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Biofilms and antibiotic therapy: Is there a role for combating bacterial resistance by the use of novel drug delivery systems?

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Abstract

The conventional view of antibiotic resistance is one where bacteria exhibit significantly reduced susceptibility to antimicrobials in laboratory tests by mechanisms such as altered drug uptake, altered drug target and drug inactivation. Whilst these mechanisms undoubtedly make a major contribution to antibiotic failure in the clinic, the phenomenon of clinical failure in spite of sensitivity in laboratory tests is also well recognised. It is in this context that attention has focussed on bacteria growing as adherent biofilms, not only as the mode of growth of device-related infections associated for example with artificial joints and venous catheters, but also with other chronic infections such as those occurring in the respiratory tract. Growth as a biofilm almost always leads to a significant decrease in susceptibility to antimicrobial agents compared with cultures grown in suspension and, whilst there is no generally agreed mechanism for the resistance of biofilm bacteria, it is largely phenotypic. That is, when biofilm bacteria are grown in conventional laboratory suspension culture they become susceptible to antimicrobials. A number of elements in the process of biofilm formation have been studied as targets for novel drug delivery technologies. These include surface modification of devices to reduce bacterial attachment and biofilm development as well as incorporation of antimicrobials—again to prevent colonisation. Electrical approaches have been used either to release antimicrobials from device surfaces or to drive antimicrobials through the biofilm. Other technologies not specifically focussed on biofilms include aerosolized delivery of antibiotics to the lung and formulation into liposome and polymer-based vehicles. Liposomal systems have been widely studied, either to target antibiotics to the surface of bacterial biofilms, or by virtue of their property of being taken up cells of the reticuloendothelial system, to target antibiotics towards intracellular bacteria. Many polymer-based carrier systems have also been proposed, including those based on biodegradable polymers such as poly(lactide-co-glycolide) as well as thermoreversible hydrogels. Their contribution to the prevention or resolution of infection is reviewed.
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1. Introduction

In addressing the question of whether use of novel drug delivery systems can overcome antibiotic resistance, it is important to view resistance in the clinical context. It may not be an all-or-nothing response and decreases in susceptibility do not necessarily mean clinical failure if sufficient antibiotic can be targeted to the infection. It is in this scenario that novel drug delivery systems may have some benefit. Unfortunately, a different scenario typically prevails in the clinic where treatment fails in spite of antibiotic sensitivity in laboratory tests. In other words, clinical failure is often due not to infections with bacteria harbouring mechanisms resulting in high-level antibiotic resistance, but rather to bacteria that are phenotypically resistant in vivo.

2. Biofilms in infection

There is now widespread recognition of the contribution of biofilms to human infection. Previously thought to be the concern only of industrial and environmental microbiologists interested in phenomena such as biofouling, it is now clear that microbial biofilms are largely responsible for the recalcitrance of many infections to conventional antimicrobial therapy [1,2]. A microbial biofilm is broadly defined as adherent microorganisms within a polymeric matrix, typically comprising exopolysaccharide that develops into a complex community [3]. The composition is often heterogeneous with water channels occurring between glycocalyx-enclosed microorganisms in stalk- or mushroom-like structures. The structure is also a dynamic one and may include single or multiple microbial species [4]. Cases of biofilm infection include the well-known examples of device-related infections such as those associated with artificial joints, prosthetic heart valves and catheters. Even with the use of perioperative antimicrobial prophylaxis and a laminar air-flow surgical environment, the risk of intraoperative infection is still around 1% for hip and shoulder replacement and 2% after knee replacement [5]. With more than 200,000 hip replacements and 200,000 knee replacements each year in the United States alone, the healthcare costs are high. Recent surveys also indicate that catheter-associated bacteremia following catheter-related infection, is by far the leading cause of nosocomial bloodstream in-

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