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Risk assessment of antibiotic resistance development by antibiotic-loaded bone cements: is it a clinical concern?

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- Because of the risk of bacterial biofilm infections, prophylactic use of antibiotics in orthopaedic procedures involving the implantation of large prosthesis systems is considered mandatory.
- A strategy based on the rationale that local antibiotics released from bone cement or other carriers establish a second antibacterial frontline in and around the prosthesis is considered complementary to the administration of systemic antibiotics.
- Although less common as a consequence of the initially very high drug concentrations of local antibiotics in the tissues, a selection process of previous high resistance bacteria may occur, leading to antibiotic resistance.
- The use of antibiotic combinations in bone cement is generally accepted to improve antibiotic efficacy and minimizes the treatment failure risk due to antibiotic resistance. This is important in septic revisions and/or in patients at particularly high risk of infection.
- On an individual basis, the benefit of a lower infection probability with combined systemic and local antibiotic application should outweigh the risk of the selection of more resistant bacteria. Each prevented infection means that a complex and extended antibiotic therapy with risk of resistance development over time has been avoided.
- On an epidemiological level there is no clinical evidence that the routine use of bone cement impregnated with appropriate bactericidal antibiotics promotes the widespread development of antibiotic resistance and thereby puts the successful treatment of a prosthetic joint infection at higher risk.

Keywords: antibiotic-loaded bone cement; antibiotic resistance; prosthetic joint infection

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Introduction

Periprosthetic joint infection is a rare, but devastating complication after total joint replacement. Because of the growing numbers of arthroplasty procedures in general, the trend to operate on older patients with high co-morbidities together with the increasing spread of resistant pathogens, prevention is gaining increasing importance.

Peri-operative antibiotic prophylaxis during implant surgery is a recognized necessity. Further addition of local antibiotics eluting from bone cement is often considered a complementary prophylactic strategy. Cement spacers carrying high doses of antibiotics are often employed during two-stage treatment of infected prosthetic joints. However, in view of concerns regarding growing antibiotic resistance, the use of antibiotic-loaded bone cement remains controversial. The aim of this review is to summarize and discuss the available evidence derived from experimental, preclinical and clinical studies on whether antibiotic-loaded bone cement does drive antibiotic resistance and, if so, whether this is of clinical relevance.

Rationale and principle of antibiotic prophylaxis in orthopaedic surgery

The implantation of foreign material in orthopaedic procedures increases the potential risk of deep infections due to bacterial colonization and biofilm formation on implant surfaces. Among the strategies taken to prevent these feared infections, peri-operative antibiotic prophylaxis (PAP) is widely accepted as a potent anti-infective measure in joint replacement procedures.[1–3] The choice of antibiotics used for prophylaxis requires an understanding of the common micro-organisms that cause surgical site infections (SSI) in orthopaedic procedures. Numerous studies have shown that gram-positive staphylococci are the most frequent bacteria causing prosthetic joint infections (PJI).[4,5] Enterococci, Streptococci and gram-negative

Table 1. Summary of advantages and disadvantages of local antibiotic use

Advantage	Disadvantage
High local antibiotic concentrations in situ may kill bacteria which are only susceptible at very high antibiotic levels (not achieved with systemic use).	There is a risk of local cytotoxicity because of high local drug concentrations.
High local antibiotic concentrations may target biofilm-associated and/or intracellular bacteria.	After a high initial peak concentration, the elimination phase varies according to the delivery system. Antibiotic resistance may occur if concentrations remain for a longer period below minimal inhibitory concentrations (MIC).
Antibiotic delivery is not dependent on vascularization of target tissue.	
Rapid bactericidal antimicrobial efficacy leaves less time for resistance development.	
Local antibiotics lead to low systemic exposure so that side effects are rare and systemic antibiotic resistance selection is low.	

organisms are less common but are also clinically relevant. Epidemiological studies from various hospitals have provided evidence that methicillin-resistant *S. aureus* (MRSA) is still a major problem pathogen in PJI[6] and that the prevalence of multi-drug resistant gram-negative bacteria is growing in some institutions.[7] The expertise guiding the recommendation as to which antibiotic(s) should be used for PAP is based on a combination of clinical and laboratory research, experience, safety issues and cost–benefit evaluations. Because of their broad antimicrobial spectrum, good safety profile, low costs and ease of administration, cephalosporins of the first and second generation are recommended in many orthopaedic guidelines for PAP.[8,9] However, as the prevalence of gram-positive and gram-negative pathogens as well as the proportion of resistant bacteria in a given hospital may vary with time and region, it is recommended to regularly re-evaluate the antibiotic guidelines. The probability of developing an infection is drastically increased if the initial contaminating flora in open wounds is not targeted by the prophylactic antibiotic regimen.

An additional anti-infective strategy is based on the rationale that local antibiotic carriers, such as bone cement, deliver huge drug concentrations in situ where contamination may have occurred and where the organism is most vulnerable to infections. Buchholz and Engelbrecht were the first to report the incorporation of antibiotics into the biomaterial Polymethylmethacrylate (PMMA) bone cement.[10] The idea was fascinating: after a high initial peak elution the antibiotic is gradually released by the cement, acts at the desired site and can reach far higher concentrations than systemic therapy without causing notable systemic side effects (see Table 1). By implementing this additional prevention measure Buchholz achieved an impressive reduction in deep infections of total hip replacements in both primary and revision surgery.[11] Neut and co-workers demonstrated later, in an in vitro model, antibiotic elution from bone cement at the cement–prosthesis and cement–bone interfaces which initially exceeds MIC (minimal inhibitory capacity) values of many bacteria by a factor of 100-fold and more.[12] Significant prolongation of the antibiotic activity in joint fluid recovered from knee arthroplasty patients was additionally shown, if the systemically administered PAP (cefazolin) was combined with antibiotic-loaded bone cement (ALBC). It was also demonstrated that only drainage fluid from the patients receiving a combination of cefazolin PAP and vancomycin-loaded bone cement was able to inhibit growth of MRSA for at least 50 hours while the fluid from control patients did not (see Fig. 1).[13]

Based on this important observation, it can be concluded that ALBC establishes a second prophylactic 'front-line' against bacterial contamination, which is of particular importance if the systemic prophylaxis fails to kill resistant bacteria.

Several clinical studies have evaluated the effect of combining antibiotic-loaded bone cement (ALBC) in total hip (THA) and in total knee arthroplasty (TKA) with systemic antibiotic prophylaxis. Evaluations from the Norwegian Hip Arthroplasty Register and from the Finnish Knee Register have demonstrated a significant beneficial effect from additional use of antibiotic-loaded cement. In both registries the lowest risk of revision was found where the antibiotic prophylaxis was given both systemically and locally in the cement.[14,15] On a single hospital level, the implementation of routine use of ALBC for all cemented primary hip and knee procedures has demonstrated a reduction of PJI cases by 60–70%, while the infection rate of uncemented prostheses in the observation period remained unchanged.[16] Based on the available clinical evidence, a recent meta-analysis concluded that antibiotic-loaded bone cement may reduce the infection risk by 50%.[17] In line with these observations, a prophylactic regime relying on the application of systemic and local antibiotics has become the surgical standard in many European countries for cemented arthroplasty.

Although antibiotic-loaded bone cement represents the best studied modality for local delivery of antibiotics, other carrier systems are also in clinical use, including bone cement beads, collagen fleeces or impregnated bone grafts and their synthetic substitutes. Even local intra-wound administration of antibiotic powder has been

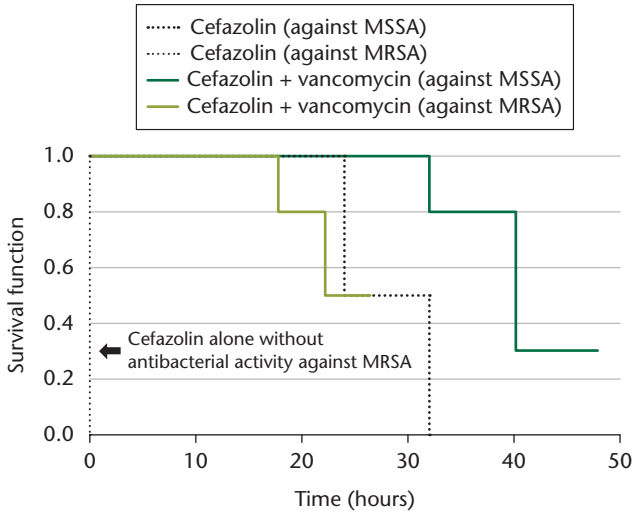


Fig. 1 The effect and the duration of the antibacterial activity (determined in the drainage fluid of cemented total knee arthroplasty procedures) is dependent on the prophylactic regimen with antibiotics. All patients received three doses of cefazolin i.v. for 24 hours. The control group received the systemic antibiotic only. In the vancomycin group, antibiotic-loaded bone cement (ALBC) loaded with 1 g of vancomycin per 40 g of cement was additionally used with the systemic cefazolin. The graph shows the effect and the duration against methicillin-sensitive *S. aureus* (MSSA) and against methicillin-resistant *S. aureus* (MRSA).
Source: Adapted from Ueng et al.[13]

described as a method capable of reducing the rate of SSI in spinal surgery.[18]

Because of their potential to provide high intra-wound concentrations without exposing the systemic circulation to toxic drug levels, local antibiotics are also an attractive option in medical fields beyond surgery, such as prevention and treatment of burn infections, treatment of acne vulgaris, treatment of chronic otitis media and treatment of bacterial keratitis in the eye.[19–22] In these situations, local antibiotic application is recommended as a therapeutic option in clinical guidelines if the risk for infection or the manifestation of the infection is considered to be serious.

Taken together, the rationale of use and the available clinical evidence supports the hypothesis that the combination of systemic and local antibiotics is an important complementary anti-infective strategy in those settings where the infection risk is particularly high. This holds true for many implant-related orthopaedic or trauma procedures. Although the experiences with local antibiotics appear relatively convincing, there is an ongoing controversy as to whether the potential benefit of infection risk reduction outweighs the risk of possible antimicrobial resistance development. This concern is more pronounced in those countries already suffering from a huge burden of antibiotic resistance.

Differences in susceptibility or resistance between systemically and locally applied antibiotics

Predictions of antibiotic success or failure are clinically based on the antibiogram which determines whether the micro-organism is in vitro susceptible or resistant to the antibiotics tested in different concentrations. For systemic antibiotic therapy, information on the typical tissue concentrations reached with standard antibiotic doses is integrated with the minimal inhibitory concentrations (MIC) of a pathogen to determine the MIC breakpoints (MICBP) which are reported for each antibiotic drug. The relationship between the measured MIC for the infective organism population and the reported MICBP for a particular antibiotic determines whether the infection is reported as susceptible, intermediate, or resistant to antibiotic therapy in a patient. This system has been established both to guide individual therapy and to ensure that across the patient population, exposure to sub-therapeutic antibiotic concentrations is minimized.

While the therapeutic framework for systemic antibiotics is relatively well established, no such equivalent system applies to antibiotics administered locally into the surgical wound bed or used to coat cement or implants. The antibiotic concentrations achieved locally are often much higher than those that typically result from systemic administration (see schematic illustration in Fig. 2). Thus, standard susceptibility reporting criteria and MICBP often do not apply in this situation. The pharmacokinetics (change of drug concentrations over time) of the local antibiotic therapy is also very different to systemic therapy, with a profile typically characterized by the rapid onset of a strong concentration peak followed by a variable elimination phase.

Translating these principles into clinical practice means that some of the bacterial strains which are classified as intermediate or resistant in antibiograms based on systemic delivery may still be killed at the locally high concentrations in situ after peak elution from local antibiotic carriers. This is particularly true for those antibiotics which show a bactericidal and concentration-dependent action, such as the aminoglycosides (see Fig. 3) Given the observation that some coagulase-negative staphylococci have experienced a significant shift towards higher MICs in recent years,[24–26] which may be beyond concentrations typically achieved via systemic antibiotic use, it can be expected that only the initially high concentrations of some local antibiotics exert an antimicrobial effect on these bacteria in the prosthetic joint compartment (see schematic illustration of MIC changes in Fig. 4). The new European Committee for Antimicrobial Susceptibility Testing (EUCAST) proposal from 2018 to modify the susceptibility and resistance categories into the new definitions

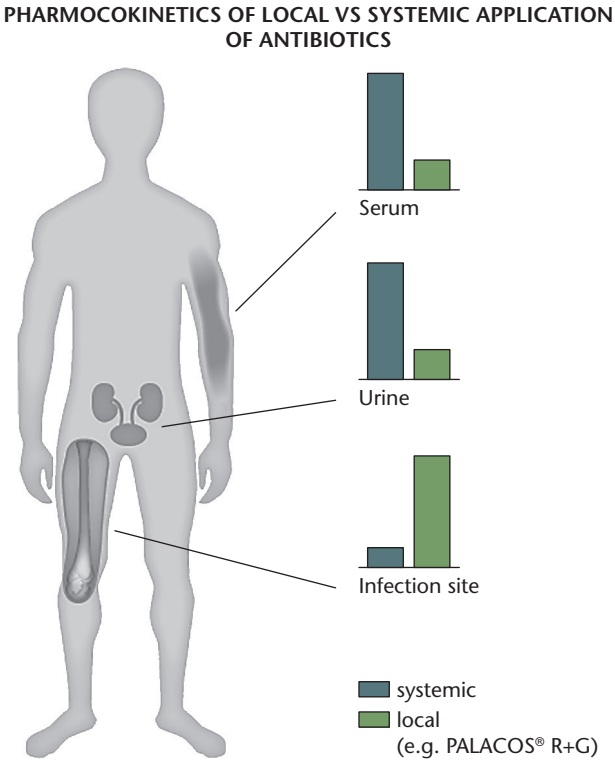


Fig. 2 Schematic illustration of different pharmacokinetics of local vs. systemic use of antibiotics. Local antibiotics reach high peak concentrations at the application site and only low concentrations in systemic circulation.

'susceptible at standard dosing regimen', 'susceptible at increased exposure' and 'resistant with high clinical failure' might therefore take this observation better into account.[27]

Use of local antibiotics and antibiotic resistance development

Any exposure to an anti-infective drug applies a selection pressure on the infective organism. Of particular concern is persistent systemic exposure at sub-inhibitory levels of antibiotics, which may lead to the emergence of resistant strains over time. In principle, the risk of resistance induction should be less for locally delivered antibiotics because of their special pharmacokinetics with enormous peak levels in situ combined with very low systemic levels which often drop under the detectable threshold after 48 hours.[28,29] However, if a highly resistant bacterial strain manages to survive the initial elution burst, a selection process may also occur. Proof of this concept was provided by Hendriks et al in their experimental interfacial gap model mimicking the space between antibiotic-loaded bone cement and bone tissue: if challenged with a huge inoculum of gentamicin-susceptible *S. epidermidis* bacteria, all bacteria were killed by the antibiotic gentamicin released from cement; if challenged with a strain of high level resistant *S. epidermidis* mutants, bacteria were able to survive.[30] Comparing the infection rate on the one hand and the percentage of antibiotic resistance development on the other in an experimental animal model, Thomes et al demonstrated that the price of a significant reduction of infections in the gentamicin-loaded bone cement group was a higher rate of gentamicin-resistant bacteria in those cases where the infection was not eradicated (see Fig. 5).[31] However, it is important to note that the amount of antibiotic loaded into the cement in this in vivo experiment was far lower compared with the antibiotic concentrations in commercially available ALBC. Based on these observations the authors therefore issued the recommendation not to use the same ALBC in revision procedures if it had been already used in previous surgery.

Consistent with these preclinical studies, it was not surprising to see that viable bacteria may persist on bone cement spacers retrieved from PJI patients treated with a two-stage revision protocol as an indication of the high tolerance of biofilms to antibiotics.[32,33] Similarly, Anagnostakos et al demonstrated bacterial growth on antibiotic-loaded PMMA beads.[34] It is of major clinical relevance to note that culture-positive tissue samples or spacers at the time of re-implantation were found by some authors to be a predictive factor for treatment failure of the septic revision procedure.[35,36]

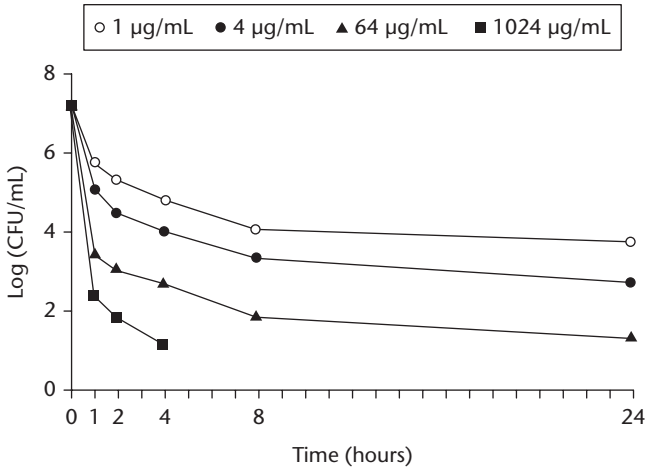


Fig. 3 Time-kill curves over 24 hours in wound fluid for gentamicin against *S. aureus*. The concentrations of gentamicin tested were 1 to 1024 ug/ml.
Source: Adapted from Sørensen et al.[23]

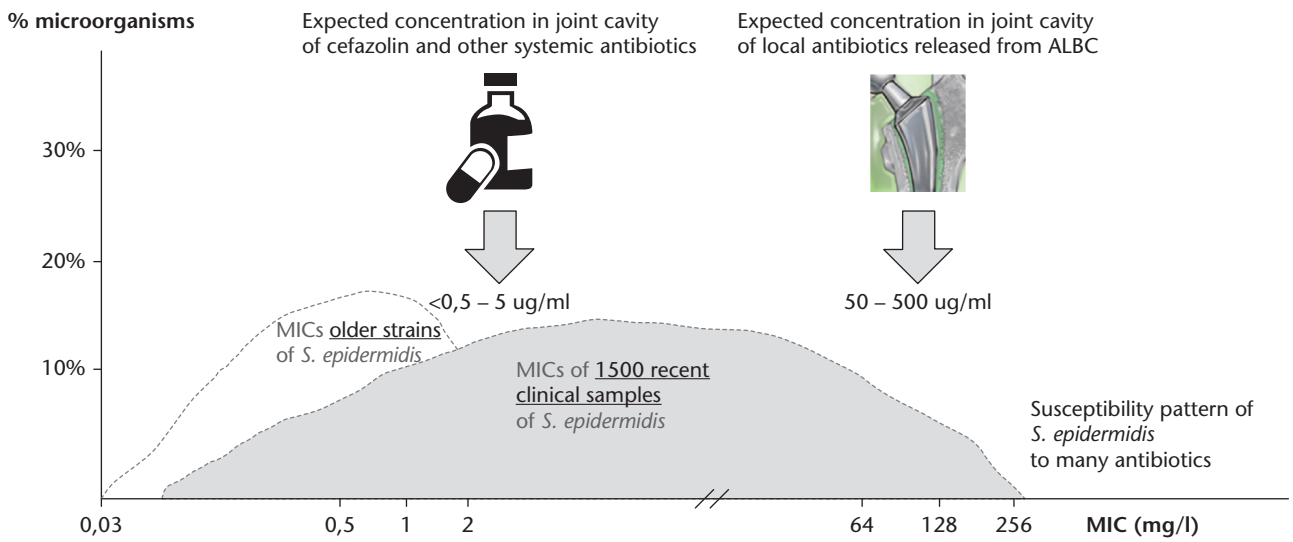


Fig. 4 Schematic illustration of the shift in minimal inhibitory concentrations (MICs) of *S. epidermidis* against several antibiotics used for peri-operative antibiotic prophylaxis (PAP). Compared are older strains vs. 1500 recent clinical isolates retrieved from several European hospitals.[24–26] MICs are compared with expected antibiotic bone and joint tissue levels achieved with systemic antibiotics and local antibiotics eluted from antibiotic-loaded bone cement (ALBC).

These findings further emphasize the need for meticulous surgical debridement in order to decrease the bacterial load in the infected site and put emphasis on the antibiotic elution capacity of the local carrier system. One strategy to overcome the risk of persistent microbial growth on bone cement in septic treatment situations is the combination of at least two antibiotics in the delivery system. The advantage of such combinations does not only lie in the frequently observed synergistic release kinetics from the carrier matrix and the broader antimicrobial efficacy but may also counteract the selection of bacterial mutants which have become resistant to one antibiotic. Concomitant antibiotic resistance of a given pathogen against two antibiotics acting at different bacterial target structures is far less frequent than resistance to one of the two (see Fig. 6). In fact, a recent retrospective analysis of a large number of septic revision cases at two major hospitals in Spain and the US has shown evidence that the combination of vancomycin with gentamicin in the bone cement spacer correlated with a lower number of culture-positive tissue samples taken at the time of re-implantation. The strongest effect was observed for *S. epidermidis* positive cultures which dropped from 17% (spacer with gentamicin only) to 2% (spacer with gentamicin plus vancomycin).[36]

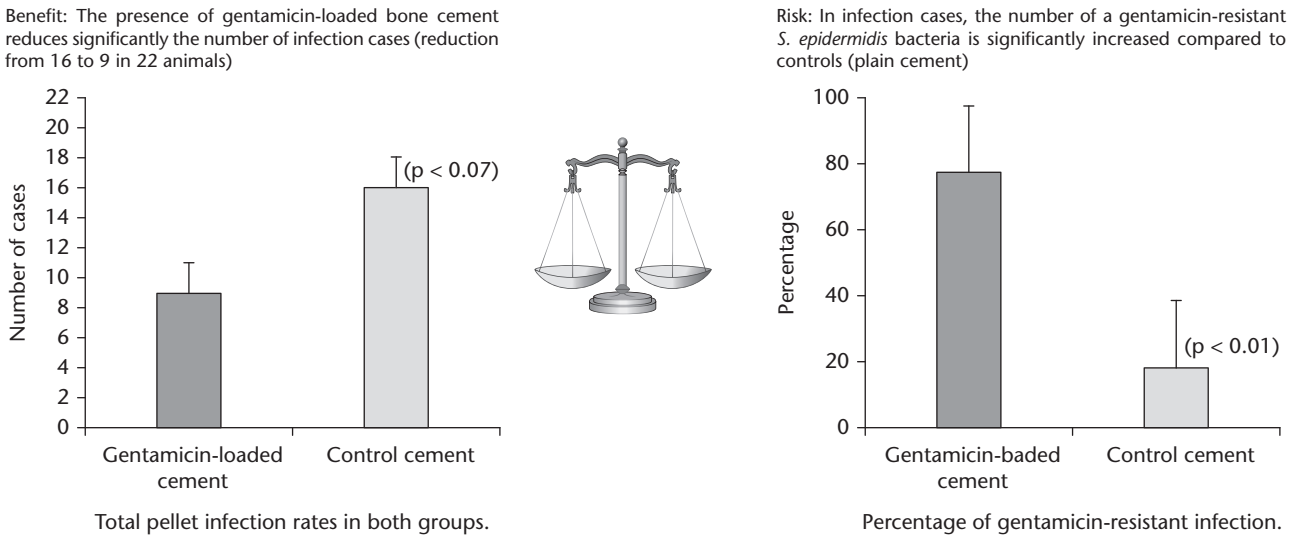
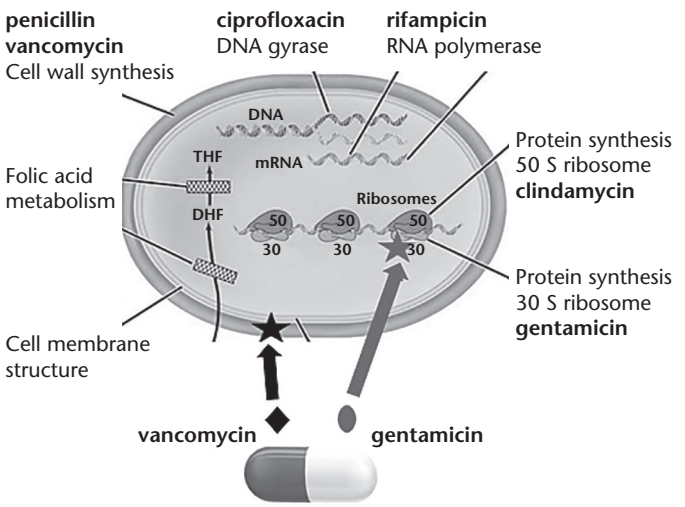


Fig. 5 Pellets made of gentamicin-impregnated bone cement (80 mg gentamicin per 20 g cement) were subcutaneously implanted in one group of 22 Sprague Dawley rats, and pellets made of saline solution-impregnated cement in another group of 22 Sprague Dawley rats. The subcutaneous pocket with the bone cement was inoculated with 2 x 10^3 bacteria (*S. epidermidis*). After 14 days the rats were re-anaesthetized, the wound re-opened and the pellets retrieved. Pellets were vortexed to dislodge any colonized bacteria into a broth and plated after 24 h onto Columbia blood agar. Left graph: Pellet infection rates in both groups. Right graph: Percentage of gentamicin-resistant infection as determined by agar diffusion tests.
Source: Adapted from Thomes.[31]



PRINCIPLE OF COMBINATION THERAPIES

Imagine that the probabilities of spontaneous **resistance to drugs A and B are 1×10^{-6} and 1×10^{-7}**, respectively.

If spontaneous resistance to drugs A and B are independent events, then the **probability of spontaneous resistance to the A+B combination** will be the product of the two rates, or 1×10^{-13}.

Fig. 6 An antibiotic combination consisting e.g. of gentamicin and vancomycin does not only increase the antimicrobial efficacy but also inhibits different metabolic pathways in the bacterial cell. Spontaneous co-resistance against both antibiotics is therefore much rarer than against only one antibiotic.

Observations of a synergistic benefit of antibiotic combinations are not new. Combination therapies with at least two or more anti-infective drugs are a cornerstone of treatment for other major infectious diseases which bear a high risk of resistance development, including Malaria, HIV, Tuberculosis or *Helicobacter pylori* infections. Most of these infections have in common that they involve an anti-infective treatment for longer time periods, as is also true for prosthetic joint infections.

After careful screening of the scientific literature, only a few clinical studies could be found which have directly addressed the question of whether routine use of ALBC in arthroplasty has an epidemiological impact on the pattern of infecting bacteria and their antibiotic resistance profiles. The results are relatively contradictory. On the one hand, Hope et al reported that the number of PJI cases caused by gentamicin-resistant coagulase-negative Staphylococci increased with prior exposure to antibiotic-loaded bone

Table 2. Number of gentamicin/clindamycin-resistant infections in patients receiving a low dose single antibiotic cement vs. a high dose dual antibiotic cement

	Low dose single antibiotic cement	High dose dual antibiotic cement	Chi squared test, p =
1941 hemiarthroplasty cases in total	681	1260	
Deep SSI cases (rate)	23 (3.40%)	15 (1.20%)	0.003
Deep SSI resistant to clindamycin	14 (2.06%)	15 (1.19%)	0.134
Deep SSI resistant to gentamicin	10 (1.47%)	12 (1.00%)	0.305
Deep SSI resistant to both	8 (1.17%)	12 (1.00%)	0.643

Note. SSI, surgical site infections.
Source: Adapted from Tyas et al.[39]

cement (gentamicin resistance found in 30% of all 91 PJI cases).[37] On the other hand, Hansen et al did not find any notable increase in the percentage of antibiotic resistance and changes in pathogens grown from 173 PJI cases over a period of nine years after they switched to routine ALBC use in their primary joint arthroplasties.[38] They therefore concluded that routine prophylactic use of ALBC was safe and did not lead to the widespread emergence of antimicrobial resistance in the orthopaedic unit. In a very recent analysis within a large clinical trial designed to compare the infection rates in neck-of-femur fracture patients as a function of the antibiotic-loaded bone cement used for the fixation of the hemiprosthesis, Tyas et al reviewed the cases of deep surgical site infections with regard to the causative pathogens and their antibiotic resistance profiles.[39] It was found that the reduction in deep infection cases was such in patients receiving a high dose antibiotic-loaded cement (HDAC) (infection rate: 1.2% in HDAC group = bone cement with 1 g gentamicin and 1 g clindamycin) as compared with a low dose antibiotic cement (LDAC) (infection rate: 3.4% in LDAC group = bone cement with 0.5 g gentamicin; p = 0.003) that there was a trend towards a lower rate of resistance with the use of HDAC. The authors therefore concluded that the concomitant prophylactic use of two antibiotics in the cement did not drive antibiotic resistant infections (see Table 2). Even in those few remaining cases of gentamicin and clindamycin-resistant pathogens susceptibility to antibiotics used for treatment of PJI remained largely unchanged, including rifampicin, daptomycin and vancomycin against gram-positive bacteria or ciprofloxacin, meropenem and ceftazidime against gram-negative bacteria.

Conclusions

Careful use of antibiotics is of the highest importance to control the growing problem of antibiotic resistance. However, because of the high risk of bacterial biofilm infections, their prophylactic use in invasive orthopaedic implant procedures appears justified. Antibiotic-loaded bone cement and other local antibiotic carrier systems may be complementary to systemic antibiotics, as the local peak concentrations do not depend on factors such as tissue vascularization or bone penetration. Any antibiotic application may lead to the development of antibiotic resistance. However, the risk is assumed to be lower for the controlled system of antibiotic-loaded bone cement because of the initially very high drug concentrations in situ, followed by retarded elution without considerable passage into the systemic circulation. The use of antibiotic combinations in bone cement has been related to lower treatment failures in septic revision protocols due to the higher antibiotic release, synergistic antibiotic efficacy and lower risk of concomitant resistance development. The benefit of a lower infection probability with combined systemic and local antibiotic application should outweigh the risk of more resistant bacteria. There is no clinical evidence that the routine use of bone cement impregnated with appropriate bactericidal antibiotics promotes the widespread development of antibiotic resistance among the pathogens causing PJI.

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ICMJE CONFLICT OF INTEREST STATEMENT

CB is an employee of the company Heraeus Medical GmbH which is a manufacturer of antibiotic-loaded bone cements and bone graft substitutes. He is responsible for the training and medical education activities provided to orthopaedic surgeons and theatre staff. The training contents developed by the author and independent experts in the field are neutral in product statements and reviewed by third parties for neutral educational contents, in order to receive certification points for the training participants.
PSR reports no conflict of interest.

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