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Guest Editorial

EMERGING PROBLEMS IN THE MANAGEMENT OF INFECTIOUS DISEASES : THE BIOFILMS

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Undoubtedly, one of the greatest accomplishments of modern medicine has been the development of antimicrobials for the treatment of infectious diseases. The first antibiotic, penicillin, was discovered by Alexander Fleming in 1928 and, now after more than five decades of intense research and development, even the most acute bacterial infections can be treated effectively with a variety of antibiotics.

However, emergence of resistance to antibiotics in several pathogenic bacteria in the past two decades has gradually rendered traditional antimicrobial treatment less effective. The horizontal transfer of resistance genes to other bacteria, even across various species, rapidly creates bacterial populations with one or more of the following antimicrobial properties; (a) an increased ability to degrade antibacterial compounds; (b) decreased permeability; (c) decreased affinity for the antibiotic; or, finally, (d) increased efflux of many different antibiotics. The microbes have evolved other mechanisms to evade antimicrobial therapy and probably the most important among them is the ability to either form or live within a biofilm. Today, a global concern has emerged that we are entering a post-antibiotic era with a reduced capability to combat microbes. Hence, the development of novel therapeutic approaches to the treatment of bacterial infections has become a global emergency in the management of infectious diseases.

The purpose of this editorial note is to highlight certain important problems that have emerged recently and which demand serious attention in the management of some infectious diseases. Though not new to the environmental microbiologists, persistent infection due to biofilm formation is certainly a new and additional burden to clinicians who treat infections.

Higher organisms, including humans are known to flock together and form colonies for various reasons. That the microbes also could form colonies and function as groups and that individuals within the group could respond to the group, as a whole, was unbelievable about ten years ago. Not any more! Through hard work and creativity, a small band of microbiologists have dispelled this belief and thanks to the pioneering work of a select group of microbiologists it is now well accepted that bacteria form groups and respond as groups. This phenomenon is mediated through various chemical signals (comparable to cell signaling in higher organisms) facilitating interaction and coordination of group bacterial activities. Interestingly, chemical cross-talk has been demonstrated between *P. aeruginosa* and *B. cepacia* and between *S. liquefaciens* and *P. aeruginosa*.

This phenomenon has become known as "quorum sensing" and often results in the formation of physical structures with unique characteristics known as "biofilms". A biofilm is a surface-associated microbial community that is embedded in a self-produced, extra cellular polymeric matrix. With these discoveries a completely new field has emerged in basic and applied microbiology called "Quorum Sensing" (QS).

Quorum-sensing is widespread among several pathogenic and non-pathogenic genera. In modern clinical microbiology, the establishment of bacterial biofilms is often considered a pathogenicity trait during chronic infections. It is involved in the regulation of many host-associated phenotypes, including production of virulence factors and secondary metabolites. Emerging evidence points to the involvement of quorum sensing in biofilm formation and surface motility in the opportunistic pathogens *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *Aeromonas hydrophila*. Quorum sensing genes are critical for pathogenesis of *P. aeruginosa* infection in the cystic fibrosis (CF) lung. Storey *et al*.[1] reported for the first time that quorum sensor transcripts and then subsequently Singh *et al*[2] identified quorum sensor molecules in CF patient sputa. There is, nonetheless, the first evidence that *P. aeruginosa* grows as a biofilm in the lungs of CF patients is based on electron microscopy.[3]

Biofilms, significantly increase the ability of the pathogen to evade both host defenses and antibiotics. They are being implicated in the pathogenesis and also clinical manifestation of several infections. They cause

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a variety of persistent infections, including chronic middle ear infections, bone infections, heart valve infections, infections related to implanted medical devices, and lung infections in people with the autosomal recessive inherited disease like cystic fibrosis. The chronic nature of some urinary tract infections is being attributed to the ability of *Escherichia coli* to form a biofilm.

Quorum sensing and biofilm biology have become very active areas in microbiology, and a large group of investigators is working on these fascinating aspects of bacterial biology, hoping to understand emerging problems in the treatment of infectious diseases and also to understand the pathogenesis of infections with particular reference to refractory, persistent and re-emergent forms of infections. Of course the objective is to develop new therapeutic agents to treat such bacterial infections.

Nosocomial infections caused by enterococci have increased dramatically in the last two decades and many such nosocomial enterococcal blood stream infections are associated with medical devices such as central venous catheters. The ability to form biofilms on medical devices is a potential virulence trait that may allow enterococci to cause infections in the expanding population of patients managed with such devices. This was recently tested and reported by Jonathan *et al*[4] from The General Infirmary, Leeds, United Kingdom with *E. faecalis* isolated from catheter related infections. Quorum sensing dependent biofilms also enhance colonization in *Vibrio cholerae*.[5] Enterohemorrhagic *Escherichia coli* (EHEC) O157:H7 is the causative agent of several outbreaks of bloody diarrhea and hemolytic-uremic syndrome throughout the world. Quorum Sensing has been shown to be a Global Regulatory Mechanism in Enterohemorrhagic *Escherichia coli* O157:H7.[6]

The ability of the opportunistic pathogen *M.avium*, which is refractory to several antimycobacterial drugs, to form biofilms was tested and reported by Luiz E. Bermudez[7] and his collaborators from California Pacific Medical Center Research Institute, San Francisco, CA, USA. *P. aeruginosa* isolates from contact lens-induced microbial keratitis showed high invasiveness and were found to express high levels of protease activity in addition to secreting quorum sensing molecules as demonstrated by Hua Zhu *et al*[8] from Australia.

Community living among microbes is a nightmare to clinicians and microbiologists from treatment and disease management point of view. The worst challenge is probably yet to come as we face cross species protection among biofilm producing microbes against antibiotics. Berit *et al* from Institute of Biomedical and Life Sciences, University of Glasgow, UK showed that the extracellular polymer produced by *S. epidermidis* RP62A could inhibit fluconazole penetration in mixed fungal-bacterial biofilms.[9] Conversely, the presence of *C. albicans* in a biofilm appeared to protect the slime-negative Staphylococcus against vancomycin. Overall, the findings suggest that fungal cells can modulate the action of antibiotics, and that bacteria can affect antifungal activity in mixed fungal-bacterial biofilms. This finding has very important consequences in the management of biofilm producing bacterial and fungal infections.

The armament of therapeutic agents available to treat bacterial infections today is restricted to antibiotics developed specifically to kill or stop the growth of individual bacteria. The development of these agents did not take into account the unique biology of bacterial groups. Bacteria growing within a biofilm lose their sensitivity to antibiotics quickly. Thus biofilms result in persistent infections that cannot be resolved with standard antibiotic treatments. Because we have not considered the problem of group biology in bacteria until recently, good therapeutic strategies to treat biofilm infection are not available. The observation that quorum sensing is linked to virulence factor production and biofilm formation suggests that many virulent organisms could potentially be rendered nonpathogenic by inhibition of their quorum-sensing systems. Research into quorum sensing, and inhibition thereof, may provide a means of treating many common and damaging chronic infections without the use of growth-inhibitory agents, such as antibiotics, preservatives, and disinfectants, that unavoidably select for resistant organisms. One might imagine that bacterial communication systems represent an Achilles' heel, a fragile target for potential new anti-infective drugs. This idea is catching up the imagination and attention of both academic investigators and scientists in the drug industry.

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