CLINICALUPDATE

Biofilm:
Secret Refuge of the Microbial World

By Steve Bierman, MD

Regardless of when you graduated, there was a surprising omission in your medical education, one that could jeopardize the very life and limb of your patients. It's difficult to imagine, but somehow a fundamental element of our understanding of infectious diseases was simply not included in the curriculum. That element is bacterial biofilms.

Did you know, for example, that all devicerelated infections involve bacterial biofilms? Or that the reason vegetations are so refractory to antibiotics is because the biofilm that forms such vegetations is protective of its bacterial components? Or that the three major device-related infections targeted this year by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), namely, ventilator-acquired pneumonia, catheter-related bloodstream infection, and catheter-associated urinary tract infection, all entail biofilm formation?

You probably did not know that, because you were not taught about biofilms in school. Fortunately, it is never too late to learn. With nosocomial infections running rampant in our nation's hospitals, there is now some urgency. Chances are, one of your present patients is harboring a biofilm infection right now.

Here's an example from 1975. An intern is charged with the daily management of a ventilator-bound, fully-instrumented ICU patient with multiple-systems failure. He is dutifully concerned with the patient's fluid status and so accounts for intake and output (I&O) assiduously. A Foley catheter is placed to assure accuracy of output measurements. A central line is in place to assess central venous pressure. Days go by, some good, some bad. Now and again, the patient spikes a fever. A septic workup discloses 10-log-4 bacteriuria, negative culture on CVC tip, and persisting pseudomonas on tracheal aspirate. An infectious disease consult recommends triple antibiotic therapy and removal of the Foley catheter. Antibiotics are administered; the Foley remains. For a few days, there are no further fever spikes. Then, the patient crashes: overwhelming pseudomonas sepsis, all systems fail, and then death ... death from overwhelming infection, despite triple-drug therapy and perfect fluid balance.

What was the source of the infection? Was it the respiratory tract or ventilator apparatus? Was it an indwelling vascular catheter or the Foley catheter? The answer is, we do not know. What we *do* know is that the offending organism took refuge under cover of a biofilm, developed resistance, proliferated, and then emerged with lethal force. We know that without a doubt, the Foley was encased in biofilm, the vaporous ventilator tubes had biofilm encrustations, and, in all likelihood (and regardless of the negative culture), the CVC had biofilm on it.

Couldn't happen today, you say. Here's an example from April 2005. The intern is now a seasoned physician, at the ICU bedside of a critically ill friend. He notes that the friend's Foley has been in for eight days. Diapers or an external catheter would suffice. "I'd like you to remove the Foley," he tells the young intensivist. "I can't," is the reply, "We need it to assess his I&O." The patient dies two days later of Enterococcal sepsis. The physicianfriend requests the lab give him the Foley. It is sent to a biofilm expert at USC. It is found to be encrusted with biofilm over 85 percent of its surface.

Biofilm Basics

A bacterial biofilm is defined as a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface. You may be more familiar with biofilm's vernacular name ... slime.

Many species of bacteria implicated in disease states form biofilm. These include certain Streptococci, Staphylococci, Enterococci, Pseudomonas species, and enteric bacteria. Some biofilms involve a single bacterial species; others involve multiple bacterial species and, sometimes, fungi.

One may think of biofilm formation as progressing through four functional states: adhesion, aggregation/micro-colonization, biofilm formation, and detachment/dispersal. The process proceeds, schematically, as follows. Freely mobile (so-called "planktonic") bacteria recognize and attach to a hospitable surface (i.e., moist and free of biocides). Once attached, the bacteria aggregate into micro-colonies. Thereafter, chemical signals are released within and between microcolonies and biofilm formation — exopolysaccharide encasement — begins. Once biofilm is formed, "a natural pattern of programmed detachment" of planktonic bacteria ensues, and the process recommences elsewhere.[1]

It is critically important to understand that planktonic bacteria, freely afloat and unshielded by protective excretions, are generally susceptible to endogenous antibodies and exogenous antibiotics. Sessile bacteria, encased in biofilm, are generally not susceptible to either. Thus, device-related infections that initially respond to antibiotics and then recur upon cessation of therapy are, in fact, reflecting the vulnerability of planktonic bacteria and the invulnerability of sessile forms. This is why removal of the biofilm-encased device is usually the only means to effect a lasting cure.

Anti-Biofilm Strategies

Biofilm prevention and treatment can theoretically be achieved by interfering with any of the aforementioned phases. Regrettably, we are so early in biofilm science that many approaches have yet to make if from the laboratory to the bedside. As you will see, the key clinical approaches now in place center on prevention of bacterial attachment and on limitation of detachment and dispersal.

What follows is a brief overview.

Attachment: A great deal of effort is currently being dedicated to the prevention of bacterial attachment. Of course, the best approach is primary prevention, meaning the scrupulous avoidance and elimination of surfaces on which bacteria might attach. Eliminating sutures or staples, electing to use an external urinary catheter, early removal of a CVC — these are all examples of primary prevention of bacterial attachment to artificial surfaces. Another primary prevention strategy in common use is prophylactic antibiotics for selected surgical procedures. Especially where prosthetics are being placed, this strategy has proven effective. Kill the planktonic bacteria before attachment can occur and the device will not become the substrate for biofilm development.

It should be noted, however, that prophylactic antibiotics often do not work to discourage bacterial attachment and colonization, as in the case of indwelling urinary catheters. How, then, do we further prevent (known as secondary prevention) attachment of bacteria to these surfaces?

A silver-hydrogel coating, as one example, is already being employed for this purpose in medical device manufacturing of selected Foley catheters. Foley catheters inevitably become encased in bacterial biofilm if left in place for several days or more. Randomized, prospective, controlled clinical trials, with catheter-associated urinary tract infections (CAUTIs) as the principal endpoint, have proven a 25 percent or better anti-infective efficacy with silver-hydrogel. [2]

Other silver ion coatings and impregnations, as well as several antibiotic coatings, are also in commercial use. The intent of all these technologies is to kill planktonic bacteria that arrive at the surface of the device, thus preventing attachment. Antibiotic-coated central venous catheters are another highly efficacious example.

Aggregation: Formation of micro-colonies on a device or biological surface is, again, the focus of much study. In addition to various kinds of chemical interference, novel electrical and biologic interference strategies are currently under investigation.[3] To date, however, bacterial aggregation is best prevented by strategies that kill planktonic bacteria before attachment and aggregation can occur.

Biofilm formation: Strategies disrupting this phase of bacterial implantation divide into two categories: intralumenal strategies and extralumenal strategies. Perhaps the oldest extralumenal strategy is to prevent accumulation of fluid which could predispose to biofilm formation. When applicable, as in certain surgical settings, this approach is effective. Think surgical drains. However, no such applicability exists for indwelling devices like urinary or vascular catheters. In such cases, it must be said that extralumenal strategies to interfere directly with biofilm formation (following attachment and aggregation) are sorely wanting.

Intralumenal strategies to affect biofilm formation are early stage, but promising. Two prominent researchers have recently disclosed novel flushing solutions, tetra-sodium EDTA and high-concentration ethyl alcohol, that appear to disrupt intralumenal biofilm.[4] The prospect of phyto-chemical interference is also under study.

Detachment and dispersal: Paradoxically, bacterial detachment and dispersal from biofilm is perhaps the least-well understood phase of biofilm activity, and yet the one in which the most successful clinical interventions can be achieved. We simply do not understand fully how a bacterial biofilm grows, differentiates and then "programmatically" releases planktonic fragments into the environment. What are the genetically determined messengers or signals involved in these processes? What are the triggers for activation? Not known.

What we do know is that shearing forces — mechanical or hydrodynamic — applied to biofilm literally "shave off" slices or shards of infectious material. For example, such shearing forces are regularly generated by pistoning of CVCs and jerking or tugging of urinary drainage catheters. A patient turns suddenly, their IV line or drainage tubing snags, and for that brief moment, tremendous shearing forces are transmitted down the line. Suddenly, briefly, a shower of bacterial shards is liberated from the traumatized biofilm. Infection often results.

Limitation of shear forces can have dramatic effects on the infectivity of biofilm. (Remember, if left quiescent and undisturbed, bacterial biofilm can often coexist in a host with relatively little adverse effect.) In this regard, surprising new data has emerged from several well-designed clinical trials demonstrating that fixation of vascular and urinary catheters (such that shearing forces are not transmitted down the catheter and into the bloodstream or bladder) does, in fact, reduce infectious complications. A novel mechanical fixation device was shown in two studies to reduce catheter-related bloodstream infections up to 88 percent (from 9.4 percent to 1.1 percent),[5] while in one multi-center trial, the same brand of fixation device resulted in a 45 percent reduction in CAUTIs.[6]

In the years to come, we hope to see devices whose surfaces more effectively discourage bacterial attachment and aggregation; technologies that interrupt biofilm formation; and approaches that interfere with biofilm detachment and dispersal. In the meantime, a good understanding of biofilm behavior will alert us to clinical situations that might predispose to this danger and guide us to treatments that sensibly address what is a ubiquitous issue in modern medicine.

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