Are antibiotics and surgery sufficient to treat biofilm-associated infections?

¿Son suficientes los antibióticos y la cirugía para tratar las infecciones asociadas a biofilms?

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The biofilm phenotype has been recognized relatively recently in medical history but it has rapidly become clear that the development of many, if not the majority of bacterial infections depend upon the formation of biofilms. Moreover, as the adherence of microorganisms to tissues is part of the process of acute infection, the impact of biofilm formation in infection might in fact be underestimated. Medical device-related infections are one of the clearest examples of biofilm-dependent infections. Such infections are most frequently caused by Staphylococcus epidermidis, Staphylococcus aureus, Pseudomonas aeruginosa and Enterobacteriaceae. Biofilm-associated infections contribute to patient morbidity and healthcare costs, as well as to the emergence and dissemination of antibiotic resistance in nosocomial settings.

At the phenotype level, a microbial biofilm can be characterized as a community of surface-adherent cells that exhibits tolerance to many antimicrobial agents and disinfectants that are otherwise active against the cells of the biofilm once dispersed into their planktonic state. Biofilms contain so-called persister cells, which are dormant cells capable of tolerating very high levels of antimicrobial agents.\textsuperscript{3} These persister cells are not resistant to antimicrobials in the classic sense, but instead appear to escape killing through what is hypothesized to be a transient dormant state. Even if the majority of the bacteria within a biofilm are killed by antimicrobial therapy, persister cells are capable of reestablishing infection after the threat is removed. The mechanism of dormancy of persister cells is not fully understood, but may be due to the expression of toxin–antitoxin systems.\textsuperscript{4} Consequently, global mechanisms of toxin–antitoxin system regulation and persister formation are potential targets for successful elimination of these dormant cells.

No definitive studies have addressed whether there is a systematic difference between the activities of bacteriostatic and bactericidal agents against biofilm-associated infections in vivo. Experimental biofilms formed by staphylococci are highly resistant to antibiotics that target cell wall biosynthesis while remaining susceptible to antibiotics that target RNA synthesis.\textsuperscript{5} Such a response is consistent with a diminished role for cell wall biosynthesis in the biofilm population and may reflect an ongoing role for transcription in biofilm establishment, maturation, and propagation. In addition to a growth-inhibiting effect, antimicrobial agents are signaling molecules. Exposure of bacteria to a subminimum inhibitory concentration of various classes of antimicrobials with diverse cellular targets globally affects gene expression regulating not only biofilm formation, but also stress response, virulence and motility.\textsuperscript{6} For example, the beneficial effect of low-dose chemotherapy with the macrolide azithromycin for the treatment of lung infection with P. aeruginosa may be partially due to its inhibition of biofilm formation.

The results of in vitro investigations of biofilm formation in clinical isolates have not been entirely consistent with the findings from in vivo studies. This might be due to the poor correlation between in vitro and in vivo biofilm formation.\textsuperscript{5} Recommendations for antibiotic therapies for the management of biofilm-associated infections have been driven largely by empiric observations and typically involve the use of surgery and antimicrobial combination regimens over extended periods.\textsuperscript{7} However, the existing regulatory climate does not provide a clear path toward the design and implementation of clinical trials to evaluate the efficacy of antimicrobials (or potentiators) in biofilm-related infection settings. Besides, there is limited current evidence of the pursuit of this approach in the pharmaceutical industry.

Clearly, we need novel strategies for the management of biofilm-associated diseases. Although in vitro investigation of biofilm formation has made significant progress over the last decade, the in vivo molecular mechanisms underlying biofilm pathogenesis remain poorly understood.\textsuperscript{8} To increase the activity of new treatment strategies against bacterial and fungal infections, factors that lead to biofilm growth inhibition, biofilm disruption, or biofilm eradication are being sought. These factors could include enzymes, sodium salts, metal nanoparticles, new antimicrobials,
cation chelators, chitosan derivatives, plant extracts, etc., which influence biofilm structure via various mechanisms and with different efficiencies. Many potential antibiofilm agents are under development, but at this point most are experimental, have not undergone clinical trials, and lack comprehensive pharmacodynamics analysis. In this journal issue, Leite et al. present the results of a study designed to determine the susceptibility of S. epidermidis biofilm cells to linezolid in combination with a non-antimicrobial drug (N-acetylcysteine), wherein each of which has different modes of action. Leite et al. show that the combination linezolid plus N-acetylcysteine has a synergistic effect, resulting in a 5-log reduction in the number of biofilm viable cells. This combination could be a potential candidate to combat S. epidermidis biofilm infections. Previous studies have shown that N-acetylcysteine decreases biofilm formation by a variety of bacteria including Escherichia coli, S. epidermidis, and P. aeruginosa. N-acetylcysteine inhibits bacterial adherence and reduce the production of extracellular polysaccharide matrix, while promoting the disruption of mature biofilms and reducing sessile cell viability. Antibiofilm therapies have a high potential of working synergistically with traditional antimicrobial agents and certain agents may exhibit increased efficacy if used in combination with a second antibiofilm that targets a different biofilm component. It is possible that certain antimicrobial agents may exhibit increased efficacy if used in combination with N-acetylcysteine.

Inhibition and/or reversal of the biofilm phenotype have become the focus of research efforts to develop new prophylactic and therapeutic agents. The biofilm phenotype is an attractive target because inhibition of biofilm formation or dispersal of established biofilms would result in maintenance of cells in or reversion of cells to a planktonic structure, which would be amenable to treatment with conventional antimicrobial agents, and to the host immune system. However, the complexity of biofilm formation makes it difficult to develop a compound that will affect this process. Dispersal strategies are attractive because they hold the promise of efficacy in established infections and do not need to be administered prophylactically. Because the biofilm matrix is composed of DNA, proteins, and extracellular polysaccharides, recent studies have indicated that the disruption of the biofilm structure could be achieved via the degradation of individual biofilm compounds by various enzymes (e.g., dispersin B, N-acetylcysteine, proteinase K, deoxyribonuclease). These strategies are therapeutically promising because once a biofilm is successfully dispersed, the resident bacterial cells lose the resistance mechanism inherent to biofilm growth, and their susceptibility to antimicrobial agents and immune defenses is restored.

Another promising antibiofilm strategy is the use of lysostaphin and staphyloolysin, microbial endopeptidases capable of breaking the pentaglycine bridge in the staphylococcal cell wall peptidoglycan. Targeting quorum sensing with farnesol or similar substances is also appealing as a therapeutic approach because inhibition is generally not detrimental to growth, relieving selective pressure to acquire resistance. Antimicrobial peptides are produced by a variety of multicellular organisms as a part of the innate immune response and are important to the host defense against infections. The combination of the ability to kill slow-growing or dormant cells, which predominate in biofilms, low rate of spontaneous resistance, and synergistic activity with certain antibiotics makes antimicrobial peptides attractive candidates for new approaches to biofilm therapy. At this point, they are clinically approved only for topical usage, but significant research effort is being invested to develop non-topical therapeutic uses. Phage therapy which, in the preantibiotic era, was used to treat bacterial infections has recently been shown to be effective in treating biofilm infections. In the same way, vaccine development may lead to the generation of vaccines against pathogenic biofilm bacteria.

Finally, medical devices that emit low-energy surface acoustic waves, electrical current, or pulsed ultrasound have been reported to either reduce device colonization or enhance the release and/or effectiveness of locally applied antimicrobials. In the latter category are the so-called intelligent implants, which are designed to locally release agents when they detect microbial colonization. In addition to such device modifications, new studies have evaluated the effectiveness of new antibiotic or microbiode immersion practices with medical devices to suppress surgical-site infections.

As a conclusion, increased knowledge about the molecular mechanisms of biofilm formation is important for the development and analysis of in vivo biofilm models and to establish innovative treatment strategies for biofilm infections. Personalized antimicrobial treatment strategies are likely to emerge in a future.

References