

Pending a comprehensive analysis, the best estimates must be made and acted on, a response reflected in the current move to increase US medical school capacity. Given the time required to train competent physicians and the growing reliance on other nations to provide physicians, it would seem in the national interest to err on the side of expanding US medical schools. The alternative is to risk the devastating effects of a physician shortage—effects almost certain to be felt most acutely by those in the greatest need—that would require many years to reverse.

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Biofilms and Chronic Infections

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THE PREVAILING PARADIGM OF INFECTIOUS DISEASE IS based on the work of Koch and colleagues, who more than 150 years ago isolated individual strains of bacteria and developed the pure culture method that is still used today. That work enlightened medicine by firmly establishing the germ theory of transmissible diseases and demonstrated that diseases like dysentery, tuberculosis, and anthrax are caused by microbiological agents.¹ Hence, the field of microbiology developed around Koch's methods with clinical microbiologists working overwhelmingly with pure log-phase cultures in nutrient-rich media because this approach provided such a powerful tool for the study of acute epidemic bacterial diseases. However, this approach that examines only planktonic bacteria (free-floating, single cell phenotype) may have limited development of a more thorough understanding of microbial processes. In most natural environments and in chronic bacterial infections, the planktonic phenotype generally exists only transiently, and usually as a minor population.

Emerging evidence describes bacterial populations as predominantly polymicrobial, sessile, community-based aggregations embedded in a self-secreted matrix that provides numerous advantages for persistence in the face of

environmental and host challenges. Therefore, biofilms and the existence of a complex bacterial life cycle provide a new perspective through which to view infectious diseases. Much of the support for this perspective has come about through the application of new detection and visualization methods that have provided evidence for the theory that chronic infections are fundamentally different than acute infections, and that different interventional approaches are necessary to treat these biofilm infections more efficiently.

What Is a Biofilm?

A biofilm is a thin layer of microorganisms that adhere to the surface of an organic or inorganic structure, together with their secreted polymers. Biofilms are the predominant phenotype of nearly all bacteria in their natural habitat, whether pathogenic or environmental. The biofilm provides a bulwark against environmental stressors and can include organisms from multiple kingdoms as in the case of mixed bacterial-fungal biofilms. Thirty years ago, Costerton et al² was the first to examine the attributes of biofilms, examining the extracellular polymeric substances (EPS) that holds these community bac-

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teria together. He and other researchers have since implicated biofilms in diverse abiotic and biotic systems, including oil pipelines, hot tubs, teeth, and mucosa. Thus biofilms, with their community defenses, are a ubiquitous feature of bacteria in nature and in some bacterial infections.

The resident bacterial community in a biofilm has added defenses and multiple mechanisms for survival, such as defenses against phagocytosis, UV radiation, viral attack, shear stress, and dehydration, as well as against biocides, antibiotics, and host immunity. Biofilms have demonstrated the ability to persist in 100 to 1000 times the concentrations of antibiotics and biocides that can inhibit planktonic cells.³ Similarly, granulocytes, macrophages, and other phagocytes are unable to engulf a biofilm as they would individual planktonic cells. The genotypic and phenotypic diversity of the biofilm allow adaptation to overcome multiple stresses and to survive most sequential therapies.

The hallmark of biofilms is genetic and phenotypic diversity, which enhances the robustness of the bacterial community.⁴ An increasing body of evidence suggests that laboratory cultivated bacteria share few characteristics with infectious biofilms. When bacteria naturally transition from individual planktonic cells to a community of biofilm tissue, the transcriptional expression of the bacteria radically changes. Although this phenotypic transition is occurring, the bacteria are excreting protective polymers and incorporating environmental molecules that bind the bacterial community to a surface and to each other. The biofilm bacterial community uses secreted pheromones (eg, quorum-sensing molecules) and other molecules for cell-cell signaling, even between species. These coordinated activities render the biofilm a formidable opponent for the host.

Biofilms as a Novel Focus

There are 3 significant limitations of continuing to operate within the planktonic paradigm. First, because planktonic cells have fewer defenses than biofilm communities, a treatment such as an antibiotic might provide excellent *in vitro* test results, when tested on planktonic cells only, but poor *in vivo* results, in which the biofilm phenotype may predominate. The same strain of bacteria can be hundreds or thousands of times more resistant to antibiotics if part of a biofilm community.^{3,5} This planktonic bias undoubtedly accounts for at least some of the discrepancy that can occur between *in vitro* test results and *in vivo* response to antibiotic therapy.⁶

Second, current culture methods do not identify the majority of bacteria now known to be in host infections.⁷ Researchers have developed molecular, genomic, metagenomic, transcriptomic, and proteomic methods because they determined that only approximately 1% of the cells they observed in ecosystems actually produced colonies by conventional culture methods.⁸ The conclusion of these DNA-based and RNA-based studies is that culture methods detect only a small minority of organisms actually present in natural and

pathogenic bacterial communities. Therefore, treatment based on conventional cultures may address only 1 or 2 bacterial species in a complex biofilm community that may include dozens of other species of bacteria, or even of fungi.

Third, planktonic techniques such as culturing may lead to an inaccurate or incomplete diagnosis because cultures do not detect biofilm cells that are viable but not culturable. Diseases that yield only intermittent positive cultures (eg, otitis media, prostatitis) have been suggested to be “sterile inflammations” or viral infections.⁹ An example of a serious result from reliance on standard cultures is that revisions of the Sulzer acetabular cup continue to be treated as “sterile loosening,” although this process probably represents a biofilm infection that does not yield positive cultures but can be detected by molecular methods.¹⁰

New Perspectives, Options for Detection, and Treatments

Changing the perspective about chronic infectious disease to include biofilm enables 2 important insights. First, it opens new methods for detection and treatment. Second, it provides a global reconceptualization of many chronic infectious diseases as resulting from a biofilm, allowing biofilm principles to be shared across disciplines.

Recent studies have investigated new methods for detecting the components of a biofilm. Several investigations have used modern molecular methods, such as denaturing gradient gel electrophoresis and denaturing high-performance liquid chromatography, along with imaging techniques including fluorescent *in situ* hybridization. Also, molecular methods such as polymerase chain reaction (PCR) and pyrosequencing in conjunction with conventional culture methods have been used to determine the bacterial species composition of chronic infections.⁷

Performing molecular tests as part of routine bacterial analysis is becoming a real option for clinical laboratories. These tests could include methods such as PCR, reverse transcriptase-PCR, microarrays, antigen testing, and rapid sequencing. Only a few of these methods are being used to test for certain pathogens, but culture-free identification of all pathogens and their corresponding resistance markers may soon become routine.¹¹

A biofilm focus also provides new strategies for treatment of chronic infections. Biofilm-based treatments might block initial bacterial attachment to a surface, block or destroy EPS formation, interfere with cell-cell signaling pathways, and use bacteriostatic or bactericidal agents at the same time. Concomitant therapies that not only attempt to eradicate bacteria but also affect the biofilm's community structure and communications may prove more effective than a single or sequential strategy such as antibiotic therapy.⁴ This multimodality approach to therapy is commonly used in other areas of medicine, such as the treatment of human immunodeficiency virus for which combination antiretroviral therapy is used to achieve the best clinical outcome.

Chronic Bacterial Disease as Biofilm Disease

Another main benefit the biofilm model allows is the reconceptualization of multiple chronic diseases as biofilm diseases. Biofilm disease has been viewed as various diseases that affect a variety of tissues and structures, including ear, nose, throat, mouth, eye, lung, heart, kidney, gall bladder, pancreas, nervous system, skin, bone, as well as virtually every implanted medical device. The Centers for Disease Control and Prevention estimates that more than 65% of infections are caused by bacteria growing in biofilms,¹² and Lewis¹³ suggests that the proportion is 80%—by far the majority of infections are estimated to be caused by biofilms. Thus, when biofilm infections are combined into a single disease category, the prevalence of the disease is significant and the mortality associated with biofilm disease is substantial.

Additionally, the disease processes and management strategies of biofilms are related. For example, the biofilm diseases of cystic fibrosis, pneumonia, and an infected knee replacement prosthesis are different, but strategies used to manage the biofilm in the lung will be similar to the strategies used for the biofilm on an infected knee implant.

Typical and Familiar Biofilms

The typical biofilm disease manifests with common features. The initial infection is subtle and usually not immediately life threatening, and antibiotics usually are prescribed. Subsequent exacerbations occur and are again usually treated with antibiotics and adjunct therapies such as corticosteroids. However, the infection worsens when treatment is withdrawn. If the patient's clinical status worsens or if the disease progresses to the point that function of the affected tissue or device is sufficiently impaired, a decision often is made to remove the infected tissue or component by surgery. The goal of the physician when addressing the disease is to manage the symptoms and signs, and to suppress exacerbations with the understanding that disease eradication is unlikely without surgical intervention.

Perhaps the most commonly encountered biofilm disease is dental plaque, a condition that can be managed effectively by dental professionals. Periodontal disease and tooth loss have greatly diminished over the last century due to the multiple concurrent strategies espoused by dentists. The suppression of biofilm in the oral cavity begins with frequent removal of the biofilm by daily brushing and flossing, coupled with periodic dental visits for plaque removal. If the bacterial biofilm load is too great and disease progresses, the frequency of biofilm management is increased in an attempt to overcome the disease. Dentistry has successfully confronted biofilm disease, and similar approaches may be used as a model for medicine to manage chronic infections.

Conclusions

Treating chronic infectious diseases cannot be limited to infectious disease specialists any more than the management of diabetes can be limited to endocrinologists. By shifting away

from the planktonic model of microbiology to the biofilm model, new methods for detection and treatment become available. Because of molecular methods, science now has the ability to detect biofilms and understand the implications of interspecies chaos that contribute to infections. With these new scientific approaches along with coordination of clinical and laboratory efforts, education, and research, it is possible to imagine overcoming much of biofilm disease.

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