PMMA BONE CEMENT: WHAT IS THE ROLE OF LOCAL ANTIBIOTICS?

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INTRODUCTION

Recently, PMMA bone cement has celebrated the 50th anniversary of its clinical use. During this time, surgeons have appreciated the product’s unique mechanical properties for the fixation of implants into joints and weak bone structures leading to the long-term success of joint prostheses after both primary and revision surgery.

Due to its primary fixation purpose antibiotic loaded bone cement (ALBC) has been classified as a class III medical device according to the CE standard for the fixation of primary or revision implants. Because of the high initial release of local antibiotics into the joint cavity, ALBC has also been successfully used for decades for prophylactic reasons aimed at prevention of bacterial colonisation of the prosthesis. Gentamicin is generally chosen because of the controlled diffusion out of the cement mantle and the broad spectrum bactericidal effect against a wide variety of gram-positive or gram-negative bacterial contaminants. However, in times of increasing bacterial resistance, empiric use of antibiotics (AB) has become a controversial discussion point, and it appears justified to ask the following question: Does the addition of one or several AB to bone cement really add benefit to the common practice of systemic AB prophylaxis and to AB treatment protocols in cases of already established prosthetic joint infections?

Fortunately, prosthetic joint infection (PJI) is a rare pathology, but treatment of the infection is often complex and increasingly difficult in view of the growing prevalence of difficult-to-treat pathogens and higher patient risk factors. Apart from the surgical challenge and the impact on the patient, PJI treatment involves high costs which are often more than twice the cost of an aseptic joint replacement.

European registries have shown longer survival data of cemented arthroplasty, particularly when looking at the endpoint revisions due to infection [1] (see Figure 1, 2). It has to be pointed out, however, that important parameters, such as patient-, pathogen- and treatment-related risk factors can rarely be compared across the different groups. Since larger randomised controlled clinical trials with ALBC involving thousands of patients with long clinical observation periods have not been performed, the clinical evidence regarding its efficacy and safety is still limited and is largely derived from the analysis of registries or retrospective single-centre studies.
To circumvent the problem of a low statistical power typically associated with clinical studies of rare pathologies, so called surrogate markers and surrogate endpoints are often used to evaluate the efficacy of a particular treatment concept. Therefore, in case of ALBC it has been proposed to evaluate their efficacy as local AB carrier in addition to its fixation quality by assessing their potential to inhibit biofilm formation on the implant surface. To provide an overview and to deepen the knowledge of this concept, this review focuses in the following on the role and clinical evidences of ALBC in orthopaedic surgery.

**A MEDICAL BLOCKBUSTER FOR A LONG TIME**

Chemically, PMMA cement is acrylic plexiglas made of PolyMethylMethAcrylate (= PMMA). When this material was used in the 1940s in surgery for the first time, it was intended to fill gaps in the skull. Many clinical investigations have proven the non-toxicity of PMMA in this indication. Thanks to its outstanding compatibility with human tissue, PMMA later found its place in the fixation of femoral implants since the 1950s.

PMMA cement has now been successfully used in orthopaedic surgery for more than two generations. Its excellent biomechanical properties have been evaluated in many scientific studies [2-6]. The main role of cement is to quickly stabilise the implant in bone tissue, improve the load distribution on the contact surface, fill and level off the implant-bone interface and also stiffen the spongy bone around the implant. All these properties improve the anchorage of the implant in bone, or more generally said, they improve the ideal integration of a foreign body in a biological medium.

Today, several million orthopaedic procedures are conducted worldwide and more than half of them routinely use PMMA cements. Thanks to the ease of use, but above all, thanks to the confirmed long-term survivorship of cemented implants, PMMA cement is recognised as a reliable and well tolerated anchorage material. The unique properties of PMMA cements ensure rapid and simple fixation of the joint implant, even in patients with active osteoporosis. As proof of concept, international arthroplasty registers demonstrate the excellent long-term outcomes of a cemented prosthesis [7-12, 107].

Since its introduction, PMMA cement has been combined with an AB agent, which is in the majority of cases the aminoglycosides gentamicin or tobramycin. The first such commercially available ALBC were introduced in the 70ies in the market as pharmaceutical products. In order to further improve the function of PMMA as a local drug delivery system and to adapt the anti-infective spectrum to a special pathogen profile, other AB than gentamicin and combinations of at least two AB are often added. Certain combinations of AB are particularly interesting because of the synergistic elution effect which leads to a higher mutual AB release. This holds true for e.g. vancomycin combined
with gentamicin [14, 15] and clindamycin combined with gentamicin [14]. The release of the antibiotics from the outer cement mantle follows the law of diffusion and correlates directly with the hydrophilic properties of the cement polymers. For primary arthroplasties bone cement containing gentamicin represents in most countries the gold standard for the local prevention of prostatic joint infections due to its broad-spectrum and strict concentration-dependent antimicrobial effect.

The main advantage of using PMMA as local delivery system for AB is the finding that the site of application is the strict site of the effect. Pharmacokinetic studies have shown that an initially very high and effective local concentration of the AB is obtained at the implant-cement-bone interface without significant systemic burden which is evident in the only transiently increased AB levels in urine and serum. Applying the same AB via oral or intravenous route has, however, the exact opposite effect with high concentrations in urine and serum, but only low AB levels in bone tissue and joint spaces, often below the minimal inhibitory concentration of a bacterial pathogen [16]. The higher the concentration of an AB such as gentamicin, the better its bactericidal action and its capacity to decontaminate the prosthesis and its surroundings from possible bacteria introduced into the surgical site. The observation that high local concentrations of some AB such as clindamycin may additionally eradicate intracellular persistent forms of Staphylococcus aureus in already established PJI cases [14] adds additional arguments to the assumption that local AB in combination with systemic AB have a benefit (4,3,49,107, 108, 110).

A broad range of gram-positive and gram-negative bacteria have been identified as causative agents of PJI. Although being rare cases, even fungi, such as Candida, have been found as part of a polymicrobial infection flora in immunocompromised patients. Table 1 shows which pathogens are most relevant in PJI:

### BIOFILM FORMATION AND BACTERIAL COLONISATION OF IMPLANTS

Most research into bacterial pathogenesis has focused historically on acute infections, but these diseases have now been supplemented by the new category of chronic infections caused by bacteria growing in slime-enclosed sessile aggregates known as biofilms. Biofilm infections associated with chronic wounds and implants or catheters affect millions of people. The hallmark of chronic biofilm infections is the extreme resistance of the highly growth-retarded sessile bacterial phenotypes to AB and other antimicrobial agents. In addition, the slimy biofilm layers made of carbohydrates and proteins provide a safe habitat in which the germs are physically and chemically protected from killing by the host immune defence mechanisms [18].

Pathomechanisms of PJI: Every surgical operation bears the risk of a bacterial contamination which may subsequently turn into an infection if not cleared. Joint replacement poses the patient at a particularly high risk for infections due to the additional presence of the implant or bone cement (if not loaded with AB) which can be easily colonised. PJI is often associated with severe joint pain and often reduces patient mobility. In extreme cases it may even lead to the loss of a limb or even to death if a generalised septic situation evolves from the local infection focus. In all cases treatment of PJI is associated with more extensive and time-consuming surgical interventions and high costs.

Biofilms form when bacteria of e.g. the skin or intestinal flora contaminate the surgical site and start to adhere to surfaces in aqueous environments. They subsequently excrete a slimy substance that can anchor them to all kinds of material - metals, plastics, soil particles, medical implant materials and necrotic tissue. The first bacterial colonists to adhere to a surface initially do so by inducing weak, reversible bonds. If the colonists are not immediately cleared from the surface, they can anchor themselves more permanently using cell adhesion molecules on their surfaces that bind other cells in a process called cell adhesion [19]. It is thought, that in the course of the following hours the bacterial pioneers facilitate the arrival of other pathogens by providing more diverse adhesion sites. They begin to build the matrix that holds the biofilm together and transform into growth-retarded sessile forms.

In the presence of foreign material the minimum number of microorganisms required to initiate a Staphylococcus (S) aureus infection has been experimentally shown to decrease by more than 100,000 times [20]. This can be partly explained by the lack of locally acting granulocytes in the non-vascularised material [21]. In animal models the presence of 100 colony forming units of S. aureus was sufficient to infect 95% of subcutaneous implants [22]. Although S.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Coagulase-negative Staphylococcus</td>
<td>30 - 43</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>12 - 23</td>
</tr>
<tr>
<td>Streptococci</td>
<td>9 - 10</td>
</tr>
<tr>
<td>Enterococci</td>
<td>3 - 7</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>10 - 17</td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td>2 - 4</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>1 - 3</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>10 - 20</td>
</tr>
<tr>
<td>Unknown (false negative culture)</td>
<td>10 - 30</td>
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Table 1: Prevalence (%) of pathogens in periprosthetic implant infections [17]
Staphylococcus aureus belongs to the more virulent pathogens, similar pathomechanisms also exist for commensals of the human skin flora, such as Staphylococcus epidermidis or Propionibacterium acnes, the latter being a grossly underestimated pathogen in chronic low grade joint infections [23, 24].

Because of the biofilm-associated life cycle, detection of such low virulent bacterial pathogens is often difficult in fluid or biopsies making the confirmation or exclusion of a joint infection a real clinical challenge. In particular, anaerobic Propionibacterium acnes is often not detected, as its growth in culture requires not only a sufficient number of free living (planktonic) bacteria in the specimen, but, in addition, a significantly longer incubation time of up to 14 days compared to “quick growers”. However, once properly diagnosed, Propionibacterium acnes infections are not difficult to treat [23-30].

Diagnosis of PJI is further complicated by the observation that some bacterial species, such as S. aureus, are able to completely change their phenotype from planktonic into highly growth-retarded, so-called small colony variant (SCV) forms growing at an approximately 10 times lower reproduction rate. Furthermore, mixed polymicrobial infections which are increasing at an alarming trend in PJI with numbers exceeding 30% make the diagnosis and treatment even more difficult [31].

From these acute early or chronic delayed infections which are mainly due to perioperative contaminations, the category of acute late infections must be clearly distinguished. Any implant-carrier is, during life-time, at a higher risk of an implant-infection as a consequence of haematogenous seeding of bacteria from remote infection sites. This can occur at any time [32].

A direct relationship between the risk for PJI and the time of the operation is evident. Therefore, revision surgery leads to a higher number of PJI cases than primary arthroplasty following the “rule” that the more the vitality of bone and soft tissue is affected by previous revision(s), the higher is the infection risk. The presence of severe patient comorbidities, such as cardiovascular disease, poorly controlled glucose levels in diabetes mellitus or excess body weight, also plays a major role as risk factors in the development of PJI [33, 34]. A study in the US showed that only 12% of joint replacement patients were not suffering from other concomitant diseases, and that two out of three patients scheduled for knee joint replacement surgery had more than three comorbidities [35, 36]. The need for a biofilm-directed prevention strategy is therefore biologically plausible and urgent [37, 38].

The high “vulnerability” of any implant for bacterial colonisation and the increasing demand for knee and hip replacement serves to emphasise the importance of implementing strategies to minimise the risk of infections. However, as long as there is nothing commercially available which may fulfil this aim, surgeons still have to rely on “old” strategies for infection prevention which includes strict theatre hygiene, quick operation times and appropriate systemic and local antibiotics.

Use of appropriate AB is key for a successful prevention or treatment strategy of bacterial infections because of their specific action against bacteria. All medical guidelines emphasise the need to first identify the pathogen and then take the decision on the surgical and antibiotic approach to be adopted according to the type of intervention, the type of germ and the hospital setting [39]. Despite this wide consensus a recent study has shown that in at least 20% of cases therapy is not in line with recommendations and about 40% of hospitals do not properly code the pathogen [33]. It is obvious that improved diagnostic tools including for example the more and more

![Figure 3: Norwegian Hip Registry: Lowest revision risk if combining both, systemic and local antibiotic prophylaxis.](image-url)
used sonication technique of explanted prosthesis material to dislodge bacteria from biofilms [37, 38, 40] enable a better treatment of in particular difficult-to-detect bacteria such as Propionibacterium acnes.

Provided that the causative microorganism is identified in PJI and the AB resistance and susceptibility profile of the germs are known, even resistant bacteria can be efficiently fought in the majority of cases [32, 41, 42, 111]. However, this requires a close interaction between an infection disease specialist and/or microbiologist and the orthopaedic surgeon, in order to make the best decisions on the type of AB, route and time of administration. The use of systemic as well as local AB completes the surgical therapy which is the radical debridement of infected tissue.

Although being an essential part in arthroplasty, the efficacy of systemically administered AB against infections in the bone and prosthesis interface is often limited as a consequence of poor bone penetration.

**ANTIBIOTIC PROPHYLAXIS - LOCALLY**

The topical application of AB should be generally considered with caution because of the non-specific and difficult-to-control mode of action which may lead to an increased risk of antimicrobial resistance development. This has become evident in acute treatment with AB-containing creams or mupirocin-based MRSA decontamination strategies often leading to higher than usual AB resistance rates among skin pathogens after topical treatment. To circumvent this problem, techniques and solutions such as negative pressure therapy in wound care have been encouraged as alternatives for topical antibiotics [44, 46].

This concept, however, does not apply for the musculoskeletal system because of the high dose effect of local AB in the bone and joint compartments compared to the limited concentrations achieved here by systemically applied AB. Local administration of active ingredients in these compartments may therefore be justified as adjuvant prophylaxis and treatment strategy and is, in fact, clinically relevant [17, 34, 47].

A recently published meta-analysis of available clinical data has highlighted the crucial role of ALBC in lowering the risk for prosthetic joint infection by up to 50% [48]. Similar conclusions were also drawn from large European registry studies [43, 45, 49, 50]. In light of these observations it can be stated that PMMA-based bone cement has proven clinical efficacy as a local carrier of active ingredients acting as a surgical and pharmaceutical adjuvant.

**ANTIBIOTIC-LOADED PMMA CEMENT (ALBC)**

The combination of systemic and local AB prophylaxis “works” best, can be considered the data from several arthroplasty registers. The Norwegian hip register looked at the general revision risk over an observation period of 16 years comparing the risk of the group “no prophylaxis”, “systemic prophylaxis alone”, “local prophylaxis alone” and “combination of systemic and local prophylaxis” (43, 106, 109). It was found that the revision rate was lowest in the latter group (see Figure 3). Similar results were also obtained from the Finnish knee register concluding that no, or inappropriate local antibiotic prophylaxis, is an even higher risk factor than no systemic AB prophylaxis (see Figure 4), (49, 51, 52).

Recent results from the National Joint Registry (NJR) of England, Wales and Northern Ireland (the largest arthroplasty registry worldwide) add further evidence to the efficacy of ALBC in the prevention of revision surgery. The data, spanning the years 2004 – 2015, comprised 717,339 cemented total knee and 421,604 cemented total hip arthroplasty procedures. Of those, 47% and 59% of primary hip and knee arthroplasties, respectively, were performed using Palacos® R+G. A statistically significant reduction in the number of both hip and knee arthroplasty revisions was observed when using ALBC, specifically Palacos® R+G, compared to other bone cements (113), (see Figure 5).

As proof of concept that the combination of both systemic and local AB prophylaxis “works” best, can be considered the data from several arthroplasty registers. The Norwegian hip register looked at the general revision risk over an observation period of 16 years comparing the risk of the group “no prophylaxis”, “systemic prophylaxis alone”, “local prophylaxis alone” and “combination of systemic and local prophylaxis” (43, 106, 109). It was found that the revision rate was lowest in the latter group (see Figure 3). Similar results were also obtained from the Finnish knee register concluding that no, or inappropriate local antibiotic prophylaxis, is an even higher risk factor than no systemic AB prophylaxis (see Figure 4), (49, 51, 52).

Another recent data set is derived from a French cohort study with 100,200 patient data showing a clear association between total hip replacement characteristics and the survivorship of the implants. Cemented THA, in general, did not only show a lower revision risk compared to uncemented THA, but the use of ALBC added an additional survival benefit to the...
cemented hip implants (see Figure 6) [45].

Last but not least, the results from a recent randomised clinical trial with 848 intracapsular neck fracture patients in the UK have added strong evidence to which extent a high dose double AB-loaded bone cement is able to reduce the infection rate in high risk patients. If the bone cement Copal® G+C (containing 1g of gentamicin and 1g of clindamycin in 40g of cement) was used for cemented hemiarthroplasty procedures instead of the low dose cement Palacos® R+G (containing 0.5 g of gentamicin), the incidence rate of superficial and deep infections was drastically reduced from 5.0% to 1.7% [53].

Because of the favourable clinical data for ALBC, many clinical guidelines including the most recent guideline issued by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [55, 107] recommend to consider the use of ALBC to reduce the incidence of prosthesis-associated biofilm infections.

Use of ALBC has also been common practice for long time for the fixation of revision implants after two-stage revision procedures and for the manufacture of interim spacers in the time interval between the first and second stage as a strategy for the reduction of the risk of infection relapses.

As already mentioned, AB locally released from

![Figure 4: Adapted from Jämsen 2009 (49). The rate of reoperations for the treatment of infection was lowest when a combination of intravenous antibiotic prophylaxis and prosthesis fixation with antibiotic-impregnated cement was used](image)

![Figure 5: Registry results from the NJR 2015 comparing Palacos® R+G with other antibiotic-loaded bone cements](image)
bone cement do not result in a significant systemic uptake of the active ingredient into organs and body compartments other than bone and joint tissue [56, 57]. This can be explained by the specific kinetics of release of the antibiotic from the PMMA surface with a high initial elution rate followed by constant release over several days [16]. An absolute prerequisite of the antimicrobial effect of ALBC is a local AB concentration well above the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of those bacteria which may cause PJI after implantation of the prosthesis. Low dose (0.5-1g of antibiotic) ALBC used in primary arthroplasty should in principle fulfill the requirement to act as a colonization barrier. However, according to several in vitro and clinical studies, the quantity of eluted AB and the duration of the AB release vary significantly among different commercial brands of ALBC, thus suggesting careful selection of the brand of ALBC [3-5, 9, 12, 57-59].

Being a strict concentration-dependant bactericidal AB, the absolute concentration of gentamicin is an important parameter of its efficacy to prevent biofilm formation of even intermediate resistant germs in the “race for the surface” [60] together with the systemic AB prophylaxis. Once a biofilm has been formed, the MIC is increased by a factor of at least 1000 because of the sessile bacterial phenotype (108). Eradication of biofilm bacteria is therefore a great challenge requiring the complete explantation of the biofilm-contaminated prosthesis and cement followed by radical surgical debridement of neighbouring bone and soft tissue. To further support the eradication of the bacterial pathogens, the combination of anti-biofilm-active systemic AB, such as rifampicin, and high-dose local AB are then needed.

**A CLOSER LOOK INTO ALBC USED IN PRIMARY SURGERY**

ALBC used in primary arthroplasty are so-called low dose antibiotic cements (typically 0.5-1g of antibiotic per 40g cement powder) containing a broad spectrum AB active against a variety of gram-positive and gram-negative bacteria which are frequent in orthopaedic infections. Bactericidal AB are clearly preferable because of their rapid killing activity which is not restricted to actively multiplying germs. ABs with only a bacteriostatic activity are not suitable.

Gentamicin, an aminoglycoside, is the AB of choice in such low dose cements, as it perfectly fulfills this criteria. On the one hand it acts against a wide spectrum of germs including Staphylococci, Enterococci and Enterobacteriaceae targeting more than 70% of the relevant pathogens in PJI [16] with a strict concentration-dependant bactericidal effect. On the other hand, it has an excellent elution profile from the PMMA bone cement matrix. Local gentamicin-induced cell toxicity is of no concern at concentrations released from ALBC [16].

Studies show that the drug release rate is initially high and then declines after a few days. Release from PMMA cement takes place according to the laws of diffusion from the material. The release of the active ingredient is directly proportional to the water absorption capacity (hydrophilicity) of PMMA and also depends on the existing surface area. All commercially available ALBC differ with respect to their polymer composition and the production process leading to large differences with respect to their antibiotic release rates [6, 59, 112]. Figure 7 compares different AB release from commercially available bone cements:

A recurrent controversy is the concern that the routine use of gentamicin-containing bone cement in arthroplasty might promote the development of bacterial resistance. Although this cannot be completely ruled out - especially if using a bone cement matrix with low AB release capacity - this phenomenon doesn’t appear to be of major clinical importance. Both, in Scandinavia and in Germany, two regions where ALBC have been in widespread use for many years, there is no indication of a higher gentamicin resistance rate in the orthopaedic ward. Recent
AB resistance mapping studies have even shown a trend to lower resistance rates of the germ *S. aureus* to gentamicin [61]. The issue whether routine use of ALBC in primary arthroplasty favours AB resistance has also been addressed in a recent study at one of the most active clinics in the US regarding the number of hip and knee replacement procedures. It was found that the shift from plain cement to ALBC in 2003 had no impact on the number and pattern of AB resistances of bacterial germs in the orthopaedic ward [62].

Consideration of all available clinical evidence, it must be concluded that ALBC has proven its additional benefit in infection prophylaxis in primary arthroplasty [56, 63-65].

### REVISION SURGERY AND TARGETED AB-LOADED CEMENTS

Septic revisions due to PJI are already a huge burden with incidence rates probably underestimated in the arthroplasty registers [66-70]. Effective infection control with the aid of ALBC is therefore even more essential. Typically, high-dose AB cements (2g and more per 40g cement powder) are used in this indication either for the anchorage for the revision prosthesis in one or two stage protocols or for the manufacture of ALBC spacers in the interim period of 2-stage protocols following the rationale, the more AB you add the more AB might potentially be eluted. Which of the surgical options is the best depends on the course of infection, the pathogen, the amount of bone loss and on further patient risk factors. A multi-disciplinary team including an infectious disease specialist and/or a microbiologist may advocate for the best patient- and germ-adapted treatment approach [32, 44, 71].

In contrast to low dose ALBC in primary procedures, such high dose ALBC should contain an AB (or better combinations of AB) which allow the rational targeting of bacterial pathogens based on the prior antibiogram. However, it must be pointed out that high amounts of added AB to the cement powder may compromise the mechanical stability of the bone cement. It is therefore critical not to exceed a certain amount of added AB (typically max. 10% of cement powder), if the cement is used for the fixation of the revision prosthesis. The mechanical aspects are not as much of a concern when using high dose ALBC for spacer manufacture.

Another strong argument for a high local concentration of some particular AB has been provided by a recent study comparing the intracellular killing activity of several AB. It was shown that clindamycin exhibits a potent antimicrobial effect on intracellular *S. aureus*, suggesting...
that this mainly bacteriostatic AB at systemic concentrations can become bactericidal when delivered directly in local bone environment (see Figure 8).

Combination of Gentamicin and Vancomycin in ALBC

Methicillin resistant S. aureus (MRSA) is an important factor of hospital morbidity and mortality. Of equal or even higher clinical concern is, however, the growing methicillin resistance rates of S. epidermidis (MRSE). Current records indicate that MRSA/MRSE infections lead to significantly longer hospital stays, higher costs and an overall increase in mortality.

In all those PJI cases in which a MRSA/MRSE pathogen has been identified, vancomycin-loaded PMMA cement is the AB of choice for local administration during revision arthroplasty. The highly synergistic effect of both AB gentamicin and vancomycin has been well known to the infectious disease specialist for many years [15,77-80]. Figure 10 shows the time-kill curve of this synergism.

Again, it is highly recommended to combine vancomycin with gentamicin, as vancomycin alone diffuses very slowly out of the cement matrix because of size, structure and the relative hydrophobicity of this molecule [81]. The synergistic elution effect with gentamicin ensures a far better diffusion of vancomycin (and gentamicin) leading to the strongest antimicrobial effect against various MRSA strains [6,82,83]. Figure 11 indicates the efficacy of this combination measured by the bacterial inhibition zone for a “wildtype” S. aureus (methicillin-sensitive) and different clinical MRSA isolates over a period of 7 days.

Manual Admixing of Antibiotics to Bone Cement

In view of the growing in vitro antimicrobial susceptibility of pathogens involved in PJI it is obvious that AB-bone cement mixtures must sometimes be customised to the specific germ profile. Multi-drug resistancies do not only refer to MRSA/MRSE, but refer also more and more to gram-negative bacteria and difficult-to-treat polymicrobial infections.

As mentioned earlier, the identification of the causative organism and the assessment of possible antibiotic resistance is of paramount importance for a successful infection management. If it proves necessary to admix an AB to PMMA cement in septic revision surgery, it is recommended to contact a specialist to ensure that the chosen antibiotic is sufficiently effective with PMMA. An inadequate quantity may compromise the stability of the prosthesis or a too low elution of the cement matrix may generate the emergence of resistant bacteria [19].

The AB powder must be soluble in water and a maximum dose of 4g per 40g of polymer powder (10%) should not be exceeded if ALBC is used for fixation purpose. In case of ALBC used as temporary spacer the mechanical strength of the AB-cement mixture is of less importance [84]. It must always be kept in mind that the manual addition of antibiotics can have a significant effect on the different mechanical properties of the cement [85]. Inhomogeneous mixtures in particular reduce the stability of the matrix and can significantly reduce implant life span [6]. Similarly, it is difficult to predict any synergy and antagonism in terms of diffusion. When directly comparing manually AB-admixed bone cement with industrially manufactured commercial ALBC differences regarding antimicrobial elution rate and in vitro-antimicrobial efficacy have been found (see Figure 12) [86].

Another in vitro comparison between commercially and manually mixed ALBC (Palacos® as control, Palacos® R+G, and Palacos® R with gentamicin manually added) revealed that the inhibition zone for bacterial growth was larger with the commercial ALBC cement compared to the cement to which the antibiotic had been manually admixed [87]. Septic revisions due to PJI are already a huge burden with incidence rates probably underestimated in the arthroplasty registers [66-70]. Effective infection control with the aid of ALBC is therefore even more essential. Typically, high-dose AB cements (2g and more per 40g cement powder) are used in this indication either for the anchorage for the revision prostheses in one or two stage protocols or for the manufacture of ALBC spacers in the interim period of 2-stage protocols following the rationale, the more AB you add the more AB might potentially be eluted. Which of the surgical options is the best depends on the course of infection, the pathogen, the amount of bone loss and on further patient risk factors. A multi-disciplinary team including an infectious disease specialist and/or a microbiologist may advocate for the best patient- and germ-adapted treatment approach [32,44,71].

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Combination of Gentamicin and Clindamycin in ALBC

Gentamicin and clindamycin combined in bone cement act synergistically with respect to the spectrum of antimicrobial action [14]. This combination also targets anaerobic bacteria which are gaining growing importance as PJI pathogens, as well as streptococci often found in late haematogenous infections. Another clear advantage of this AB combination is its synergistic effect via a mutually increased elution from the PMMA matrix [6, 14, 72, 73] (see Figure 9). Because of their high local diffusion, the concentration of these two AB gentamicin and clindamycin is significantly higher than the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) for several days and weeks at the surface of the cement [73, 74]. In addition, being a rather small sized molecule, clindamycin shows excellent bone penetration and exerts an intracellular bactericidal activity [14].

As proof of concept for the clinical benefit of such a synergistic high release profile of two AB serve the observations that 1. the Copal® G+C bone cement is more effective against biofilm formation than Palacos® with only gentamicin [75] and 2. the incidence of superficial and deep infections is markedly reduced in the presence of this double-loaded cement if hemiarthroplasty procedures in intracapsular neck fracture patients were done with Copal® G+C instead of Palacos® R+G [53, 76].

In light of the clinical data, this AB combination can therefore be recommended not only in all those septic revision cases where the antibiogram reveals sensitivity of the germ(s) for gentamicin and clindamycin, but also in high risk patients where the risk of infection is significantly higher than normal. Another indication for use could be those revision cases where the diagnosis is difficult and «uncertain» (e.g. culture-negative PJI cases) or in those situations where anaerobic bacteria such as Propionibacterium cannot be ruled out.

Another hallmark of AB combinations is the observation that the presence of two AB with different modes of action virtually rules out the risk of development of concomitant resistance to these two substances.

Despite the high local concentration of both AB, systemic side effects are not a concern as evidenced by a clinical study showing that gentamicin and clindamycin peak only transiently in serum and urine after local use of Copal G + C and then quickly fall below detectable levels [73]. Infection was resolved in all analysed patients during the observation period of one year.

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In view of the growing antimicrobial resistances it is obvious that AB-bone cement mixtures must sometimes be customised to the specific pathogen profile.
involved in PJI cases. Multi-drug resistances do not only refer to MRSA/MRSE, but refer also more and more to gram-negative bacteria and difficult-to-treat polymicrobial infections.

As mentioned earlier, the identification of the causative organism and the assessment of possible antibiotic resistances is of paramount importance for successful infection management. If it proves necessary to admix an AB to PMMA cement in septic revision surgery, it is recommended to contact a specialist to ensure that the chosen antibiotic is sufficiently effective with PMMA. An inadequate quantity may compromise the stability of the prosthesis or a too low concentration of the cement matrix may generate the emergence of resistant bacteria [81].

The AB powder must be soluble in water and a maximum dose of 4g per 40g of polymer powder (10%) should not be exceeded, if ALBC is used for fixation purpose. In case of ALBC used as temporary spacer the mechanical strength of the AB-cement mixture is of less importance [84]. It must always kept in mind, that the manual addition of antibiotics can have a significant effect on the different mechanical properties of the cement [85]. Inhomogeneous mixtures in particular reduce the stability of the matrix and can significantly reduce implant life span [6]. Similarly, it is difficult to predict any synergy and antagonism in terms of diffusion. When directly comparing manually AB-admixed bone cement with industrially manufactured commercial ALBC differences regarding antimicrobial elution rate and in vitro-antimicrobial efficacy have been found (see Figure 12) [86].

Another in vitro comparison between commercially and manually mixed ALBC (Palacos R® as control, Palacos® R+G, and Palacos® R with gentamicin manually added) revealed that the inhibition zone for bacterial growth was larger with the commercial ALBC cement compared to the cement to which the antibiotic had been manually admixed [87].

**WHICH PMMA SPACER FOR TWO-STAGE REVISION SURGERY?**

Two-stage revision protocols treat the joint infection by using a temporary AB spacer as a temporary prosthesis before insertion of the definite revision implant [5, 88].

Apart from local high AB elution, articulating ALBC spacer also allow a temporary joint function. By this, tissue retraction is avoided and the joint space maintained, which often facilitates the subsequent implantation of the revision prosthesis [82, 83, 86, 89, 90]. An at least partial joint function is not possible with a non-articulating spacer which is still in use. With respect to the efficacy of infection eradication differences between articulating and non-articulating spacers have not been observed [91].

Articulating PMMA spacers are subjected to a specific cement friction leading to abrasive cement particle wear. Such particle wear can have a negative impact on the future re-implantation of a prosthesis leading to example a higher risk of subsequent revision implant loosening. It is also discussed if particle wear in an infected and previously infected environment leads to a “circulus vitiosus” of increased cell apoptosis [92-94], as it is well known that wear particles constitute a risk factor for infection [95]. Therefore, not only the implant, but also wear particles may interact with granulocytes that are involved in such a scenario [96].

The impact of local ABs on a two-stage interim PMMA cement spacer was analysed during a prospective clinical study conducted with 68 patients presenting acute infection of the hip prosthesis (all patients with fistula formation; gram-positive bacteria were detected in 68.5% of all infections and gram-negative bacteria in 31.5%). 30 of the 68 patients were treated during the intermediate period after removal of the infected prosthesis without spacer (Girdlestone resection) and 38 patients were treated with an ALBC spacer (with 1g of vancomycin/40 g).

The infection recurrence rate in the Girdlestone group was particularly high after primary surgery with 23.3% versus 5.2% in the group with spacer [97] (see Figure 12). This result confirms prior studies suggesting that the local concentration of AB achieved at the site of infection can be much higher than that achievable with systemic therapy, without significant toxicity [98, 99].

Taken together, this data suggest that the placement of a spacer with high dose antibiotics (gentamicin and vancomycin) after removal of the infected implant and debridement of the joint cavity can significantly reduce the risk of reinfection (Figure 13).

Special PMMA spacer cements with low-abrasive calcium carbonate/calcium sulphate used as a contrast medium for radiology, exhibit a markedly reduced abrasion of cement particles during the intermediate period (see Figure 14). The lower visibility of calcium carbonate on X-rays compared to conventional contrast agents such as...
zirconium dioxide and barium sulphate, is not a major concern, since the lower visibility of calcium carbonate is compensated for by the large size of the spacer.

In addition, because of the significantly higher hydrophilicity of such a cement matrix, these spacers elute antibiotics much better than “conventional” bone cement spacers.

**ECONOMIC IMPACT OF ALBC**

In view of the predicted ageing of the world’s population and the changes in lifestyle factors, such as increased obesity and lack of physical activity as a consequence of urbanisation and motorisation, it is estimated that the number of people affected by musculoskeletal disorders and the numbers of subsequent joint replacement surgeries will drastically increase. In the United States alone, a doubling of the number of arthroplasty procedures is possible by 2030 [100]. The overwhelming success of arthroplasty is evident by the high patient satisfaction scores and the long life span of prostheses with 88-95% of the primary implants still functioning well after 10 years [101, 102].

Complications of arthroplasty procedures are rare [17]. However, surgeons and patients are increasingly faced with the problem of implant-associated infections. The consequences for patients and for the health service budgets are dramatic, mainly because of the longer hospital stays which often exceed 30 days compared to only a few days in primary or aseptic revision procedures [103]. Also, the re-operation rate increases sharply, if the first infection intervention fails. A crucial point in health economic evaluations is to analyse how medical interventions can create maximum benefit and output with a limited budget.

Many countries try to control their health spending with methods that require calculations to show the relationship between the differences in the average costs of a technology compared with the best alternatives. The consequences not only in “physical terms” must therefore be measured with a cost-effectiveness analysis (CEA), but a cost-utility analysis (CUA) is required for a valuation of individual assessments of the consequences. This is expressed in QALY units meaning health related quality adjusted life years. This corresponds to a weighting of the time passed in good health (= utility). The results of cost-utility studies have so far not been a decisive factor for access to treatment reimbursement. However, this kind of analysis is becoming increasingly important for medical payers.

In Australia for instance ALBC was the subject of an incremental cost effectiveness ratio analysis (ICER). The result of the comparison between systemic AB therapy with and without concomitant use of ALBC revealed a gain of 32 QALY equivalent to a sum of AUD$ 123,000 [104]. A similar result was obtained in a study in the UK comparing AB cement with plain cement. ALBC used for local prophylaxis resulted in £37,355 per QALY [105].

Preventing deep SSI with AB prophylaxis and ALBC has shown to improve health outcomes, save lives, and enhance resource allocation [45]. The observation that the use of high dose gentamicin- and clindamycin-loaded bone cement not only reduces the rate of superficial and deep SSI in hemi-arthroplasty procedures, but also reduces the number of days in ICU from 18 days to 3 days can be considered of major health economic impact [76]. Another cost/benefit study (level II evidence) showed that the use of ALBC in primary hip replacement is cost-effective if assuming a significantly lower PJI incidence rate and costs for the treatment of septic revision case being approximately 3.5 times higher than the primary intervention [105].

**CONCLUSION**

Gaining deeper knowledge about the properties and the application of bone cement is of paramount importance to all orthopaedic surgeons. Although bone cement had been considered for a long time as a key biomaterial in the field of joint replacement surgery, its use has somewhat decreased because of the introduction of press-fit implants which encourage bone in-growth. The main purpose of bone cement is still a long-lasting fixation of prostheses. Since AB elute relatively well from PMMA, it must also be considered as a modern drug delivery system that delivers the required drugs directly to the surgical site. In view of the increasing challenges of more resistant bacterial pathogens and higher patient risk factors, the antibiotic carrier function gains additional importance to prevent the formation of bacterial biofilms and to suppress the incidence of infection relapses. The industry has reacted to these challenges by developing bone cements with tailored antibiotic combinations aimed at targeting different germ profiles.
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