Progress of antibiotic-loaded bone cement in joint arthroplasty

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Abstract

Bone cement, consisting of polymethyl methacrylate, is a bioinert material used for prothesis fixation in joint arthroplasty. To treat orthopedic infections, such as periprosthetic joint infection, antibiotic-loaded bone cement (ALBC) was introduced into clinical practice. Recent studies have revealed the limitations of the antibacterial effect of ALBC. Moreover, with the increase in high infection risk patients and highly resistant microbes, more researches and modification of ALBC are required. This paper reviewed latest findings about ALBC for most popular and destructive pathogens, summarized the influence of antibiotic kind, drug dosage, application method, and environment towards characteristic of ALBC. Subsequently, new cement additives and clinical applications of ALBC in joint arthroplasty were also discussed.

Keywords: Polymethyl methacrylate; Bone cement; Antibiotic; Modification

Introduction

Periprosthetic joint infection (PJI) is a catastrophic adverse complication of joint arthroplasty. Both local and systemic antibiotic delivery are required for treatment of this refractory infection.[1] Bone cement, a polymer named polymethyl methacrylate (PMMA), has been used for prothesis fixation of cemented joint arthroplasty since 1960.[2] The cement fills gaps between the joint prosthesis and bone but has no antimicrobial capacity, and thus, the concept of antibiotic-loaded bone cement (ALBC) was introduced in 1970 by Buchholz and Engelbrecht to address this limitation.[3] Although ALBC has been used for decades, recent studies have cast a shadow on its actual effectiveness. A retrospective study showed no decrease in infection rates with ALBC in primary total knee arthroplasty (TKA),[4] while a similar study found that ALBC was associated with a significantly lower rate of revision caused by infection.[5] Meta-analysis indicated that ALBC might be related to an increase in PJI risk in the early post-operative period of TKA, and the risk was lower in ALBC total hip arthroplasty (THA).[6,7] With the aging of the population, more patients receiving joint arthroplasty have high infection risk factors, such as obesity and diabetes.[8] As a result of natural selection, highly resistant microbes, such as methicillin-resistant *Staphylococcus aureus* (MRSA), began to appear in PJI.[9] All of the above factors call for a modified, more powerful ALBC. Based on associated papers in recent years, the purpose of this review was to introduce the latest progress in the antibiotic capacity, drug-elution properties, and mechanical performance of ALBC. New ideas for clinical application of ALBC will also be discussed.

Antimicrobial Capacities of Antibiotics in ALBC

Anti-Staphylococcus agents

According to a retrospective study based on 278 monomicrobial PJI cases from 2003 to 2017, the most frequent pathogens were *Staphylococcus epidermidis* (35%) and *S. aureus* (21%).[10] So antibiotics against Staphylococcus are the most urgent need. Although simulation on dissolvable alginate beads still proved gentamycin's eradication ability towards Staphylococcus biofilm, this common choice in ALBC was being challenged by drug resistant microbes.[11] An *in vitro* test of 93 Staphylococcus species obtained from PJI patients found a resistant percentage of 66%.[12] Combination with other antibiotics was a possible choice. In double antibiotic beads containing gentamycin and daptomycin, vancomycin or ciprofloxacin, the minimal biofilm eradication concentration (MBEC) decreased, indicating enhancement of bioactivity. In contrast, the MBEC decreased when gentamycin was applied with rifampin, clindamycin, or linezolid.[11] In another test, it was found that 40 g PMMA with 1.5 g daptomycin and 0.5 g gentamycin was the optimal choice for treatment of PJI caused by gram-

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positive bacteria.[13] Changing of drug could be another ideal choice. As another classical antibiotic choice in ALBC, vancomycin was still effective towards some updated pathogen. During an *in vitro* comparative research towards MRSA, vancomycin group maintained the inhibition zone for 4 weeks.[14] When compensated with vancomycin, daptomycin exhibited better resistance towards *S. aureus* in ALBC than vancomycin-linezolid group.[15] Teicoplanin, an alternative for vancomycin, also scored an eradication rate of 96% (24/25) in a cohort study mainly composed by Staphylococcus PJIs.[16] There are still other candidates. The combination of 4 g ceftazidime and 40 g PMMA showed antimicrobial effect to Staphylococcus in laboratory.[17] When compensated with 3 wt% (weight percent) of ceftaroline (1.2 g drug in 40 g cement powder), a successor of ceftazidime, extraneous ALBC elution fluid can keep the drug dose above the MIC for MRSA for 6 weeks.[18]

Anti-fungi agents

Fungi are rare but intractable pathogens of PJI. Brown *et al*[19] found 31 fungal PJIs from 3525 PJI cases treated in their institution from 1996 to 2014. The survivorship of reinfection in 2 years was only 38% in hips and 76% in knees. Because of the inability of normal antibiotics, antifungal agent became a unique member of ALBC family. Plain amphotericin B showed strong mechanical performance when added in ALBC, but the drug elution was too low for clinical use.[20] The elution characteristics were significantly improved when the ALBC was made of liposomal amphotericin B. Plain amphotericin with the help of a sodium deoxycholate or N-methyl-D-glucamine/palmitate carrier led to the same outcome. Both of the modified ALBCs showed resistance against *Candida spp*., with an insignificant influence on mechanical performance.[21] Econazole and fluconazole also showed *in vitro* bioactivity towards *Candida spp*., while mechanical performance was also insufficient for weight-bearing use.[17,22]

Antibiotic Elution Kinetics of ALBC

Based on a systematic review of the current literature, there is sufficient elution of antibiotics after ALBC spacer implantation and at spacer removal.[23] The exact mechanism of antibiotic elution from ALBC remains uncertain.[24] Based on *in vitro* elution measurements, there is a hypothesis describing it as a bi-phasic process.[15,25,26] Antibiotics are usually premixed with the cement powder. After mixing with monomer liquid, a condensed cement layer forms with uniform distribution of the antibiotic particles. Particles distributed on the surface directly dissolve in body fluid, resulting in a short "burst elution" phase. Many more particles are present inside the matrix but have difficulty penetrating the hardened PMMA structure and thus are released in a slower "continuous elution" phase. The following factors may influence elution kinetics.

(1) Kind of antibiotic: It is believed that total antibiotic release may be related to the chemical nature of the antibiotic, such as molecular size, electrical charge, and hydrophobic/hydrophilic character. When added at the same dose and incubated in the same *in vitro* environment, the antibiotics are released in the burst phase, and total elution ranks in the order of vancomycin < linezolid < daptomycin. Synergism between daptomycin and vancomycin can enhance the burst and total elution.[15]*In vitro* tests found a synergistic effect with combinations of different types of drugs. For vancomycin, tobramycin, and gentamycin, the more antibiotic types that were added into PMMA, the higher the elution rate and amount were.[27]

(2) Dosage of antibiotic: Higher drug dosage in ALBC can promote drug elution. A significant enhancement of elution velocity and total amount were seen in vancomycin-loaded cement when the drug dose increased from 1 g per 40 g PMMA to 4 g.[28] The similar phenomenon was observed in multi-drug ALBCs. In an *in vitro* test, the total release of each kind of drugs increased in both ciprofloxacin/meropenem and ciprofloxacin/ceftazidime ALBC.[26] Another study about vancomycin and tobramycin combination showed that incorporation of 1 g vancomycin resulted in an approximately 38% increase of tobramycin elution.[29] However, too much antibiotic could worse mechanical performance of cement and limit its application, which would be discussed below.

(3) Methods of mixing: Various preparations may affect the elution of antibiotics from ALBC. In Frew's experiments,[30] vancomycin-loaded ALBC was prepared using three procedures: "commercially prepared" (by the manufacturer), "manufacturer mixed" (homemade in accordance with the manufacturer's instructions), and "homemade" (all the drugs added into the cement powder at once). Then, the three cement groups were mixed and tested. *In vitro* experiments recorded the highest elution in the "homemade" group, likely the result of an increase in the porosity caused by clumping of vancomycin embedded in the cement. A long mixing time (mixing 90 s, doughing 30 s) significantly enhanced drug elution compared with a short mixing time (mixing 30 s, doughing 90 s) in gentamycin-loaded ALBC, and an obvious increase in total drug elution of 7 days was detected in the vacuum mixing group.[31]

(4) Environment temperature: Lower temperature extends the polymerization reaction, causing an increase of air pore collected in cement matrix. So, it will be easier for antibiotic particles to penetrate the cement. Tai *et al*[32] found a higher proportion of vancomycin release from ALBC cured at 0°C than samples cured at 50°C.[32] A relatively higher temperature could also benefit drug elution, Sundblad *et al*[33] reported increase of drug elution in tobramycin/vancomycin loaded ALBC at both high (37°C) and low (8°C) polymerization temperature than room temperature.[33] Frozen storage affected drug elution of ALBC. Compared with ALBC spacers stored in room temperature, the frozen stored sample showed no effect in drug elution and antimicrobial ability.[34] On the contrary, low temperature was an optical environment for the preservation of prefabricated ALBC spacer. The degradation of drug was less than 1% after 3-month' storage at −80°C in such spacer.[35]

(5) Thermogenesis of polymerization: The polymerization of PMMA is an exothermic reaction,[36] and thus, it is believed that only "heat-stable" antibiotics could tolerate the partial high temperature caused by polymerization. An *in vitro* test for 38 frequently used antibiotic agents found aminoglycoside, glycopeptide, tetracycline, and quinolone as "heat-stable" and β-lactam as "heat-sensitive."[37] Carli *et al*[38] conducted thorough research in this field. They measured temperatures of PMMA cured inside silicone molds of the distal femur and proximal tibia and then incubated vancomycin (representing "heat-stable") and ceftazidime (representing "heat-sensitive") in accordance with the temperature curves collected from molds. Finally, the MICs were tested in both groups. The results indicated that the MIC of ceftazidime increased by only two-fold and the bioactivity was reserved. Whether more "heat-sensitive" antibiotics could be utilized clinically should be further discussed.

(6) Ultrasound sonication: Antibiotic remaining in cement can be released during sonication.[39] Ultrasound sonication is a common way to promote solute dissolution in chemistry. A 6-week *in vitro* simulation test was performed with ALBC spacers produced with formulations used in clinical practice. The sonication was performed at 2, 4, and 6 weeks for 5 min at a frequency of 40 kHz. Antibiotic concentrations were determined every week. Compared with the control group, with sonication, there was an increase in elution of the antibiotics.[25] Another study using different sonication times and frequencies demonstrated that a lower frequency and longer sonication time could benefit antibiotic elution, with a clinically acceptable mechanical performance.[40]

Mechanical Performance of ALBC

Chemical bonds are formed during PMMA polymerization, determining the mechanical performance. However, antibiotic molecules do not generally take part in this reaction. For instance, in econazole-loaded ALBC, no compound except PMMA and econazole was detected via magnetic resonance spectroscopy.[22] Due to the absence of strengthened bonds, antibiotics diminish the internal strength of cement, thus decreasing mechanical performance. *In vitro* tests showed a significant decline in the yield strength of ALBCs loaded with cefazolin, cefuroxime, ceftazidime, meropenem, vancomycin, gentamycin, and clindamycin at ratios used in clinical practice. Among them, gentamycin and clindamycin led to substantial decreases, resulting in failure to meet the threshold for weight-bearing use.[41] With drug particles gradually leaving the cement, the remaining gaps become weak points in the structure and lead to initiation of cracks. After 2 weeks of incubation at 37°C in natural saline, the impact strength of gentamycin/vancomycin-loaded ALBC decreased by nearly 40%.[42] An *in vitro* fatigue test to investigate gentamycin-loaded ALBC and plain PMMA found a difference in their fatigue crack propagation. Cracks began to propagate in ALBC specimens before its failure, showing slow growth with fatigue cycles. In contrast, cracks either did not appear to propagate or propagated extremely slowly in plain specimens until close to failure, ending with rapid crack propagation.[43]

The following factors may influence mechanical performance.

(1) Kind of antibiotic: Differences in chemical nature among various antibiotics influence changes in mechanical performances. The yield strength of 5wt% cefazolin-loaded ALBC was 85.43 MPa compared with 92.30 MPa in 5wt% ceftazidime-loaded cement.[41] It is noteworthy that antibiotic molecules are radical scavengers, which inhibit polymerization. The most prominent example is hydroquinone in the rifampin structure. When rifampin is added, PMMA showed a serious reduction in compressive strength, with a prolonged setting time, decreased exothermic output in the curing process, and an increase in toxicity due to MMA monomer release, indicating incomplete polymerization.[44]

(2) Dosage of antibiotic: As a destroyer of cement structure, the more antibiotic molecules that are embedded, the worse the mechanical performance of ALBC is. An *in vitro* test of vancomycin showed a negative correlation between bending strength and antibiotic dose.[45] In tobramycin, gentamycin, and vancomycin systems, an increase in both type and quantity significantly decreased the compressive and bending strength.[27] Another study using tobramycin and vancomycin demonstrated the same phenomenon, along with a decrease in cement porosity, confirming degradation of the structure.[29]

(3) Physical state of the drug: In general, antibiotics are added into PMMA powder in the solid state, but some are added in the liquid state. The impact strength was reduced under the weight-bearing threshold with a mixture of 240 mg gentamycin solution and 40 g plain PMMA,[41] while the strength was above the threshold with a mixture of 1 g gentamycin powder and 40 g PMMA.[42]

ALBC Modification Additives

Porogen

The inclusion of porogens to generate open porosity is considered an effective way to improve the elution behavior of cement. Carboxymethylcellulose successfully enhanced the porosity and bioactivity of econazole-loaded ALBC. Unfortunately, the compression strength was significantly decreased under the threshold necessary for weight-bearing applications.[22] Hollow titanium dioxide nanotubes are also in this family and showed the same effect in gentamycin-loaded cement, retaining sufficient strength for use at weight-bearing sites.[46]

Sustained drug release systems

Sustained drug release systems mediate slow but continuous drug elution via a changing elution profile. Daptomycin-loaded cement with poly D, L-lactic-co-glycolic acid copolymer (PLGA) exhibited altered elution profiles. In the

initial stage, a moderate burst (close to 10%) was still observed in the first 3 h. Then, a progressive elution in the next 35 days was observed, followed by a sudden elution increase, which was prolonged in the following 20 days. This change might be ascribed to biodegradation of the inner PLGA microparticles. Overall, PLGA obviously enhanced release of the drug.[15,47] Silicon dioxide nanoparticles can also act as drug carriers. *In vitro* experiments investigating this additive showed an increase in the drug release rate, total elution, and antimicrobial activity, with no significant changes in mechanical performance or biocompatibility.[48-50] Calcium polyphosphate, an analog of bone tissue, extended the elution time, with a significant decrease in the initial elution and maintenance of bioactivity.[51] When coated on PMMA in combination with alginate-chitosan nanoparticles, vancomycin prolonged drug elution for 60 days.[52] Rifampin-filled β-cyclodextrin particles achieved a longer effect time but no longer met the weight-bearing standard.[53] To modify the characteristics, microcapsules of rifampicin containing alginate, polyhydroxybutyratehydroxyvalerate, ethyl cellulose and stearic acid were introduced. They relieved the mechanical antimicrobial activity of ALBC and improved the compression strength.[54] Personalized drug release systems are designed for particular conditions. According to Ikeda design, a vancomycin-loaded calcium phosphate cement core was embedded in a PMMA shell with prefabricated holes. *In vitro* experiments verified its superiority in antibiotic elution time and bioactivity compared with conventional ALBC spacers.[55]

Inorganic antimicrobial agents

The history of inorganic antimicrobial agent was even longer than antibiotics. Some of them were still ideal candidates for cement additive. Silver is the most famous antibacterial metal. The development of nanotechnology made it possible to apply silver into PMMA without severe damage of physical properties. When incorporated with silver nanoparticles, this complex cement demonstrated substantially no difference in mechanical and material properties. In test against *S. epidermidis*, the cement showed significant ability of biofilm eradication.[56] NanoSilver, PMMA loaded with metallic silver nanoparticles, showed high-antibacterial activity against MRSA and methicillin-resistant *S. epidermidis* with no significant cytotoxicity towards osteoblast.[57] Silver nanoparticles capped with tiopronin showed similar characters when encapsulated in bone cement.[58] Copper is another type of antibacterial material. Copper-doped bioactive glass powder appeared well distribution in PMMA. The copper-doped cement showed good bioactivity, released a significant amount of copper in simulated body fluid.[59]

Although many researches illustrated a promising future of inorganic antibacterial material, there were also some studies reporting negative results. During *in vivo* tests on *S. aureus* contaminated rabbit femur model, bone cement with 0.6% or 1% silver did not show better bioactivity than tobramycin-loaded ALBC, because silver could only kill pathogens on cement surface and was useless for pathogens in surrounding tissues.[60] The toxicity of heavy metal element could be another potential danger for metallic antimicrobial agents like copper.

Organic antimicrobial agents

Despite antibiotics, some organic antimicrobial materials were also suitable for bone cement. Quaternary ammonium monomers with N-alkyl chain lengths varying from 6 to 18, namely, MEIM-x ($x = 6–18$), have shown significant antibacterial activity. Under laboratory conditions, $x \geq 10$ was recognized as a prerequisite for adequate bioactivity, and at that time, 2wt% was enough for bioactivity. This compound inhibits polymerization and endures through the hardening time. However, a minor effect on mechanical performance and biocompatibility was seen in tests.[61] An antimicrobial quaternary ammonium dendrimer containing iodine was found to have an *in vitro* antimicrobial effect towards gram-positive bacteria within 30 days at a dose of 10%.[62] When added in osteomyelitis models generated through damage to the femoral head, bone cement with short, linear, α-helical antimicrobial peptides added showed inhibitory activity against biofilm formation.[63] The elution fluid of ozonized sunflower oil-loaded PMMA collected in the first 24 h inhibited the growth of *Pseudomonas aeruginosa* for 20 h.[64] Nature organics, such as blood and synovial fluid, were also applied into bone cement. *In vitro* tests showed inhibition of drug release from cement beads coated with heparin coagulative blood or synovial fluid, but the total release was not influenced.[65]

Clinical Applications of ALBC

Multidrug ALBC

Application of multiple antibiotics broadens the antimicrobial spectrum but leads to defects in mechanical performance, and thus, this type of ALBC is usually used as beads or spacers. Hsu *et al*[66] produced bone cement specimens loaded with 4 g of either vancomycin or teicoplanin and 4 g of ceftazidime, imipenem or aztreonam and then measured the *in vitro* elution characteristics and antibacterial capacities of the specimens. The most effective combination was implanted into eight chronic PJI patients to assess *in vivo* drug dose and bioactivity. Vancomycin and ceftazidime, the elected best choice, exhibited good capacities in both the laboratory and clinical practice.[66] In another prospective study investigating gentamycin-clindamycin loaded cement, 32 subjects were divided into two groups: PJI patients underwent a one-stage exchange, and aseptic loosening patients underwent revision or primary arthroplasty but were considered at high risk for infection. At the end of a 5-year follow-up, no reinfection was found.[67] A retrospective study on daptomycin- and tobramycin-loaded cement reported a cure rate of 92% (11/12) for patients who had any MRSA infection during the evaluation period compared with 62% (13/21) for patients with MSSA. The difference might stem from systemic use of antibiotics that could not be balanced in this type of trial. An improvement in daptomycin release in joint fluid was also seen with the presence of tobramycin.[68]

ALBC spacers

ALBC spacers play an important role in revision of PJI. As mentioned above, antibiotics primarily decrease the mechanical performance of cement, which could lead to mechanical failures, such as spacer dislocation, spacer fracture, and femoral fracture. According to a retrospective study, 45% (14/31) of patients suffered at least one spacer-related mechanical complication in the interim period, and patients who had mechanical complications were younger than those without mechanical complications. Chronic infection and utilization of the posterior approach were risk factors for the development of spacer-related complications according to univariate analysis.[69] Various methods have been applied to improve the performance of spacers. Commercial gentamycin-loaded cement spacers fixed with vancomycin-gentamycin ALBC were tried in revision TKA in one cohort study.[70] Within a mean follow-up time of 74.1 months, the average time from spacer implantation to prosthesis reimplantation was 9.1 months (range of 3–27 months). The mean American Knee Society Score improved from 68.4 pre-operatively (range of 34–108) to 112.7 at the final follow-up examination (range of 49–180). The average range of motion improved from 40.1 degrees (range of 6–90 degrees) to 79.3 degrees (range of 45–125 degrees). There are some studies on personal spacer designs. Stainless intramedullary rods were implanted to enforce spacers in infected TKA cases with extensive bone loss. The rate of success for the first reimplantation was 77% (75/97). Pathogen cultures of the spacer rods were positive in two cases, but none of them failed.[71] A custom-made spacer template was created by applying dental silicone on the surface of a bipolar femoral prothesis with the proper size, and then, ALBC was used to fill the template to complete the spacer. No recurrence was detected among patients receiving the spacer.[72] Another retrospective study comparing the outcomes of commercial spacers, hand-made spacers and a hand-made tibial spacer with reimplantation of a sterile femoral component in infectious revisions of TKA resulted in no significant differences among the three groups, and the lowest financial cost was recorded for the hand-made spacer group.[73] A new spacer technique called "ENDO technique" was introduced by Lausmann *et al*[74] The technique involves a dual mobility liner and a downsized stainless cemented straight stem fixed with ALBC in a "deliberately poor cementing technique" (covering only the proximal 4/5 of the stem). Data from a retrospective study of 30 cases showed a mean spacer duration time of 53.6 days (ranging from 14 to 288 days). The incidence of spacer-related complications was 6.7% (2/30), and the Harris hip score was significantly improved from 34.0 (ranging from 3 to 62) to 48.1 (ranging from 11 to 73) ($P = 0.0008$).

Partial revision

Partial revision simplifies some steps of the conventional two-stage revision and retains the original uninfected prosthesis components; thus, more bone resource can be restored with less time of operation. There are two surgical techniques for partial revision.

The first is retainment of an ALBC spacer as a prosthesis in a one-stage operation. A simulation test demonstrated the wear-resistance of an ALBC spacer after a cyclic test on a knee wear simulator for 500,000 walking cycles.[75] Examinations of prolonged implanted vancomycin-PMMA intramedullary rods (117 days) and beads (210 days) found them effective for *P. aeruginosa* and *S. aureus*.[76] The ALBC spacer was found to be an optional successor for an infected prosthesis. Beaupre *et al*[77] measured the health-related quality of life (HRQL) of patients who received a revision THA. It was found that improvements in the HRQL appeared 3 to 6 months after spacer implantation. Patients desiring better motion capacity (7 of 22 patients) received a second-stage operation after 24 months, while others kept the spacer. A 24-month follow-up found no significant difference between the two groups ($P > 0.32$), and thus, one-stage revision using ALBC showed the same effect in low-activity need patients. In Lee's retrospective study,[78] the eradication rate for one-stage revision (92.3%) was slightly lower than that for the two-stage revision (94.9%). Similar differences were found in Visual Analogue Score (VAS) and Harris scores. However, motion abilities showed no difference between the two groups. Researchers concluded that a two-stage revision was still a standard option but a one-stage revision is suitable for patients of advanced age or who were unable to receive the standard revision.

The second is preservation of some prosthesis components. Chen *et al*[47] conducted a prospective study of partial revision in chronic PJI patients of biotype THA. During the first surgical stage, they retained the stem or cup that was unable to be removed and replaced others with ALBC spacers. The second stage was conducted when infection was controlled. At a mean follow-up time of 5 years, the infection cure rate was 81.3% (13/16), and two of the remaining three patients received further prosthesis-removing surgery due to detection of high-virulence organisms. This type of operation is only recommended for those who are not immunocompromised and are infected with a low-virulence organism.[47] Crawford *et al*[79] applied hand-made or commercial ALBC acetabular spacers in patients with chronic PJI and failed to remove the femoral component. A retrospective review reported that 95% (39/41) of patients received implantation of a new acetabular component in an average period of 9.2 weeks, and two cases received a two-stage revision. If the failure was defined as infection recurrence, Kaplan-Meier survival was 77% at a mean follow-up time of 5.5 years.

Although partial revision can benefit subjects with severe complications (ie, advanced aged or osteoporosis) by minimizing surgical trauma and accelerating post-operative recovery, special attention should be paid during the treatment. (1) ALBC can never take the place of systemic antimicrobial treatment. Animal experiments confirmed the effect of ALBC only within the joint space,[80] and the placement of a spacer without the auxiliary step could not eradicate pathogens in a murine osteomyelitis model.[81] A prospective study in humans measured a serum drug dose

lower than the effective threshold in the first 6 months after implantation of vancomycin-loaded ALBC, regardless of the prevention or treatment dose used.[82] Based on these discoveries, it is necessary for ALBC to be applied in conjunction with systemic antibiotic treatment. (2) The risk of hepatic or renal defection should be considered. Edelstein *et al* conducted prospective studies in primary revisions using ALBC spacers containing vancomycin, gentamycin, or tobramycin. The results suggested a detectable serum dose of drugs 8 weeks after implantation. The risk factors for an increased vancomycin dose include diabetes, high blood urea nitrogen, a high amount of ALBC, and systemic drug delivery. In another group of 37 patients, during the 8 weeks after ALBC spacer implantation, ten patients (27%) fitted risk, injury, failure, loss, end-stage kidney disease (RIFLE) criteria for kidney injury, and two patients (5%) fitted the criteria for kidney failure.[83,84]

In conclusion, the application of antibiotics in bone cement has been broadly regarded as a simple and economic cure for PJI and other orthopedic infections. As a classical filler and fixture, ALBC is continuously being used for new applications. Meropenem or ceftazidime ALBCs have been used to treat melioidosis of the musculoskeletal system.[85] Multi-antibiotic-loaded cement played an essential role in application of a total femur spacer and filling.[86,87] New bone defect filling and cement fixation techniques are still being designed.[88-91] Some questions have developed in the process and remain unsolved. For instance, one prospective study found an increase in immunological factors (ie, soluble interleukin-6 [SIL-6] and C-reactive protein [CRP]) in gentamycin-loaded cement implant patients, which may indicate that unknown immunomodulatory pathways are altered by ALBC.[92] In response to the increasing achievements in medical and material science, further researches should be conducted to investigate the antimicrobial bioactivity, pharmaceutical elution, and mechanical enhancement activity of ALBC. Therefore, more options will be provided to surgeons, which will contribute to the lifespan of joint prostheses and improve post-operative quality of life.

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Conflicts of interest

None.

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