Infections With Biofilm Formation

Selection of Antimicrobials and Role of Prolonged Antibiotic Therapy

Trevor Beaudoin, PhD, and Valerie Waters, MD, MSc

Biofilms are groups of bacteria attached to themselves and/or a surface and encased in a self-secreted matrix or slime. The National Institute of Health in the United States estimates that 80% of all infections are associated with organisms forming biofilms. The process driving biofilm formation from planktonic (free-swimming) bacterial populations is complex and arises as an adaptation of the bacteria to environmental cues. A general biofilm model for the formation of a bacterial biofilm can be described. In brief, the process consists of 5 genetically distinct steps: (1) initial bacterial attachment, (2) surface formation of a bacterial monolayer, (3) migration of bacteria to form microcolonies, (4) increased production of extracellular matrix and (5) maturation of the 3-dimensional architecture of the biofilm (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C438). In addition, bacterial biofilms can undergo dispersion by releasing planktonic cells, allowing for dissemination of the biofilm to other locations in the environment or the body.

Biofilms are a particular concern to clinicians primarily because they contribute significantly to antimicrobial resistance, rendering these infections difficult to treat. Many studies have shown that bacterial biofilms have the ability to survive following exposure to high levels of various antibiotics. This has been attributed to a number of factors including interaction of the antibiotic with the extracellular matrix, an increase in the expression of efflux pumps during initial attachment of bacteria and the slow growth of bacteria within areas of the biofilm. As a result, biofilms are up to 1000 times more resistant to antibiotic treatment when compared with traditional, planktonic susceptibility testing. In addition, several studies have noted the inability of host immune cells to eradicate biofilm infections, resulting in a nidus for recurrent infections.

INFECTIONS IN WHICH BIOFILMS PLAY A ROLE

Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disease resulting from mutations in the cystic fibrosis transmembrane conductance regulator gene, leading to defective chloride ion transport at the epithelium. Although it is a multisystemic disease, the primary cause of morbidity and mortality in patients results from repeated bacterial infections of the airways, ultimately resulting in respiratory failure. Although the etiology and consequences of these infections go beyond the scope of this review, chronic infection with Pseudomonas aeruginosa has been identified as a biofilm-based infection. In fact, it is one of the most well-characterized biofilm infections described in the literature. Both electronic microscopy and in vivo analysis of bacterial signaling molecules indicate that P. aeruginosa grows as a biofilm. Biofilms grown in the CF lung seem to consist of aggregates of bacteria distal from the airway surface, embedded within the thick mucus layer of the airways. Initial infection can usually be eradicated with antibiotic treatment, with rates of clearance reported to be 80%–85%. Once chronic P. aeruginosa infection develops, however, eradication is much more difficult and the aim of treatment shifts to chronic suppressive treatment, typically with inhaled antibiotics. Delivering antibiotics via aerosolization allows for higher pulmonary drug concentrations to be achieved, which have been shown to inhibit and even kill cells within the biofilms of many Gram-negative CF pathogens.

BIOFILM INFECTIONS ON Biotic SURFACES

Bacteria can attach directly to biotic surfaces, such as the skin, to form biofilms. Biofilms have been shown to be important...
in chronic wounds derived from pressure or diabetic ulcers, with >60% of these wounds harboring biofilm bacteria, compared with <6% of acute wounds.4 Numerous bacteria have been implicated in burn wound infections, derived from the normal flora of the skin (predominately Staphylococcus aureus) and from environmental sources such as water (primarily P. aeruginosa). These biofilm infections cause delayed epithelial maturation and wound closing, leading to increased scar tissue and chronic wounds. Invasion of microorganisms into the tissue layers below the dermis may also result in bacteremia and sepsis.

Biofilms have also been shown to play an important role in cases of chronic otitis media with effusion, one of the most common illnesses for which a child will see a physician or receive antibiotics. Chronic otitis media with effusion results from persistent bacterial infection despite the absence of culturable bacteria and recurrence is attributable to the original infecting organism, both hallmarks of biofilm-based infections.5

Endocarditis, frequently caused by S. aureus or Streptococcus spp., is another common example of a biofilm formation on a biotic surface. The valve lesion consists of a complex biofilm formed from bacterial and host-derived factors, such as fibrin and platelets. Not only does this biofilm disrupt the function of the valve, it acts as a bacterial reservoir leading to persistent bacteremia, despite antibiotic treatment.6 Biofilms may also be involved in the pathogenesis of chronic osteomyelitis. At least 1 study has shown direct evidence for biofilm formation in bone infection, and biofilm infection is hypothesized to play a role due to the behavior and recurrent nature of the infection.7 Of interest, a recent study has shown that secreted products from bacterial biofilms can inhibit osteoblast formation in vitro, which could potentially lead to bone destruction and explain some of the consequences of the disease.8

DEVICE-RELATED INFECTIONS

Indwelling medical devices, including catheters (urinary and intravascular) and endotracheal tubes, as well as implanted surgical devices, are sources of microbial colonization and biofilm infection. In one study, the incidence of catheter-related blood stream infections and catheter-related urinary tract infections in the pediatric intensive care unit was reported to be as high as 10.6% and 26%, respectively.9 A wide variety of pathogens have been associated with indwelling medical devices including Klebsiella pneumoniae, P. aeruginosa, Acinetobacter baumannii, Escherichia coli and Staphylococcus spp.; these can originate from commensal flora or be hospital-acquired. Prosthetic implants, such as spinal rods, are also susceptible to infection by biofilm-producing organisms.10 Postoperative colonization of surgically implanted devices can occur as a result of bacteremia, as the device offers a surface that the bacteria can seed or during the procedure to insert the device. New methods of prevention and treatment, including antibiotic biomaterials, are currently being studied including new materials that use antiadhesive material (such as a hydrogel or superhydrophobic polymer chains) or are infused with bactericidal agents directly bound to the device.

ANTIBIOTIC SELECTION AND DURATION OF TREATMENT

The selection and method of administration of antibiotics are crucial in the treatment of biofilm-based infections. Several considerations should thus be taken into account when selecting antibiotic treatment courses for biofilm infections (Table, Supplemental Digital Content 2, http://links.lww.com/INF/C439). First, the growth rate of bacteria within biofilms is a major factor in the ability of many antibiotics to effectively kill. In particular, the efficacy of β-lactam antibiotics is dependent on bacterial growth rate, with the rate of kill being proportional to the rate of growth of the bacteria, as they target the cell wall of dividing cells. Because the bacterial population in a biofilm is stratified, with faster growing cells on the surface and slower growing populations in the biofilm core, β-lactams are only effective on the outer portion of biofilm cells. It has been reported that meropenem and imipenem (carbapenems), as well as gentamicin, work better against very slow-growing Gram-negative bacteria, whereas fluoroquinolones (such as ciprofloxacin) can work against both slow-growing and nongrowing bacteria.11 In addition to slow growth, the surrounding environment of the bacteria within the biofilm can affect the efficacy of antibiotics. Localized acidosis at the site of biofilm infection, as a result of increased inflammation, may alter the pH and inactivate antibiotics. The biofilm matrix is another major barrier to several classes of antibiotics commonly used. In particular, aminoglycosides such as a tobramycin have been shown to directly interact with the biofilm matrix or secreted products produced specifically by biofilms. This sequesters the antibiotics outside the cell where they are unable to target bacterial cell functions such as protein synthesis. It has also been shown that in vitro efflux pump expression is up-regulated during the initial attachment phase of biofilm formation, increasing resistance to a number of classes of antibiotics, including aminoglycosides and fluoroquinolones. Macrolide antibiotics have been shown to be effective against alginate-producing, Gram-negative organisms within biofilms, specifically P. aeruginosa. However, in biofilms of Gram-positive species such as Staphylococcus spp., they may induce increased adhesion and biofilm formation. Trimethoprim/sulfamethoxazole is often used in CF for the treatment of patients with Burkholderia cepacia complex pulmonary infection. Linezolid (2 mg/mL), alone or in combination with rifampin, has also been shown to be effective in clearing mature biofilms from catheters in vitro. However, this requires exposure with high doses for up to 10 days to prevent relapse and so is more suitable for lock therapy.12 Glycopeptides, such as vancomycin (10 mg/mL) showed a similar effect when given for 10 days. In addition to these barriers to effective antibiotic treatment, biofilms can harbor populations of “persister” cells within the biofilm. These cells (bacteria) are embedded within the biofilm matrix and are not actively growing, thus they can withstand the majority of the initial antibiotic treatment. They are also protected from the immune system by being within the biofilm. It is thought that these persister cells can act as a reservoir to reestablish infection, making the biofilm harder to clear. To overcome these cells, new antibiotic classes that target biofilm barriers and the extracellular matrix are required.13

There have been no systematic studies of the optimal dose and duration of antibiotic treatment of biofilm infections. Ideally, the goal is to prevent the establishment of bacterial biofilms such as with successfully eradication of initial P. aeruginosa infection in children with CF. In vitro experiments have shown that “young” biofilms (24-hour biofilms) are easier to treat compared with more mature biofilms.14 In addition, the current evidence suggests that biofilm infections require higher doses of antibiotics to achieve eradication. Therefore, using the optimal delivery method (such as aerosolized antibiotics for airway infections or topical antibiotics for skin infections) to achieve the highest possible concentration at the site of the biofilm infection is warranted. In addition to high-dose antibiotics, in vitro evidence suggests that combination therapy may be useful for biofilm infections. The resistance of Staphylococci biofilms was shown to be high for individual antibiotics; however, a number of different combinations were found to be effective at eradicating these biofilms, with rifampin being the most common drug used in combination.15 Because biofilms are difficult to eradicate once established, there may be a role for prophylactic antibiotic treatment in the case of surgical implantation of devices; however, it is currently unclear how
long this should be given to prevent biofilm infections from forming. Once bacterial biofilms are established, controlling the source of infection, by removal of colonized prosthetic devices, for example, is the most effective way of clearing biofilms. In instances when source control of the infection cannot be achieved, chronic suppressive therapy may be required, for months to years in cases of indwelling medical device infections, and potentially lifelong for persistent P. aeruginosa pulmonary infections in CF patients.

There is also some evidence to suggest that during periods of acute pulmonary exacerbations, some CF patients respond more slowly to therapy and are thus treated with antibiotic durations beyond the standard 14 days. It is important to note, however, that prolonged antibiotic exposure is associated with cumulative drug toxicity and bacterial adaptations such as increased efflux pump expression, among other biofilm antimicrobial resistance mechanisms.

CONCLUSIONS

Chronic infections in children highlight the importance of bacterial biofilm formation and its impact on the efficacy of antibiotic treatment. It is important to understand the barriers biofilms pose to the delivery and activity of antimicrobials to select therapeutic regimens with the highest chance of success. Methods of drug administration that can help achieve high concentrations within bacterial biofilms, such as liposomal encapsulation of antibiotics, are currently under investigation. However, further research is needed to develop additional compounds that can penetrate the extracellular matrix of biofilms to permit the entry of antimicrobials and allow clearance of these infections.

REFERENCES