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Antibiotic Release Enhancement Methods for Antibiotic-Loaded PMMA Bone Cement for Periprosthetic Joint Infection Prophylaxis in Cemented Total Joint Arthroplasties: Current Status and Future Prospects

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Author's contribution

Author designed the study, performed the literature search and wrote the manuscript.

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Review Article

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ABSTRACT

Background: It is widely acknowledged that peri-prosthetic joint infection (PJI) is the most devastating and challenging complication of total joint arthroplasty. As such, over the years, myriad aspects of this problem have been studied, among which are methods to increase the resistance of the arthroplasty to PJI by enhancing the profile of release of the antibiotic from an antibiotic-loaded poly(methyl methacrylate) bone cement (ALBC) when it is used to anchor the prosthesis to the bone.
Purpose: This was to conduct a detailed and critical state-of-the-art review of the literature on all aspects of enhancement methods, with a view to identify the most effective of these methods.
Methodology: Keywords, such as PJI, ALBC, and cemented arthroplasties, and publicly-available databases, such as Google Scholar and MEDLINE, were used to search for relevant English-language articles published in the open literature between January 1985 and August 2020.
Findings: From the results presented in the studies, a number of indices of enhancement were calculated. These included increases in 1) the cumulative amount of antibiotic released during the course of a release test, 2) the duration of the burst phase of release of the antibiotic, 3) the time at

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the start of the exhaustion phase of the release of the antibiotic and 4) effectiveness of the released antibiotic against microorganisms commonly found in PJI cases (herein, referred to as "clinically-relevant" bacterial strains), notably *S. aureus*. These calculated values indicated that the most effective enhancement method involves adding fillers to the cement powder.

Summary: An assortment of enhancement methods have been used, among which were adding fillers to the cement powder and ultrasonication of the cement specimen. Although many results were reported in the studies reviewed, the literature has a number of limitations.

Among these are a dearth of studies on determining activity of the released antibiotic against clinically-relevant bacterial strains and against biofilm formation. Expositions on these limitations lead to identification of potential areas for future research, such as studies of antibiotic enhancement from ALBCs that have innovative architecture and on relationship between an enhancement method and quorum quenching (a mechanism that is postulated to be involved in resistance to biofilm formation).

Keywords: Poly (methyl methacrylate) bone cement; periprosthetic joint infection; orthopaedic bacterial strains.

1. INTRODUCTION

It is widely acknowledged that the most serious, challenging and potentially devastating complication following total joint arthroplasty (TJA) is peri-prosthetic joint infection (PJI) [1-6]. As such, there is a very large body of literature on myriad aspects of PJI, including definition, clinical presentation, etiology, incidence, risk factors, diagnostic methods, prevention methods, treatment/management methods, and economic impact. Several definitions of PJI have been put forward by various professional organizations, such as Musculoskeletal Infection Society, Infectious Diseases Society of America, European Bone and Joint Infection Society, and The World Association Against Infection in Orthopedics and Trauma, covering a wide collection of scoring systems and criteria [1]. Common clinical presentations are severe pain, high fever, and presence of a sinus tract connecting with the joint replacement [2]. The etiology of PJI invariably involves introduction of a bacterial strain, most commonly, *Staphylococcus aureus* (through direct contact or aerosolized contamination of prosthesis component(s) or peri-prosthetic tissue, at time of surgery) [2-5]. The 2015 unweighted mean PJI burdens accompanying total hip and knee arthroplasties, between 6 arthroplasty registers, are 0.97% and 1.03%, respectively [7]; however, a concern is that the burden increases with increase in the number of years since the procedure [8]. Among risk factors for PJI are patient characteristics (notably, diabetes mellitus [9], high body mass index (> 35) [9], rheumatoid arthritis [2], smoking [9], young age (<50 years) [10], preoperative use of opioids [11]) and long surgery time [3]. A "gold standard" for diagnosis of PJI is lacking; as such, there are myriad diagnostic methods, each displaying varying degree of sensitivity, specificity, and reliability. Examples of these methods are determination of the level of a coagulation-related indicator (usually, plasma D-dimer or plasma fibrinogen) [12], use of an imaging method (such as [^{18}F] fluoro-2-deoxyglucose positron emission tomography [13] and single photon emission computed tomography [14]), use of a molecular analytical method (such as polymerase chain reaction (PCR) electrospray ionization mass spectrometry [15] and a PCR assay using the restriction length polymorphism technique [16]), determination of the level of a biomarker (such as synovial fluid procalcitonin [17]), determination of the viscosity of the synovial fluid [18], and next-generation sequencing assaying [19]. Prevention of PJI involves perioperative parenteral therapy, oral therapy, or initial parenteral therapy followed by oral therapy of prophylactic antibiotic(s) and anchoring the prosthesis in a bed of an antibiotic-loaded bone cement (ALBC) [2,4,20-26]. Use of ALBC in a cemented TJA has two advantages over systemic administration of antibiotics. First, the cement helps treat/prevent infections by releasing antibiotic(s) locally at high levels that are not possible with systemic administration, thereby killing the bacteria before they form biofilms on the implant surface [27]. Second, with the cement, there is no systemic toxicity by the antibiotic. In the absence of a gold standard for diagnosis of PJI, a recent approach to treatment is to use an algorithm [2,28] or to rely on guidelines derived from evidence-based and validated criteria [29]. PJI treatment/management options include infection control with no continued antibiotic therapy [30,31], infection

control with patient on suppressive antibiotic therapy [30,31], debridement, antibiotic, and implant retention (DAIR) [25,32] and revision surgery (one- or two-stage exchange total joint arthroplasty (TJA) [2,33,34]). In exchange TJA, ALBC also plays a crucial role [33-35]. A major economic ramification of PJI is increased burden on a health care system in terms of cost and resource allocation [7,36-40]. For example, 1) in the United States, in 2010, annual hospital cost incurred for treating PJI hip and knee cases was estimated to be between ~$769 million and ~$802 million (amounting to ~$27,000 per case), with it projected to be ~$1.62 billion in 2020 [36]; 2) in Andalusia, Spain, in the period January 2005-January 2010, mean total cost of treating a patient with knee PJI was ~ $52,000 [37]; and 3) in Rome, Italy, in 2018, estimated hospital costs for treating hip and knee PJI were ~$44,000 and ~$25,000, per case, respectively [38].

While there is much debate on the clinical evidence supporting use of ALBC for TJA/PJI, it is used by nearly all TJA surgeons for a variety of indications, namely, all cemented primary arthroplasties, primary arthroplasties with patients at risk for infection, and for revision arthroplasties, particularly in PJI cases [41-43]. For example, in the period 2014-2016 ~65% of primary total hip arthroplasties (THAs) in Sweden, ~80% of primary total knee arthroplasties (TKAs) in the United States, and ~80% of revision THAs in Australia were cemented [41-43]. In contemporary clinical practice, one of two approaches is taken with regard to the ALBC used. In one approach, an approved ALBC brand is used (in most of these brands, the antibiotic is gentamicin sulfate) and the method used for mixing the antibiotic into the cement powder is proprietary [44,45]. In the other approach, a custom formulation is prepared (the antibiotic is mixed into the powder in the operating room, under the direction of the surgeon, but there are no published guidelines for selecting the amount of antibiotic used) [44,45].

There are three shortcomings of ALBC relative to its use to prevent PJI. First, the antibiotic release profile (amount released and duration of release) is sub-optimal. Specifically, it is characterized by: an initial burst phase (one in which antibiotic particles at or close to the surface are released), followed by a phase in which the release rate noticeably decreases, and, finally, an exhaustion phase (one in which release reduces to a very low level that may, in fact, be below a therapeutically effective value, and, in due course, stops). Typically, the duration of the initial burst phase (DBP) is ~8 h-~8 d and the time at the start of the release exhaust phase (TSEP) is~4 d-~ 2 mo [46-56]. It is worth noting the the cumulative amount of antibiotic released (CAAR) is very low, on the order of $\leq$ ~7% of the initial mass of the antibiotic in the cement powder after ~1 wk release in 1X phosphate buffered saline (PBS) solution, at 37°C [46-56]. In other words, most of the antibiotic remains trapped in the cement (it is assumed, in the matrix). Second, the antibiotics commonly used in ALBC brands approved by relevant regulatory bodies for use in primary TJAs (hereafter, referred to as "approved brands") or in commercially-available ALBC brands (that is, gentamicin, tobramycin, and vancomycin) are becoming resistant to clinically-relevant bacterial strains [3]. This resistance is the consequence of the formation of a biofilm on the implant component surface, which shelters the bacteria and encourages persistence of infection through reduction of the antibiotic concentration/amount to a sub-therapeutic level [3,57]. Third, there are reports of depreciation of some mechanical properties of an ALBC (relative to those of its no-antibiotic-loaded or plain counterpart), examples being compressive strength and fatigue strength [58].

Although there is a large body of literature on enhancement of release of antibiotic from ALBCs, only three reviews of this body have appeared [21,59,60], with each having its shortcomings. Anagnostakos and Kelm [59] mainly focused on influence of additives/fillers, antibiotic combination, and ultrasound and was limited to CAAR. Arora et al. [21] devoted only a short section to the use of three nano-sized particles in enhancing the effectiveness of the released antibiotic against clinically-relevant bacterial strains, notably *S. aureus*, methicillin-resistant *S. aureus* (MRSA), and *S. epidermidis.* Similarly, in the review by Bistolfi et al. [60], the coverage of the section devoted to the literature on enhancement methods was very limited. The purpose of the present contribution was to perform a comprehensive, critical, and up-to-date review of the literature on enhancement of release of antibiotics from ALBC; as such, CAAR, DBP, TSEP and effectiveness of the released antibiotic against clinically-relevant bacterial strains are considered. There are two caveats attached to the present review. First, it is limited to the literature on use of ALBC to prevent PJI in primary TJA; thus, the literature on

spacers and beads is not included because these devices are used in treatment of PJI via revision arthroplasty [61-65]. Second, studies involving biantibiotic ALBCs [64-66] were not included because the vast majority of ALBC brands approved by the appropriate regulatory body (such as the US Food and Drug Administration) for use in TJAs contain only one antibiotic (for example, Cemex Genta® (gentamicin), Palacos R+G® (gentamicin), and Simplex with Tobramycin™).

The present review is organized into five sections. Following the introduction, succinct descriptions of the most salient findings in the literature on enhancement methods are given in the second section. Here, CAAR, DBP, TSEP, and indices of released antibiotic effectiveness are considered. Summarized presentations on details of postulated mechanisms for the most widely-used antibiotic release enhancement method are given in the third section. Expositions on limitations of the literature (shortcomings and gaps) are presented in the fourth section. The fifth section comprises a summary of the key points made.

2. INDICES OF ENHANCEMENT

2.1 Release Profile

Results given in the literature on enhancement methods [54,56,67-107], with specific reference to CAAR, DBP, and TSEP are summarized in Table 1, with the computed means of these indices of enhancement being given in Table 2.

From these results, two key findings emerge. The first is that there are four methods that yield promising results in terms of CAAR, these being additive(s) to the cement powder, method of mixing antibiotic powder and cement powder, direct impregnation of antibiotic into a nano-additive, and ultrasonication. A summary of postulated mechanisms that account for the enhancement in CAAR provided by these methods as well with others is presented in Table 3. The second key observation is that there is a dearth of results on DBP and TSEP.

Table 1. Summary of three calculated indices of enhancement of antibiotic elution profile provided by various enhancement methods

Enhancement method	Agent/technique	Calculated increase in inhibition index[a]		
		CAAR[b,c] (%)	DBP (%)	TSEP (%)
Addition to cement powder	20 wt./wt.% lactose [69]	325		
	20 wt./wt.% lactose [70]	700	NMI[d]	300
	10 wt./wt.% lactose [71]	240	NMI	80
	0.75 vol./vol.% xylitol [72]	470	NMI	114
	1.66-6.13 wt./wt.% xylitol [73]			94
	20 wt./wt% xylitol [74]	440	NMI	1400
	4.76 wt./wt.% xylitol [74]	200	200	NMI
	1 wt./wt.% gelatin sponge [77]	420	NMI	150
	17 wt./wt.% ceramic capsules [77]	240	NMI	150
	2.5 wt./wt.% antimicrobial peptide[e] [78]	370		NMI
	5.0 wt./wt.% antimicrobial peptide[e] [78]	275	200	NMI
	Emulsifier[f] [56]	320		
	12.5 wt./wt.% MSNPs[g] [79,80]	775-970	150	700
	90.9 wt./wt.% bioactive borate glass particles [81]	70	NMI	200
	Silica nanoparticles (layer-by-layer technique[h]) [54]	160		
	Silica nanoparticles (layer-by-layer technique[i]) [82]	300, 400		360
	47.5 wt./wt.% strontium-containing hydroxyapatite particles [83]	1700	600	600
	20 wt./wt.% 26% HACC[j] [84]	785	44	NMI
	20 wt./wt.% chitosan particles [84]	115	NMI	NMI
Additive to cement	Extruded liposomes coated with a non-toxic,	160	NMI	NMI

Enhancement method	Agent/technique	Calculated increase in inhibition index[a]		
		CAAR[b,c] (%)	DBP (%)	TSEP (%)
liquid	neutral surfactant [85]			
Direct impregnation of antibiotic into a nano-additive	Gentamicin loaded into 10.2 wt./wt.% MSNPs [87,88]	860	725	285
	Gentamicin loaded into 32.3 wt./wt.% HANRs[k] [87,88]	1380		
	Gentamicin loaded into 5.4 wt./wt.% CNTs[l] [87,88]	1240		
	Gentamicin loaded into 25.2 wt./wt.% TNTs[m] [87,88]	1600		
Method of mixing cement powder and antibiotic powder	Industrial/proprietary method [49,89]	22-740		
	"Dough-phase" mixing[n] [90]	80-190		
Ultrasonication (US)	Low-intensity, low-frequency US (time-averaged acoustic intensity (I) = 167 mW cm^{-2}; frequency (freq) = 46.5 Hz; duration (t) = 18 h)) [93]	6-24		
	Continuous-wave US (acoustic output = 100 or 300 mW cm^{-2}; t = 0.5 h) [94]	2.5-28		
	Intermittent watt-level US (US applied with a pause of 10 min between US application period (40 min)) [98]	88-94		
	I = 300 mW cm^{-2}; freq = 1 MHz; 3:10 duty cycle (VAN+US study group) [99]	31		
	Microbubbles-mediated US (Same US conditions as for VAN+US study group but with addition of a microbubbles contrast agent to the antibiotic release test solution and refreshment of the solution every 4 h during the test, which lasted 24 h) [99].	240		100
	I = 3 W cm^{-2}; freq = 40 kHz; t = 10 min [101]	500		
	(a)Cement powder and vancomycin powder mixed; mixture vacuum-mixed with cement liquid (-30 kPa), at 1 Hz, for 90 s ("standard antibiotic addition" technique); low-frequency (25.5 Hz) US (LFUS) applied for 45 min versus (b)cement powder and liquid vacuum-mixed (-30 kPa), at 1 Hz, for 60 s; vancomycin powder added to dough, followed by 30 s of vacuum mixing ("delayed antibiotic addition" technique); LFUS applied for 45 min [104].	68		
Timing of addition of antibiotic powder to cement powder	"Delayed antibiotic addition" technique versus "standard antibiotic addition" technique [105]	30		
	"Delayed antibiotic addition" technique versus "standard antibiotic addition" technique [104]	NMI		
Method of addition of antibiotic liquid to cement liquid	(a)Antibiotic powder added to distilled water, the solution vortexed for 30 s and, then, powder of a plain cement brand added ("powder component"); antibiotic liquid added to liquid of plain cement and mixed	300	200	NMI

Enhancement method	Agent/technique	Calculated increase in inhibition index[a]		
		CAAR[b,c] (%)	DBP (%)	TSEP (%)
	manually before powdered component was added; this mixture was mixed manually for 2 min versus (b)antibiotic powder and plain cement powder mixed and, then, cement liquid added [75].			
Combination method	"Standard antibiotic addition" technique followed by LFUS for 45 min versus "standard antibiotic addition" technique only [104]	169		
	"Delayed antibiotic addition" technique followed by LFUS for 45 min versus "delayed antibiotic addition" technique only [104]	300		
	Gentamicin added to powder of an approved plain cement brand ("GS-powder blend") and, then, the blend (90 wt./wt.%) mixed with PVP[o] (10 wt./wt.%). The liquid obtained by mixing the liquid of the plain cement brand (50 wt./wt.%) and HEMA[p] (50 wt./wt.%). This experimental cement is herein designated (PVP+HEMA) cement [106].	6400	NMI	NMI

[a]With respect to value of index when enhancement agent/technique was not used; that is, value when specimens of control cement (ALBC powder and liquid mixed using a manual method) were used
[b]CAAR: cumulative amount of antibiotic released at a specified time during test; DBP: Duration of the burst phase of release of the antibiotic; TSEP: time at the start of the exhaustion phase of release of the antibiotic
[c]Although across the literature reports reviewed, a number of different measures of CAAR were used (for example, mass of antibiotic released per surface area of test specimen, mass of antibiotic released per surface area of test specimen per test duration, and mass of antibiotic released as a % of mass of starting mass of antibiotic in the antibiotic powder + cement powder mixture), within a given study the same measure was used. Increase in CAAR was based on release measure at a specified time during the test (T). Across the literature reports reviewed, different Ts were used but, within a given study, the same T was used to compute index of enhancement for results using control cement specimens and enhancement method specimens
[d]NMI: No measurable increase
[e]Dhvar-5 (made by solid-phase peptide synthesis using (9-fluorenyl-methoxycarbonyl) chemistry)
[f]Obtained by dissolving 8 mL of the liquid of the control cement and 1 g gentamicin sulfate powder in 1 mL deionized water and 1 g of a surfactant
[g]Mesoporous silica nanoparticles
[h]Using poly-beta-amino-ester as the polycation and alginate as the polyanion.
[i]Using a positively-charged and hydrolyzable polyectrode (poly-b-amino-ester)
[j]Hydroxypropyltrimethyl ammonium chloride chitosan
[k]Hydroxyapatite nanorods
[l]Carbon nanotubes
[m]Titania nanotubes
[n]Powder and liquid of a plain cement brand were mixed using a manual method (mixing in bowl, open to the atmosphere, using a spatula, for 3 min) to produce a dough to which the antibiotic powder was added without breaking up the chunks
[o]Poly(N-vinyl-2-pyrrolidone)
[p](2-hyrodroxethyl methacrylate)

2.2 Effectiveness of Released Antibiotic

Several observations are made on literature studies on this issue. First, in many studies, the amount of released antibiotic as a function of test time was obtained but no tests were conducted that would have allowed determination of an index of effectiveness of the released antibiotic [56,69,70,72,78,85,87,88]. Second, a variety of instrumentation was used to determine

effectiveness, among which was high-performance liquid chromatograph [71], spectrophotometer [80], isothermal microcalorimeter [103] and size/diameter of the bacterial inhibition zone [85]. Third, in the preponderance of these tests, catalog *S. aureus* and catalog *S. epidermidis* strains were used, strains that are commonly encountered in PJI cases [71,74,80,82,85]. Fourth, in some studies, the results were presented in a such a way that did not allow calculation of an index of effectiveness [71,79,80].

Table 2. Overall means of calculated indices[a] of a selection of methods of enhancement of antibiotic release profile

Enhancement method	CAAR[b]	DBP[b]	TSEP[b]
Additive(s) to cement powder	460	235	375
Direct impregnation of antibiotic into a nano-additive	1270	NC[c]	NC
Method of mixing antibiotic powder and cement powder	250	NC	NC
Ultrasonication	110	NC	NC

[a]Expressed as increase of index relative to value when enhancement agent/method was not use
[b]CAAR: cumulative amount of antibiotic released at a specified time during test
DBP: duration of the burst phase of release of the antibiotic; TSEP: time at the start of the exhaustion phase of release of the antibiotic
[c]NC: insufficient number of results in literature reports did not allow calculation of index

Table 3. Summary of salient features of postulated mechanisms for enhancement of cumulative amount of antibiotic released

Enhancement method	Postulated mechanism
Additive(s) to cement powder	A poragen (for example, lactose) acts as an antibiotic release modulator; specifically, the poragen leads to creation of an irregular surface on the cement specimen, characterized by a series of “ink well” pores and voids [69,70].
	Xylitol acts as a soluble poragen and, as such, increases the porosity of the cement specimen, thereby creating a porous network, which facilitates the permeation of the cement matrix by the test solution, resulting in dissolution of antibiotic particles located deep within the cement matrix [72-74].
	An antimicrobial peptide (Dhvar-5) disperses and, subsequently, dissolves within the matrix of the cement which, in turn, allows release of the antibiotic from deeper zones within the cement matrix [78].
	A surfactant-stabilized emulsifier allows the liquid microbial agent to be loaded to the cement without separation during polymerization, leading to a homogeneously porous cement matrix, which, in turn, facilitates release of the antibiotic [56].
	With MSNP or TNT content ≥ 8 wt./wt.%, the nanoparticles facilitate formation of a nano-network path for diffusion of the antibiotic from the cement matrix, from which it is released [79,80,87,88].
	Bioactive borate glass particles act as a water-soluble poragen; that is, the dissolved particles allow for further contact with the incoming test solution and exchange with the previously entrapped antibiotic powder particles [81].
	When gentamicin is loaded on surface of silica nanoparticles (SNPs) using a layer-by-layer technique, the gentamicin is first released from the coating on the SNPs before it migrates through the cement matrix [54,82].
Additive to cement liquid	Gentamicin incorporated into extruded liposomes (105 ± 25 nm diameter) coated with a non-toxic, neutral surfactant leads to creation of small, well-dispersed pores, which facilitate gradual

Enhancement method	Postulated mechanism
	and controlled release of the gentamicin from the cement specimen [85].
Direct impregnation of antibiotic	With gentamicin loaded into halloysite nanotubes using a vacuum cycling method, the nanotubes isolate the gentamicin from the cement liquid and act as nanocontainers for slow release of the gentamicin [86].
Method of mixing antibiotic powder and cement powder	Industrial mixing leads to a homogeneous dough [49].
	Industrial mixing leads to increased porosity [89].
	In "dough-phase mixing", the antibiotic powder chunks that survive polymerization act as a porogen [90].
Method of mixing blended powder mixture and cement liquid	Increase of surface porosity of specimens mixed using a mixing drill device [91].
Ultrasound	Enhancement effect of low-intensity, low-frequency US or continuous-wave US attributed to easy diffusion of the antibiotic from the cement matrix by microstreaming and localized temperature increase of the specimen [93,94,96].
	Enhancement effect of intermittent watt-level US attributed to stable cavitation and radiation pressure, which generate multidirectional microstreams [98]. These microstreams produce a high shear stress at the vancomycin powder-cement matrix interface, which facilitates detachment of vancomycin grains from the specimen surface [98]. During the rest phase, these grains diffuse out of the craters and pores created in the specimen during the US application phase [98].
	Enhancement effect of microbubbles-mediated US attributed to stable cavitation and associated ultrasonic pressure produced by exposure to the US [104], increased rate of mass transfer from the cement matrix [104], and rupture of microbubbles by exposure to the US [99].
Timing of addition of antibiotic powder to cement powder	The "delayed antibiotic addition method" leads to decreased interference of the vancomycin with the initial stages of the cement polymerization process, which increases the porosity of the cement specimen [105].
Combination technique	Enhanced gentamicin release profile of (PVP + HEMA) cement specimens attributed to dissolution of PVP within the HEMA matrix, creating a series of interconnected pores through which gentamicin is released [106].

From the results presented in the literature studies, various indices of effectiveness were calculated (Table 4). As expected, the trends in these indices parallel those in CAAR (Table 1). Because of the sparseness of the data in Table 4, it is not useful to highlight enhancement methods that lead to marked improvement in the effectiveness of the released antibiotic. Consequently, it is difficult to identify the enhancement methods that have the best potential from this perspective.

3. DETAILS OF POSTULATED RELEASE ENCHANCEMENT MECHANISMS

In cases where enhancement of CAAR is achieved by adding an agent to the powder of the ALBC (see Table 1), many workers have presented details of the postulated enhancement mechanism operational during each of the three phases of release of the antibiotic. These may be summarized as follows: initial burst (attributed to dissolution/wash-off of the antibiotic particles in the near-surface region of the specimen (mechanism 1)); Fickian diffusion of the antibiotic from accessible pores and voids (mechanism 2); and dissolution of the antibiotic within the cement matrix, creating a network of pores/internal pathways in the matrix through which the antibiotic elutes [70,74] (mechanism 3) (Fig. 1).

The associated kinetics equation for variation of amount of antibiotic released (M_t) from the test

specimen with time of immersion of the specimen in the test solution (t) is:

$$M_t = a + b\sqrt{t} + c[1-e^{-(kt)}] \quad (1)$$

where a, b, c, and k are process constants.

Each of the three terms on the right-hand side of Eq. (1) is associated with each of the aforementioned mechanisms; that is, burst (first term), diffusion (second term), and dissolution (third term).

4. METHODOLOGICAL ISSUES AND GAPS IN KNOWLEDGE BASE

Various methodological issues with some of the studies reported in the literature as well as gaps in the knowledge base (underexplored and unexplored topics) on aspects considered in the present review suggest potential areas for future research. Brief comments on these aspects are now presented.

Table 4. Summary of five calculated indices of effectiveness of released antibiotic

Enhancement method	Agent/technique	Calculated change in effectiveness index (%)				
		ABC[b]	TAB[d] (%)	TPI[f]	DAA[i]	CAA[l]
Addition to cement powder	2.4 wt./wt.% xylitol[a] [74]	~0				
	20 wt./wt.% xylitol[a] [74]	~0				
	10 wt./wt.% lactose[c] [71]		86			
	8.2 wt./wt.% MSNPs[e] [80]			100		
	Gentamicin loaded on silica nanoparticles using a layer-by-layer technique and POLY1[g,h] [82]				85	
	Gentamicin loaded on silica nanoparticles using a layer-by-layer technique and POLY2[g,h] [82]				69	
	26 %HACC[j] [84]	88				
	Chitosan macroparticles [107]	35[k]				
	Chitosan nanoparticles [107]	74[k]				
	Quaternary ammonium chitosan derivative nanoparticles [107]	89[k]				
Method of mixing blended antibiotic powder and cement powder and cement liquid	Vacuum mixing versus hand mixing [92]					
	Cobalt GHV					7
	Palacos R+G					8
	Simplex with Tobramycin					7
Ultrasonication	Ultrasound (US) [99]	90[m]				
	US + microbubbles [99]	99[m]				

[a] *Inoculation with a catalog bacterial strain (MRSA; n315 strain)*
[b] *ABC: reduction of amount of bacterial colonization of specimen surface by released antibiotic (expressed in CFU/cm^2 or CFU/mm^2)*
[c] *Inoculation with a catalog bacterial strain (S. aureus; ATCC® 25,923)*
[d] *TAB: increase in time until biofilm appeared on test specimen (expressed in days)*
[e] *Inoculation with a catalog bacterial strain (S. aureus; NCTC® 7447)*
[f] *TPI: increase in time over which inhibition of inoculate is preserved, after immersion of specimen in PBS, at 37 °C, for 4 wk (expressed in days)*
[g] *POLY1: piperazine; POLY2: 4,4-trimethylendiperidine*
[h] *Inoculation with clinical isolate of S. aureus*
[i] *DAA: increase of duration of antimicrobial activity of released antibiotic (expressed in days)*
[j] *HACC: a water-soluble chitosan derivative (hydroxypropyltrimethyl ammonium chloride chitosan)*
[k] *Inoculation with S. aureus; reduction in amount of bacterial colonization of specimen surface by released antibiotic, after 3 wk in PBS at 37 °C (expressed in CFU/cm^2)*
[l] *CAA: increase in cumulative antimicrobial activity, as determined using a zone of bacterial growth inhibition test (S. aureus 6538P; 5-day test) (expressed in mm).*
[m] *Reduction of surviving amount of S. aureus in adult New Zealand white rabbits*

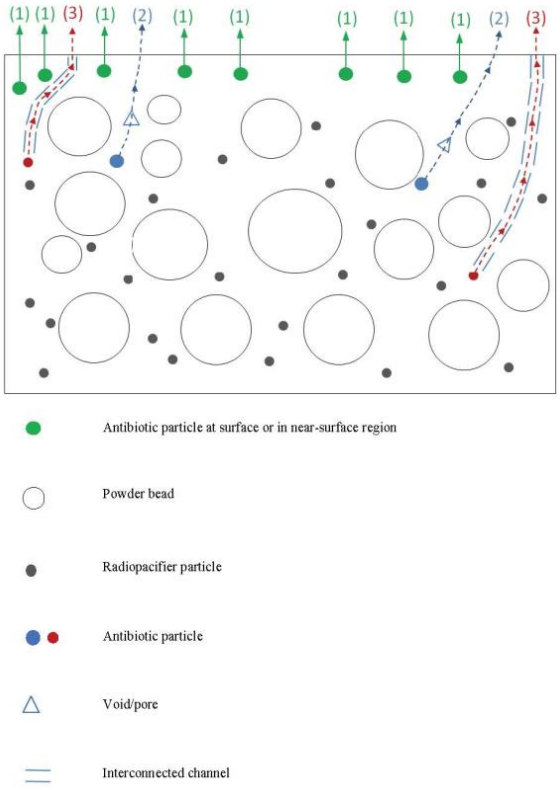

Fig. 1. Schematic presentation of postulated mechanisms of *in vitro* release of an antibiotic from antibiotic-loaded bone cement (the numbers refer to the postulated mechanism)

At the moment, it is very difficult, almost impossible, to make comparisons between the results presented in various literature reports. This is because workers used a variety of protocols and presented the results in many different formats (Tables 1 and 4). A remedy for this situation is to develop an international testing standard for antibiotic release testing on ALBC specimens. At the minimum, this standard should specify antibiotic loading (expressed as %vol./vol.%), specimen configuration and dimensions (for example, short solid cylinder, diameter and height = 6 mm and 12 mm, respectively), specimen fabrication conditions (such as device to use to mix antibiotic powder with cement powder, in the case of experimental ALBC formulations; evacuation pressure in vacuum mixing chamber; speed of mixing; and duration of mixing of cement powder mixture and liquid), post-fabrication conditions for specimen (aging medium and duration (for example, 1X PBS solution, at 37°C, for ≥ 24 h)), release test conditions and minimum duration of test (for example, immersion of specimens in 10 mL of 1X PBS solution, at 37°C; test duration ≥ 60 d), method of determining amount of antibiotic released (for example, use fluorescence polarization immunoassay to determine mass of antibiotic present in 3-mL assays), and format for reporting release test results (for example, cumulative amount of antibiotic released (M; in μg) normalized by dividing M by the product of initial mass of test specimen (in mg), the assay volume used (3 mL), and the volume fraction of the antibiotic in the cement powder blend).

Studies involving experimental ALBC formulations in which an antibiotic and a filler are added to the powder of an approved plain cement brand but the formulation includes one or more constituents of the starting cement liquid that are not present in approved plain cement or ALBC brands should be re-done with the necessary corrections to the composition of the liquid. An example of such a filler is polyamide of trans-4-hydroxy-L-proline (PAT4HLP) [108]. Details have been provided of the steps in the synthesis of this filler and its characterization (using Fourier transform infrared spectroscopy, ^{1}H nuclear magnetic resonance spectroscopy,

and viscosity measurements (to determine the molecular weight of its oligomers)) [108]. When incorporated into a bone cement powder, this filler was shown to be a poragen [108]. No antibiotic release study involving a cement that contains PAT4HLP has been reported. Another example is an experimental cement formulation in which strontium-containing hydroxyapatite (Sr-HA) particles and gentamicin were added to the powder of an experimental plain cement (SrHA-Gen cement) [83]. At any time point during a gentamicin release test, release from SrHA-Gen specimens was significantly more than from specimens of the control cement (only gentamicin added to powder) (by between 7- and 18-fold) [83]. However, the constituents of the liquid in the experimental plain cement were bisphenol A diclycidylether methacrylate (Bis-GMA), triethylene glycol dimethacrylate (TEGDMA), and N,N-dimethyl-p-toluidine [83] but neither Bis-GMA nor TEGMA is present in liquids in approved plain cement or ALBC brands. This means that comparison of antibiotic release profiles between specimens of a cement in which Sr-HA particles are added to the powder of an approved ALBC brand versus those fabricated using the approved ALBC brand is needed.

There are a number of emerging fillers that warrant examination of their suitability for incorporation into ALBC as antibiotic release enhancement agents. Three examples of such fillers are given. The first comprises mesoporous organosilica nanoparticles [109]. The second example comprises hybrid nanofibers (HNFs), which have a drug-free thin layer of glycerol monostearate as the shell and a nanocomposite containing a drug (berberine hydrochloride (BHC)) and ethylcellulose as the core, with the production being accomplished using a monoaxial electrospinning method [110]. Over the course of a 32-hour BHC release study, a marked difference in BHC release profile was found: in the initial time period (up to 2 h), BHC amount was significantly more from particles containing BHC (raw particles) compared to BHC released from HNFs, but release from raw particles ended after this initial period whereas release from HNFs continued slowly throughout the test period, culminating in ~97% of the loaded BHC being released at the end of the test [110]. The third example comprises curcumin nanoparticles [111].

There are no studies involving ALBCs formulated using an innovative architecture; that is, not simply blending an antibiotic with either the powder or the liquid of a starting cement (as is done with the current generation of approved cement brands or experimental formulations). In this regard, evaluations of two systems are suggested. The first is a cement in which cross-linked poly (methyl methacrylate-acrylic acid sodium salt) particles are incorporated in the powder that contains an antibiotic [112]. The second is a cement in which β or γ-cyclodextrin microparticles are filled with an antibiotic, dried, and, then, added to the mixture of the cement powder and liquid as it is polymerizing [113].

Chemical modification of the antibiotic, through chemical conjugation, has been investigated as a means of enhancing antibiotic release from a polymer matrix. Two examples of this approach are summarized here. One, Edwards et al. [114] postulated that by linking an antibiotic directly to the polymer backbone of a bone cement, the release of the antibiotic will be determined by the hydrolysis of the intramolecular ester bond in the system. This is determined by the properties of the neighboring groups, which can be changed as needed. Results of a study involving three different conjugates into methyl methacrylate in a bone cement loaded with nalidixic acid showed release of the acid over a period of 60 days which, it was contended, demonstrated that this method has promise in enhancing antibiotic release from an ALBC specimen. An investigation of this method is warranted. Two, Cyphert et al. [115] reported a study in which adamantane-1(AD)-carbohydrazide was covalently bonded to an antibiotic (erythromycin (EM)) via a pH-degradable hydrazine bond (AD-EM material). In both acidic (pH = 5.0) and neutral (pH = 7.4) test solutions, over the test period of 40 days, erythromycin released from specimens in which AD-EM was loaded into cyclodextrin polymer discs (AD-EM material-loaded group specimens) was higher than from specimens that only contained EM, with the difference being marked at test period $\geq$ 20 days. This result was attributed to the presence of the extra-high-affinity AD group in AD-EM material [115].

In cemented TJA surgery, two practices are common. In one case, the orthopaedic surgeon (or an authorized member of the operating room/surgical team) prepares an *ad hoc* ALBC formulation by mixing antibiotic(s) with the powder of an approved brand, obtaining what is sometimes referred to as a “physician-directed” ALBC formulation. Alternatively, an approved ALBC brand is used. In the case of physician-

direction formulations, issues such as the optimal timing when the delayed antibiotic addition method [105] is employed and the influence of mixing device (for example, a simple spatula versus a commercially-available mixer [116]) remain unexplored. When an approved ALBC brand is used, five examples of variables for investigation are temperature at which the cement unit (powder and liquid) is stored prior to vacuum mixing; the length of time between taking the cement unit out of the storage medium and commencement of vacuum mixing; the magnitude of the evacuation pressure in the vacuum mixing chamber; the speed at which the powder and liquid are vacuum mixed; and the length of the vacuum mixing operation. It is realized that such a study would be very time-consuming and, possibly, expensive (for example, with three values of each of the aforementioned five variables and three replicates per test, 729 specimens would be required). The results should then be analyzed using an appropriate statistical method, such as response surface methodology [117], leading to the combination of the values of these five variables that yield optimal antibiotic release measure (for example, cumulative amount of released amount after a specified time). It is possible that results from both of these studies may change clinical practice.

Wendling et al. [101] reported on the conjoint influence of frequency (f) and duration of application of US (τ) on release of an antibiotic from an ALBC specimen. A shortcoming of this study is that it did not elucidate the influence of each of these variables separately. In this respect, it is to be noted that in addition to f and τ, another key process variable is acoustic intensity.

There is scope for design of agents to be added to the powder and/or liquid of an ALBC that would affect the values of the process coefficients in Equation (1) (namely, a, b, c, and k) so that the antibiotic release profile is significantly improved; that is, there is marked reduction of antibiotic release rate in the burst zone, increase in TSEP and decrease in the rate at which exhaustion of release is achieved.

A shortage of complementary data on effectiveness of released antibiotic (compare Table 1 and Table 4) precludes meaningful comparison of enhancement methods that may lead to identification of the ones that show the best promise and, hence, deserve evaluation for clinical use.

The issue of increased resistance of pathogenic species among clinical isolates of implant-associated infections (most frequently, gram-positive bacteria, including *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus,* and coagulase staphylococci, as well as, for example, extended-spectrum beta-lactamase-producing *Enterobacteriaceae* [118]) to gentamicin, vancomycin, and tobramycin, which are the antibiotics present in nearly all approved ALBC brands or, commonly, utilized in preparing "physician-directed" ALBC formulations, is extensively discussed in the literature [119]. Thus, over the past few years, there have been many reports on the design, synthesis, and characterization of a new generation of antibiotics which, it is postulated, would be less susceptible to this antibiotic resistance problem and, thus, may find use in preventing and/or treating PJI. Although there are many of these so-called new-generation single antibiotics (such as levofloxacin [71], daptomycin [120,121], dalbavancin [122], telavancin [123], omadacycline [124-126], ceftobiprole [127], optimized arylomycin analogs [128], ceftraoline fosamil [129], and second-generation lipophosphonoxins [130]) and antibiotic hybrids (such as CBR-2092 (a rifamycin-quinolone hybrid) [131]) and trimethoprim (TMP)-sulfamethoxazole (SMX) [132]), only a few of them have been the subject of *in vitro* antibiotic release studies [50,55,71,73,103,129,130] and in none of these studies was enhancement of antibiotic release investigated. These gaps should be filled.

An overarching consideration in the design of all future studies must be to avoid shortcomings of the present body of literature. Seven of these shortcomings are highlighted here. First, in a number of reports, statistical methods were either not used to analyze the results [69,79,87,88,106] or were mentioned as used but the outcomes of the analysis were not given [70,71,77,85,86]. Additionally, and more importantly, with very few exceptions [70,74,98], a parametric statistical method (usually, the Student *t*-test or ANOVA) was used to perform test of comparison of populations (sets of results. Such methods should be used only if it is first shown that each of the populations is a normally-distributed set. To avoid the extra work that this entails, it is best to use a non-parametric method with an appropriate *ad hoc* correction method,

such as Kruskal-Wallis test with Bonferroni correction.

Second, in some studies, a plain cement brand/formulation, rather than an ALBC brand/formulation, was used as the control cement [133]. Third, with very few exceptions [82], in all the studies in which effectiveness of the released antibiotic was determined, a catalog bacterial strain, rather than a clinical isolate, was used. Fourth, the cement brand used in the study by Faber et al. [78] (Osteopal G; Heraeus Medical GmbH, Wehrheim, Germany) is one that is more suited for use in vertebral augmentation procedures (specifically, balloon kyphoplasty) [134] rather than in anchoring TJAs. Fifth, in some reports, explicit values of the effectiveness of the released antibiotic were not given (for example, size of zone of bacterial inhibition [83]). Sixth, even though Simplex P with Tobramycin is an approved ALBC brand that is very widely used in primary and revision THA and TKA cases [43], it has been the subject of very few antibiotic release studies [92]. Seventh, there is a glaring dearth of determination of the extent to which a released antibiotic resists formation of a biofilm on test surfaces on which there is a clinically-relevant bacterial strain. This gap is surprising given the widely recognized role that biofilms play in PJI and in the development of resistance of the clinically relevant bacterial strains to the current generation of antibiotics. Thus, in the design of future studies, it should be ensured that, among other features, 1) cement brands or formulations that are relevant to preventing and/or treating PJI are used, 2) at least one of the cement brands used be Simplex with Tobramycin; 3) performance of the released antibiotic with respect to biofilm formation be included; in that regard, evaluation should include determination of ability to demonstrate quorum quenching, a mechanism that has been postulated to significantly reduce quorum sensing, which, in turn, has been presented as being critical to the formation of biofilm [135-138]; 4) clinical isolates of bacterial strains that are obtained from PJI cases be used in the biofilm work and other determinations of the effectiveness of the released antibiotic; and 5) appropriate statistical methods are used to analyze the results.

After *in vitro* investigations, the next stages in the evaluation of an enhancement method prior to clinical use are preclinical study and a clinical trial. There have been no preclinical studies (that is, studies in which an animal model of PJI was used; for example, mouse [139] Dutch Belted rabbit [140], or sheep [141] model) and no clinical trials on this subject. These gaps point to opportunities for future research.

5. CONCLUION

The following are the key points made in this review:

- Peri-prosthetic joint infection (PJI) remains a relatively rare but overwhelmingly challenging complication of total joint arthroplasties. Antibiotic-loaded PMMA bone cement (ALBC) is widely used for preventing and/or treating/managing PJI.
- The sub-optimal profile of release of the antibiotic from ALBC specimens in *in vitro* tests is well known. Among other features, this profile is characterized by i) an initial burst phase (which occurs during the first few hours to days) followed by a marked decrease in the release rate and, then, exhaustion of release (after, typically, ~1 mo); and ii) the cumulative amount of antibiotic released at the end of test (which, typically, lasts ~40 days) is ≤ ~7% of the starting amount of the antibiotic powder in the cement powder.
- Methods or approaches to enhance the antibiotic release profile have been the subject of a miscellany of literature studies, but, it appears that the most effective one involves incorporating an additive, such as xylitol powder, chitosan macroparticles, or silica nanoparticles, into the cement powder.
- There is a dearth of studies in which the effectiveness of the released antibiotic against bacterial strains commonly encountered in PJI cases, such as *S. aureus*, was determined.
  This, therefore, limits identification of the enhancement methods that have the most promise for simultaneous maximization of all the indices of enhancement; in particular, antibiotic release and effectiveness of the released antibiotic against aforementioned bacterial strains. A collection of other shortcomings of and gaps in the literature are highlighted, among which are need for the development of an international standard for *in vitro* antibiotic release testing and evaluation of an enhancement method that involves linking the antibiotic directly to the

backbone of the polymer bead in the powder.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Romano CL, Al Khawashki H, Benzakour T, Bozhkova S, del Sel H, Hafez MH, et al. The W.A.I.O.T. definition of high-grade and low-grade peri-prosthetic joint infection. J Clin Med. 2019;8(5):650(13).
2. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev. 2014;27:302-5.
3. Otto-Lambertz C, Yagdiran A, Wallscheid F, Eysel P, Jung N. Periprosthetic infection in joint replacement: Diagnosis and treatment. Dtsch Arztebl Int. 2017;114:347-53.
4. Kuhn H-D, Editor. Management of periprosthetic joint infection. Berlin, Germany: Springer-Verlag; 2018.
5. Abad CL, Haleem A. Prosthetic joint infections: An update. Cur Infect Dis Reports. 2018;15(13):20.
6. Mussa M, Manciulli T, Corbella M, Mariani B, Cambieri P, Gipsz N, et al. Epidemiology and microbiology of prosthetic joint infection: a nine-year, single-center experience in Pavai, Northern Italy. Musculoskeletal Surg; 2020. Available:https://doi.org/10.1007/s12606-020-00638-y
7. Springer BD, Cahue S, Etkin CD, Lewallen DG, McGory BJ. Infection burden in total hip and knee arthroplasties: An international registry-based perspective. Arthroplasty Today. 2017;3:137-40.
8. Kurtz SM, Lau EC, Son M, Chang ET, Zimmerili W, Parvizi J. Are we winning or losing the battle with periprosthetic joint infection: Trends in periprosthetic joint infection and mortality risk for the Medicare population. J Arthroplasty. 2018;33:3238-45.
9. Alamanda VK, Springer BD. The prevention of infection: 12 modifiable risk factors. Bone Joint J 2019;101-B(1Suppl A):3-9.
10. Meehan JP, Danielsen B, Kim SH, Jamali AA, White RH. Younger age is associated with a higher risk of early periprosthetic joint infection and aseptic mechanical failure after total knee arthroplasty. J Bone Joint Surg Am. 2014;96:529-35.
11. Bell KL, Shohat N, Goswami K, Tan TL, Kalbian I, Parvizi J. Preoperative opioids increase the risk of periprosthetic joint infection after total joint arthroplasty. J Arthroplasty. 2018;33:3246-51.
12. Li R, Shao H-Y, Hao L-B, Yu B-Z, Qu P-F, Zhou Y-X, et al. Plasma fibrinogen exhibits better performance than plasma D-dimer in the diagnosis of periprosthetic joint infection: a multicenter retrospective study. J Bone Joint Surg Am. 2019;101:613-9.
13. Kwee TC, Kwee RM, Alavi A. FDG-PET for diagnosing prosthetic joint infection: Systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2008;35:2122–32.
14. Tarabichi M, Shohat N, Parvizi J. New technologies for diagnosis of periprosthetic hip infection. J Hip Surg. 2018;02:068-075.
15. Greenwood-Quaintance KE, Uhl JR, Hanssen AD, Sampath R, Mandrekar JN, Patel R. Diagnosis of prosthetic joint infection by use of PCR electrospray ionization mass spectrometry. J Clin Microbiol. 2014;52:642-9.
16. Moshirabadi A, Razi M, Arasteh P, Sarzaeem MM, Ghaffari S, Aminiafshar S, et al. Polymerase chain reaction assay using the restriction fragment length polymorphism technique in the detection of prosthetic joint infections: A multi-centered study. J Arthroplasty. 2019;34:359-64.
17. Chisari E, Parvizi J. Accuracy of blood-test and synovial fluid-tests in the diagnosis of periprosthetic joint infections. Anti-Infective Therapy. DOI: 10.1080/14787210.2020.1792771
18. Fu J, Ni M, Chai W, Li X, Hao L, Chen J. Synovial fluid viscosity test is promising for the diagnosis of periprosthetic joint infection. J Arthroplasty. 2019;34:1197-1200.
19. Li M, Zeng Y, Wu Y, Si H, Xianchao BX, Shen B. Performance of sequencing assays in diagnosis of prosthetic joint infection: A systematic review and meta-analysis. J Arthroplasty. 2019;34:1514-22.

20. Shahi A, Eajazi A. Prevention of periprosthetic joint infection: Pre- and intraoperative considerations. Orthopedics. 2015;38:219-21.
21. Arora M, Chan EKS, Gupta S, Diwan AD. Polymethylmethacrylate bone cements and additives: A review of the literature. World J Orthop. 2013;4:67-74.
22. Sa Y, Yang F, wang Y, Wolke JGC, Jansen JJ. Modifications of poly(methyl methacrylate) cement for application in orthopedic surgery. In: Chun HJ, et al., editors. Cutting-edge enabling technologies for regenerative medicine, advances in experimental medicine and biology; 1078.
Available:https://doi.org/10.1007/978-981-13-0950-2_7
23. Ghandi R, Backstein D, Zywiel MG. Antibiotic-laden bone cement in primary and revision hip and knee arthroplasty. J Am Acad Orthop Surg. 2018;26:727-34.
24. Martínez-Moreno J, Merino V, Nácher A, Rodrigo JL, Climente M, Merino-Sanjuán M. Antibiotic-loaded bone cement as prophylaxis in total joint replacement. Orthop Surg. 2017;9:331-41.
25. Ricciardi BF, Muthukrishnan G, Masters EA, Kaplan N, Daiss JL, Schwartz EM. New developments and future challenges in prevention, diagnosis and treatment of prosthetic joint infection. J Orthop Res. 2020;38:1423-35.
26. Sebastian S, Liu Y, Christensen R, Raina DB, Tagil M, Lidgren L. Antibiotic containing bone cement in prevention of hip and knee prosthetic joint infections: A systematic review and meta-analysis. J Orthop Translation. 2020;23:53-60.
27. Arciola CR, Campoccia D, Montanaro L. Implant infections: Adhesion, biofilm formation and immune evasion. Nature Rev Microbiol. 2018;16:397-409.
28. Sukeik M, Haddad FS. Periprosthetic joint infections after total hip replacement: an algorithmic approach. SICOT-J. 2019;5(2S):5.
DOI: 10.1051/sicotj/2019004
29. Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 definition of periprosthetic hip and knee infection: An evidence-based and validated criteria. J Arthroplasty. 2018;33:1309-14.
30. Bolia IK Tsiodras S, Chloros GD, Kaspiris A, Sarlikiotis T, Savvidou OD, et al. A review of novel antibiotic regimens for the treatment of orthopedic infections. Orthopedics. 2018;41:323-8.
31. Abblitt WP, Ascione T, Bini S, Bori G, Brekke AC, Chen AF, et al. Hip and knee section, outcomes: Proceedings of international consensus on orthopedic infections. J. Arthroplasty. 2019;34:S487-S495.
32. Shah NB, Hersh BL, Kreger A, Sayeed A, Bullock AG, Rothenberger SD, et al. Benefits and adverse events associated with extended antibiotic use in total knee arthroplasty periprosthetic joint infection. Clin Infect Diseases; 2019.
DOI: 10.1093/cid/ciz261
33. Srivastava K, Bozic KJ, Silverton C, Nelson AJ, Makhni EC, Davis JJ. Reconsidering strategies for managing chronic periprosthetic joint infection in total knee arthroplasty. J Bone Joint Surg Am. 2019;101:14-24.
34. Kunutsor SK, Whitehouse MR, Blom AW, Kay P, Wroblewski BM, Zeller V, et al. One- and two-stage surgical revision of peri-prosthetic joint infection of the hip: A pooled individual participant data analysis of 44 cohort studies. Eur J Epidem. 2018;33:933-46.
35. Miller R, Higuera CA, Wu J, Klika A, Babic M, Piuzzi NS. Periprosthetic joint infection: A review of antibiotic treatment. J Bone Joint Surg Reviews. 2020;8(7):e19.00224.
Available:http://doi.org/10.2106/JBJS.RVW.19.00224
36. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. 2012;27(8 Suppl 1): 61-65.
37. Garrido-Gomez J, Arrabal-Polo MA, Giron-Prieto MS, Cabello-Salas J, Torres-Barroso J, Parra-Ruiz J. Descriptive analysis of the economic costs of periprosthetic joint infection of the knee for the public health system of Andalusia. J Arthroplasty. 2013;28:1057-60.
38. Efremov K, Valentini MB, de Maio F, Potenza V, Caterini R, Farsetti P. Periprosthetic hip and knee infections: comparison of etiology, perioperative management and costs. Eur Rev Med Pharmacol Sci. 2019;23(Suppl.):217-23.
39. Leite PS, Figueiredo S, Sousa R. Prosthetic joint infection: Report on the one versus two-stage exchange EBJIS survey. J Bone Joint Infection. 2016;1:1-6.

40. Schwarz EM, McLaren AC, Sculco TP, Brause B, Bostrom M, Kates SL, et al. Adjuvant antibiotic-loaded bone cement: Concerns with current use and research to make it work. J Orthop Res. 2020;1-13. Available:https://doi.org/10.1002/jor.24616
41. Karrholm J, Lindahl H, Malchau H, Mohaddes M, Nemes S, Rogmark C, et al. Swedish Hip Arthroplasty Register; Annual Report 2016; Gothenburg, Sweden; 2018.
42. Daines BK, Dennis DA, Amann S. Infection prevention in total knee arthroplasty. J Amer Acad Orthop Surg. 2015;23:356-64.
43. Australian Orthopaedic Association (AOA). National Joint Replacement Registry. Cement in Hip and Knee Arthroplasty. Supplementary Report, AOA; 2017.
44. Jiranek WA, Hanssen AD, Greenwald AS. Antibiotic-loaded bone cement for infection prophylaxis in total joint replacement. J Bone Joint Surg Am. 2006;88:2487-500.
45. Lewis G. Properties of antibiotic-loaded acrylic bone cements for use in cemented arthroplasties: a state-of-the art review. J Biomed Mater Res Part B: Appl Biomater. 2009;89B:558-74.
46. Kuechle DK, Landon GC, Musher DM, Noble PC. Elution of vancomycin, daptomycin and amikacin from acrylic bone cement. Clin Orthop Rel Res. 1991;264:302-8.
47. Penner MJ, Duncan CP, Masri BA. The in vitro elution characteristics of antibiotic-loaded CMW and Palacos-R bone cements. J Arthroplasty. 1999;14:209-13.
48. Van de Belt H, Neut D, Uges DRA, Schenk W, van Horn JR, van der Mei HC, et al. Surface roughness, porosity and wettability of gentamicin-loaded bone cements and their antibiotic release. Biomater. 2000;21:1981-7.
49. Neut D, van de Belt H, van Horn JR, van der Mei HC, Busscher HJ. The effect of mixing on gentamicin release from polymethylmethacrylate bone cements. Acta Orthop Scand. 2003;74:670-6.
50. Kaplan L, Kurdziel M, Baker KC, Verner J. Characterization of daptomycin-loaded antibiotic cement. Orthopedics. 2012;35: e503-e509.
51. Samuel S, Mathew BS, Veeraraghavan B, Fleming DH, Chittaranjan SB, Prakask JAJ. *In vitro* study of elution kinetics and bio-activity of meropenem-loaded acrylic bone cement. J Orthopaed Traumatol. 2012;13:131-136.
52. Lee S-H, Tai C-L, Chen S-Y, Chang C-H, Chang Y-H, Hsieh P-H. Elution and mechanical strength of vancomycin-loaded bone cement: *in vitro* study of the influence of brand combination. PLoS ONE. 2016;11(11):e0166545. DOI: 10.1371/journal.pone.0166545
53. Paz E, San-Ruiz P, Abenojar J, Vaquero-Martin J, Forriol F, Del Real JC. Evaluation of elution and mechanical properties of high-dose antibiotic-loaded bone cement: Comparative “in vitro” study of the influence of vancomycin and cefazolin. J Arthroplasty. 2015;30:1423-9.
54. Thaher YA, Yang L, Jones SA, Perni S, Prokopovich P. LbL-assembled gentamicin delivery system for PMMA bone cements to prolong antimicrobial activity. PLoS ONE. 2018;13(12):e207753. Available:https://doi.org/10.1371/journal.pone.0207753
55. Meeker DG, Cooper KB, Renard RL, Mears SC, Smeltzer MS, Barnes CL. Comparative study of antibiotic elution profiles from alternative formulations of polymethylmethacrylate bone cement. J Arthroplasty. 2019;34:1458-61.
56. Miller RB, McLaren A, Leon CM, Vernon BL, McLemore R. Surfactant-stabilized emulsion increases gentamicin elution from bone cement. Clin Orthop Rel Res. 2011;469:2995-3001.
57. Taha M, Abdelbary H, Ross FP, Carli AV. New innovations in the treatment of PJI and biofilms-clinical and preclinical topics. Curr Rev Musculoskel Med. 2018;11:380-8.
58. Bishop AR, Kim S, Squire MW, Rose WE, Ploeg H-L. Vancomycin elution, activity and impact on mechanical properties when added to orthopedic bone cement. J Mech Beh Biomed Mater. 2018;87:80-6.
59. Anagnostakos K, Kelm J. Enhancement of antibiotic elution from acrylic bone cement. J Biomed Mater Res Part B: Appl Biomater. 2009;90B:467-75.
60. Bistolfi A, Ferracini R, Albanese C, Verne E, Miola M. PMMA-Based Bone cements and the problem of joint arthroplasty infections: status and new perspectives. Materials. 2019;12:4002. DOI: 10.3390/ma12234002
61. Guild GN, Baohua W, Scuderi GR. Articulating vs. static antibiotic impregnated spacers in revision total knee arthroplasty for sepsis; a systematic review. J Arthroplasty. 2014;29:558-63.

62. Bitsch RG, Kretzer JP, Vogt S, Buchner H, Thomsen MN, Lehner B. Increased antibiotic release and equivalent biomechanics of a spacer cement without hard radio contrast agents. Diagnos Microbiol Infect Dis. 2015;83:203-9.
63. Likine EF, Seligson D. Rifampin and tobramycin combination with PMMA antibiotic cement. Eur J Orthop Surg Traumat. 2019;29:499–500.
64. Parra-Ruiz FJ, Gonzalez-Gomez A, Fernandez-Gutierrez M, Parra J, Garcia-Garcia J, Azuara G, et al. Development of advanced biantibiotic loaded bone cement spacers for arthroplasty associated infections. Int J Pharmaceut. 2017;522:11-20.
65. Boelch SP, Rueckl K, Fuchs C, Jordan M, Knauer M, Steinert A, et al. Comparison of elution characteristics and compressive strength of biantibiotic-loaded PMMA bone cement for spacers: Copal® Spacem with Gentamicin and Vancomycin versus Palacos® R+G with Vancomycin. BioMed Res Int. Article ID 4323518. 2018;2018:5.
66. Adelaziz H, von Förster G, Kuhn K-D, Gehrke T, Citak M. Minimum 5 years' follow-up after gentamicin- and clindamycin-loaded PMMA cement in total joint arthroplasty. J Med Microbiol. 2019;68:475-9.
67. McLaren AC, McLaren SG, Smeltzer M. Xylitol and glycine fillers increase permeability of PMMA to enhance elution of daptomycin. Clin Orthop Rel Res. 2006;451:25-28.
68. McLaren AC, Mclaren SG, Hickmon MK. Sucrose, xylitol and erythritol increase PMMA permeability for depot antibiotics. Clin Orthop Rel Res. 2007;461:60-63.
69. Virto MR, Frutos P, Torrado S, Frutos G. Gentamicin release from modified acrylic bone cements with lactose and hydroxypropylmethylcellulose. Biomater. 2003;24:79-87.
70. Frutos G, Pastor JY, Martinez N, Virto MR, Torrado S. Influence of lactose addition to gentamicin-loaded acrylic bone cement on the kinetics of release of the antibiotic and the cement properties. Acta Biomaterialia. 2010;6:804-11.
71. Matos AC, Ribeiro IAC, Guedes RC, Pinto R, Vaz MA, Goncalves LM, Almeida AJ, Bettencourt AF. Key-properties outlook of a levofloxacin-loaded acrylic bone cement with improved antibiotic delivery. Int J Pharmaceut. 2015;485:317-28.
72. Nugent M, McLaren A, Vernon B, McLemore R. Strength of antimicrobial bone cement decreases with increased poragen fraction. Clin Orthop Rel Res. 2010;468:2101-6.
73. Salehi A, Cox Parker A, Lewis G, Courtney HS, Haggard WO. A daptomycin-xylitol-loaded polymethylmethacrylate bone cement: How much xylitol should be used? Clin Orthop Rel Res. 2013;47:3149-57.
74. Slane JA, Vivano JF, Rose WE, Squire MW, Ploeg H-L. The influence of low concentrations of a water soluble poragen on the material properties, antibiotic release, and biofilm inhibition of an acrylic bone cement. Mater Sci Eng C. 2014;42:168-76.
75. Chang YH, Tai CL, Hsu HY, Hsieh PH, Lee MS, Ueng SWN. Liquid antibiotics in bone cement: An effective way to improve the efficiency of antibiotic release in antibiotic loaded bone cement. Bone Joint Res. 2014;3:246-51.
76. Tunney NM, Brady AJ, Buchanan F, Newe C, Dunne NJ. Incorporation of chitosan in acrylic bone cement: Effect on antibiotic release, bacterial film formation and mechanical properties. J Mater Sci: Mater Med. 2008;19:1609-15.
77. Wu K, Chen Y-C, Hsu Y-M, Chang C-H. Enhancing drug release from antibiotic-loaded bone cement using porogens. J Am Acad Orthop Surg. 2016;24:188-95.
78. Faber C, Hoogendoorn RJW, Lyaruu DM, Stallman HP, van Marle J, van Nieuw Amerongen A, et al. The effect of the antimicrobial peptide, Dhvar-5, on gentamicin release from a polymethyl methacrylate bone cement. Biomater. 2005;26:5717-26.
79. Shen S-C, Ng WK, Shi Z, Chia L, Neoh KG, Tan RBH. Mesoporous silica nanoparticle-functionalized poly(methyl methacrylate)-based bone cement for effective antibiotics delivery. J Mater Sci: Mater Med. 2011;2283-92.
80. Letchmanan K, Shen S-C, Ng WK, Kingshuk P, Shi Z, Wang W, et al. Mechanical properties and antibiotic release characteristics of poly(methyl methacrylate)-based bone cement formulated with mesoporous silica nanoparticles. J Mech Beh Biomed Mater. 2017;72:163-70.
81. Funk GA, Burkes JC, Cole KA, Rahaman MN, McIff TE. Antibiotic elution and mechanical strength of PMMA bone

cement loaded with borate bioactive glass. J Bone Joint Infec. 2018;3:187-96.
82. Perni S, Caserta S, Pasquino R, Jones SA, Prokopovich P. Prolonged antimicrobial activity of PMMA bone cement with embedded gentamicin-releasing silica nanocarriers. ACS Appl Bio Mater. 2019;2:1850-61.
83. Liu WC, Wong CT, Fong MK, Cheung WS, Kao RYT, Luk KDK, et al. Gentamicin-loaded strontium-containing hydroxyapatite bioactive bone cement — an efficient bioactive antibiotic drug delivery system. J Biomed Mater Res Part B: Appl Biomater. 2010;95B:397-406.
84. Tan H, Peng Z, Li Q, Xu X, Guo S, Tang T. The use of quaternised chitosan-loaded PMMA to inhibit biofilm formation and downregulate the virulence-associated gene expression of antibiotic-resistant staphylococcus. Biomater. 2012;33:365-77.
85. Ayre WN, Birchall JC, Evans SL, Denyer SP. A novel liposomal drug delivery system for PMMA bone cements. J Biomed Mater Res Part B: Appl Biomater. 2016;104B:1510-24.
86. Wei W, Abdullayev E, Hollister A, Mills D, Lvov YM. Clay nanotube/poly(methyl methacrylate) bone cement composites with sustained antibiotic release. Macromol Mater Eng. 2012;297:645-53.
87. Shen S-C, Ng WK, Dong Y-C, Ng J, Tan RBH. Nanostructured material formulated acrylic bone cements with enhanced drug release. Mater Sci Eng C. 2016;58:233-41.
88. Shen S-C, Letchmanan K, Chow PS, Tan RBH. Antibiotic elution and mechanical property of TiO_2 nanotubes functionalized PMMA-based bone cements. J Mech Beh Biomed Mater. 2019;91:91-98.
89. Miola M, Bistolfi A, Valsania MC, Bianco C, Fucale G, Verne E. Antibiotic-loaded acrylic bone cements: an *in vitro* study on the release mechanism and its efficacy. Mater Sci Eng C. 2013;33:3025-32.
90. Miller R, McLaren A, Leon C, McLemore R. Mixing method affects elution and strength of high-dose ALBC: A pilot study. Clin Orthop Rel Res. 2012;470:2677-83.
91. Shiramizu K, Lovric V, Leung A, Walsh WR. How do porosity-inducing techniques affect antibiotic elution from bone cement? An *in vitro* comparison between hydrogen peroxide and a mechanical mixer. J Orthopaed Traumatol. 2008;9:17-22.
92. Meyer J, Piller G, Spiegel CA, Hetzel S, Squire M. Vacuum-mixing significantly changes antibiotic elution characteristics of commercially-available antibiotic-impregnated bone cements. J Bone Joint Surg. 2011;93:2049-56.
93. Hendriks JGE, Ensing GT, van Horn JR, Lubbers J, van der Mei HC, Busscher HJ. Increased release of gentamicin from acrylic bone cements under influence of low-frequency ultrasound. J Control Release. 2003;92:369-74.
94. Yan SY, Cai X, Yan W, Dai X, Wu H. Continuous wave ultrasound enhances vancomycin release and antimicrobial efficacy of antibiotic-loaded acrylic bone cement *in vitro* and *in vivo*. J Biomed Mater Res Part B: Appl Biomater. 2005;82B:57-64.
95. Ensing GT, Hendriks JGE, Jongsma JE, van Horn JR, van der Mei HC, Busscher HJ. The influence of ultrasound on the release of gentamicin from antibiotic-loaded acrylic beads and bone cements. J Biomed Mater Res Part B: Appl Biomater. 2005;75B:1-5.
96. Ensing GT, Neut D, van Horn JR, van der Mei HC, Busscher HJ. The combination of ultrasound with antibiotics released from bone cement decreases the viability of planktonic and biofilm bacteria: An *in vitro* study with clinical strains. J Antimicrob Chemotherap. 2006;58:1287-90.
97. Cai X-Z, Yan S-G, Wu H-B, Dai X-S, Chen H-X, Yan R-J, et al. Effect of delayed pulse-wave ultrasound on local pharmokinetics and pharmodynamics of vancomycin-loaded acrylic bone cement *in vivo*. Antimicrob Agent Chemotherap. 2007;51:3199-204.
98. Cai X-Z, Chen X-C, Yan S-G, Ruan Z-R, Yan R-J, Ji K, et al. Intermittent watt-level ultrasonication facilitates vancomycin release from therapeutic acrylic bone cement. J Biomed Mater Res Part B: Appl Biomater. 2008;90B:11-17.
99. Lin T, Cai X-Z, Shi M-M, Ying Z-M, Hu B, Zhou C-H, Wang W, Shi Z-L, Yan S-G. *In vitro* and *in vivo* evaluation of vancomycin-loaded PMMA bone cement in combination with ultrasound and microbubbles-mediated ultrasound. BioMed Res Internat.; 2015. Article ID: 309739:(7).
100. Cai Y, Wang J, Liu X, Wang R, Xia L. A review of the combination therapy of low frequency ultrasound with antibiotics.

BioMed Res Internat; 2017;14. Article ID: 2317846.
101. Wendling AC, Mar DE, Burkes JC, McIff TE. Effect of ultrasound frequency and treatment duration on antibiotic elution from polymethylmethacrylate bone cement. Kansas J Med. 2019;12:45-9.
102. Masri BA, Duncan CP, Beauchamp CP, Paris NJ, Arntorp J. Effect of varying surface patterns on antibiotic elution from antibiotic-loaded bone cement. J Arthroplasty. 1995;10:453-9.
103. Arias PP, Tafin UF, Betrisey B, Vogt S, Trampuz A, Borens O. Activity of bone cement loaded with daptomycin alone or in combination with gentamicin or PEG600 against Staphylococcus epidermidis biofilms. Injury. 2015;46:249-53.
104. Wendling A, Mar D, Wischmeier N, Anderson D, McIff T. Combination of modified mixing technique and low frequency ultrasound to control the elution profile of vancomycin loaded acrylic bone cement. Bone Joint Res. 2016;5:26-32.
105. Amin TJ, Lamping JW, Hendricks KJ, McIff TE. Increasing the elution of vancomycin from high-dose antibiotic-loaded bone cement: a novel preparation technique. J Bone Joint Surg Am. 20114;94:1946-51.
106. Frutos P, Diez-Pena E, Frutos G, Barrales-Rienda JM. Release of gentamicin sulphate from a modified commercial bone cement. Effect of (2-hydroxyethyl methacrylate) comonomer and poly(N-vinyl-2-pyrrolidone) additive on release mechanism and kinetics. Biomater. 2002;23: 3787-97.
107. Shi Z, Neoh KG, Kang ET, Wang W. Antibacterial and mechanical properties of bone cement impregnated with chitosan nanoparticles. Biomater. 2006;27:2440-9.
108. Puska M, Yli-Urpo A, Vallittu P. Synthesis and characterization of polyamide of trans-4-hydroxy-L-proline used as porogen filler in acrylic bone cement. J Biomater Appl. 2005;19:287-301.
109. Yang B, Chen Y, Shi J. Mesoporous silica/organosilica nanoparticles: Synthesis, biological effect and biomedical application. Mater Sci Eng: R: Reports. 2019;137:66-105.
110. Hai T, Wan X, Yu D-G, Wang K, Yang Y, Liu Z-P. Electrospun lipid-coated medicated nanocomposites for an improved drug sustained-release profile. Mater Design. 2019;162:70-79.
111. Peng K-T, Chiang Y-C, Huang T-Y, Chen P-C, Chang P-J, Lee C-W. Curcumin nanoparticles are a promising anti-bacterial and anti-inflammatory agent for treating periprosthetic joint infections. Int J Nanomed. 2019;14:469-81.
112. Nien Y-H, Lin S-w, Hsu Y-N. Preparation and characterization of acrylic bone cement with high drug release. Mater Sci Eng C. 2013;33:974-8.
113. Cyphert EL, Learn GD, Hurley SK, Lu C-y, von Recum HA. An additive to PMMA bone cement enables post-implantation drug refilling, broadens range of compatible antibiotics and prolongs antimicrobial therapy. Adv Healthcare Mater. 2018;7:1800812(13).
114. Edwards CR, Gorman SP, Jones DS, McCoy CP. Antibiotic release from a novel bone cement. Trans 19th Eur Conf Biomater, Sorrento, Italy; 2005.
115. Cyphert EL, Wallat JD, Pokorski JK, von Recum HA. Erythromycin modification that improves its acidic stability while optimizing it for local drug delivery. Antibiotics. 2017;6(11):15.
DOI: 10.3390/antibiotics6020011
116. Bormann N, Schwabe P, Smith MD, Wildemann B. Analysis of parameters influencing the release of antibiotics mixed with bone grafting material using a reliable mixing procedure. Bone. 2014;59:162-72.
117. Chelladurai SJS, Murugan K, Ray AP, Upadhyaya M, Narasimharaj V, Gnanasekaran S. Optimization of process parameters using response surface methodology: a review. Mater Today: Proc; 2020.
Available:https://doi.org/10.1016/j.matpr.2020.06.466
118. Antony SJ, Parikh MS, Soto-Ruiz E, Cameron C, Mody R. Extended-spectrum beta-lactamase infections in orthopedic-related devices and prosthetic joints. Orthopedics. 2016;39(4):e668-e678.
119. Bolia IK, Tsiodras S, Chloros GD, Kaspiris A, Sarlikiotis T, Savvidou OD, et al. A review of novel antibiotic regimens for the treatment of orthopedic infections. Orthopaedics. 2018;41:323-8.
120. Licitra CM, Crespo A, Licitra D, Wallis-Crespo MC. Daptomycin for the treatment of osteomyelitis and prosthetic joint infection: Retrospective analysis of efficacy and safety in an outpatient infusion center. Internet J Infect Dis. 2010;9(2):9.
DOI: 10.5580/215c

121. Joseph C, Robineau O, Titecat M, Putman S, Blondiaux N, Loiez C. Daptomycin versus vancomycin as post-operative empirical antibiotic treatment for prosthetic joint infections: A case-control study. J Bone Joint Infect. 2019;4:72-5.
122. Huang V, Cheung CM, Kaatz GW, Rybak MJ. Evaluation of dalbavancin, tigecycline, minocycline, tetracycline, teicoplanin and vancomycin against community-associated and multidrug-resistant hospital-associated methicillin-resistant *Staphylococcus aureus*. Int J Antimicrob Agent. 2010;35: 25-9.
123. Kaushal R, Hassoun A. Successful treatment of methicillin-resistant *Staphylococcus epidermidis* prosthetic joint infection with telavancin. J Antimicrob Chemotherap. 2012;67:2052-3.
124. Macone AB, Caruso BK, Leahy RG, Donatelli J, Weir S, Draper MP, Tanaka SK, Levy SB. *In vitro* and *in vivo* antibacterial activities of omadacycline, a novel aminomethylcycline. Antimicrob Agent Chemotherap. 2014;58:1127-35.
125. Rodvold KA, Burgos RM, Tan X, Pai MP. Omadacycline: A review of the clinical pharmacokinetics and pharmacodynamics. Clin Pharmokinetics. 2020;59:409-25.
126. Zhanel GG, Esquivel J, Zelenitsky S, Lawrence CK, Adam HJ, Golden A, et al. Omadacycline: A novel oral and intravenous aminomethylcycline antibiotic agent. Drugs. 2020;80:285-313.
127. Duployez C, Wallet F, Migaud H, Senneville E, Loiez C. Ceftobiprole: a potential empirical post-operative monotherapy in prosthetic joint infections. Ann Clin Microbiol Antimicrob. 2020;19:9.
Available:https://doi.org/10.1186/s12941-020-00351-5
128. Smith PA, Koehler MFT, Girgis HS, Yan D, Chen Y, Chen Y, et al. Optimized arylomycins are a new class of gram-negative antibiotics. Nature. 2018;561:189-94.
129. Haseeb A, Singh VA, The CSJ, Loke MF. Addition of ceftaroline fosamil or vancomycin to PMMA; an *in vitro* comparison of biomechanical properties and anti-MRSA efficacy. J Orthop Surg. 2019;27:1-9.
130. Zborníková E, Gallo J, Večeřová R, Bogdanová K, Kolář M, Vítovská D, et al. Evaluation of second-generation lipophosphonoxins as antimicrobial additives in bone cement. ACS Omega. 2020;5:3165-71.
131. Fedorowicz J, Saczewski J. Modifications of quinolones and fluoroquinolones: Hybrid compounds and dual-action molecules. Monatsh Chem. 2018;149: 1199-245.
132. Bakdach D, Elajez R. Trimethoprim-sulfamethoxazole: New lessons on an old antimicrobial; a retrospective analysis. J Pharm Health Services Res. 2020;1:269-74.
133. Deb S, Doiron R, DiSilvio L, Punyani S, Singh H. PMMA bone cement containing a quaternary amine comonomer with potential antibacterial properties. J Biomed Mater Res Part B: Appl Biomater. 2008;85B:130-9.
134. Opalko M, Bosebeck H, Vogt S. Properties and clinical application safety of antibiotic loaded bone cement in kyphoplasty. J Orthoped Surg and Res. 2019;14:238(9).
135. Shoji MM, Chen AF. Biofilms in periprosthetic joint infections: A review of diagnostic modalities, current treatments, and future directions. J. Knee Surg. 2020;33:119-31.
136. Mahamuni-Badiger PP, Patil PM, Badiger MV, Patel PR, Thorat-Gadgil BS, Pandit A, et al. Biofilm formation to inhibition: Role of zinc oxide-based nanoparticles. Mater Sci Eng C; 2019.
Available:https://doi.org/10.1016/j.msec.2019.110319
137. Mooney JA, Pridgen EM, Manasherob R, Suh G, Blackwell HE, Barron AE, et al. Periprosthetic bacterial biofilm and quorum sensing. J Orthop Surg. 2018;36:2331-9.
138. Paluch E, Rewak-Soroczynska J, Jedrusik I, Mazurkiewicz E, Jermakow K. Prevention of biofilm formation by quorum quenching. Appl Microbiol Biotech. 2020;104:1871-81.
139. Carli AV, Bhimani S, Yang X, Shirley MB, de Mesy Bentley KL, Ross FP, et al. Quantification of peri-implant bacterial load and in vivo biofilm formation in an innovative, clinically representative mouse model of periprosthetic joint infection. J Bone Joint Surg Am. 2017;99:e25(1-8).
140. Miller RJ, Thompson JM, Zheng J, Marchitto MC, Archer NK, Pinsker BL, et

al. *In vivo* bioluminescence imaging in a rabbit model of orthopaedic implant-associated infection to monitor efficacy of an antibiotic-releasing coating. J Bone Joint Surg Am. 2019;101:e12(1-11).

141. Ferrell Z, Grainger DW, Sinclair KD. Antibiotic-eluting resorbable bone-void filler evaluated in a large animal infection prevention model. Eur Cell Mater. 2019;37:265-76.

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