Journal of Infection (2014) 69, S47—S52

BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

New approaches to the treatment of biofilm-related infections

Matthew Wilkins [a,b], Luanne Hall-Stoodley [b,c], Raymond N. Allan [a,b], Saul N. Faust [a,b,*]

[a] *Academic Unit of Clinical and Experimental Sciences, Faculty of Medicine and Institute of Life Sciences, University of Southampton, Southampton, UK*
[b] *NIHR Wellcome Trust Clinical Research Facility, C Level, West Wing, Mailpoint 218, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD, UK*
[c] *Microbial Infection and Immunity, Centre for Microbial Interface Biology, The Ohio State University, 793 Biomedical Research Tower, 460 W. 12th Avenue, Columbus, OH, 43210-2210, USA*

Accepted 18 July 2014
Available online 17 September 2014

KEYWORDS
Clinical biofilm infection;
Bacterial infection;
Pathophysiology;
Diagnosis;
Treatment

Summary Bacteria causing chronic infections predominately grow as surface-attached, sessile communities known as biofilms. Biofilm-related infections including cystic fibrosis lung infection, chronic and recurrent otitis media, chronic wounds and implant- and catheter-associated infections, are a significant cause of morbidity and mortality and financial cost. Chronic biofilm-based infections are recalcitrant to conventional antibiotic therapy and are often unperturbed by host immune responses such as phagocytosis, despite a sustained presence of host inflammation.

The diagnosis of clinically important biofilm infections is often difficult as Koch's postulates are rarely met. If treatment is required, surgical removal of the infected implant, or debridement of wound or bone, is the most efficient means of eradicating a clinically significant biofilm. New approaches to treatment are under investigation.

Discovery and definition

The concept that bacteria exist as single, free-floating ("planktonic") organisms in nature was radically overturned in the 1970s upon the observation that bacteria were capable of attaching to and growing on a surface, and that these adherent bacteria predominate numerically in natural, clinical and industrial aquatic ecosystems.[1] It is now widely

* Corresponding author. NIHR Wellcome Trust Clinical Research Facility, C Level, West Wing, Mailpoint 218, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD, UK.
E-mail address: s.faust@soton.ac.uk (S.N. Faust).

http://dx.doi.org/10.1016/j.jinf.2014.07.014
0163-4453/

accepted that biofilms represent a mode of bacterial growth, allowing survival in hostile environments and colonisation of new niches through dispersal.[2] Biofilms are associated with a self-produced hydrated matrix of extracellular polymeric substances (EPS),[3,4] comprised of polysaccharides, proteins, lipids and extracellular DNA (eDNA).[5] This matrix confers structure and protection to the complex biofilm community against changing environmental conditions.

Biofilms — the clinical importance and burden on public health

Bacteria in biofilms can specifically mediate infections which differ from those caused by planktonic bacteria.[6] Aside from surface association, aggregation, and the production of a matrix, there are two main differences between biofilm-associated microorganisms and their planktonic counterparts. Biofilms are inherently more tolerant to antibiotics and other forms of antimicrobial treatment, and to host immune responses, despite a sustained presence of inflammatory cells and effector functions.[7–9] Clinically, this can result in chronic or recurrent infections such as chronic and recurrent otitis media (COM),[10] chronic wounds,[11] cystic fibrosis lung infection[12] and chronic rhinosinusitis[13] (Table 1).

Biofilm contamination occurs in a range of indwelling medical devices leading to hospital-acquired infections (Table 1). The US Centres for Disease Control and Prevention (CDC) estimates that biofilms are responsible for more than 65% of such nosocomial infections.[14] Currently, the most effective means of treating these infections, and often the only feasible solution, is to physically remove the infected medical device.

Why do bacteria form biofilms?

There are a number of evolutionary advantages for bacterial cells to aggregate and attach to a surface.

Table 1 Biofilm-associated clinical infections.[48]

Chronic Otitis media
Recurrent tonsillitis
Chronic wounds
Cystic fibrosis lung infection
Urinary tract infections
Chronic rhinosinusitis
Dental caries
Periodontitis
Device-related infections
Urinary catheters
Mechanical heart valves
Prosthetic joints
Contact lenses
Intrauterine devices
Pacemakers
Endotracheal tubes
Voice prostheses
Tympanostomy tubes

Defence

In the process of infection or colonisation, bacteria come up against a variety of host defence mechanisms, including pH changes, phagocytic attack, and the presence of antimicrobial agents (natural and administered). Biofilm bacteria can withstand these mechanisms far better than planktonic bacteria, displaying enhanced resistance to cell lysis by complement, opsonisation and phagocytosis.[4] Phagocytes that attempt to engulf and ingest bacteria in a biofilm may harm surrounding healthy tissue, through the secretion of toxins, in a process known as "frustrated phagocytosis".[4] In *Pseudomonas aeruginosa* biofilms, phagocytic killing has also been reported to be reduced despite polymorphonuclear leukocytes (PMN) penetrating through the EPS and apparent phagocytosis occurring.[15]

Interactive communities and quorum sensing

Bacteria in biofilms are often described as living in a community comparable to those of multicellular organisms. Individual bacterial cells in biofilms are capable of sensing environmental conditions and, through cell-to-cell communication, undergoing changes in their gene expression to increase survival. However, such phenotypic change after adaption of gene expression is only transient and, depending on the conditions, biofilm bacteria may convert back to planktonic growth. Nevertheless, the communal existence and closely packed environment within a biofilm is ideal for intercellular interactions between cells of either the same or different species, benefitting other members of the community and the biofilm as a whole.

To communicate with one another, bacteria synthesise and respond to signalling molecules in a process known as quorum sensing (QS). In low density, as in planktonic populations, bacteria secrete low molecular weight, highly diffusible, signal molecules (autoinducers, such as oligopeptides in Gram positive bacteria and *N*-acyl-L-homoserine lactones in Gram negative bacteria) at levels that are too low to induce changes in gene expression. Once the close proximity bacterial population reaches a critical mass, the increased concentration of autoinducer molecules in the EPS allows individual bacterial to sense the presence of other bacteria. Physiological processes under QS control include surface attachment, EPS production, competence, bioluminescence and secretion of virulence factors.[16]

Biofilm formation

The biofilm life cycle is regarded as a dynamic, continually evolving process characterised by several distinct phases, each regulated by a number of specific genes (Fig. 1).

Attachment

When free-floating, planktonic bacteria initially attach to a surface they are not irreversibly bound and are susceptible to antibiotic treatment, gentle rinsing, or changes in conditions.

Bacterial surface attachment is complex. The rate and extent of microbial attachment is not simply dependent on the properties of the bacteria, but of the surface itself and