New ways to stop biofilm infections

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As the use of indwelling medical devices has increased in the past few decades, so has the occurrence of persistent infections associated with these implants.[1] Biofilms are at the root of these troublesome infections. Biofilms are bacteria and yeast that congregate on surfaces, in multicellular aggregates, in which they are protected from host defences and from killing by antibiotics.[2,3] The only sure way to resolve a biofilm infection is to remove the infected device. What can be done to improve this situation?

There are reasons to be optimistic that new antibiotics, which would be effective against microbes in biofilms, can be discovered. But there are also alternative approaches that beg to be developed. Four come to mind: stopping microbial attachment, preventing microbial growth, disrupting cell-to-cell communication, and disintegrating the biofilm matrix. Even if one of these strategies were only partly effective at limiting biofilm formation or weakening biofilm structures, such effects might be enough to tip the balance and allow existing antibiotics to eliminate the infection.

Much has been published on attempts to understand bacterial attachment in physicochemical terms by modelling microbial cells as bald, spherical colloids and invoking electrostatic and hydrophobic interactions. This effort has borne little fruit. One explanation for this failure is that microbial attachment is an active biological process rather than a passive chemical interaction. A second explanation is that attachment is often mediated by proteinaceous appendages such as pili, flagella, and fimbriae, not by bulk chemical properties of the cellular particle. With this insight in mind, there are many ways that attachment via such appendages might be prevented. As an example, *Pseudomonas aeruginosa* uses type IV pili to locomote on surfaces by twitching motility. Singh et al[4] reported that, under conditions of iron restriction, *P aeruginosa* never stop twitching enough to settle down and form mature biofilm structures. A biomaterial that incorporated an iron-chelating agent might be able to reduce biofilm formation by this organism.

In this issue of *The Lancet*, Mark Lyte and colleagues show that certain drugs, namely catecholamine inotropes such as norepinephrine, promote growth and biofilm formation of *Staphylococcus epidermidis*. This finding is in the preventing growth category of biofilm control because it opens the door to suppressing biofilm formation by simply limiting the availability of substances required for growth. Of particular interest is the suggestion, supported by preliminary data, that the inotropic drugs stimulate biofilm growth by facilitating the transfer of iron to the bacteria. For a second time, an iron-scavenging biomaterial emerges as an attractive anti-infective design.

One of the most exciting developments about biofilms was the discovery that bacterial cell-to-cell communication, known as quorum sensing, is required for normal biofilm formation.[5] Diffusible signal molecules produced by the bacteria accumulate locally when a quorum of cells is present, triggering elaboration of virulence factors including biofilm. This finding raises the prospect of manipulating biofilm formation by interfering with this signalling process. Analogues of natural signal molecules, that jam bacterial communication, could prove to be effective antibiofilm drugs. This strategy has shown some promise in laboratory tests[6] and is the premise of a few young commercial ventures.

Another alternative approach to biofilm control, and one that is rife with opportunity, is to target the matrix of the biofilm rather than the cells themselves. Dissolving the matrix polymers, or blocking their synthesis, might cause a biofilm to become unglued. For example, macrolide antibiotics have therapeutic efficacy against some lung infections even though these agents are only weakly bactericidal. One explanation of the mode of action is that these antibiotics cripple the biofilm by reducing matrix polysaccharide synthesis.[7] It may suffice to block a single, seemingly minor, step in matrix polymer elaboration. Acetylation of polysaccharides changes their physical properties dramatically; mutant strains of bacteria that are unable to modify the polymer backbone by acetylation are deficient in biofilm formation.[8,9] New drugs that block enzymatic acetylation of biofilm polymer chains could be effective antibiofilm agents.

When dealing with biofilms, a single-minded strategy of extermination may be a prescription for frustration. It may be better to learn how to dismantle these protective fortresses by preventing attachment, stopping growth, disrupting communication, and dissolving the biofilm matrix.

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Diagnosing smallpox in possible bioterrorist attack

Smallpox as a possible agent for bioterrorism is much in the news of late,[1,2] although there is no evidence of use so far. If an incident occurs which might be due to smallpox released by bioterrorism, two aspects of diagnosis will be paramount: accuracy and speed, as the following example shows. In 1969, when smallpox was still endemic in several parts of the world including East Africa, I was rung at 4 pm one Friday afternoon by a colleague at another London teaching hospital who told me that a young man with a vesicular rash had been waiting all afternoon to be seen in the outpatients department. He had recently returned from Kenya and claimed to have had chickenpox as a boy. The public-health implications did not need spelling out and an urgent diagnosis was imperative. Some vesicle fluid was aspirated into a tuberculin syringe with a fine needle and the syringe arrived by taxi 20 min later. Preparing an electron microscopy grid took another 5 min and, within seconds of putting it in the instrument, numerous herpesvirus particles were seen. The patient had varicella and was mistaken in thinking he had had it already; consequently, all public-health anxiety evaporated, together with the need to trace any contacts.