Clinical abstract

The significance of biofilm in implant-associated infections

The use of implants in surgical procedures is increasing and with it, the number of complications. Implant-associated infection is one risk that is particularly feared. Not only is it detrimental to the patient, it also results in considerable expense. For example, the costs to be covered by health insurance providers in the United States for anti-microbial and surgical treatment of implant-associated infection average at $30,000 per case (1–3). Moreover, the formation of bacterial biofilm also complicates the diagnosis and treatment of implant-associated infections.

Why do implant-associated infections present such difficulties?

In theory any medical implant can become populated with bacteria. One possible consequence of this is infection. On average, around 5% of all surgical implants become infected (3). Implant infections are for the most part associated with biofilm. Foreign body contamination generally occurs perioperatively (4, 5). In the case of biomaterial implants such as orthopaedic prostheses, catheters or artificial heart valves, the host cell population attempts to colonise the foreign body during cell and tissue integration. Host cells and bacteria compete with each other in the colonisation of the surface of the foreign object ("race for the surface") (6–8) (Fig. 1).

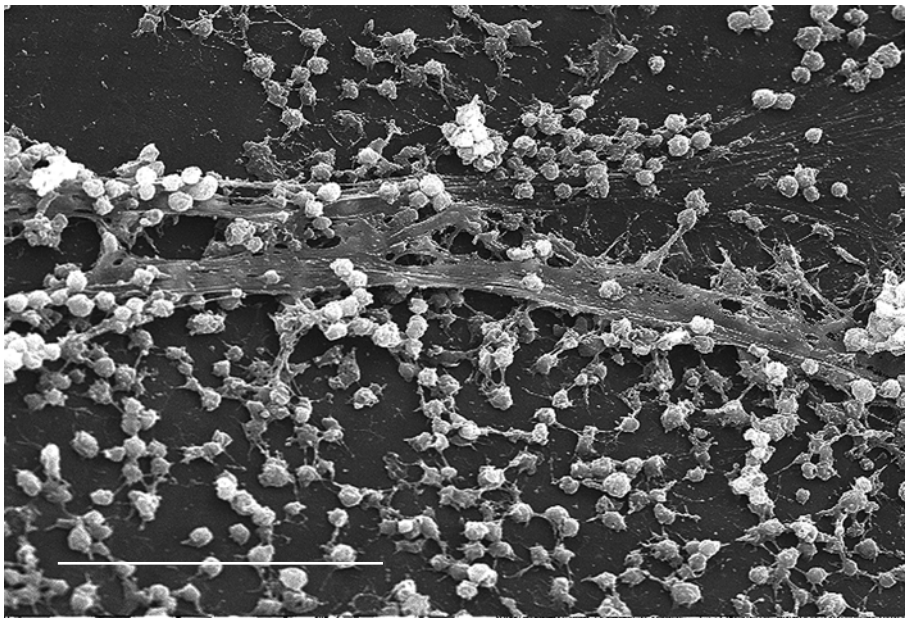

Fig. 1. Electron microscope image of staphylococcal biofilm; streak length 20 µm.
With the kind permission from Janice Carr, Centres for Disease Control and Prevention.

Which microorganisms can contribute to implant-associated infection?

The microorganisms most commonly identified on implants are: coagulase-negative staphylococci (30 –43 %) – particularly *staphylococcus epidermidis* – and *staphylococcus aureus* (12–23%), followed by mixed bacterial flora (10 – 11 %), streptococci (9 – 10 %), gram-negative bacteria (3– 6 %), enterococci (3 – 7 %) and anaerobes (2 – 4 %). (9 – 13) (Fig. 2). Different bacteria favour different implants. Orthopaedic implants, as well as intravascular catheters and artificial heart valves, are generally colonised by coagulase-negative staphylococci (*staphylococcus epidermidis*). Coagulase-positive staphylococci such as *staphylococcus aureus* are the main cause of infection in haemodialysis systems, stents and metal implants, which include dental implants and metallic osteosynthesis implants (4, 14).

Bone cement also comprises a biomaterial that microorganisms could colonise. Adding an antibiotic to bone cement can provide effective protection against bacterial colonisation. Subinhibitory concentration of the antibiotic released in-situ by the bone cement matrix also promotes the potential development of resistance. (15, 16).

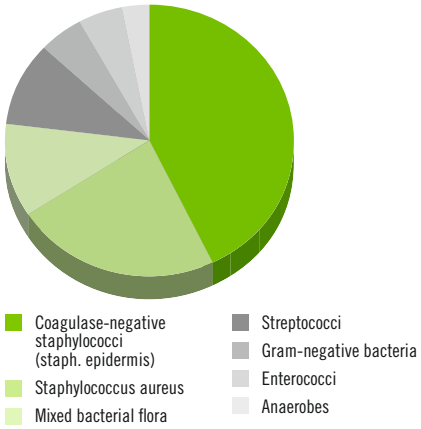

Fig. 2. Bacterial spectrum of implant-associated infection (13).

Why are implants prone to bacterial colonisation?

The risk of infection increases significantly with the implantation of biomaterial. In accordance with its biomimetic properties, biomaterial triggers an immune response by the immunocompetent cells of the host. Following placement of implants containing titanium, nickel or chrome, histolytic tissue, connective tissue membranes or fibrous capsules, for example, will form. These provide the ideal lead compound for the formation of bacterial biofilm. The implanted foreign body also triggers excessive activation of the complement system with a corresponding inflammatory response. This reduces the ability of the organism to eliminate foreign bodies by way of phagocytosis (17).

Early diagnosis with reliable identification of the bacteria is essential for the treatment of implant-associated infection. Once bacteria have won the war of colonisation of the biomaterial ("race for the surface") and have established themselves, biofilm will begin to form. This allows them to avoid the immune response of the host and to protect themselves against anti-microbial substances. (18)

What is biofilm and how does it develop?

Bacteria can exist in planktonic and sessile form. Sessile bacteria are associated with surfaces and live in biofilm. At the same time, biofilm is defined as a natural survival strategist and structured community of microorganisms that is distinguished by various factors including the limitation of an immune response from the host.

Biofilm is encapsulated in a polymer matrix comprising glycolipids and glycoproteins (exopolysaccharide gel, "slime") that adheres to a living or inert surface (19–21).

Biofilm formation comprises five phases (22–24) (Fig. 3):

Phases 1 and 2: Adhesion – the adhesion of microorganisms on solid surfaces is a common natural phenomenon (19, 25), for example in the colonisation of epithelial cells. Adhesion to an implant takes approx. 1–2 hours. It is determined by numerous factors, for example by the type of cell surface and the receptors of the microorganism, the physiochemical properties of the surface or the environment (26). In this respect, the bacteria compete with the host cells in the colonisation of the surface (27).

Phase 3: Proliferation – after approximately 2–3 hours the bacteria begin to proliferate. The increasing proliferation and maturing of the bacteria and the formation of a network comprising several cell layers results in greater adhesion to the foreign material (28).

Phase 4: Maturing – after a further day, the stable biofilm itself takes form, with the formation of a gel matrix comprising several layers in which the bacteria embed themselves (26). Nutrients are reserved and bacteria protected against immune response or antibiotics (29).

Phase 5: Separation – individual bacteria may separate from the biofilm, colonise remote regions and establish additional sources of infection (30).

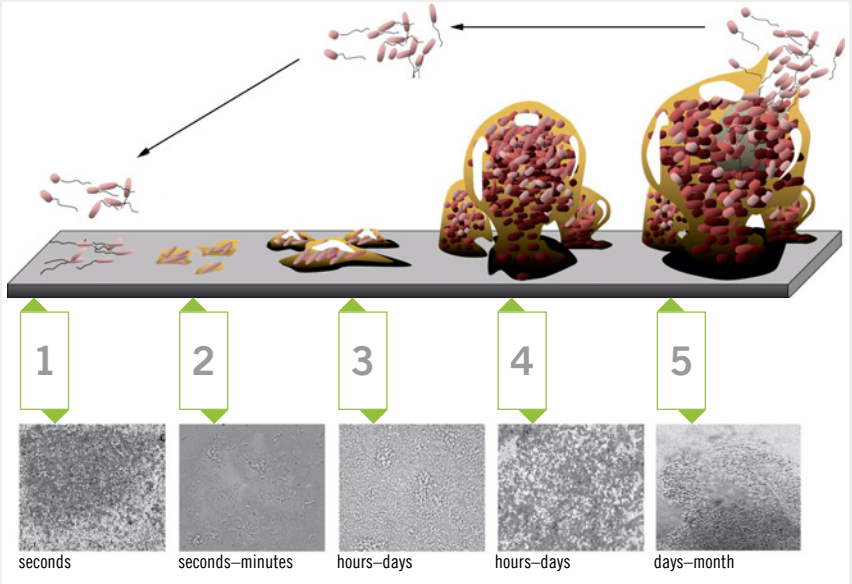

Fig. 3. Biofilm formation: **1.** Reversible adhesion of bacteria, **2.** Irreversible binding on the surface of the foreign material, **3.** Bacterial growth, **4.** Maturing and formation of the polymer matrix, **5.** Separation, with kind permission of D. Davis (22).

Why are antibacterial antibiotics almost completely ineffective in biofilm?

The formation of biofilm is a dynamic process that is determined by external factors as well as the micro-environment in the biofilm (31). Immune system access to the bacteria in the biofilm is limited at best or not possible at all, and the "layer of slime" also restricts phagocytosis as well as proliferation of the body's own immune cells (28). The relative hypervascularity in the area around the implant, which is increased by infection, promotes this process and further reduces the immunocompetence of the host (32).

Intrinsic resistance

Intrinsic protection against antibiotics is based on physical mechanisms and the reduced growth rate of bacteria in biofilm (33). The exopolysaccharide gel acts as a physical barrier as it can prevent the penetration of certain antibiotics either through binding and inactivation or by limiting diffusion. Bacteria that are affected by a high cell density proliferate more slowly or are in a sessile phase (19, 34). The slower growth rate and clearly reduced metabolism allows them to withstand a restricted supply of nutrients, changes in the pH value and oxygen radicals (26, 31). The low-oxygen environment in the deeper layers of the biofilm also promotes the development of resistance due to the reduced uptake of antimicrobial substances (35).

The reduced bacterial growth in biofilm appears to play a critical role in the development of resistance to antibiotics that rely on growth phases, particularly with regard to cell wall activity (36). Bacteria in biofilm tolerate antibiotic concentrations that are 10–1000 times greater than the concentrations required to kill off comparable plankton life forms. As a result, it is virtually impossible to successfully combat bacteria organised in biofilm. (20, 37–39).

Acquired resistance

Acquired resistance is based on phenotypic differences between the microorganisms in biofilm that have a particular impact on their growth rate and gene expression (20, 33). Regulatory systems adapt the gene expression to the changing environmental conditions, including the increase in cell density in the biofilm. This process of regulation (40, 41) is described by cell-to-cell communication known as "Quorum sensing". Quorum sensing plays a critical role in the synchronisation of gene expression and in the functional coordination of bacterial communities and is crucial to the formation of biofilm (42). The exchange of genetic material between bacteria enables the spread of phenotypes that are resistant to antibiotics (20, 33).

Sub-populations of the microorganisms in biofilm ("small-colony variants") have the ability to become metabolically dormant (43). They are also less sensitive to antibiotics. They most probably form as the biofilm continues to develop and act as a barrier for oxygen and nutrients. It is also assumed that biofilm contains a type of specialised bacteria known as "persister cells" (44, 45) that neither proliferate nor die off in the presence of antibiotics. Once antibiotic treatment has been concluded, (46) "persister cells" and "small-colony variants" can metamorphose into "normal" bacteria (47, 48) and are probably the primary reason for the development of resistance to antibiotics.

The mechanisms of bacterial resistance in biofilm are based on a number of factors:

Intrinsic resistance

- Reduced penetration of anti-microbial substances through the biofilm
- Chemically-altered micro-environment, e.g. lack of oxygen, changes in the pH value

Acquired resistance

- Reduced growth rate of the bacteria in the biofilm
- Modified, multiresistant phenotypes with resistance gene expression
- "Persister cells" and "small-colony variants"

How can infections associated with biofilm be diagnosed?

In orthopaedic surgery, implant infections are classified in accordance with when they occur following surgery:

- Early infection: <3 months
- Low-grade infection: 3–24 months
- Late infection: >24 months

Early and low-grade or delayed infection generally occurs during surgery, while late infection can generally be attributed to spreading via the bloodstream (49).

What findings are indicative of infection?

Patients with an early infection generally show typical signs such as pain, redness, swelling, hyperthermia and secretion from the wound. Low-grade and late infections present a diagnostic challenge however, as the definitive indications of infection are not exhibited. The cardinal symptom of pain occurs in nearly all infections. It is caused by the loosening of the implant and is therefore also evident in the case of aseptic loosening. As a result, only a combination of clinical, laboratory (chemical), histopathological, microbiological (Fig. 4)

and radiological findings can be used to arrive at the diagnosis of an infection associated with biofilm (50). Nevertheless, the preoperative distinction between aseptic and septic loosening remains difficult; many implant infections associated with biofilm go unrecognised (19, 51, 52).

Can intraoperative diagnostics help establish the pathogen?

Bacteriological and histopathological cultures from tissue samples that are taken intraoperatively at different locations can help improve the identification of bacteria. To this end, antibiotics must be discontinued at least two weeks prior to surgery and samples should be taken before perioperative administration of antibiotics (38, 53).

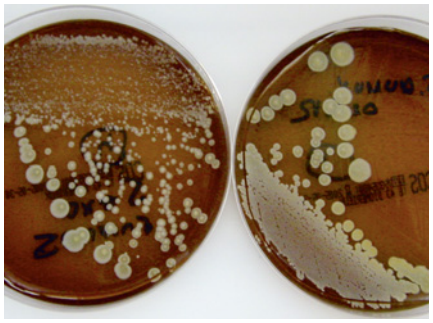

Fig. 4. Pathogen bacteria: culture in petri dishes (Dr. Miguel Pons Cabrafiga, Barcelona, Spain).

Why does biofilm hinder the identification of an infection?

Optimum surgical and antibiotic treatment requires that the original pathogen is identified. However, it is difficult to identify bacteria in biofilm during routine examinations because of their reduced metabolic function and slow growth rate. Low-grade infection in particular can be misinterpreted as aseptic implant loosening. The surgeon and microbiologist must therefore actively look for "small-colony variants" (43). Cultures for the detection of "small-colony variants" and slow-growing bacteria such as propionibacterium species require an incubation period of at least 10 to 14 days (54), and may also require the addition of hemin and menadione to the culture medium in order to increase the growth rate (55, 56).

Optimised identification of the bacteria through:

- Histopathological and bacteriological cultures of samples taken intraoperatively
- Cultivation of removed implants in an enriched growth medium
- Removal of microorganisms from the surface of a removed implant using ultrasound
- Incubation period of at least 10 to 14 days

What prophylactic measures can prevent the formation of biofilm?

Once an implant infection associated with biofilm has been established, removal of the implant with radical debridement in combination with extended antibiotic treatment is generally the only remaining treatment option in order to effectively eliminate microorganisms. The primary goal should therefore be to prevent the formation of biofilm. In addition to sterile management during surgery and care, materials have also been developed that have anti-microbial properties intended to prevent colonisation by microorganisms.

Surface modifications with an anti-microbial impact

Modifications to the surface of implants can prevent colonisation by microorganisms. For this purpose, different technologies have been developed for the modification of polymer surfaces and the impregnation of medical implants with anti-microbial agents. The manufacture of bactericidal or bacteriostatic surfaces is one particular goal (57–59). Ideally, implants are required that essentially comply with three anti-microbial principles:

1. Barrier protection to prevent microbial adherence
2. Active, selective delivery of active agents
3. Deep penetration of the active agent

Passive surface coatings can contain polyethylene glycol, polyethylene oxide or hydrophilic polyurethane (60–62). However, these are limited in terms of their effectiveness, which depend heavily on the micro-organism in question. Alternative approaches include active coatings or local excipients. As drug-delivery systems, these ensure the ongoing release of active agents such as antibiotics, antiseptics or heavy-metal ions (63–65) directly in-situ.

Drug-delivery systems

The basic strategy is based on the broad prophylactic impact of antibiotics, antiseptics or heavy-metal ions that are primarily intended to protect the medical implant against microbial colonisation and the formation of biofilm. For this purpose, special local release systems are used with a combination of biomaterial and anti-microbial additives or active agents (8, 66). During the critical perioperative and postoperative phase in the hours following implantation, high concentrations of the active agent should be reached at the implant site. As application is local, the risk of side-effects developing as a result of the active agent is negligible (14, 67–71).

Drug-delivery systems based on non-biodegradable polymers, for example polyurethane, silicone or polymethyl methacrylate (PMMA) facilitate a lower quantity of active agent overall in comparison with biodegradable excipients such as biodegradable gentamicin beads or bone graft substitutes containing gentamicin, however the release period is often longer relative to the quantity used.

Examples of local excipients:

- PMMA bone cement
- PMMA beads containing gentamicin
- Biodegradable gentamicin beads
- Absorbable collagen sponge containing gentamicin
- Bone graft substitute containing gentamicin
- Absorbable suture materials impregnated with an active ingredient
- Implant coating made of polymer, silicone, polyhydroxyalkanoate, polylactide, silver or copper

Gentamicin example: why is the initial release of high local concentrations of antibiotics after implantation so important?

Within the first 72 hours, the bactericidal aminoglycoside antibiotic gentamicin, for example, allows high active agent concentrations to be achieved (Fig. 5) (39, 72). These can prevent the formation of biofilm and reduce the frequency of implant-associated infections (73–75).

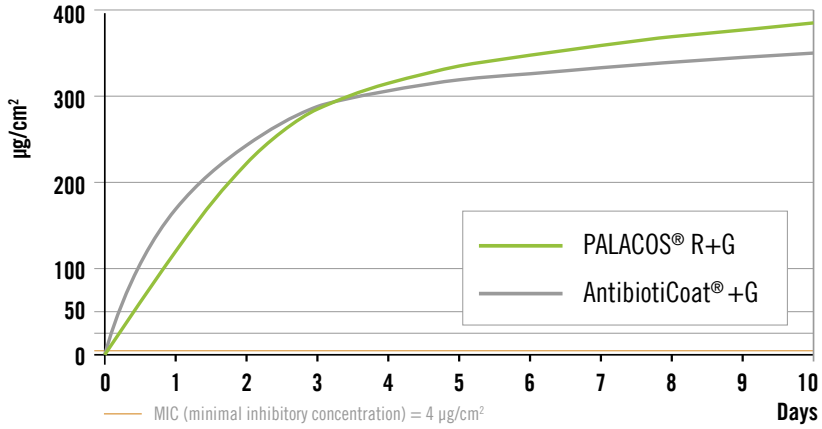

Fig. 5: Progress of the elution of gentamicin from PALACOS® R+G and AntibiotiCoat® +G on a titanium implant. (76)

A high local concentration of active agents often allows even pathogens that are classified as having little or no sensitivity according to conventional antibiograms, such as certain staphylococcus strains or gram negative resistant bacteria, to be treated (77, 78).

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