spectrum of coverage than many other penicillins, including coverage of several gram-negative species. The additional amino group also confers greater activity against resistant strains of bacteria. It is safe and effective in Stimulan™ at doses up to 570 mg and non-medicated Simplex™ HV up to 1450 mg [30].

Clindamycin

Clindamycin is a lincosamide antibiotic active against many gram-positive organisms, including MRSA. It is also effective against anaerobes. Clindamycin is safe and effective at doses of up to 6 g in non-medicated Simplex™ HV [31].

Linezolid

Linezolid is an oxazolidinone antibiotic with excellent gram-positive coverage, including MRSA, CoNS, and vancomycin-resistant enterococcus (VRE) [47], making it an essential antibiotic for use in complex cases with resistant gram-positive bacteria. Linezolid was found to be safe up to 4 g, representing 10% of standard 40 g PMMA mass in applications of Simplex™ HV. Linezolid also demonstrated safety at doses up to 1.2 g in Simplex™ P [48, 49]. Palacos™ Bone Cement as another viable medium through which Linezolid showed extended elution [45].

Fusidic acid

Fusidic acid is a bactericidal antibiotic with a spectrum of activity featuring mainly gram-positive coverage, including activity against MRSA, but also against anaerobes, *Neisseria* spp., *Mycobacterium leprae*, and others [46]. In a 2008 study, Panagopoulos et al. showed in vitro activity of fusidic acid up to 1 g in Stimulan™ [50].

Quinupristin/Dalfopristin (Synercid)

This combination of two streptogramin antibiotics has activity against severe gram-positive infections, including VRE. Synercid is effective in non-medicated Simplex™ HV at doses of up to 3 g [45].

Teicoplanin

Teicoplanin is a glycopeptide antibiotic effective against virulent and resistant strains of gram-positive bacteria. It is not currently approved by the FDA for use in the USA but remains widely used elsewhere [51]. Teicoplanin was found to have clinically significant antibacterial activity, especially against VRE at doses of 200 mg in Simplex™ P spacer [52]. Additionally, teicoplanin is safe at doses of up to 4 g in non-medicated Simplex™ HV [53]. In Stimulan™, teicoplanin is safe and effective at doses up to 400 mg [29].

Daptomycin

Daptomycin is a lipopeptide with excellent gram-positive coverage, including virulent and resistant strains. Given the promise of utilizing this drug in recalcitrant cases of infection with gram-positive organisms, Cortes et al. described the safe and successful use of daptomycin-impregnated Simplex™ P (PMMA + aminoglycoside) bone cement in the treatment of a case of recurrent prosthetic joint infection in a patient with multiple antibiotic allergies and past colonization with multiple antibiotic-resistant organisms. Daptomycin exhibited safety and efficacy at 2 g in Simplex™ P [54]. In non-medicated Simplex™ HV, doses up to 8 g are safe and effective [45]. In Stimulan™, daptomycin demonstrated efficacy and safety at doses up to 1 g [29].

Broad-spectrum coverage/empiric therapy

This section will address broad-spectrum and empiric therapies for treating FRIs and PJIs. The quality of evidence in the 41 supporting studies is varied with four Level I evidence studies, one Level III study, six Level IV studies, three Level V studies, and 27 foundational evidence in vitro studies in accordance with AAOS Levels of Evidence. Although gram-positive staphylococci predominate on the skin, bacterial infection, including gram-negative organisms, may present when microorganisms colonize bone or orthopedic implants via hematogenous seeding, direct inoculation as with

unsterile surgical instrumentation, or airborne contamination [14]. See Table 1 for dosing recommendations based on carrier and Fig. 2 for supported antibiotic use and coverage.

Colistin

Colistin is a potent antibiotic often reserved as a last-line treatment for resistant gram-negative infections [55]. Laycock et al. performed an in vitro experiment to examine the compatibility of colistin with calcium sulfate beads. They found colistin is a feasible option with safety at 400 mg and efficacy against 100% of *Pseudomonas* and *A. baumannii* isolates [56].

Due to its remarkable activity against gram-negative organisms, colistin is also used with other empiric therapy antibiotics. Within the first years after Bucholz and Engelbrecht introduced the idea of antibiotic-loaded PMMA spacers, Rosenthal et al. evaluated the in vitro efficacy of erythromycin and colistin in combination as empiric therapy. They noted effectiveness in inhibiting 98% of anaerobic and aerobic test isolates when applying 500 mg of erythromycin and 240 mg of colistin in Simplex™ P.

More recently, Krajewski et al. presented a case report of multidrug-resistant *Pseudomonas* osteomyelitis that was successfully treated with 1920 mg (24,000,000 IU) of colistin in tobramycin-loaded PMMA (Simplex™ P) with elution present 30 days after implantation [57]. In non-medicated Simplex™ HV, colistin demonstrated efficacy and safety at 960 mg (12,000,000 IU) for seven days and at 240 mg (3,000,000 IU) for three days [53].

Meropenem

Meropenem is a carbapenem antibiotic with a broad spectrum of activity, including against anaerobes and multidrug-resistant infections. Thus, it is a popular choice for empiric therapy [58]. It is stable, safe, and effective at doses of up to 5 g in Simplex™ P bone cement [59]. Andollina et al. showed total eradication in vitro of *Pseudomonas* with 1 g in Stimulan™. Notably, when combined with vancomycin, the elution kinetics of both drugs was unaffected [60]. Additionally, meropenem elutes and is safe up to 8 g in Simplex™ HV [61].

Ertapenem

Ertapenem possesses a similar spectrum of coverage to meropenem, with notable differences being that ertapenem covers neither *Enterococcus* spp. nor *Pseudomonas* spp[62]. Ertapenem can be successfully used at doses of up to 4 g of Simplex™ P [63]. It is safe and retains antimicrobial activity in Simplex™ HV up to 8 g [64].

Imipenem/Cilastatin

Imipenem is another carbapenem antibiotic with a similar spectrum of activity to meropenem but slightly inferior gram-negative and superior gram-positive coverage. Since the kidney quickly inactivates it, imipenem is given with cilastatin, a dihydropetidase-1 inhibitor. Imipenem is safe and effective at doses up to 500 mg in Stimulan™ [29] and 4 g in non-medicated Simplex™ HV [65].

Rifampin/Rifamycin Derivatives

Rifamycin derivatives are a family of bactericidal antibiotics that possess activity against a broad spectrum of bacteria, including some gram positives, including *S. aureus*, some gram negatives, anaerobes, and most famously, *mycobacteria*. When applied to calcium sulfate beads, 600 mg of rifampin demonstrated suitable elution for the 42-day study, supporting its use in eradicating infections with select microorganisms [66]. Rifampin is also effective in Simplex™ HV bone cement at doses up to 8 g, with at least 4 g required for suitable elution beyond 14 days [53]. Rifampin is a feasible option for treating S. aureus infection; however, other rifamycin derivatives are not recommended due to poor or absent elution from PMMA bone cement. In a 2015 study, rifabutin and rifapentine eluted much lower in vitro over 14 days than rifampin, while rifaximin did not elute at detectable limits past the first 24 h [67].

Tigecycline

Tigecycline is an antibiotic structurally related to tetracyclines; however, it has alterations that allow for a greater spectrum of activity and increased activity against resistant organisms, including VRE and MRSA, making it an intriguing option for consideration in empiric therapy [68]. In the literature, tigecycline eluted and retained activity when placed in a PMMA spacer; however, it was grossly cytotoxic and caused damage to the surrounding bone and construct. Thus, the available literature does not support tigecycline when loading hip spacers [48].

Piperacillin

Piperacillin is a carboxypenicillin with a broad spectrum of activity, including against *Pseudomonas.* Piperacillin is safe and effective at doses up to 8 g in non-medicated Simplex™ HV [10].

Ticarcillin

Ticarcillin is a carboxypenicillin with a broad spectrum of activity, including against Pseudomonas. Ticarcillin is safe

and effective at doses up to 12 g in non-medicated Simplex™ HV [31].

Cefuroxime

Cefuroxime is a second-generation cephalosporin with a broad spectrum of activity and a greater ability to cover gram negatives than with first-generation cephalosporins and anaerobic coverage. Cefuroxime has greater resistance to beta-lactamase-producing strains of bacteria than many of its fellow cephalosporins [69].

Cefuroxime is safe and effective in Stimulan™ at doses up to 1500 mg [29]. It is safe and effective at doses of up to 4 g in non-medicated Simplex™ HV [28]. In Simplex™ P, 4.5 g of antibiotic was found to be safe, though the flexural and structural strength of the construct were compromised with higher doses; therefore, the maximum dose applicable to Simplex™ P is 1.5 g [70].

Ceftriaxone

Ceftriaxone is a third-generation cephalosporin with a broad spectrum of activity, though it does not cover *Pseudomonas.* It is safe and effective at doses up to 1000 mg in Stimulan™ [29] and 4 g in non-medicated Simplex™ HV [53].

Ceftazidime

Ceftazidime is a third-generation cephalosporin with a broad spectrum of activity, including against Pseudomonas. It is safe and effective at doses up to 4 g in non-medicated Simplex™ HV and Simplex™ P [71, 72].

Ceftaroline

Ceftaroline is a fifth-generation cephalosporin with a broad spectrum of activity that is a vital piece of the infectious disease armamentarium as it is effective in treating MRSA and other extensively resistant strains, such as vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA (hVISA), and vancomycin-resistant *S. aureus* (VRSA) [73]. A recent in vitro study demonstrated superior bioactivity and elution characteristics of ceftaroline compared with vancomycin and recommended using up to 1.8 g in Simplex™ HV against MRSA [74].

Gentamicin

Gentamicin is an aminoglycoside antibiotic characteristically associated with ototoxicity and nephrotoxicity when administered systemically at high doses. It possesses activity primarily against gram-negative bacteria, including *Pseudomonas*, yet notably also covers *S. aureus,* making it a good option for empiric treatment of orthopedic infections. Gentamicin is safe to use at doses up to 1 g of powder or 240 mg of liquid (6 ml of 40 mg/milliliter) in Stimulan™ [29, 66]. In the novel product Cerament G (dissolvable calcium sulfate + calcium phosphate), gentamicin demonstrated good elution kinetics and bioactivity up to 175 mg/10 ml [75]. In non-medicated Simplex™ HV, gentamicin is safe at doses up to 8 g.

Vancomycin + Tobramycin

As previously mentioned, vancomycin is a commonly utilized antibiotic for application to implants, and its familiarity lends it to combination applications. Much research supports combined vancomycin and tobramycin, owing to their complementary activity spectra and general effectiveness. Vancomycin is a potent antibiotic employed against gram-positive organisms, while tobramycin demonstrates excellent gram-negative coverage, including resistant strains and *Pseudomonas*.

In combination, vancomycin and tobramycin are effective and safe in Stimulan™ at 1 g of vancomycin to either 240 mg liquid tobramycin [76] or 600 mg powder tobramycin [43]. In non-medicated Simplex™ HV, vancomycin and tobramycin are safe at doses up to 4 g and 4.8 g, respectively [77]. In Simplex™ P, vancomycin and tobramycin are the same at 1 g and 600 mg [43].

Aztreonam

Aztreonam is a narrow-spectrum antibiotic that is only effective against gram-negative bacteria, including Pseudomonas. In a study where aztreonam was combined with vancomycin for empiric coverage, aztreonam exhibited safety and efficacy at 4 g in non-medicated Simplex™ HV [78].

Doxycycline

Doxycycline is a tetracycline antibiotic with a broad spectrum of coverage, including several atypicals. It is safe and effective at doses up to 100 mg in non-medicated Simplex™ HV [79].

Sulfamethoxazole/Trimethoprim (SMX/TMP)

SMX/TMP is a combination antibiotic that inhibits multiple enzymes in the genesis of tetrahydrofolate. It possesses a broad spectrum of activity. It exhibits good bioactivity and safety in its liquid form in non-medicated Simplex™ HV at 400 mg SMX to 80 mg TMP [79].

Moxifloxacin

Moxifloxacin is a fluoroquinolone antibiotic with a broad spectrum of activity, including MRSA and *M. tuberculosis*, making it suitable for exploration as empiric therapy. It demonstrated safety and efficacy up to 1 g in Stimulan™ [50]. It is effective in non-medicated Simplex™ HV at doses of up to 8 g [64].

Ciprofloxacin

Ciprofloxacin is a fluoroquinolone antibiotic with a similar spectrum of activity to moxifloxacin but with better pseudomonas coverage [80]. Ciprofloxacin is safe in Stimulan™ up to 1 g [81]. It is safe in non-medicated Simplex™ HV up to 6 g [31].

Amikacin

Amikacin is an aminoglycoside antibiotic with a broad spectrum of activity, including resistant strains of *Pseudomonas, Klebsiella,* and *Staphylococcus,* making it a worthy choice for empiric antibiotic prophylaxis [82]. Amikacin is safe and effective in Stimulan™ at 1000 mg/4 ml [29]. In non-medicated Simplex™ HV, 1 g of amikacin dissolved in 4 ml of liquid showed suitable elution but only sustained suitable elution for seven days [83]. At this institution, 5 g powder is utilized for both applications.

Targeted Antibiotic Therapies

In the literature, select case reports outlined therapies for targeted and rare fracture-related, implant-associated, and periprosthetic infections with either *Candida* or *Mycobacterium tuberculosis*. Fungal infection accounts for 1–2% of periprosthetic joint infections [84], which occur in about 1–2% of joint surgeries [8], or between 1 in every 2,500–10,000 cases. Musculoskeletal *Mycobacterium tuberculosis* is one of the more common extrapulmonary manifestations of tuberculosis (TB) in the USA but is still rare. *M. tuberculosis* infection of an orthopedic implant is exceptionally infrequent. The quality of evidence in the two supporting studies is poor, with two Level V evidence studies in accordance with AAOS Levels of Evidence.

Isoniazid

Isoniazid is a staple in the treatment of TB. In a 2013 study, Han et al. demonstrated good elution kinetics and antimycobacterial activity of isoniazid, safe up to 4 g in non-medicated Simplex™ HV [85].

Streptomycin

Streptomycin was the first aminoglycoside antibiotic, discovered in 1943. Today, it is used primarily with other antibiotics for treating pulmonary TB. A 1995 case report details its applicability to tuberculosis osteomyelitis and found it safe and effective at doses up to 7 g in non-medicated Simplex™ HV [86].

Additional antibiotics not recommended for effective use

Ampicillin, amoxicillin/clavulanate, cefepime, oritavancin, and piperacillin/tazobactam [87] are antibiotics with poor elution characteristics that are not recommended for treating bacterial FRI or PJI (see Table 2) [64, 88]. The quality of evidence in the 5 supporting studies is poor, with one Level V evidence study and four foundational evidence in vitro studies in accordance with AAOS Levels of Evidence.

Antifungals

Fungal infection is another rare yet devastating complication of FRIs and PJIs. Treating these infections is often protracted and significantly burdens the patient and health care system. Recommendations for the evidence-based treatment of fungal infection of an implant or fracture site are made based on the available data in this review. The quality of evidence in the 17 supporting studies is poor, with two Level IV evidence studies, seven Level V studies, and eight foundational evidence in vitro studies in accordance with AAOS Levels

Table 2 List of antibiotics not supported for use in the treatment of FRI and PJI and the reason for their exclusion

NOT RECOMMENDED	**PMMA**
Ampicillin	Does not elute
Amoxicillin/clavulanate	Does not elute
Cefepime	Does not elute
Oritavancin	Does not elute after 24 h
Rifabutin	Does not elute
Rifaximin	Does not elute
Rifapentine	Does not elute
Tigecycline	Does not elute after 24 h
Zosyn (piperacillin/tazobactam)	Case report of use resulted in drug fever verified in pt with IV rechallenge positive

Table 3 List of antifungals supported for use in the treatment of FRI and PJI and their respective doses in common carriers

Antifungals in Bone Cement	Stimulan (dissolvable calcium sulfate) Amount per 20 gm 10 ml = 20 gm Dissolves over 3 weeks	Simplex HV (PMMA) (Cobalt HV in outpatient) Amount per 40 gm Non-dissolvable	Simplex P (PMMA with Tobramycin 1gm) Amount per 40 gm Non-dissolvable
Amphotericin B (fungizone)	Up to 100 mg In Vivo 500 mg In vitro	Up to 1200 mg In Vivo See notes below	
Amphotericin B LIPOSOMAL (ambisome)		Up to 200–800 mg In vitro Elutes well but not compressive	
Fluconazole		Up to 4000 mg	
Voriconazole	Up to 200 mg 1000 mg In Vitro	Up to 1000 mg	Up to 1000 mg 3000 mg In Vitro

of Evidence. See Table 3 for dosing recommendations based on carrier.

Amphotericin B

Amphotericin B is a polyene antifungal used to treat severe fungal and protozoal infections, including mucormycosis, coccidioidomycosis, cryptococcosis, severe candida, and life-threatening leishmaniasis. It has a well-documented history of severe side effects when utilized systemically. In several case studies [10, 89–91], Amphotericin B deoxycholate eliminated severe recalcitrant fungal infections of the implant while causing no severe side effects seen with its systemic use. It is safe and effective at doses up to 100 mg in vivo [89] and 500 in vitro [92] when added to Stimulan™ and at doses up to 1.2 g when applied to non-medicated Simplex™ HV [10]. Amphotericin in its liposomal form was safe and effective at doses up to 800 mg, with greater elution kinetics than the amphotericin deoxycholate; however, the drug compromised the compressive ability of the cement [93]. Some studies did not support the utility of amphotericin B deoxycholate due to poor or short elution duration [90, 94, 95].

Voriconazole

Voriconazole is a triazole antifungal with a broad spectrum of activity, including Aspergillus spp., and more robust activity against Candida species than other triazoles [96].

It is safe and effective when added to Stimulan™ in vivo up to 200 mg and in vitro up to 1000 mg [92, 97]. Voriconazole demonstrated safety and efficacy at doses up to 1000 mg in vivo [98] and 3000 mg in vitro [99] when applied to Simplex™ P and up to 1000 mg when applied to non-medicated Simplex™ HV.

Fluconazole

Fluconazole is a triazole antifungal widely used for treating candida infections, both local and systemic. Fluconazole is safe and effective, up to 4 g in non-medicated Simplex™ HV [100].

Additional antifungals not recommended for effective use

Anidulafungin, flucytosine, itraconazole, micafungin, and terbinafine are antifungals with poor elution characteristics that are not recommended for use in treating fungal FRIs or PJIs (see Table 4). The quality of evidence in the six supporting studies is poor, with two Level V studies and four foundational evidence in vitro studies in accordance with AAOS Levels of Evidence [89, 99, 101, 102].

Discussion

Since local antibiotic concentrations must reach up to 1000 times the usual bactericidal concentration to effectively eliminate bacteria in a biofilm, systemic antibiotic treatment of implant-related infections, such as FRI and PJI, is often ineffective [15–18]. Antibiotic-loaded acrylic bone cement has a storied history, beginning with Bucholz and Engelbrecht in 1970 [25]. It is considered by many to be the gold standard for treating infections with associated orthopedic implants [26, 27]. The application of antibiotics directly to the site of infection allows for high local concentrations of the given drug relative to oral or intravenous applications while minimizing serum drug levels, which may lower systemic side effects and the incidence of antimicrobial resistance [28–30]. Polymethylmethacrylate (PMMA) is a cement utilized in temporizing implant-related infections, allowing

Table 4 List of antifungals not supported for use in the treatment of FRI and PJI and the reason for their exclusion

NOT RECOMMENDED	PMMA
Amphotericin B (fungizone)	Up to 200 mg in PMMA with tobramycin (not detectable at 168 h) forms bonds with PMMA 750 mg mixed in 4 batches of PMMA [200 mg × 2, 250 mg × 1, 100 mg × 1] (implanted dose estimated at 675–725 mg or 9 mg/kg) had detectable levels for up to 50 h, then rapid decline over the next 24 h (0.51 mg/L to day 5) 1500 mg mixed in PMMA had decent elution for 22 h in vitro
Anidulafungin	Does not elute (up to 3600 mg)
Flucytosine	Does not elute
Itraconazole	Does not elute
Micafungin	Does not elute
Terbinafine	Does not elute

for steady elution of an impregnated drug for several weeks [31].

One major drawback of using bone cement is the conventional necessity to remove it when used in orthopedic trauma and fracture surgery, as the cement is not absorbable. Due to this limitation, resorbable carriers of antimicrobials became available, obviating the need for a second surgery for removal. Calcium sulfate beads are a resorbable option that has shown efficacy in decreasing infection rates, and they have been demonstrated to elute antibiotics for a longer duration than PMMA [33, 34]. There have been concerns regarding prolonged wound drainage in the setting of the use of calcium sulfate beads [35] that has caused some surgeons to be wary of their use due to increased length of hospital stay and concern that persistent drainage may augment the risk of infection [36]. However, a 2014 study showed no increased risk of infection in these patients [37]. In a 2021 study, resorbable constructs comprised of both calcium sulfate and calcium phosphate were found to have the potential to stimulate osteogenesis by acting as a scaffold while simultaneously protecting against biofilm infection [38].

This evidence-based systematic review offers the most up-to-date and comprehensive practice guidelines for using antimicrobial-loaded cements and beads as prophylaxis or treatment of FRI and PJI. While first-line treatment modalities for use in targeted therapy against gram positives and broad-spectrum empiric therapy are described, this review 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.

This review has some notable limitations. As with any systematic review, it is only as strong as its constituent studies. All included studies were published in English, leading to a potential language bias. A majority of included studies were conducted in vitro. While these studies are valuable, they cannot perfectly emulate real clinical scenarios. Many clinical studies cited here are case studies or case series, which provide low-level evidence to support claims; however, they offer valuable information when approaching unique or resistant pathogens. Due to the quality of the included studies, the authors elected not to conduct a meta-analysis. The authors acknowledge the value that a meta-analysis brings yet assert that a meta-analysis may in and of itself be misleading when analyzing studies at high risk of bias. Additionally, there is no standardized method for applying the antimicrobials described in this review, which is an inherent limitation. Finally, available antibiotics and bacterial resistance profiles are dynamic, which could affect this review's accuracy and comprehensiveness. As such, it is advisable to communicate with institutional infectious disease specialists and reference sensitivity panels for each infection when deciding on the optimal agent choice.

Conclusion

These results encapsulate valuable 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 to create institutional protocols for antibiotic-eluting implants and close comanagement to ensure efficacy and patient safety.

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Declarations

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References

1. Rimondini L, Fini M, Giardino R (2005) The microbial infection of biomaterials: A challenge for clinicians and researchers A short review. J Appl Biomater Biomech 3(1):1–10
2. Metsemakers WJ, Reul M, Nijs S (2015) The use of gentamicin-coated nails in complex open tibia fracture and revision cases: A retrospective analysis of a single centre case series and review of the literature. Injury 46(12):2433–2437
3. Darouiche RO (2004) Treatment of Infections Associated with Surgical Implants. N Engl J Med 350(14):1422–1429
4. Okike K, Bhattacharyya T (2006) Trends in the management of open fracture A critical analysis. J Bone Joint Surg Am 88(12):2739–2748
5. Spencer J, Smith A, Woods D (2004) The effect of time delay on infection in open long-bone fractures: a 5-year prospective audit from a district general hospital. Ann R Coll Surg Engl 86(2):108–112
6. Springer BD et al (2017) Infection burden in total hip and knee arthroplasties: an international registry-based perspective. Arthroplast Today 3(2):137–140
7. Shichman I et al (2023) Projections and Epidemiology of Primary Hip and Knee Arthroplasty in Medicare Patients to 2040–2060. JB JS Open Access. https://doi.org/10.2106/JBJS.OA.22.00112
8. Ahmed SS, Haddad FS (2019) Prosthetic joint infection. Bone Joint Res 8(11):570–572
9. Lenguerrand E et al (2017) Revision for prosthetic joint infection following hip arthroplasty: Evidence from the National Joint Registry. Bone Joint Res 6(6):391–398
10. Wu MH, Hsu KY (2011) Candidal arthritis in revision knee arthroplasty successfully treated with sequential parenteral-oral fluconazole and amphotericin B-loaded cement spacer. Knee Surg Sports Traumatol Arthrosc 19(2):273–276
11. Collinge CA et al (2018) Acute Compartment Syndrome: An Expert Survey of Orthopaedic Trauma Association Members. J Orthop Trauma 32(5):e181–e184
12. Chiller K, Selkin BA, Murakawa GJ (2001) Skin Microflora and Bacterial Infections of the Skin. Journal of Investigative Dermatology Symposium Proceedings 6(3):170–174
13. Grice EA, Segre JA (2011) The skin microbiome. Nat Rev Microbiol 9(4):244–253
14. Nelson CL (2004) The current status of material used for depot delivery of drugs. Clin Orthop Relat Res 427:72–78
15. Luppens SB et al (2002) Development of a standard test to assess the resistance of Staphylococcus aureus biofilm cells to disinfectants. Appl Environ Microbiol 68(9):4194–4200
16. Davies D (2003) Understanding biofilm resistance to antibacterial agents. Nat Rev Drug Discov 2(2):114–122
17. Stewart PS, Costerton JW (2001) Antibiotic resistance of bacteria in biofilms. Lancet 358(9276):135–138
18. Verderosa AD, Totsika M, Fairfull-Smith KE (2019) Bacterial Biofilm Eradication Agents: A Current Review. Front Chem 7:824
19. Lodise TP et al (2008) Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 52(4):1330–1336
20. Filippone EJ, Kraft WK, Farber JL (2017) The Nephrotoxicity of Vancomycin. Clin Pharmacol Ther 102(3):459–469
21. Downes KJ, Goldman JL (2021) Too Much of a Good Thing: Defining Antimicrobial Therapeutic Targets to Minimize Toxicity. Clin Pharmacol Ther 109(4):905–917
22. Mouton JW, Aarnoutse RE (2014) Therapeutic drug monitoring of antimicrobials. Ned Tijdschr Geneeskd 158:A7520
23. Segal JA et al (1999) Aminoglycoside neurotoxicity involves NMDA receptor activation. Brain Res 815(2):270–277
24. Roberts JA et al (2012) Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol 73(1):27–36
25. Buchholz HW, Engelbrecht H (1970) Depot effects of various antibiotics mixed with Palacos resins. Chirurg 41(11):511–515
26. Gogia JS et al (2009) Local antibiotic therapy in osteomyelitis. Semin Plast Surg 23(2):100–107
27. Inzana JA et al (2016) Biomaterials approaches to treating implant-associated osteomyelitis. Biomaterials 81:58–71
28. Hughes S et al (1979) Cephalosporins in bone cement: studies in vitro and in vivo. J Bone Joint Surg Br 61(1):96–100
29. Laycock PA et al (2018) In Vitro Efficacy of Antibiotics Released from Calcium Sulfate Bone Void Filler Beads. Materials (Basel) 11(11):2565
30. Bowyer GW, Cumberland N (1994) Antibiotic release from impregnated pellets and beads. J Trauma 36(3):331–335
31. Adams K et al (1992) In vitro and in vivo evaluation of antibiotic diffusion from antibiotic-impregnated polymethylmethacrylate beads. Clin Orthop Relat Res 278:244–252
32. Masters, E.A., et al., *Evolving concepts in bone infection: redefining "biofilm", "acute vs. chronic osteomyelitis", "the immune proteome" and "local antibiotic therapy"*. Bone Res, 2019. **7**: p. 20.
33. Thahir A et al (2022) The Use of Calcium Sulphate Beads in the Management of Osteomyelitis of Femur and Tibia: A Systematic Review. Arch Bone Jt Surg 10(4):320–327
34. Cooper J et al (2016) Elution profiles of tobramycin and vancomycin from high-purity calcium sulphate beads incubated in a range of simulated body fluids. J Biomater Appl 31(3):357–365
35. Ziran BH, Smith WR, Morgan SJ (2007) Use of calcium-based demineralized bone matrix/allograft for nonunions and posttraumatic reconstruction of the appendicular skeleton: preliminary results and complications. J Trauma 63(6):1324–1328
36. Saleh K et al (2002) Predictors of wound infection in hip and knee joint replacement: results from a 20 year surveillance program. J Orthop Res 20(3):506–515
37. Ferguson, J.Y., et al., 2014 *The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases* Bone Joint J, **96-b** (6) 829–36.
38. Jiang N et al (2021) Antibiotic loaded β-tricalcium phosphate/calcium sulfate for antimicrobial potency, prevention and killing efficacy of Pseudomonas aeruginosa and Staphylococcus aureus biofilms. Sci Rep 11(1):1446
39. Seidelman JL, Mantyh CR, Anderson DJ (2023) Surgical Site Infection Prevention: A Review. JAMA 329(3):244–252
40. Masri BA, Duncan CP, Beauchamp CP (1998) Long-term elution of antibiotics from bone-cement: an in vivo study using the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. J Arthroplasty 13(3):331–338
41. Agarwal S, Healey B (2014) The use of antibiotic impregnated absorbable calcium sulphate beads in management of infected joint replacement prostheses. Journal of Arthroscopy and Joint Surgery 1(2):72–75
42. Howlin RP et al (2015) Antibiotic-loaded synthetic calcium sulfate beads for prevention of bacterial colonization and biofilm formation in periprosthetic infections. Antimicrob Agents Chemother 59(1):111–120
43. McConoughey SJ et al (2015) Comparing PMMA and calcium sulfate as carriers for the local delivery of antibiotics to

infected surgical sites. J Biomed Mater Res B Appl Biomater 103(4):870–877
44. Funk GA et al (2018) Antibiotic Elution and Mechanical Strength of PMMA Bone Cement Loaded With Borate Bioactive Glass. J Bone Jt Infect 3(4):187–196
45. Jagodzinski, J.T., JR; Ludwig, BJ; Andes, DR; Squire, MW, *ANTIBIOTIC ELUTION OF SYNERCID, LINEZOLID, AND DAPTOMYCIN FROM PALACOS BONE® CEMENT*, in *Orthopedic Research Society 53rd Annual Meeting*. 2007: San Diego.
46. Dobie D, Gray J (2004) Fusidic acid resistance in Staphylococcus aureus</em&gt. Arch Dis Child 89(1):74
47. Zahedi Bialvaei A et al (2016) Linezolid: a promising option in the treatment of Gram-positives. J Antimicrob Chemother 72(2):354–364
48. Nichol T et al (2017) Analysis of linezolid and tigecycline as candidates for local prophylaxis via antibiotic-loaded bone cement. J Antimicrob Chemother 72(2):410–416
49. Anagnostakos K et al (2008) Antimicrobial properties and elution kinetics of linezolid-loaded hip spacers in vitro. J Biomed Mater Res B Appl Biomater 87(1):173–178
50. Panagopoulos P et al (2008) In vitro elution of moxifloxacin and fusidic acid by a synthetic crystallic semihydrate form of calcium sulphate (Stimulan). Int J Antimicrob Agents 32(6):485–487
51. Auwaerter, P.M.D. and P.P.D. Pham, *Teicoplanin.* 2022.
52. Anagnostakos K et al (2005) In vitro evaluation of antibiotic release from and bacteria growth inhibition by antibiotic-loaded acrylic bone cement spacers. J Biomed Mater Res B Appl Biomater 72(2):373–378
53. Gasparini G et al (2014) Drug elution from high-dose antibiotic-loaded acrylic cement: a comparative, in vitro study. Orthopedics 37(11):e999-1005
54. Cortes NJ et al (2013) Successful clinical use of daptomycin-impregnated bone cement in two-stage revision hip surgery for prosthetic joint infection. Ann Pharmacother 47(1):e2
55. Nation RL, Li J (2009) Colistin in the 21st century. Curr Opin Infect Dis 22(6):535–543
56. P.A.Laycock, J.J.C., M.J.Brayford, *Elution and Efficacy of Colistin when Combined with a Synthetic Calcium Sulfate*, K.S.P. Biocomposites Ltd., UK, Editor. 2019.
57. Krajewski J et al (2014) Successful treatment of extensively drug-resistant Pseudomonas aeruginosa osteomyelitis using a colistin- and tobramycin-impregnated PMMA spacer. Int J Antimicrob Agents 44(4):363–366
58. Baldwin CM, Lyseng-Williamson KA, Keam SJ (2008) Meropenem: a review of its use in the treatment of serious bacterial infections. Drugs 68(6):803–838
59. Solomon AW et al (2010) Elution and antibacterial activity of meropenem from implanted acrylic bone cement. J Antimicrob Chemother 65(8):1834–1835
60. Andollina A et al (2008) Vancomycin and meropenem in acrylic cement: elution kinetics of in vitro bactericidal action. Chir Organi Mov 91(3):153–158
61. Samuel S et al (2012) In vitro study of elution kinetics and bioactivity of meropenem-loaded acrylic bone cement. J Orthop Traumatol 13(3):131–136
62. Zhanel GG et al (2007) Comparative review of the carbapenems. Drugs 67(7):1027–1052
63. Radoicic D et al (2016) Ertapenem Articulating Spacer for the Treatment of Polymicrobial Total Knee Arthroplasty Infection. Can J Infect Dis Med Microbiol 2016:5753489
64. Gálvez-López R et al (2014) Elution kinetics, antimicrobial activity, and mechanical properties of 11 different antibiotic loaded acrylic bone cement. Diagn Microbiol Infect Dis 78(1):70–74
65. Cerretani D et al (2002) The in vitro elution characteristics of vancomycin combined with imipenem-cilastatin in acrylic bonecements: a pharmacokinetic study. J Arthroplasty 17(5):619–626
66. Aiken SS et al (2015) Local release of antibiotics for surgical site infection management using high-purity calcium sulfate: an in vitro elution study. Surg Infect (Larchmt) 16(1):54–61
67. Sanchez CJ Jr et al (2015) Rifamycin Derivatives Are Effective Against Staphylococcal Biofilms In Vitro and Elutable From PMMA. Clin Orthop Relat Res 473(9):2874–2884
68. Greer ND (2006) Tigecycline (Tygacil): the first in the glycylcycline class of antibiotics. Proc (Bayl Univ Med Cent) 19(2):155–161
69. Neu HC, Fu KP (1978) Cefuroxime, a beta-lactamase-resistant cephalosporin with a broad spectrum of gram-positive and -negative activity. Antimicrob Agents Chemother 13(4):657–664
70. Mohd Fuad, D., et al., *Biomechanical properties of bone cement with addition of cefuroxime antibiotic.* Med J Malaysia, 2006. **61 Suppl A**: p. 27–9.
71. Hsu YH et al (2017) Vancomycin and Ceftazidime in Bone Cement as a Potentially Effective Treatment for Knee Periprosthetic Joint Infection. J Bone Joint Surg Am 99(3):223–231
72. Morejón Alonso L et al (2018) Evaluation of acrylic bone cements with single and combined antibiotics: Release behavior and in vitro antibacterial effectiveness. Int J Polym Mater Polym Biomater 67(14):830–838
73. Duplessis, C. and N.F. Crum-Cianflone, *Ceftaroline: A New Cephalosporin with Activity against Methicillin-Resistant Staphylococcus aureus (MRSA).* Clin Med Rev Ther, 2011. **3**.
74. Haseeb A et al (2019) Addition of ceftaroline fosamil or vancomycin to PMMA: An in vitro comparison of biomechanical properties and anti-MRSA efficacy. J Orthop Surg (Hong Kong) 27(2):2309499019850324
75. Stravinskas M et al (2016) Pharmacokinetics of gentamicin eluted from a regenerating bone graft substitute: In vitro and clinical release studies. Bone Joint Res 5(9):427–435
76. McPherson, M.D.F.E., B.A.M. Dipane, and M.D.S. Sherif, *Dissolvable Antibiotic Beads in Treatment of Periprosthetic Joint Infection and Revision Arthroplasty - The Use of Synthetic Pure Calcium Sulfate (Stimulan®) Impregnated with Vancomycin & Tobramycin.* Reconstructive Review, 2013. **3**(1).
77. Iarikov D et al (2012) Choice and doses of antibacterial agents for cement spacers in treatment of prosthetic joint infections: review of published studies. Clin Infect Dis 55(11):1474–1480
78. Hsieh PH et al (2006) High concentration and bioactivity of vancomycin and aztreonam eluted from Simplex cement spacers in two-stage revision of infected hip implants: a study of 46 patients at an average follow-up of 107 days. J Orthop Res 24(8):1615–1621
79. Dr. Michael Mazurek, D.J.C., Dr. Carl Carrano, Dr. Dale Chatfield *Antibiotic Impregnated Bone Cement for the treatment of Osteomelitis and Severe Open Fractures: Expanded Options for Surgeons.* 2008.
80. Follath F et al (1986) Use of ciprofloxacin in the treatment of Pseudomonas aeruginosa infections. Eur J Clin Microbiol 5(2):236–240
81. DiMaio FR, O'Halloran JJ, Quale JM (1994) In vitro elution of ciprofloxacin from polymethylmethacrylate cement beads. J Orthop Res 12(1):79–82
82. Gonzalez, L.S., 3rd and J.P. Spencer, *Aminoglycosides: a practical review.* Am Fam Physician, 1998. **58**(8): p. 1811–20.
83. Atilla A et al (2010) In vitro elution of amikacin and vancomycin from impregnated plaster of Paris beads. Vet Surg 39(6):715–721
84. Chisari E et al (2022) Fungal periprosthetic joint infection: Rare but challenging problem. Chin J Traumatol 25(2):63–66
85. Han CD et al (2013) Isoniazid could be used for antibiotic-loaded bone cement for musculoskeletal tuberculosis: an in vitro study. Clin Orthop Relat Res 471(7):2400–2406

86. Masri BA et al (1995) Streptomycin-loaded bone cement in the treatment of tuberculous osteomyelitis: an adjunct to conventional therapy. Can J Surg 38(1):64–68
87. Park HB et al (2011) Drug fever due to piperacillin/tazobactam loaded into bone cement. J Korean Med Sci 26(2):301–303
88. Schmidt-Malan, S., et al., *Oritavancin polymethylmethacrylate (PMMA)—compressive strength testing and in vitro elution.* Journal of Orthopaedic Surgery and Research, 2019. **14**.
89. Zhu ES et al (2013) Amphotericin B-impregnated bone cement to treat refractory coccidioidal osteomyelitis. Antimicrob Agents Chemother 57(12):6341–6343
90. Houdek MT et al (2015) Elution of High Dose Amphotericin B Deoxycholate From Polymethylmethacrylate. J Arthroplasty 30(12):2308–2310
91. Marra F et al (2001) Amphotericin B-loaded bone cement to treat osteomyelitis caused by Candida albicans. Can J Surg 44(5):383–386
92. Karr JC, Lauretta J (2015) In vitro activity of calcium sulfate and hydroxyapatite antifungal disks loaded with amphotericin B or voriconazole in consideration for adjunctive osteomyelitis management. J Am Podiatr Med Assoc 105(2):104–110
93. Cunningham B et al (2012) Liposomal formulation increases local delivery of amphotericin from bone cement: a pilot study. Clin Orthop Relat Res 470(10):2671–2676
94. Goss B et al (2007) Elution and mechanical properties of antifungal bone cement. J Arthroplasty 22(6):902–908
95. Kweon C et al (2011) Amphotericin B delivery from bone cement increases with porosity but strength decreases. Clin Orthop Relat Res 469(11):3002–3007
96. Greer ND (2003) Voriconazole: the newest triazole antifungal agent. Proc (Bayl Univ Med Cent) 16(2):241–248
97. Harvey D., T.J., Cooper A., Buckley S., Townsend R., Kerry R., Oliver D., *Voriconazole-impregnated beads in the treatment of candidal prosthetic joint infection*, in *19th European Congress of Clinical Microbiology and Infectious Diseases*. 2009.
98. Deelstra JJ, Neut D, Jutte PC (2013) Successful treatment of Candida albicans-infected total hip prosthesis with staged procedure using an antifungal-loaded cement spacer. J Arthroplasty 28(2):374.e5–8
99. Rouse MS et al (2011) Are anidulafungin or voriconazole released from polymethylmethacrylate in vitro? Clin Orthop Relat Res 469(5):1466–1469
100. Martínez-Moreno J et al (2017) Bioactivity of Ceftazidime and Fluconazole Included in Polymethyl Methacrylate Bone Cement for Use in Arthroplasty. J Arthroplasty 32(10):3126-3133.e1
101. Sealy PI et al (2009) Delivery of antifungal agents using bioactive and nonbioactive bone cements. Ann Pharmacother 43(10):1606–1615
102. Percival K, Brock J, Peterson N (2016) Delivery of Antifungal Agents from Bone Cement. Current Fungal Infection Reports 10:30–36