G86 – Should antimicrobial treatment target Minimal Inhibitory Concentrations (MIC) or Minimal Biofilm Eradication Concentration (MBEC) of organisms?

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Response/Recommendation: MIC susceptibility testing is utilized for identifying antibiotic-resistant strains and selecting effective therapeutic strategies for planktonic infections. If the causative microorganism can form biofilm *in vitro*, MBEC susceptibility testing may provide a more realistic insight into the empirical success of a specific antibiotic. Currently, however, the MBEC value is not a clinically available metric and has not been definitively linked to any impact on treatment recommendations. Future clinical studies are needed to evaluate if MBEC-guided treatment improves treatment success and patient outcomes.

Level of Evidence: Limited

Delegate Vote:

Rationale:

The minimum biofilm eradication concentration (MBEC) is a measure that is increasingly being evaluated as an indicator of antibiotic susceptibility *in vitro* biofilms. The growing recognition of biofilm resistance in implant-related and non-implant related infections has prompted interest in MBEC as a potential measure to guide treatment. There are currently no standardized measurement parameters (surface, age, duration of exposure) for MBEC susceptibility testing. This is counter to the minimum inhibitory concentration (MIC), a well-established value both clinically and microbiologically, which is assessed via a standard set of methods and breakpoints, such as those offered by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[1, 2] These MIC methods of susceptibility testing, although validated and reproducible, focus on the planktonic state of bacteria rather than bacteria within a biofilm state.[3]

A comprehensive literature search was conducted using PubMed and Embase databases, initially identifying 535 studies. Five hundred nineteen abstracts were screened, and 157 studies were assessed for eligibility as potentially relevant studies, of which 21 were selected for in-depth review.

Studies have shown that the MIC of pathogens can be achieved in surgical tissues at the time of implantation. For example, Komatsu *et al.* reviewed the pharmacokinetics of cefazolin in serum and hip joint capsule tissues during primary total hip arthroplasty and showed that cefazolin maintained supra-MIC levels for up to 3 hours.[4] MIC values for therapeutics have been detected in antibiotic spacers during the initial implantation and at the time of revision or reimplantation surgery.[5-8] Von Baum *et al.* and others have found that antibiotic concentrations within bone (both cancellous and cortical) can achieve MIC values for common pathogens.[9, 10] Favorable clinical outcomes have been achieved with quinolones, mainly when the peak serum/MIC ratio is ≥ 12, resulting in good bone penetration.[11] The amount of fluoroquinolones (2-6 μg/ml), cephalosporins (267-356 μg/ml) and amikacin(92-215 μg/ml) needed to achieve $MIC_{90}$of *Pseudomonas aeruginosa* biofilm from implant associated infections was significantly different than the same bacteria in planktonic form (fluoroquinolones 0.8 μg/ml, 19 μg/ml for cephalosporins, and amikacin 3) μg/ml.[12] In a preclinical model of

methicillin-resistant Staphylococcus aureus osteomyelitis, intramuscular moxifloxacin has been shown to improve outcomes at levels above the MIC (43 times) but below the minimum bactericidal concentration (MBEC).[13] Certain antibiotics have been found to have more effect than others in the treatment of implant-related infections. Tunney *et al.*. found that bacteria isolated from revision hip surgery were more susceptible to vancomycin and ciprofloxacin than to gentamicin. Minimum bactericidal concentrations (MBC, 99.9% killing) were significantly higher (10-1000 x) than MIC values.[14, 15] Additional work by Brady *et al.*. found that 20 staphylococcal isolates from implant infections had MBEC values higher than their MIC values and recommended MBEC testing in clinically relevant situations where implants or devices had to remain *in situ*.[15] While some antibiotics are ineffective against bacteria in biofilm,[16] rifampicin has shown the lowest MBEC/MIC ratios in staphylococcal strains causing periprosthetic joint infections. [17] The suggestion that antibiotics delivered at levels that achieve MBEC would improve clinical outcomes is made but not yet supported in the literature. The reporting of MBEC values can also vary based on clinical isolates, antibiotic selection, and antibiotic synergistic or antagonistic activity.[18] [19, 20] Meléndez-Carmona *et al.* found no relationship between antibiofilm activity (defined as biofilm-embedded cells recount and crystal violet staining) of levofloxacin, rifampin, and their combination, and the MBEC value when evaluating *S. aureus* isolates from patients with PJI who had undergone debridement and retention of components.[21] Subinhibitory treatments have led to increased biofilm formation and upregulation of genes related to biofilm formation.[22-25] Additionally, the susceptibility of biofilms to antibiotics may change over time with exposure. [24-27] This could be due to changes within the biofilm or the rapid emergence of small colony variants. However, this can vary depending on the bacterial species, clinical isolate, or location within a biofilm.[28] Clinical isolates, when in biofilm form, may also respond differently to combinations of antibiotics and adjuvants.[29, 30]
Malchau *et al.* demonstrated that strong biofilm production is associated with increased antibiotic resistance and a higher recurrence rate of periprosthetic joint infections.[31] Therefore, the characterization of biofilm abilities and MBEC susceptibility testing of clinical strains could serve as relevant clinical diagnostic tools to guide treatments or indicate when specific treatments are futile. The development of the MBEC, or methods to determine antimicrobial biofilm activity, has been described. [32] [15, 31, 33, 34] However, clinical studies need to verify the clinical relevance of the MBEC method.[28] A retrospective study found that in six out of seven patients with treatment failure, staphylococcal and enterococcal strains exhibited high minimum bactericidal concentrations (MBECs) against the antibiotics used to treat osteomyelitis associated with percutaneous orthopaedic implants. [34] A prospective clinical trial, where MBEC guides oral antibiotic therapy in the intervention arm, is currently underway; however, no data are yet available for review.[35] Moreover, not only the treatment success but also the tolerability of antibiotics at the required doses to achieve MBEC will be critical, as the amount of antibiotics needed to achieve the MBEC in vitro is often higher than what can be safely achieved *in vivo*. [36] While *in vitro* assessment of MBEC is possible, the measurement of biofilm eradication is reliant on more variables than that of MIC testing. Before the definition of breakpoints for clinical resistance is redefined, the parameters surrounding the MBEC method should be further identified and standardized. In the future, MBEC testing will become increasingly relevant in cases where implants cannot be removed or when dealing with recalcitrant infections. In cases where the MBEC is too high, alternative treatment strategies may need to be considered.

Conclusion: Strong biofilm production is associated with increased antibiotic resistance and a higher recurrence rate of periprosthetic joint infections. MBEC susceptibility testing could guide therapeutic treatments, though its clinical relevance needs validation. An ongoing clinical trial aiming to assess MBEC-guided therapy is currently underway. Standardizing MBEC testing parameters is crucial, and their relevance may increase in managing implant-related infections. Incorporating MBEC testing could improve treatment outcomes by providing accurate antibiotic dosing guidelines, but further research is needed to confirm its benefits.

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