

## Biofilms in the ICU

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### WHAT ARE BIOFILMS?

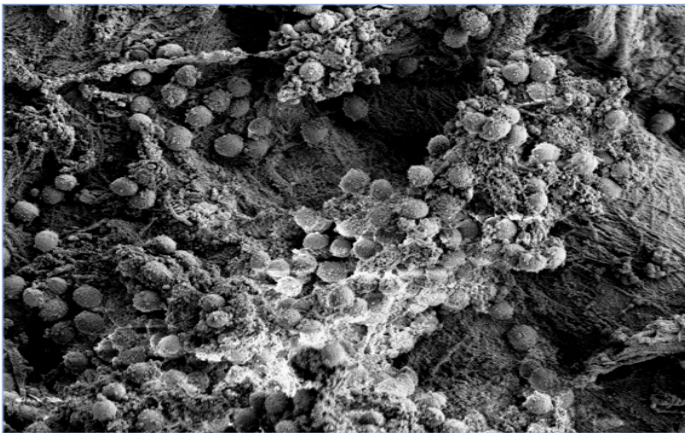
Biofilms are communities of microorganisms that are adherent to a surface and/or each other and are surrounded by a self-secreted, hydrated matrix composed of polysaccharides, proteins, water, and nucleic acid, often referred to as extracellular polymeric substance or EPS (Figure 1).<sup>1</sup> These communities can be homogeneous but are often polymicrobial and may include bacteria and fungi. Biofilms are not a new problem, but the perspectives of the microbiologists studying them are relatively new. Since Robert Koch developed the methodology of pure culture, microorganisms have been removed from their native

environments and propagated for study under completely artificial conditions. We now know that these techniques create a selection bias for cells growing in the planktonic, or 'free-living', phenotype, while the biofilm phenotype is the dominant mode of growth for most microorganisms on the planet.

### WHY ARE BIOFILMS SO DIFFICULT TO TREAT?

The differences between bacteria in a biofilm versus the planktonic phenotype are striking. Compared to planktonic cells, biofilm cells have modified doubling times and transcriptional profiles and significantly reduced susceptibility to antimicrobials. Of course, it is this reduced susceptibility to antimicrobials that makes them clinically important. Bacterial cells in biofilms can be up to 1000 times more tolerant to antibiotic agents than free-living planktonic cells.<sup>2</sup> Biofilm-related antibiotic tolerance is a transient, non-heritable phenotype distinct from conventional mechanisms of antibiotic resistance, which are genetically transferable. Several mechanisms may explain drug tolerance within biofilms.<sup>3</sup> The two most widely accepted theories are that bacterial cells adopt a sessile or dormant state when living in a biofilm rendering them less susceptible to antibiotics that act only on proliferating cells, and that the EPS surrounding the cells provides a mechanical shield that can inhibit the penetration of antimicrobials.

The classic clinical hallmarks of biofilm infection include the 3Rs- resolution, relapse, and recalcitrance. The chronic cycle of infection begins soon after a biofilm has formed on some surface within the body (Figure 2). As planktonic cells are shed from the biofilm, symptoms of infection are apparent as the immune system mounts a defense. The immune response and antimicrobials effectively kill these planktonic cells, resolving symptoms, and seemingly

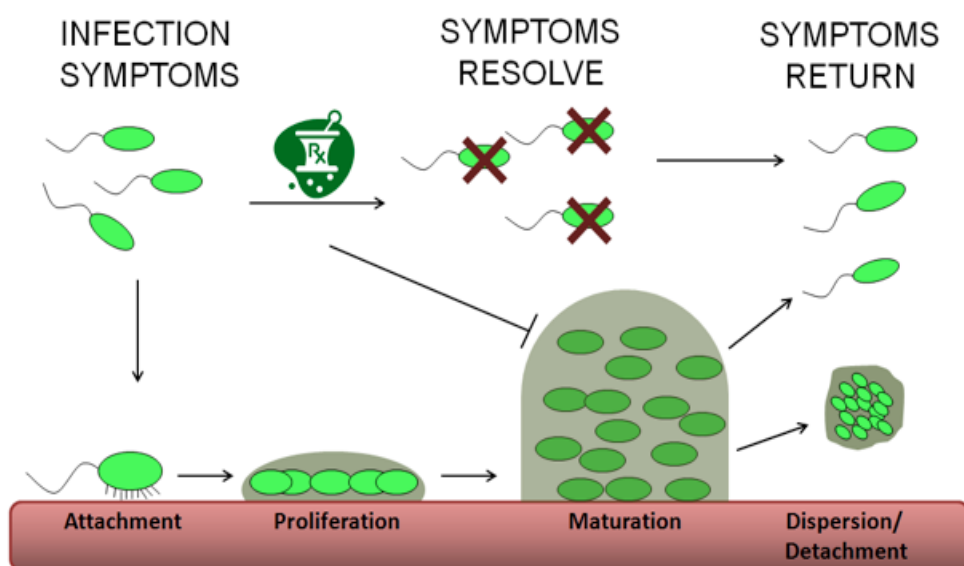


**Figure 1.** Scanning electron micrograph of a *Staphylococcus aureus* biofilm growing in an in vitro wound model. Clusters of *S. aureus* cells are coated by a stringy substance which is thought to be EPS. It should be noted that during processing for SEM the EPS becomes dehydrated and flattened. Image at X5, 000 magnification (Rumbaugh laboratory).

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clearing the infection. However, dormant biofilm cells remain, and once the antimicrobial pressure is lifted, symptoms return. This cycle can continue indefinitely through many rounds of antibiotics and is commonly seen in biofilm-related diseases, such as otitis media, tonsillitis, chronic wound infections, urinary tract infections, and sinusitis.<sup>4</sup>

establish a biofilm. It is estimated that 20% of ICU patients will get a healthcare-associated infection (HAI), which can result in considerably increased hospital stays, costs, morbidity, and mortality.<sup>5</sup> The majority of these HAIs are biofilm-based and medical device-related. It is thought that biofilms allow microbes to persist in the environment despite significant disinfection



**Figure 2.** Cycle of biofilm infection. Bacterial cells in planktonic or free-living form enter the body and proliferate, alerting the immune system and resulting in infection symptoms, such as fever and malaise. These cells may also enter the 'biofilm mode of growth' by attaching and proliferating on an abiotic or biotic surface and then differentiating into a mature biofilm community surrounded by EPS. While antibiotic and immune mediators effectively kill planktonic cells, those within biofilms remain viable. Bacterial cells can leave the biofilm community by active dispersion, returning to their planktonic form and reinitiating infection symptoms. Detachment of biofilm cells by mechanical disruption can also result in biofilm growth at other locations.

## WHY ARE BIOFILMS PARTICULARLY PROBLEMATIC IN THE ICU?

Several aspects of intensive care units (ICUs) make them the ideal environment for very dangerous biofilm infections. First, the hospital environment is notoriously associated with microorganisms that cause nosocomial infections, many of which already possess multidrug resistance. Second, ICUs typically house the frailest and most immunocompromised patient populations. And last, the insertion of many types of foreign bodies (e.g. catheters, endotracheal tubes, central lines, etc.) provide an ample variety of surfaces to which microbial cells can adhere and es-

tion efforts. A recent study demonstrated that multi-drug resistant microbes in biofilms persisted on clinical surfaces in an ICU even after terminal cleaning, indicating that conventional disinfection procedures are not adequate.<sup>6</sup> Consequently, urinary tract infections, which are the most common HAI, affect over 400,000 patients/yr in U.S. hospitals.<sup>7</sup> Bloodstream infections related to central venous catheters (CVC) affect 200,000 patients/yr and 30% of CVC infections in ICU patients are associated with septic shock.<sup>8</sup>

## HOW CAN WE DETECT BIOFILMS ON SURFACES?

Biofilms can form on virtually any environmental surface, but porous or uneven surfaces and those

with grooves, pits, or other imperfections and/or surfaces that are located in humid areas are more prone to biofilm contamination. Once formed, biofilms can persist in the environment despite stringent cleaning efforts and desiccation and detecting them is a major challenge.<sup>6</sup> There are no specific tests, stains, or indicators for biofilms; although, researchers are working towards this goal. Furthermore, cells that are in biofilms can become metabolically dormant, making infection control surveillance, which relies on culturability, ineffective. Thus biofilms may be present even when surfaces are ‘culture negative’. Contemporary methods for identification of biofilm-contaminated surfaces rely on visualization with electron microscopy and/or detection of microbial nucleic acids, techniques that are not commonly available at most hospitals.<sup>6,9</sup>

**WHAT CAN BE DONE TO PREVENT AND/ OR TREAT BIOFILM-RELATED INFECTIONS?**

This question is the subject of intense research in academia as well as in the pharmaceutical industry and was the subject of a recently-published book.<sup>10</sup> The major strategies being pursued to prevent and/or treat biofilm-related infection are listed

in Table 1. Most of these agents are designed to be used in conjunction with conventional antibiotics that kill planktonic cells. Unfortunately, most of these interventions are in the research and development stage and face a long, expensive road to commercialization, filled with many regulatory hurdles. Currently, the most effective treatment option is removal of the biofilm-affected surface. While this is relatively easy to do in device-related infections, biofilms established on human tissue, such as in chronic wounds, often require the amputation of a limb.

In summary, biofilms are a significant problem for hospitals in general and even more so for ICUs. Researchers now have a good understanding about how and where biofilms form, but large gaps in our knowledge remain about prevention, detection and treatment of biofilms. As the medical costs spent on biofilm-related infections and the number of patients they affect continue to rise, scientists hope that funding agencies will make available more support for research in this field.

**KEYWORDS:** Biofilm, ICU, hospital-acquired infection, antibiotic tolerance, antibiofilm agents

Strategy	Target(s) and examples
Degradation or penetration of EPS	Enzymes that catalyze the hydrolysis of exopolysaccharides or physical strategies that disrupt the EPS allowing better antibiotic penetration (e.g. electric current, ultrasound waves, photosensitizers, nanoparticles)
Quorum sensing inhibitors	Disrupts the cell-to-cell signaling systems used by some bacteria to facilitate biofilm formation (e.g. chemical analogues, antibodies to signals or signal receptors)
Bacteriophage	Highly specific natural bactericidal viruses that are being engineered to express EPS-degrading enzymes
Antimicrobial surfaces	Inhibition of bacterial adherence with various surface coatings (e.g. hydrophilic polymers and impregnation of antimicrobial agents)
Dispersing agents	Agents that promote the dispersion of bacterial cells from the biofilm so they can be killed in their planktonic form by conventional antibiotics

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