ANTIMICROBIAL RESISTANCE IN BIOFILMS: A STICKY SITUATION

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1 BIOFILMS—A CLINICAL AND INDUSTRIAL PERSPECTIVE

In many environments, microbial cells are found associated with surfaces and form conglomerate structures termed *biofilms* [1]. During human infections, the formation of biofilms has been implicated, for example, in periodontitis, otitis media, cystic fibrosis pneumonia, endocarditis, and osteomyelitis. In addition, biofilms are often found on indwelling medical devices such as prostheses and catheters, leading to a high incidence of infections associated with the use of such biomaterials [2]. It is estimated that at least 60% of all microbial infections involve biofilms [3]. For pathogens, the beneficial associations with biofilm formation include protection against stresses by antimicrobial agents and host defenses. As a consequence of its key role in pathogenesis, biofilm formation is a significant determinant of infectivity and persistence [3–5].

Outside the medical domain, biofilm formation causes serious problems for industries, particularly in food-processing and water distribution systems [6, 7]. For example, when biofilms are established on the interior of metal pipes in the production lines, accelerated corrosion of the pipes and contamination of pipe contents may occur. Additionally, increased tolerance of microorganisms in biofilms to disinfecting agents such as chlorine, peroxides, and quaternary ammonium compounds has been frequently reported. As a result, billions of dollars are spent annually to rectify biofilm-related repercussions in the industries [8].

The increased recognition of the impact that biofilm formation has in the clinical and industrial settings has led to an explosion in the field of biofilm research over the past two decades. These studies led to the generation of several hypotheses to account for the exceptional ability of biofilm populations to resist antimicrobial killings. In this review, the various mechanisms of antimicrobial resistance will be examined with a specific emphasis on the predominant pathogens involved in biofilm-associated infections, that is, staphylococci, *Pseudomonas aeruginosa*, and the fungal pathogen *Candida albicans*.

2 ANTIMICROBIAL RESISTANCE IN BIOFILMS DIFFERS FROM THAT IN PLANKTONIC CULTURE

It has become clear in several studies that mechanisms of resistance to antibiotics can differ significantly between biofilm and planktonic cells. A classic example is the resistance to β-lactam antibiotics such as ampicillin. In biofilms of *Klebsiella pneumoniae*, resistance to β-lactams was not correlated with the production of β-lactamase [9]. The penetration of ampicillin was impaired in the biofilms of wild-type cells, whereas biofilms formed by a β-lactamase mutant were fully penetrated by the antibiotic. Despite that, biofilm cells of the β-lactamase mutant were resistant to ampicillin, suggesting that mechanisms other than degradation by β-lactamase were responsible for the observed β-lactam resistance. The findings obtained in this and similar studies have prompted researchers to take a more detailed look at the specific mechanisms of antimicrobial resistance in biofilms (Fig. 1).

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