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Understanding Biofilms and Novel Approaches to the Diagnosis, Prevention, and Treatment of Medical Device-Associated Infections

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Summary

Treatment of medical device-related infections is challenging, and recurrence is common. The main reason for this is that microorganisms adhere to the surfaces of medical devices, and enter into a biofilm state in which they display distinct growth rates, structural features, and protection from antimicrobial agents and host immune mechanisms compared with their planktonic counterparts. This article reviews how microorganisms form biofilms and mechanisms of protection against antimicrobial agents and the host immune system provided by biofilms. Also discussed are innovative strategies for diagnosis of biofilm-associated infection, and novel approaches to treatment and prevention of medical device-associated infections.

Keywords

Biofilm; extracellular polymeric substance; tolerance; medical device-associated infection; surface-coating or eluting substrate; physical–mechanical approach; extracellular polymeric substance targeting therapy

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Introduction

Device-associated infections are one of the most common and feared complications in medical practice. Treatment of medical device-related infections is notoriously challenging, and recurrence is common.[1] The main reason for this is that microorganisms adhere to surfaces of medical devices and enter into a biofilm state in which they display distinct structural features, growth rates, and microenvironments, when compared with planktonic organisms.[2,3] Decreased susceptibility to antimicrobial agents and the host immune system is observed in microorganisms in biofilms compared with planktonically-grown organisms.[4] The biofilm structure itself, decreased growth rate, antimicrobial-destroying enzymes within the matrix, upregulation of stress-response genes and horizontal transfer of antimicrobial resistance genes are involved in reduced antimicrobial susceptibility.[3,4] Microorganisms in mature biofilms over 7 days old are 500–5000 times less susceptible to killing by antimicrobial agents compared to planktonic organisms.[5]

Many controversies and uncertainties exist in the diagnosis, prevention and treatment of biofilm-associated infection.[6] Once a biofilm develops on a medical device, eradication of microorganisms becomes extremely challenging and cost can be substantial due to the frequent need for prolonged hospitalization, surgery, and long-term antimicrobial treatment.[7] Bacterial biofilms are associated with approximately 1.7 million hospital-acquired infections annually in the United States, incurring an annual economic burden of approximately 11 billion dollars.[8] Biofilm formation is now accepted as one of the most important virulence factors in medical device-associated infections.[2]

This article reviews the means by which microorganisms develop biofilms and their defense mechanisms against the host immune system and antimicrobial agents. Also discussed are innovative concepts for the diagnosis of biofilm-associated infection and novel approaches to treatment and prevention of medical device-associated infections.

Body of Text

Understanding of Biofilms

Definition and structure of biofilms—Biofilms appear very early in the fossil record and can be formed by a diverse range of microorganisms; they are widespread in natural, industrial and hospital settings.[9] A biofilm is generally defined as “an aggregate of microorganisms adherent to a biotic or abiotic surface, embedded within a matrix of extracellular polymeric substance (EPS) (Figure 1).[10] Interestingly, free-floating cells can also self-aggregate and form a biofilm, which can display features similar to those of a medical device-associated biofilm.[10,11] A major feature of biofilms is their self-produced EPS which consists of polysaccharides, nucleic acids and/or proteins.[3] The EPS matrix advances microbial attachment to surfaces and cell-to-cell adhesion and aggregation, and functions as a three-dimensional barrier to protect cells against from external threats, including host defense mechanisms and antimicrobial treatment.[12] Moreover, the EPS matrix can create harsh environments by modulating chemical and nutrient gradients, and contribute to important virulence attributes.[12] Host-derived components, including fibrin, platelets and immunoglobulins, may also be components of biofilms in complex host

environments. A description of biofilms as 'aggregated, microbial cells surrounded by a polymeric self-produced matrix, which may contain host components' was suggested at the 5th ASM Biofilm Conference.[10] Microorganisms can attach to almost all types of medical devices and also biotic surfaces (e.g., skin, bone, airway, connective tissue, intestinal mucosa, vascular endothelium).[9] Therefore, biofilms may be associated with various types of tissue-associated chronic infections, in addition to their association with medical devices (Table 1). Medical device-associated infections are most commonly caused by *Staphylococcus epidermidis* and *Staphylococcus aureus*, but a long list of species of bacteria and fungi can cause these infections.[13,14] While some authors suggest that *S. epidermidis* accounts for approximately 80% of the bacteria causing medical device-related infections,[15] in the hospital setting, multidrug-resistant Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa*, have emerged as serious concerns, especially in catheter-associated urinary tract infection (CAUTI).[16]

Stages of biofilms—The initial step of biofilm formation is initiated by complex interactions between surfaces and the microorganism (or microorganisms). Biofilm formation consists of several stages, beginning with attachment and progressing to detachment (Figure 2).[2] At the stage of initial attachment, surface characteristics such as hydrophobicity, charge, topography, and exposure time influence attachment of microorganisms to the surface of medical devices.[17] Adherence of microorganisms to medical devices has been reported to occur through cell surface proteins, such as biofilm-associated protein - a fimbria-like polymer -, and the protein autolysin of *S. epidermidis*, and the capsular polysaccharide/adhesion of *S. epidermidis* and other coagulase-negative staphylococci.[18–21] Host-derived proteins, such as fibronectin, fibrinogen, and vitronectin, released to aid in healing, are absorbed onto the surfaces of medical devices, producing a conditioning film, which enhances microbial colonization through interactions between microbial and host proteins.[17,18] At the stage of biofilm growth, microorganisms proliferate, and cell-to-cell adhesion on the colonized surface is enhanced. These organized structures are then surrounded by a self-produced EPS.[2,3,8] As biofilms mature, they become a structured multicellular community providing protection against from external threats, including host defense mechanisms and antimicrobial treatment. Microorganisms in biofilms release autoregulators and have altered gene expression that stimulates production of virulence factors, enhancing their own survival.[22] At the stage of cell detachment, planktonic cells may be released from the surface, potentially resulting in distant metastatic infections and/or further regional biofilm formation. Dispersed microorganisms revert to an active state, comparable to that of their planktonic counterparts, making them more susceptible to antimicrobial agents.[23] In addition, dispersed biofilm cells lose the protective effects granted by the biofilm community and its structured organization. The cyclic di-GMP (c-di-GMP) second messenger reported in *E. coli*, *P. aeruginosa*, and *Salmonella enterica*,[24] is an example of a molecule responsible for biofilm dispersal.[25]

Tolerance and resistance of microorganisms in biofilms—Biofilm-associated infections are particularly challenging to treat. Several mechanisms account for protection against the host immune system and antimicrobial agents, compared with microorganisms in

the planktonic state. This type of resistance is not mainly due to the genetic antimicrobial resistance that occurs by mutation or horizontal gene transfer but is rather better described as a reversible tolerance to antimicrobial agents.[4,26] Tolerance can be the result of entrapment or inactivation of antimicrobials, and/or of the slow growth that is characteristic of biofilms.[4,26] Restricted penetration of antimicrobial agents into the depth of a mature biofilm due to the EPS matrix of the biofilm itself can contribute to the antimicrobial tolerance.[4,26] EPS matrix has also been shown to inactivate antimicrobial substances by harboring enzymes secreted into it.[4,26] Another mechanism involves slow-growing or non-growing microorganisms due to nutrient and oxygen depletion within biofilms, particularly with regard to resistance to killing by growth-dependent antimicrobial agents.[9] This phenomenon can be amplified by the presence of phenotypic variants or "persisters".[27] Persister cells are thought to be tolerant to antimicrobial agents because they are in a particularly dormant state.[28] Importantly, dispersed planktonic microorganisms can lose tolerance and restore their susceptibility to antimicrobial agents; thus, targeting dispersal mechanisms is a potential adjuvant strategy to render conventional antimicrobial agents active against biofilms.[29] Growth within a biofilm may facilitate acquisition of genetic changes such as mutations and gene transfer.[30,31] One study showed that plasmid conjugation was up to 700–fold more efficient in biofilms compared with free-living microorganisms.[32] Similarly, hypermutability may occur in biofilms, with mutation rates for *S. aureus* and *S. epidermidis* being 4- and 60-fold higher, respectively, in biofilms than that under planktonic conditions.[31] Together, increased gene transfer and hypermutability can increase selection of genetic antimicrobial resistance.

Diagnosis of medical device-associated infections

Bearing in mind that most medical device-associated infection are associated with biofilms on the surfaces of the devices, diagnostic strategies that approach the surface of the device are preferred. Sampling surfaces of medical devices may require invasive procedures such as aspiration, biopsy, or extirpation of medical devices. However, device removal is not necessarily required for diagnosis in all situations. For central-line associated bloodstream infections (CLABSI), diagnostic methods based on qualitative (or quantitative) blood cultures, including differential time to positivity, may be used.[33–35] Swab cultures are not recommended because of the small volume of sample available for culture; negative results do not necessarily correlate with the absence of infection.[36] Nevertheless, for some medical device-associate infections, microorganisms may not be identified until the medical device is removed. Moreover, culture is not always positive even when the device is removed. Slow growth rates in biofilms can lead to the 'viable-but-nonculturable' state (VBNC state) of microorganisms.[37] *S. aureus*, for example, can enter the VBNC state in biofilms, rendering it undetectable using standard growth media;[38] daptomycin and vancomycin are particularly noteworthy for inducing a VBNC state in *S. aureus* biofilms.[39] The emergence of small colony variants (SCVs) can also render successful diagnosis difficult.[40,41] SCVs are slow growing subpopulations of microorganisms that differ from normal microorganisms in their small colonial size and biochemical characteristics.[41,42] *S. aureus* SCVs have increased intracellular persistence.[41]

Sonication may improve culture positivity of large device-related infections.[43] One study, focusing on prosthetic hip and knee infection, demonstrated that sonicate fluid cultures had a sensitivity of 79% compared with 61% for periprosthetic tissue cultures.[43] Sonication is not, however, recommended for all devices; the use of a quantitative sonication technique to detect catheter colonization has been shown to be no better than the easier-to-perform semiquantitative roll-plate culture method.[44] Combinations of sonication with certain nucleic acid amplification tests further enhance the sensitivity to diagnose infection.[45,46] Several studies show differences between findings using culture and molecular diagnostic methods; molecular methods may identify additional organisms (i.e., increased diversity) compared to culture and/or may detect microorganisms in culture-negative cases.[47,48] In culture-negative endocarditis, for example, identification of the causative bacterium by broad-range bacterial (e.g., 16S ribosomal RNA gene) PCR of heart valve tissues can be useful.[49] Some infections may be missed or their microbiology not defined because of a high rate of false negative microbiological results with conventional culture methods; an example is arthroplasty failure.[50, 51,52] As mentioned above, implant sonication can improve diagnosis. Alternatively, DL-dithiothreitol has been used as for detection of biofilms on orthopedic implants.[53] Disclosing agents have been suggested as an intra-operative strategy to visualize biofilms, but the sensitivity of this approach is not defined.[54] Confocal laser scanning microscopy (CLSM) and scanning electron microscopy (SEM) are advanced options to visualize biofilms in resected specimens,[55,56] but are not typically used in direct patient care.

Treatment and prevention of medical device-associated infections

Basic principles of infection prevention should be applied to prevent microbial contamination of implanted devices because, as mentioned, this can readily lead to biofilm formation. Device implantation and handling must be performed as outlined in current guidelines.[57] Appropriate perioperative antibiotic prophylaxis should be administered to cases of surgically implanted devices. And of course, the need for the indwelling medical device itself must be justifiable at any time.

Current preventive (and to some extent therapeutic) approaches can be divided into two broad categories, surface-coating or elution, and physical/mechanical/electrical/biological approaches. Surface modification of medical devices using antibiotics and silver has been the focus of much research to reduce microbial colonization and biofilm formation.[1,2,6,58] Minocycline-rifampin catheters, which are commercially-available, have been associated with reductions in microbial colonization and CLABSI.[59] Although impregnated and standard catheters have similar CLABSI risks over first 10 days after placement; a cost-effectiveness analysis suggested minocycline-rifampin catheters to be most attractive if the catheter is anticipated to be in place for eight or more days.[60] Chlorhexidine-silver sulfadiazine catheters also decrease microbial colonization of surfaces.[61] Antibiotic impregnated materials may reduce the incidence of orthopedic foreign body-associated infections.[62] A silver impregnated endotracheal tube (ETT) showed a maximal effect during the first 10 days of intubation and reduced mortality in patients with ventilator-associated pneumonia (VAP).[63] Water sprays and jets have been used as physical–mechanical approaches for biofilm removal (e.g., debridement of surgical-site, exudates or dental

biofilms).[64] In addition, the use of dedicated devices to mechanically remove ETT biofilm is supported by a limited number of studies.[65] Electrical and electrochemical strategies are being investigated as strategies to prevent biofilm formation on device surfaces.[66]

When confronted with therapeutic difficulties, removal of the indwelling medical device is a definitive option for curing a medical device-associated infection. However, removal of a medical device may not always be feasible or desirable and the removal procedure itself may be prone to complications and associated with substantial cost. Microorganisms in biofilms show a wide degree of tolerance to different antimicrobial agents. Antibiotics such as rifampin, for the staphylococci in particular, and the fluoroquinolones, may exhibit activity.[67,68] Conversely, antibiotics that inhibit cell wall synthesis (e.g., β-lactams) may be less active because microorganisms in biofilms display slow growth rates.[69] When using rifampin-based therapy, combination with another antimicrobial agent, rather than monotherapy, must be employed to minimize the emergence of rifampin resistance. Glycopeptides or linezolid when combined with rifampin showed enhanced effects against staphylococcal biofilms.[67,70] In a cage-associated methicillin-resistant *S. aureus* (MRSA) infection model in guinea pigs, the combination of levofloxacin or daptomycin with rifampin had higher activity than the combination of vancomycin or linezolid with rifampin.[71] Rifampin and fosfomycin or tedizolid also showed enhanced effects in treating medical device infections caused by MRSA biofilms *in vivo*.[72,73] Dalbavancin alone has recently been shown to have *in vitro* activity against staphylococcal and enterococcal biofilms, potentially providing an option to treat dalbavancin-susceptible staphylococcal and enterococcal biofilm-associated infections.[74,75] Oritavancin also demonstrates activity against staphylococcal biofilms.[76] Age of the biofilm and biofilm species composition are important variables that impact susceptibility microorganisms in biofilms. Age of *S. epidermidis* biofilms was shown to be related with activity of erythromycin, clindamycin, cephalothin, teicoplanin, and vancomycin.[77] With respect to biofilm species composition, susceptibility of *Streptococcus pneumoniae* to β-lactam antibiotics was reduced by the co-presence of β-lactamase producing *Moraxella catarrhalis* in the biofilm.[78] In a biofilm composed of *Candida albicans* and *S. epidermidis* combined, the staphylococcal EPS inhibited azole penetration into the biofilm, and *C. albicans* appeared to protect *S. epidermidis* against vancomycin.[79] High dosages of antibiotics and prolonged duration of treatment are also important when treating medical device-associated infections. The application of catheter lock solutions is a strategy to eradicate established biofilm in the catheter lumen; using this approach, antimicrobial agents dwell at supratherapeutic concentrations (but concentrations sufficient to exhibit anti-biofilm activity) in the catheter lumen for a prolonged time. Antimicrobial lock solutions have been shown to decrease the risk of CLABSI in immunocompromised hematologic patients and those undergoing hemodialysis.[80,81] Antibiotic lock therapy is used in conjunction with systemic antibiotics in the treatment of patients with uncomplicated CLABSI.[82]

Recent advances in surface technologies and materials have ushered in development of defined surface patterns of chemistry and topography that can impact biofilm formation without adding antimicrobial agents.[58] Novel materials such as zinconium oxide and electropolished stainless steel reduce bacterial adhesion.[27] Incorporation of the Sharklet micropattern (motivated by shark skin) on the surface of medical devices may reduce

microbial colonization and biofilm formation.[83] Several studies show the feasibility and efficacy of surface modification of medical devices with antifouling polyurethanes and hydrogels to reduce microbial colonization.[1,27] Bacteriophages are viruses that propagate in their bacterial host, and can kill their host and/or produce anti-biofilm substances.[84] Pretreating hydrogel-coated catheters with a single *S. epidermidis* bacteriophage or a cocktail of *P. aeruginosa* bacteriophages mitigated biofilm formation by relevant bacteria *in vitro*.[85–87]

Recent advances in understanding the complexity of biofilm biology has informed the development of novel biofilm-targeting therapeutic strategies.[1,2,27] EPS-degrading enzymes are a new strategy that may enhance efficacy of antimicrobial agents against biofilms.[88,89] Enzymes such as deoxyribonuclease 1 (DNase 1) and dispersin B (DspB) may be useful adjuvants in this regard.[88,89] Both DNase 1 and DspB are being investigated as promising options for biomedical coatings.[90] Another antibiofilm strategy is the use of lysins - bacteriophage-encoded peptidoglycan hydrolases.[91] Small molecules such as mannosides or peptides impede bacterial adhesins binding to host surfaces, thereby preventing biofilm formation.[92–94] The widespread use of quorum sensing systems of bacteria for controlling virulence and biofilm formation constitutes another target tactic for the development of novel therapeutics.[95] Nanoparticles provide yet [96] another exciting area of development of new biofilm-targeting methodologies. Nanoparticles are currently in the spotlight mainly for their intrinsic antimicrobial activity and strong anti-biofilm potential together with relatively low toxicity to the host.[97] Nanoparticles can be used for targeted delivery of antibacterial and antibiofilm agents.[98] Liposomes are widely used as representative organic nanoparticles for delivery agents for antimicrobial agents. [99–103] Recently, nanomodified ETTs have been shown to have decreased bacterial colonization compared to unmodified ETTs.[104,105] Nano- and chemical engineering approaches can be used to develop improved materials for prevention of biofilm formation. Finally, electrical and electrochemical strategies are being developed for their anti-biofilm activities.[96,106–115]

Summary

Medical device-associated infections are biofilm-associated infections related to organized communities of microorganisms embedded within a matrix of EPS of microbial and host origin. Because of the entrapment or inactivation of antimicrobial agents, and of the slow growth in biofilms, microorganisms in biofilms display tolerance to a wide range of antimicrobial agents. The VBNC state and emergence of SCVs in biofilms can make successful diagnosis difficult using standard microbiological assays. New diagnostic techniques such as sonication of large implants and molecular diagnostic methods may improve not only identification of pathogens but also reveal greater microbial diversity than previously appreciated. Although most currently available antibiotics have poor activity against microorganisms in biofilms, some, notably rifampin against staphylococci, have been shown to be active against biofilms. Surface-coating or eluting substrates and physical/mechanical/chemical/electrical/biological approaches aimed at inhibition of initial attachment and biofilm removal are two main current biofilm-targeting approaches. Recent advances in surface technologies and materials have ushered in development of material optimization and surface modification with antifouling polyurethanes, hydrogels, and

bacteriophages. Recent insights into the biofilm matrix have accelerated novel biofilm-targeting therapeutic strategies such as extracellular polymeric substance-degrading enzymes, small molecules targeting host–extracellular polymeric substance interactions, and quorum sensing systems involved in biofilm formation and dispersal. Electrical and electrochemical strategies are under development.

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Box 1

Clinical features of medical device-associated infections

- Presence of an indwelling medical device
- Clinical findings suggestive of infection, often with low-grade inflammation
- Infection lasting more than one week
- Failure of antibiotic treatment without planktonic genetic antimicrobial resistance
- Recurrence of infection (particularly if same microorganism is detected over multiple time points, and clinical findings improve/resolve with antibiotic therapy, only to recur after therapy has ceased)

(Data from Hoiby N, Bjarnsholt T, Moser C, et al. ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. *Clin Microbiol Infect.* 2015;21 Suppl 1:S1–25.)

Key Points

- Treatment of medical device-related infections is challenging because microorganisms adhere to and accumulate on the surfaces of medical devices producing biofilms. Microorganisms in biofilms display tolerance to a wide range of antimicrobial agents.
- The ‘viable-but-non-culturable’ state, alongside emergence of small colony variants, can render successful diagnosis of biofilm-associated infections difficult using standard microbiological assays. Sonication of infected implants and molecular diagnostic methods may improve not only detection and identification of pathogens but also reveal greater microbial diversity than traditionally recognized.
- Surface-coating or eluting substrates and physical/mechanical/chemical/electrical/biological approaches targeted at inhibition of initial attachment and bacterial removal are two biofilm-targeting approaches in use and/or under development.
- Recent advances in surface technologies and materials have ushered in development of material optimization and surface modification with antifouling polyurethanes, hydrogels, and bacteriophages.
- Recent insights into the biofilm matrix have accelerated novel biofilm-targeting therapeutic strategies such as extracellular polymeric substance-degrading enzymes, small molecules targeting host–extracellular polymeric substance interactions, and interventions targeting quorum sensing systems involved in biofilm formation and dispersal.

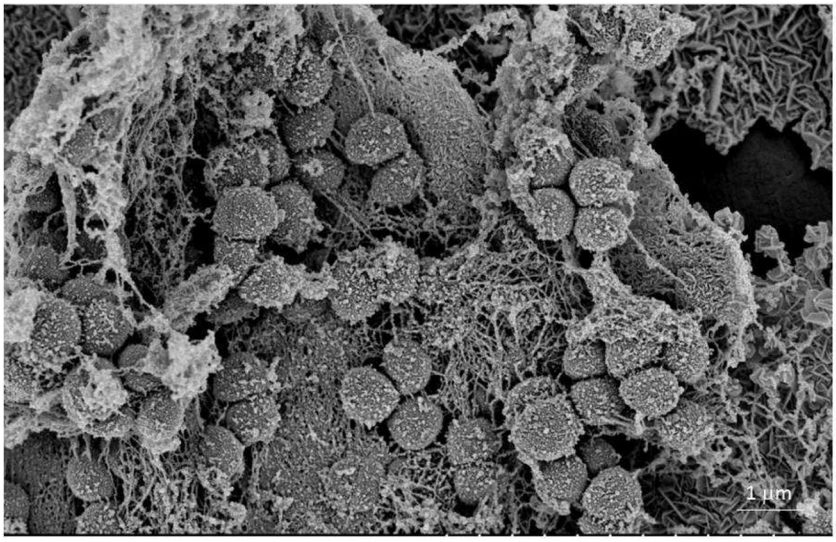

Figure 1. Scanning electron microscopy of *Staphylococcus epidermidis* biofilm

S. epidermidis was grown in the laboratory on a Teflon surface.

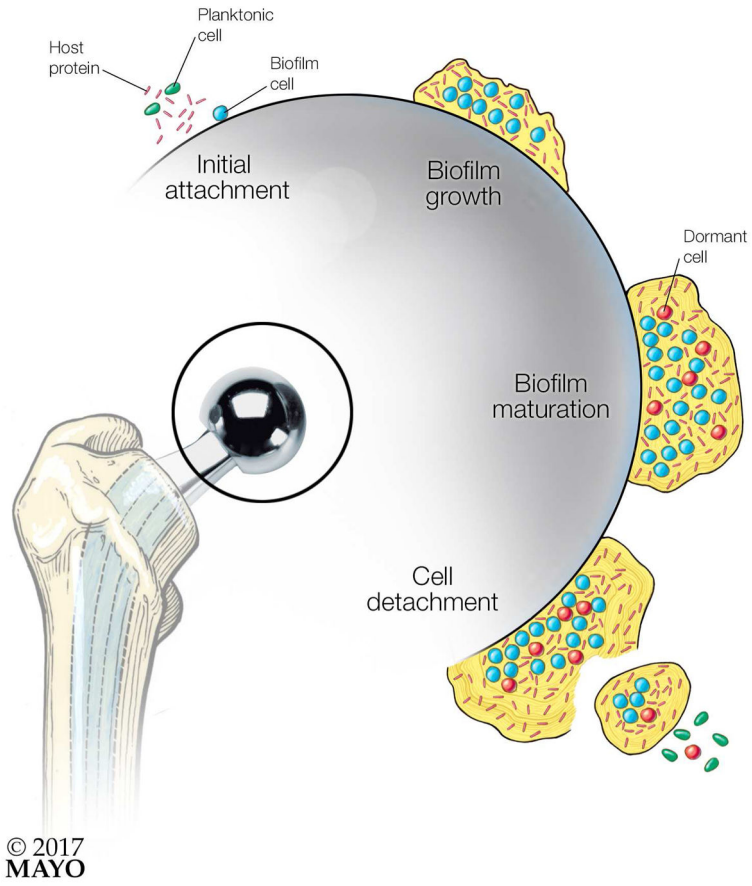

Figure 2. Steps in biofilm formation on an orthopedic prosthesis

Biofilm formation has distinct stages: **Initial Attachment**, in which microorganism attaches to an orthopedic implant through interactions between the microorganism and host molecules on the foreign body surface as well as the foreign body surface itself; **Biofilm Growth**, in which the microorganism begins to proliferate, and individual cells adhere to one another, and become surrounded by a self-produced extracellular polymeric substance; **Biofilm Maturation**, whereby the biofilm develops a structured multicellular community protecting its members against from external threats, including host defense mechanisms and antimicrobial treatments; and finally **Cell Detachment**, whereby planktonic cells may be released from the surface of large biofilms, causing distant metastatic infections and further regional biofilm establishment.

Table 1

Biofilm-associated infections.

Medical devices associated with infections	Tissues associated with infections
Cardiovascular implantable electronic devices	Biliary tract
Catheters, shunts and stents	Internal ear (chronic otitis media)
Cochlear implants	Tonsils (chronic tonsillitis)
Contact lenses	Sinuses (chronic sinusitis)
Deep brain stimulators	Wounds
Endotracheal tubes	Teeth (dental caries)
Dental implants	Heart valves (endocarditis)
Orthopedic implants	Kidney stones
Tissue fillers, including breast implants	Lung (cystic fibrosis patients)
Sutures and surgical meshes	Bone (osteomyelitis)
Vascular grafts	

(Data from Hoiby N, Bjarnsholt T, Moser C, et al. ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. *Clin Microbiol Infect.* 2015;21 Suppl 1:S1–25.)