G87: Do currently available products safely achieve local antibiotic concentrations above Minimum Biofilm Eradication Concentration (MBEC) for sufficient time to achieve eradication of infection?

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Response/Recommendation: There is no clear evidence that the current products can safely achieve local antibiotics concentrations above Minimum Biofilm Eradication Concentration (MBEC) levels for sufficient time to eradication of infection.

Level Of Evidence: Strong

DELEGATE VOTE: Agree: [% vote], Disagree: [%], Abstain: [%]

Rationale:
The Minimum Biofilm Eradication Concentration (MBEC) represents the concentration of antibiotics required to eradicate biofilms. Ceri et al. introduced the Calgary Biofilm Device in 1999, developing a novel MBEC measurement system using peg plates and reported that MBEC requires antibiotic concentrations 100 to 1,000 times higher than the Minimum Inhibitory Concentration (MIC) [1]. Biofilm formation makes implant-associated infections (IAI) in orthopedics difficult to treat, with the MIC-MBEC disparity jeopardizing successful outcomes[2-4]. The International Consensus Meeting (ICM) in 2018 highlighted the limited utility of MIC in bacteria forming biofilms and emphasized on the importance of MBEC [5]. However, achieving MBEC through systemic antibiotic administration is difficult to achieve without causing severe systemic adverse effects. Thus, there is a clear need for innovative local delivery systems or treatment strategies that can deliver high concentrations of antibiotics at the site of infection over a sustained period.

We conducted a systematic review, using specific MESH terms developed by librarians, to identify all relevant publications in the Medline and Embase databases, covering studies published up to November 2024. Search results yielded 997 publications in English language. Two of the authors went through title and abstract screening and discrepant results were reviewed by a third person. Then, 97 full articles were reviewed and 51 articles were referenced in this manuscript.

Antibiotic concentration and duration for MBEC varies by bacterial strain and antibiotic type [2, 6]. Moreover, MBEC is influenced not only by antibiotic concentration but also by the duration of exposure [7-9]. Prolonged antibiotic administration has been shown to reduce MBEC values by promoting deeper penetration and sustained bacterial eradication. Additionally, combined antibiotic therapies can effectively lower MBEC values through synergistic mechanisms[3, 10], though in some cases, a combination of antibiotics may inadvertently increase the MBEC [11]. Significant synergistic effects have been also observed when antibiotics are used in conjunction with anti-inflammatory drugs such as aspirin and ketorolac[8, 12, 13], essential oils [14], enzymes that degrade proteins, polysaccharides or DNA [15], nanoparticles [16], and antimicrobial peptides [17]. However, the challenge intensifies under in vivo conditions, where MBEC values for biofilm-associated infections on implants are significantly elevated compared to in vitro measurements [18, 19]. The synergistic effect of combination therapy has the potential to reduce the MBEC to an antibiotic concentration feasible for clinical use, however, its efficacy and safety in clinical practice remain unverified.

To achieve high local antibiotic concentrations, antibiotic-loaded bone cement (ALBC) is employed in orthopaedic procedures such as single and two-stage exchange arthroplasty [2, 20]. ALBC enable the localized delivery of high concentrations of antibiotics with sustained release over an extended period. However, this method is limited by a lack of high-quality evidence and the potential for antibiotic inactivation due to the heat generated during polymerization[21] Moreover, randomized studies have reported that most commercially available ALBC fail to maintain intra-articular antibiotic concentrations above the MBEC, with antibiotic concentration declining rapidly[22]. The use of static or articulating antibiotic spacers with high-dose antibiotic-loaded bone cement (ALBC) is widely recognized as an effective method for delivering high-concentration, sustained-release antibiotics directly to the infection site [2, 20, 23]. However, the high antibiotic concentration needed to achieve MBECs thresholds could lead to systemic toxicity and compromise the mechanical integrity of bone cement[24]. Calcium sulphate beads are also used for local antibiotic delivery, primarily in revision procedures, but have less favorable outcomes in Debridement, Antibiotics, and Implant Retention (DAIR) procedures and may increase the risk of implant surface abrasion [25].

Recent studies have demonstrated the efficacy of direct antibiotic administration into the joint or intramedullary cavity via catheters or intramedullary needles, as well as the use of biodegradable carriers for localized antibiotic delivery. Roy et al. [26] reported that intra-articular administration of vancomycin resulted in sustained high local antibiotic concentrations, while Young et al. [27] demonstrated that intraosseous administration of vancomycin achieved similar results, both when compared to intravenous administration. These methods have shown potential prophylactic benefits in total knee arthroplasty and total hip arthroplasty[27-29] . Such direct delivery techniques have been shown to maintain antibiotic concentrations exceeding the MBEC locally for a sustained period, though their use is predominantly prophylactic in elective orthopedic surgeries. In spinal surgeries, topical vancomycin is frequently employed for the prevention of surgical site infections (SSI). However, its preventive efficacy remains inconclusive [30].

Whiteside et al. investigated an intra-articular antibiotic infusion system designed for direct delivery to the infection site to disrupt biofilms in patients with periprosthetic joint infection (PJI) [31, 32]. This system achieved exceptionally high local antibiotic concentrations and demonstrated a success rate exceeding 95% in cases of PJI caused by MRSA or in patients with failed two-stage revision arthroplasty. Zou et al. highlighted that incorporating intra-articular infusion in single-stage revision procedures for PJI achieved high local antibiotic concentrations, likely exceeding the MBEC [33]. Springer et al. introduced an intra-articular antibiotic irrigation system for PJI patients and evaluated its safety through a Phase II prospective randomized comparative study using conventional two-stage revision arthroplasty as a control[34]. The study concluded that the intra-articular antibiotic irrigation system effectively elevated local antibiotic concentrations while minimizing systemic levels of antibiotics, with no significant increase in adverse events compared to conventional methods. The reported success rates of these intra-articular infusion are highly promising, achieving 90-100% in DAIR, 82-100% in single-stage revision arthroplasty, and approximately 80% in two-stage revision arthroplasty [35] . These findings suggest that intra-articular infusion may be a viable alternative to achieve sustained local antibiotic concentrations without compromising renal function[36]. Moreover, a recent study by Semeshchenko et al. examined the ability of five different irrigation solutions to achieve MBEC and reported that only povidone-iodine and silver nitrate successfully eradicated at least 99.9% of 24-hour biofilm, suggesting the potential for non-antibiotic approaches to achieve MBEC [37].

Maruo et al. developed Continuous Local Antibiotics Perfusion; CLAP, a method for treating bone and soft tissue infections by directly delivering high-dose gentamicin through intra-medullary and intra-soft tissue perfusion system while utilizing a negative pressure wound closure system to facilitate antibiotic distribution and manage dead space. The efficacy of CLAP has been firstly reported in managing fracture-related infections [38, 39] Additionally, its effectiveness in treating PJIs has also been documented [40, 41]. Choe et al. further explored the application of this method for fungal PJIs, administering micafungin at concentrations exceeding the MBEC against *Candida albicans* without observing significant adverse effects [41]. However, concerns have been raised regarding the potential cytotoxicity of such high local concentrations of antibiotics on osteoblasts [42]. Establishing an appropriate balance between effective antibiotic concentrations and minimizing cytotoxic effects remains a critical area for future research and clinical validation in direct antibiotic delivery technique.

Another approach for localized antibiotic delivery involves the use of biodegradable carriers. Ambrose et al. investigated a method of utilizing microspheres for antibiotic delivery by embedding antibiotics into polylacticglycolic acid to achieve homogeneous distribution, enabling steady-state release for up to four weeks at concentrations reaching the minimum bactericidal concentration [43-45]. These antibiotic-loaded microspheres demonstrated significant efficacy in eradicating infections and promoting favorable bone defect healing in a rabbit osteomyelitis model. Furthermore, technologies incorporating antibiotics into hydrogels have been commercialized as implant coatings and have shown utility in preventing SSI and PJI without significant adverse events [46, 47]. Hydrogels enable the delivery of high local concentrations of antibiotics over a sustained period and have the significant advantage of being biodegradable, eliminating the need for subsequent removal after their functional duration has elapsed[48-50]. Additionally, basic research is exploring methods to incorporate nanoparticles into hydrogels for more efficient localized delivery of antimicrobial agents[51]. Nanoparticles are becoming increasingly important in the treatment of biofilm-associated infections, although their clinical application has yet to be reported [52, 53].

In conclusion, currently two approaches have been explored in both basic research and clinical applications to achieve local antibiotic concentrations exceeding the MBEC: the direct infusion of antibiotics to the infection site using catheters or similar device, and the use of biocompatible carriers loaded with antibiotics to release high concentrations locally. These methods have been reported to have the potential to achieve MBEC levels at the infection site. However, the concentration and duration of antibiotics required to achieve MBEC vary greatly depending on the presence of implants, the bacterial strain, and the type of antibiotic. Furthermore, no definitive evidence currently exists to confirm that MBEC can be achieved in clinical practice. A further concern is that the high concentrations of antibiotics necessary to achieve MBEC may pose cytotoxic risks to surrounding tissues. Thus, there is still no clear evidence that MBEC has been successfully and safely achieved in clinical practice, and further clinical research is needed to address this clinical question in the future.

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