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REVIEW

Environmental, Microbiological, and Immunological Features of Bacterial Biofilms Associated with Implanted Medical Devices

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SUMMARY The spread of biofilms on medical implants represents one of the principal triggers of persistent and chronic infections in clinical settings, and it has been the subject of many studies in the past few years, with most of them focused on prosthetic joint infections. We review here recent works on biofilm formation and microbial colonization on a large variety of indwelling devices, ranging from heart valves and pacemakers to urological and breast implants and from biliary stents and endoscopic tubes to contact lenses and neurosurgical implants. We focus on bacterial abundance and distribution across different devices and body sites and on the role of environmental features, such as the presence of fluid flow and properties of the implant surface, as well as on the interplay between bacterial colonization and the response of the human immune system.

KEYWORDS biofilms, fluid flow, immune response, medical implants, microbial contamination

INTRODUCTION

Medical implants are artificial devices partly or entirely inserted into the human body and intended to remain after the procedure for diagnostic, therapeutic, and rehabilitation purposes. The wealth of functions they offer is continually expanding and evolving and demand for such implants is expected to increase due to the aging population (1–4). It was

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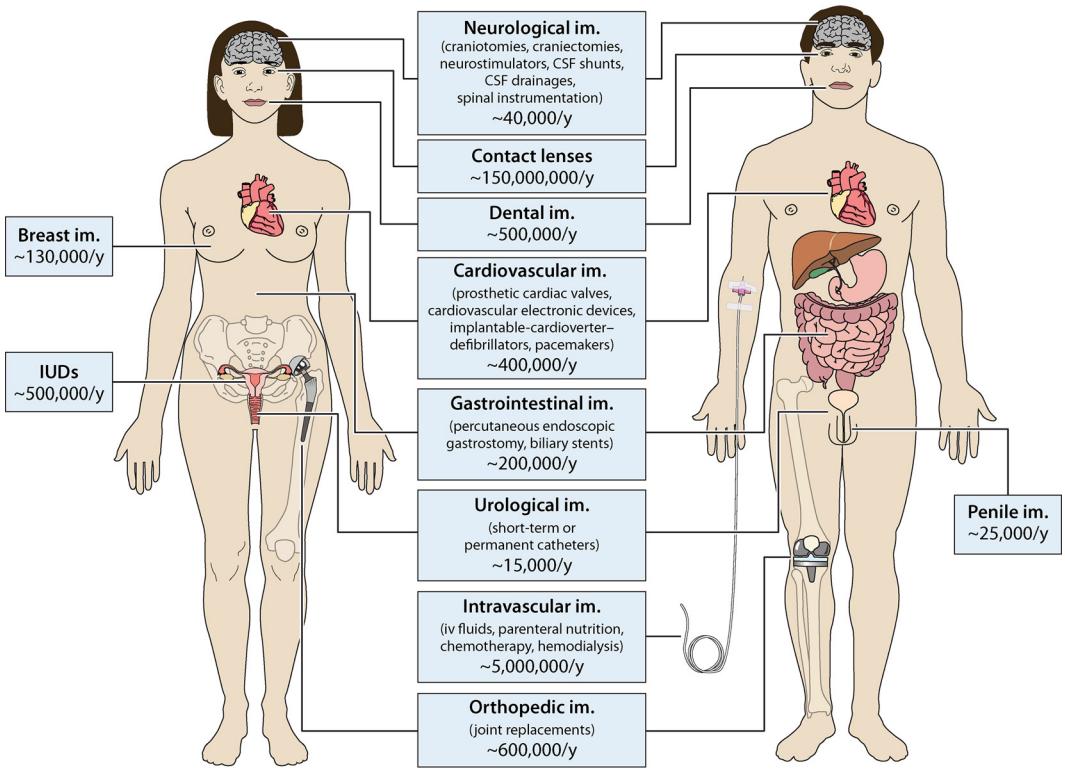

FIG 1 Most used medical devices. The figure depicts the most common medical devices, their distribution within the human body, and the number of implants employed per year (/y) in the United States (6, 402, 403). Implants commonly used in both women and men are listed in the middle, while sex-specific implants are reported at the side of each figure. The graphic work was done using Smart Servier Medical Art.

estimated that, only in 2018, the U.S. market of medical devices alone reached about 90 billion USD, while the forecast market for 2019 to 2025 would predict a compound annual growth rate (CAGR) of 6.3%, reaching by 2025 the market value of about 140 billion USD (5). Intravascular devices are the most employed, with an estimate of approximately 5,000,000 devices implanted in a single year only in the United States, followed by orthopedic implants (~600,000/year), dental implants (~500,000/year), and cardiovascular devices (~400,000/year) (Fig. 1) (6). The use of medical devices ameliorated the treatment of multiple pathologies and, ultimately, patient quality of life. Unfortunately, device-associated nosocomial infections, often related to biofilm formation (7–10), still represent a significant health concern worldwide (11–14), with substantial clinical and economic consequences. In fact, compared to planktonic cells of the same species, bacteria within a biofilm are up to 1,000 times more resistant to antimicrobial agents (15), thus becoming the primary cause of persistent and chronic infections, which in turn affect the well-being of individuals and increase the treatment costs for the national health systems (16, 17).

Biofilms are surface-associated microbial colonies, embedded in a self-secreted matrix of extracellular polymeric substances (EPS). EPS consists of many types of polymers, including polysaccharides, extracellular nucleic acids (eDNA), proteins, amyloids, and amphiphilic surfactants. Being prevalent on most wet surfaces in nature (18–20), the communal lifestyle of biofilms favors the emergence of properties substantially different from the ones exhibited by planktonic cells, mainly due to the presence of the extracellular matrix (21). The sessile mode of growth, by keeping the cells in proximity, mediates communication between bacteria (22), fosters horizontal gene transfer (23) and promotes the sharing of metabolic products within the biofilm community (24). A remarkable property in terms of biofilm survival is the increased resistance to phagocytosis (25) and biocides (26), which, in a clinical context, implies resistance to host defense mechanisms (27, 28) and treatments with antibiotics and antimicrobials (29, 30). The biofilm matrix can retard the diffusion of solutes (31, 32) and of

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some antibiotics (33) with an efficiency that strongly depends on the specific interaction between EPS components and antibiotic molecules (34, 35). Moreover, although many antibiotics can penetrate the EPS, bacterial cells inside the biofilm are often protected due to their slower metabolism, which makes them less susceptible to the effects of antimicrobials. An additional cause of the increased antibiotic tolerance in biofilms is the presence of dormant cells, which can be less susceptible to chemical attacks (36, 37). These cells, called persisters, can survive antibiotic treatments in the absence of specific resistance mechanisms (38, 39), and their existence is intrinsically related to the physicochemical biofilm heterogeneity that promotes the formation of phenotypical niches (40, 41).

An essential aspect of the biofilm-associated infection treatment is the microbiological diagnosis (42). The conventional method is to perform microbial cultures using tissue samples or fluids close to the infection site. However, a more effective approach, which can be applied when the implant is removed, is the sonication of the device to dislodge the biofilm from the surface and disperse the cells in sonicate fluid (43). The sonicate fluid culture has a higher sensitivity compared to standard tissues samples since in biofilm-associated infections cells are retained in the matrix and its dispersion increases their detectability (44, 45). Indeed, the use of conventional culture methods is not always indicative of biofilm growth: a negative result may not necessarily indicate the absence of bacterial infection but could be due to the slow proliferation rate of microbes within a biofilm. Thus, advances in sequencing methods, such as 16S rRNA gene sequencing (46, 47) or metagenomic sequencing (48–50), have begun to identify pathogens and to provide data describing their composition and function across multiple sites in the human body (51, 52). Several independent culture techniques could be employed (53). Denaturing gradient gel electrophoresis (PCR-DGGE) uses a polyacrylamide gel containing linearly increasing concentrations of a denaturing agent to separate amplicons of ribosomal DNA having the same size, but different sequences (54, 55). Terminal restriction fragment length polymorphism (T-RFLP) is based on detecting differences within the pattern obtained with a single restriction enzyme cut on the 16S rRNA gene. T-RFLP can identify the dominant community members comprising at least 1% of the total (56); both DGGE and T-RFLP can assess the community structure and variation over time or space. Fluorescent *in situ* hybridization (FISH) probes target large taxonomic groups and can quantify microbial communities even within complex environmental samples (57). Direct 16S rRNA gene sequencing can identify a single bacterium species; however, in recent years, thanks to the development of next-generation high-throughput sequencing, it is possible to analyze a PCR mix, including hundreds of different rRNAs from a bacteria community (or the rRNA gene internal transcribed spacer [ITS] regions for yeast), to identify the different bacteria present and their relative quantities within this community (48, 49). This identification step is crucial for undertaking efficacious therapeutic treatments.

This review presents an overview of biofilms associated with implanted medical devices in different parts of the human body, highlighting the most frequently colonizing microbes, the environments that promote their growth (including the presence of fluid flow and the properties of the implant surface), and the human immunological response. Despite the wealth of research studies in this field, there is a need to collect the most relevant contributions on device-associated biofilms and start pulling the threads together to guide research on this complex and critical problem.

BIOFILM FORMATION AND MICROBIAL COLONIZATION ON MEDICAL DEVICES

Cardiovascular Implants

Implantable cardiac devices are tools for patients with cardiac diseases and are used to prevent heart failure. They comprise pacemakers, implantable cardioverter–defibrillators (ICDs), cardiovascular implantable electronic devices (CIEDs), and prosthetic cardiac valves. The annual number of cardiac devices employed in medicine is constantly increasing (58). Unfortunately, many of them need to be replaced due to malfunctions or infections: it is estimated that the rate of infected devices is currently between 1.2 and 2.4% of the total implanted devices (58–60), with infection rates increasing up to 10-fold after the replacement of the device or after its upgrade (61, 62). Infections occurring within the first 12

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months postoperation are predominantly linked to colonization at the time of surgery, and 25% of these infections manifest themselves within the first month following the implantation. Overall, CIED infections are associated with morbidity, mortality (especially when comorbid conditions are present [63]), and substantial health care expenses.

The microbes most frequently identified on the infected device surface or in the skin pockets of cardiovascular implants are coagulase-negative *Staphylococcus* spp., accounting for almost 60 to 80% of the infections (64, 65), and *Staphylococcus aureus*, which is identified 11 to 29% of the time (66, 67). Moreover, *Enterococcus* spp., *Streptococcus* spp., HACEK (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.), and few fungi, particularly *Candida albicans* (68–71), have been associated with cardiovascular implants. In cardioverter defibrillators and pacemakers, polymicrobial colonization are identified 1 to 7% of the time, but the composition of these mixed communities was not investigated (70, 71). Patients with possible CIED infection undergo blood cultures to identify the aerobic or anaerobic microbe, since most of the contaminants are methicillin-resistant *S. aureus* (MRSA); vancomycin is usually the first antibiotic administered. Once the contaminant is identified, a more specific cure is undertaken for 10 to 14 days (65, 72), while the device is replaced. To reduce the chance of infections, antibiotic prophylaxis or antibacterial envelopes covering the device have been employed (73). For example, the use of a polypropylene mesh releasing minocycline and rifampin has been shown to significantly reduce the occurrence of CIED infections (73). Moreover, oral pathogens causing periodontitis, such *S. mutans* (74, 75), can also reach the heart valve from the bloodstream, causing an infection (76–78). A good oral hygiene in healthy individuals is usually sufficient to avoid these problems, but in patients at high risk of endocarditis an antibiotic prophylaxis is normally suggested before a dental procedure. In this case, amoxicillin is the most frequently utilized antibiotic (79, 80).

Despite the clinical importance of infections associated with cardiovascular implants, very little is known on the growth of biofilms on these devices. Some evidence comes from *in vitro* studies of biofilm formation from clinical isolates. For instance, *Cutibacterium* (formerly *Propionibacterium*) *acnes* strains—isolated from the surfaces of explanted pacemakers with no clinical signs of infection—can form biofilms, as shown using a microtiter plate assay (81). In addition, cytoplasmic material and a fibrous matrix of eDNA were found via electron microscopy in *C. acnes* biofilms, suggesting that eDNA may play a role in forming biofilms on pacemakers and other cardiovascular devices (81).

Gastrointestinal Implants

Percutaneous endoscopic gastrostomy (PEG) is the most common access route for enteral nutrition in pediatric and adult populations. However, PEG tubes have been recognized as risk factors for gastrointestinal colonization and biofilm formation by antibiotic-resistant bacteria in long-term care facilities (82, 83). Investigations conducted on PEG tubes always revealed the presence of bacterial and fungal biofilms (84, 85), despite their presence not being the cause for removal. Dautle et al. analyzed the microbiota associated with silicone gastrostomy devices used for long-term (3 to 47 months) enteral nutrition in children (6 months to 17 years) (84). All devices examined showed the presence of biofilms; 24 bacterial species were identified, including *Bacillus*, *Enterococcus*, and *Staphylococcus* species. In that study, scanning electron microscopy (SEM) measurements showed that defects on the surface of PEG tubes provided protected sites for initial attachment and the development of biofilms. In another study (85), PEG tubes removed from 12 patients after 4 to 233 weeks of use were sampled and examined for microbial colonization and biofilm formation. Cultures were positive for fungal contamination in all cases (*Candida tropicalis* was the species most frequently involved), while the inner walls of the tubes used for more than 12 weeks were always encrusted with a thick biofilm but with variable thicknesses that did not correlate with the PEG age (85).

Obstructive jaundice is a condition that prevents the normal flow of bile to the duodenum. It frequently correlates with symptoms of appetite loss, nausea, recurrent cholangitis, and renal failure; moreover, it is a common indication of pancreatic or periampullary cancer (86). Currently, more than 70% of the patients with obstructive jaundice are treated by biliary

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stenting in first-line centers receiving the patient under urgent conditions and later referred to specialized high-volume centers for surgery (87). Moreover, due to long waiting lists or the necessity of neoadjuvant chemoradiation therapy, the operation must be postponed by several weeks even in referral centers, and biliary stenting becomes mandatory. During this period, by gaining access to the biliary system, duodenal bacteria can attach to the stent surface and start forming biofilms, playing a critical role in the clogging of biliary stents (88, 89).

Endoscopic gastrointestinal devices are associated with a wide and diverse spectrum of microbial species. Previous works have demonstrated a clear connection between the presence of biliary stents and a dramatic increase in the contamination of bile, which was predominantly characterized by species from the duodenal microbiota such as enterococci (90, 91). In a prospective study, pigtail polyurethane stents and straight polyethylene stents were retrieved from 120 patients (62.5% males; median age, 64 years) with biliary strictures (35% malignant, 65% benign) after 1 to 1,274 days of indwelling time. The occlusion rates of the stents—which significantly increased the risk of cholangitis—were found to be around 11.5% in pigtail stents and 13% in the straight ones. Polymicrobial colonization predominated (95.8% versus 4.2%), with enterococci (79.3%), *Enterobacteriaceae* (73.7%), and *Candida* spp. (55.9%) as the leading pathogens among 95 different bacterial and 13 fungal species identified. Interestingly, *Candida* spp. were more common on stents from patients previously receiving prolonged antibiotic therapy (63% versus 46.7%) (92).

Orthopedic Implants

Total joint replacement is a safe and standard procedure that can restore functionality and improve the well-being of patients with hip and knee arthritis (93). Despite its safety, postoperative complications still occur: the most common is prosthetic joint infection (PJI), a major mechanism of failure of the implant that often requires surgical revision. In many cases, if surgical debridement and implant retention are performed or after implant removal with a two-stage procedure, the treatment of PJI fails (94). In the last decade, a new classification has been described based on the pathogenicity and etiology of the infection. PJI can be recognized as (i) an acute infection characterized by early onset and highly virulent bacteria; (ii) a low-grade infection, a chronic type of infection that arises later and is caused by low virulence or small colony-forming bacterial stains; or (iii) a late hematogenous high-grade infection.

In general, the bacterial species found most in PJIs are *S. aureus*, *Staphylococcus epidermidis*, and *Staphylococcus lugdunensis* (95, 96). Several studies identified three different mechanisms of pathophysiology in staphylococcal chronic PJIs: the formation of small colony variants (SCVs) (97), bacterial internalization in osteoblasts (98), and the formation of biofilm (99). Both SCV and biofilm formation have been observed for *S. aureus*, *S. epidermidis*, and *S. lugdunensis*. An acute PJI is usually caused by *S. aureus* and, in up to 50% of cases, by MRSA strains (93). In particular, the presence of biofilms of *S. aureus* have been observed directly from the bone cement retrieved during a revision surgery and, in synovial fluid samples, as free-floating biofilm-like aggregates (100, 101). Moreover, polymicrobial communities have been also identified in association with PJIs, comprising *P. aeruginosa-E. faecalis-K. pneumoniae*, MRSA-MSSA, and MRSE-*E. faecalis* (93, 95).

Osteomyelitis could occur because of PJIs and biofilm formation; in this case, it is referred to as contiguous-focus osteomyelitis, and it is usually caused by *S. aureus* (102). Considering that the biofilm's presence complicates the treatment of osteomyelitis, different approaches have been considered, such as the use of anti-polysaccharide intercellular adhesin (PIA) antibodies to prevent microbial attachment or PIA formation (103, 104) or the coating of medical devices before implantation. Recently, also the prosthesis surface has been investigated to prevent bacterial colonization or biofilm formation (105). Among these approaches, the most studied is silver coating (106, 107), despite its several limitations, especially its toxicity (108). For this reason, different kinds of nanoparticles with antimicrobial abilities, such as silver, copper, quantum dots, and zinc oxide, have been used on prosthesis surfaces to reduce cell viability and bacterial adhesion (109–112). For treating osteomyelitis, Bioactive Glass (BAG-S53P4), a bone substitute with proven antibacterial and bone-bonding properties (113), is used. Furthermore, Franceschini et al. found that an antibacterial hydrogel

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coating, composed of hyaluronan, poly-D,L-lactide (defensive antibacterial coating [DAC]), could be used as protective biomaterial, in association also with topic antibiotics, to prevent bacterial adhesion and biofilm formation (114).

Studies have shown that one of the biofilm persistence mechanisms involved a crosstalk with myeloid-derived suppressor cells (MDSCs), i.e., immature monocytes and granulocytes that are involved, during inflammation or injury, in the generation of a mature myeloid population (115, 116). During bacterial biofilm infection, MDSCs lose their ability to mature, and they negatively regulate inflammatory mechanisms through their suppressive actions (117, 118). Heim and colleagues found that MDSCs improve bacterial persistence during *S. aureus* orthopedic biofilm infection via interleukin-10 production (119). As described above, biofilm can protect pathogens that would otherwise be eradicated in their planktonic or free-floating form. For these reasons, the treatment of PJI is very complex because it often involves a two-stage exchange, with implant removal and antibiotic spacer placement followed by systemic antibiotic therapy and delayed reimplantation. To reduce morbidity, antibiotic therapy could be improved to a one-stage exchange, or implant retention may be more feasible. Using a mouse *in vivo* model, Niska et al. evaluated and compared efficacies of vancomycin-rifampin combination therapy for PJIs and demonstrated an increased efficacy compared to monotherapy (120).

Neurosurgical Implants

Neurosurgical devices comprise neurostimulators, cerebrospinal fluid (CSF) shunts, external ventricular CSF drainage, and external lumbar CSF drainage spinal instrumentation. The rate of infections of these devices ranges, on average, from 3 to 15%, but it can reach even higher numbers with craniectomies and external ventricular CSF drainages (6, 121–123). The consequences of these infections are often devastating for the patient and are associated with an increase in morbidity and mortality (124, 125). Management of this problem is even more difficult if we consider (i) that diagnosis of infection is challenging; (ii) that biofilms are easily formed on the implant surface, requiring prolonged antimicrobial treatment; (iii) that standardized approaches to fight the infections are lacking; and (iv) the impossibility, in some cases, of removing or replacing the implant (126–128). Most of the infections are related to microbes found in skin and mucosal flora or disturbance of the wound healing process. Indeed, preoperative infection prevention protocols have been shown to decrease infection rates (129). Acute infections present themselves within 6 weeks of operation. Since immature biofilms are present at this stage, infections are most frequently treated with prolonged antimicrobial treatment (from 4 to 12 weeks) and shunt removal. Before microbial identification, general treatment can start with intravenous vancomycin plus ceftriaxone, cefepime, or ceftazidime (127). If Gram-positive bacteria are detected, rifampicin is administrated in combination with co-trimoxazole, levofloxacin, moxifloxacin, or doxycycline to avoid the development of resistance (130), whereas fluoroquinolones are the antimicrobial agents most frequently used against Gram-negative bacteria. Whenever chronic infections present themselves more than 6 weeks after the operation, biofilms on the implant surface are usually mature and stable, and to remove these biofilms, antibiotic treatment is performed, along with removal or replacement of the device (127, 128). Overall, the most frequently identified bacteria are *Staphylococcus* spp., especially *S. aureus*, which is identified more than 50% of the time; followed by *Cutibacterium* spp., where *C. acnes* is isolated 5.4% of the time; and *Enterobacter* spp. (3.78%); among fungi, *Candida* spp. are isolated 1.63% of the time (131, 132).

Urological Implants, Nephrostomy Tubes, and Stents

Biofilm formation has been observed in the most used devices in the urogenital tract: short-term or permanent catheters, ureteral stents, nephrostomy tubes, and penile implants (133). In current clinical practice, indwelling catheters are widely used to relieve upper urinary tract obstruction, prevent stricture formation, drain urinary tract leaks, and hinder postsurgical complications (134). In indwelling stents, which are infected in most cases, fever and urinary tract infections (UTIs) are the most common complications, followed by bacteremia and even death (135, 136). Bacterial penetration is probably due to the

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permissive environment; in fact, these devices meet polysaccharides, ions, and glycoproteins, which form a conditioning film on the implant surface, allowing various planktonic bacteria to adhere and form biofilms (137, 138). This event occurs typically within 24 h of the stent insertion (136, 138). Moreover, encrustation could lead to bacterial biofilm formation. This process involves the deposition of mineral crystals onto the surface and lumen of a ureteral stent. As a result, the stent becomes calcified and loses its tensile strength, raising the risk of stent fracture or ureteral avulsion during removal.

In one of the first papers analyzing encrustation and its relationship with bacterial biofilm, Wollin et al. found a conditioning biofilm layer on indwelling stents derived from 64 patients, half of whom showed encrustation, and 13% had been coated by a bacterial biofilm (139). Though the production of urease can lead to encrustation, the relationship between these two processes is poorly understood. In fact, on one hand, bacterial biofilms may facilitate precipitation of crystals causing encrustation, and on the other hand, encrustation could constitute a niche for bacteria colonization and bacterial biofilm formation (140).

The most common biofilm-forming pathogens found on these devices are *E. coli*, *P. mirabilis*, *P. aeruginosa*, *E. faecalis*, *Staphylococcus* spp., and *C. tropicalis* (141, 142). The latter are considered strong biofilm-forming microbes and are also involved in polymicrobial infections (142), since the capacity to form a biofilm could serve as a shelter for the weak formers. There are several studies on the bacterial adhesion of uropathogens to host cells. For *E. coli*, a connection between type I pili, in particular its protein FimH, and Tamm-Horsfall protein (THP) was found. This protein is usually responsible for eliminating bacteria, but in permanent stents it becomes an anchor for *E. coli* via FimH and for *P. mirabilis* and *P. aeruginosa* via different adhesion proteins (141). Antibiotic treatment is often not sufficient to eliminate or avoid the formation of bacterial biofilms on ureteral stents (143); thus, the usual approach to eliminate the infection consists of replacement or early removal of the implants (138). Modifications of the surface material or treatment of the surface itself have been investigated as ways to prevent bacterial attachment and biofilm formation (143–145).

Different prevention strategies to avoid both encrustation and biofilm formation are currently under investigation. The most common method is to coat surface devices. The use of silver and silver nanoparticles, antibiotics, bacteriophages, chlorhexidine, triclosan, antimicrobials peptides and enzymes, hydrogel, polytetrafluoroethylene (PTFE), polyzwitterions, and polyethylene glycol (PEG) coatings are the most explored and used techniques (146–149). Moreover, changes in surface topographies have been studied to avoid bacterial attachment (146). Recently, Mosayyebi et al. proposed an innovative approach in which a microfluidic model of the stented and occluded ureter is used to study the effect of stent architecture on wall shear stress (WSS) distribution and encrustation over its surface (150). Measuring the stent thickness and the hole vertex angle, a reduction in the encrustation thickness by ~90% was detected. Penile implants are primarily used for erectile dysfunction (ED), a disease that affects 20 to 25% of men over 40 and 5 to 10% below this age. ED is predominantly linked to medical conditions such as cardiovascular disease and diabetes (151). Infectious complications are generally infrequent (about 3% of primary surgeries and up to 18% of revision surgeries [152, 153]) but can cause serious consequences from both a clinical and an emotional perspective (151). During the revision surgery, bacteria were found in 70% of cases; among these, the majority are *Staphylococcus* spp., in particular *S. epidermidis* (137, 153, 154). Recently, surgeons have improved the prosthesis insertion procedure: leveraging the experience in the orthopedic field, they are implementing the strategy employed for PJIs (151).

Intravascular Devices

Intravascular devices are used for different applications, including intravenous fluids, parenteral nutrition, antibiotic therapy, chemotherapy, and hemodialysis. It has been estimated that over 5 million devices are implanted every year in the United States only (155). Needle-free connectors, such as split septum connectors, Luer activated valves, and Luer valves with positive displacement, were introduced to reduce the risk of needlestick injuries and assist catheter management and nursing care. However, environmental contaminations, lack of disinfection procedures (70% alcohol and treatments for 5 to 60 s are suggested), and poor scrubbing

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techniques increase the risk of infection (156). Colonization of needle-free connectors causes 50% of catheter-related infections (157). To reduce the infection rate, disinfection protocols should be improved, and the predisposition to contamination of different connectors should be tested (156, 158). Overall, *S. aureus*, *S. epidermis*, *E. faecalis*, *P. aeruginosa*, and *K. pneumoniae* are the leading infectious agents in intravascular catheters. Within this environment, *C. albicans* is again the most frequently isolated fungus (159–161). These microbes are related to bloodstream infection, a major problem that in the United States alone causes almost 200,000 cases of infection per year, resulting in prolonged hospitalization and increased costs (162). The first step to solving this problem is antibiotic therapy. Since the most common source of infections are MRSA strains, vancomycin is often used since it is active against coagulase-negative staphylococci and *S. aureus*. Alternatively, when *P. aeruginosa* is detected, ceftazidime or cefepime, fourth-generation cephalosporins, are recommended. When a fungal infection is detected, the use of amphotericin B or fluconazole is recommended (155).

Often, the identified microbes form biofilms along the catheter and display a higher antibiotic tolerance. To achieve a higher local concentration of the drugs, the "lock therapy" could also be undertaken. Here, since most infections in tunneled catheters spread to the lumen, the latter gets filled with the desired drug for a few hours or even days, also intermittently, to eradicate the contaminant (163–165). Ideally, lock solutions should be directed against common pathogens or be targeted to specific bacteria, be able to disrupt a biofilm, be compatible with anticoagulants, have long chemical stability and low toxicity, induce no antibiotic resistance, and be cost-effective. Overall, the main combinations used are vancomycin with the anticoagulant heparin, taurolidine, and minocycline with EDTA, which can disrupt biofilm integrity and synergize the activity of the antibiotic, or ethanol (163, 165, 166). If this strategy fails, the infected catheter should be removed and replaced with a new one.

Breast Implants

Breast implants are used in both postmastectomy breast reconstruction and cosmetic surgical procedures. In addition to other surgical procedures, breast implants also face complications such as hematoma, seroma, infection, altered nipple sensation, asymmetry, scarring, rupture, and capsular contracture (CC) (167). Implant removal or revision is usually caused by CC (168), which is also responsible for breast pain and discomfort and affects the breast aesthetic (169). Moreover, prosthesis revision surgery is often associated with CC recurrence. Several factors may participate in CC etiopathogenesis: (i) surgical procedure, such as the choice of location and incision (170, 171); (ii) genetic predisposition (172); (iii) inflammation resulting from subclinical infection and biofilm formation (167); and (iv) implant texturization (173). Bacteria were found in 85% of breast implants that encountered CC, and biofilms, observed using SEM, were detected in more than half of them (174). *Staphylococcus* spp. are usually present in breast implants removed for CC, in particular *S. epidermidis* and *S. aureus* (174–176). However, several bacteria can survive in the periprosthetic environment and form biofilms, such as *C. acnes* (a commensal species of the skin and gut), streptococci, *Bacillus* spp., *E. coli*, *Mycobacterium* spp., *Corynebacterium* spp., and lactobacilli (174, 175, 177). These studies indicate a possible correlation between bacterial colonization, biofilm formation, and CC (178).

Another factor potentially implicated in biofilm formation and consequent CC is the breast-implant texture. Although some works did not find a correlation between bacterial colonization and the type of textured implants (175), other studies have shown, both *in vitro* and *in vivo*, that biofilm formation is more common on rough surfaces (179, 180). At the same time, smooth prostheses have also been associated with increased biofilm formation (171, 173, 181, 182). Although CC is considered one of the main problems with breast implants, anaplastic large cell lymphoma associated with a breast implant (BIA-ALCL) has also been recently investigated. BIA-ALCL was identified for the first time in 1997 (183); however, it is not known whether its formation derives from the formation of biofilms or the specific texture of the implants. Hu et al. studied the bacterial population present in BIA-ALCL compared to normal patients and found that *Ralstonia* spp. are mainly associated with tumor capsule specimens compared to nontumor ones (184). However, it was recently reported that BIA-ALCL is primarily associated with macrotextured implants (185). In order to prevent biofilm formation and

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also capsular contraction, clinicians have improved the surgical procedures by (i) administering intravenous antibiotic prophylaxis, avoiding periareolar incision (170, 186), reducing the permanence of drainage tube, and using nipple shields to prevent spillage of bacteria into the pocket (187); (ii) irrigating the pocket with a triple antibiotic solution or betadine (188); and (iii) using an antibiotic-impregnated mesh during breast reimplants and implementing the "no touch" methods by an introduction sleeve to minimize skin contact (189).

Dental Implants

The oral microbiota is highly complex since the oral cavity is the site of the human body with the most bacteria species able to colonize differently specific niches (i.e., tongue, cheeks, teeth, and gums). Mouth colonization starts at birth, and it changes over time due to aging, tooth appearance or extraction, diet, characteristics of saliva, and the use of antibiotics (190). *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Spirochaetes*, and *Fusobacteria* are among the most representative taxa. Using the methods described above, it is now possible to fully describe the microbial diversity present in the human oral cavity and to assess its composition when health problems arise. Indeed, oral bacteria have been implicated in cardiovascular disease, pneumonia, diabetes, and systemic disease (191–195). Therefore, the prevention and control of oral diseases are essential to prevent these conditions.

Biomaterial surfaces that are employed to restore optimal oral cavity functionality can be colonized by several microbes, often forming stable biofilm structures leading to peri-implantitis (196, 197). Consequences can be severe: gingival health can be compromised; composite resins could be degraded, leading to the possibility of bacterial invasion at the interface between the tooth and the restoration; and tooth enamel can demineralize (198–201). Because of several components present in the saliva, host tissue, and bacterial products, a pellicle is formed around the implant surface within minutes of its placement (202–204), and early colonization of tooth and implants has been shown to be different (205). Microbial colonization occurs immediately, with Gram-positive cocci and rod-like microbes being the primary colonizers (205, 206), producing the basic structure that enables secondary colonization thanks to interbacterial adhesion. Whenever Gram-negative anaerobic bacteria become the main colonizers, the dominant microbial species are *Fusobacterium* spp., *Porphyromonas gingivalis*, *Eikenella corrodens*, *Prevotella intermedia*, *Campylobacter* spp., and *C. albicans* (197, 202, 207, 208). Under these conditions, peri-implantitis may develop in less than a year after implant placement. Antibiotic prophylaxis could avoid this phenomenon (209). Overall, to prevent implant failure, correct planning of treatments, placement of the implant, and follow-up visits are extremely important, along with monitoring the overall health state (i.e., osteoporosis, diabetes, obesity, use of drugs, etc.). In addition, evaluation of surface modifications and different coating possibilities will help to identify materials less prone to pathogen colonization (210, 211).

Contact Lenses

Microbial keratitis is an infection of the cornea which, if not properly treated, could lead to the loss of vision. The main risk factor is the widespread use of contact lenses. Bacterial keratitis is connected to biofilm-forming bacteria and the following are the most frequently identified genera and species: coagulase-negative staphylococci, *Cutibacterium* spp., *Corynebacterium* spp., *S. aureus*, and *P. aeruginosa*. Fungal infections are more probable in tropical and subtropical climates, and *Fusarium* spp., *Aspergillus* spp., and *Candida* spp. are often isolated. Tiny amoebas have also been implicated in this pathogenesis (*Acanthamoeba*) (212–215). The origin of the infection is linked to the ability of contact lenses, even cosmetic ones, to induce alterations of the corneal epithelium and carry organisms to the ocular surface (216). Organisms on contact lenses form stable biofilms, primarily the Gram-negative bacterium *P. aeruginosa*, due to its capacity to survive different stress situations and to adhere to many different surfaces (216, 217). Physical and chemical characteristics, along with the water retention capacity of the lens' material and its hydrophobicity, are factors influencing the colonization (214, 217). Researchers are constantly looking for new materials able to inhibit this

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process (218–221). Moreover, the presence of neutrophils can enhance *P. aeruginosa* biofilms, a stimulation that can be counteracted by treatment with DNase and anionic poly-aspartic acid (222). Of course, as contact lenses are regularly removed, to avoid their contamination, special care should be taken in correctly using not only the lenses themselves but also their cases and the liquid storage solutions. Overall, the storage conditions should provide a clean environment that prevents microbial growth. The latter represents intensive ongoing research (223–227).

Other Implants

Intrauterine devices (IUDs) are effective long-term contraception methods. However, their usage period is between 4 and 5 years unless signs of pelvic inflammatory disease are detected. Indeed, IUDs represent a foreign body that biofilm-forming bacteria or fungi can colonize. The most common microbes associated with IUDs and upper genital tract infections are *S. aureus*, *E. faecalis*, *E. coli*, *Streptococcus* spp., *Actinomyces* spp., *Prevotella* spp., *Bacteroides* spp., *Clostridium* spp., and *C. albicans* (228–231).

Patients requiring mechanical ventilation can develop ventilator-associated pneumonia due to the use of breathing machines. This life-threatening infection is often linked with biofilm formation on the inserted tubes. The principal genera colonizing the oral and respiratory tract of intubated patients are *Streptococcus*, *Neisseria*, and *Prevotella* (232). Many factors contribute to the development of infections; since the tubes prevent the cough reflex, resulting in an inhibition of mucous clearance, infection damages the tracheal epithelium and finally provides an easy entrance for bacteria able to reach the lower respiratory tract and form biofilm around the surface, representing a dangerous reservoir of bacteria potentially able to migrate and develop pneumonia. The main bacteria responsible for this colonization are *S. aureus*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, and *Acinetobacter baumannii* (159), often found in a mixed population. Indeed, polymicrobial communities are identified between 8 and 58% of the time in endotracheal tubes (233). When these bacteria, all high-grade biofilm formers, stably colonize the tube, they are covered with extracellular polymeric substances typical of biofilm growth, which provides higher tolerance to antimicrobials (234).

Finally, cochlear implants are also prone to infection, and the incidence of complications due to this colonization ranges between 1.7 and 4.1% of patients, a problem that can lead to the removal of the implant and even, in severe cases, be fatal. *S. aureus* and *C. albicans* are the leading agents of such infections (235–238).

MICROBIAL DISTRIBUTION

A detailed overview of the microorganisms found in implanted medical devices is shown in Table 1. Gastrointestinal and urological implants are devices that can be colonized by the most diverse strains. *S. aureus* is the main contaminant in urological implants, along with *E. faecalis* and *E. coli*, while gastrointestinal implants are most frequently infected by the pan-antibiotic-resistant *A. baumannii*, a bacterium resistant to desiccation and nutrient deficiency (239), which forms a stable biofilm resistant to many antimicrobials. *A. baumannii* is currently one of the top microbes against which new antibiotics are being developed (240–243). Microbes colonizing dental implants are quite different from the ones found on other devices (Table 1). The microbiome colonizing the oral tract has been described as having a dynamic "biofilm lifestyle" (204), forming complex communities composed of a different combination of bacterial species (between 500 and 700 different species have been identified as members of the oral microbiome), many of which are still not cultivable (244). Disequilibrium within the microbial community, the host, and the local microenvironment results in advantageous conditions for the growth of *Fusobacterium* spp., *P. gingivalis*, *Prevotella* spp., *Selenomonas* spp., *Staphylococcus* spp., and *Streptococcus* spp. (197, 202, 207, 208, 245, 246).

Moreover, *Staphylococcus* spp. are the most frequently isolated; among these, *S. aureus* is found in essentially all implants. Among the coagulase-negative staphylococci, *S. epidermidis*, *S. haemolyticus*, *S. lugdunensis*, *S. capitis*, *S. mitis*, and *S. auricularis* are the most commonly isolated. *Streptococcus* spp. are very often found on orthopedic, cardiac, neurosurgical

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TABLE 1 Bacterial species and fungi isolated and identified from the most clinically relevant medical devices[a]

Devices	Bacteria				Fungi	References
	Most frequently isolated	Frequently isolated	Less frequently isolated	Rarely isolated (all <1%)		
Cardiac devices (~1.2–2.4%)	Coagulase-negative staphylococci (~60–80%), *S. aureus*	*S. aureus* (11–29%), *Streptococcus* spp. (~12%), *Enterococcus* spp. (~10%)	*Cutibacterium acnes* (~4%), HACEK group (~2%) (*Haemophilus*, *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella* spp.)	*Cutibacterium avidum*, *Granulicatella adiacens*, *S. lugdunensis*	*Candida* spp. (~2–6%)	58, 66, 68, 71, 81, 273, 276, 277, 404–408
Gastrointestinal implants (~11.5 [biliary stents]-100% [gastrostomy devices])[b]	Enterococci (~21.5–79.3%), (*E. faecalis*, *E. faecium*, *E. casseliflavus*, *E. avium*, *E. gallinarum*), *Enterobacteriaceae* spp. (~73.7%) (*E. coli*, *E. cloacae*, *K. pneumoniae*, *K. oxytoca*), streptococci (~7–31.5%) (*S. anginosus*, *S. parasanguinis*, *S. mitis*, *S. constellatus*)	Staphylococci (~9–11.3%), *Pseudomonas* spp. (~4–11%)	*Micrococcus* spp. (~2.5%), *M. morgana* (~2.5%), *Vibrio* spp. (~1.5%)	*Hafnia alvei*, *S. liquefaciens*, *Fusobacterium* spp., *S. liquefaciens*, *S. anaerobius*	*Candida* spp. (~7.5–55.9%) (*C. albicans*, *C. glabrata*, *C. kefyr*, *C. tropicalis*)	79, 86, 88–90
Orthopedic implants (~0.7–1.1%)	Methicillin-sensitive *S. aureus* (~30%)	Methicillin-resistant *S. epidermidis* (~16%), methicillin-sensitive *S. epidermidis* (~14%)	Methicillin-resistant *S. aureus* (~8%), *E. faecalis* (~2%), *Corynebacterium* spp. (~3%)	*S. lugdunensis*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *S. mitis*, *Streptococcus pneumoniae*, *Corynebacterium striatum*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *S. marcescens*	*Candida* spp. (~1–3%)	93, 95, 96, 100, 247
Neurosurgical implants (~1.6–25.6%)	*Staphylococcus* spp. (~76.2%) (*S. aureus*)	Coagulase-negative staphylococci (~20%), *Cutibacterium* spp. (formerly *Propionibacterium* spp.) (~5.4–21%)	*Enterobacter* spp. (~3.8%), (*E. aerogenes*, *E. cloacae*), *Streptococcus* spp. (~1.9%), *Klebsiella* spp. (~1.9%) (*K. pneumoniae*, *K. oxytoca*), *E. coli* (~2.2%), *Pseudomonas* spp. (~1.6%) (*P. aeruginosa*)	*Acinetobacter baumannii*, *S. marcescens*, *Proteus mirabilis*, *Providencia stuartii*, *Morganella morganii*	*Candida* spp. (~1.6–15%) (*C. albicans*, *C. parapsilosis*)	131, 132
Urological implants (~3–18%)	Coagulase negative staphylococci (~70–77%) (*S. lugdunensis*, *S. capitis*, *S. haemolyticus*, *S. mitis*, *S. auricularis*), *E. faecalis* (~55%), *E. coli* (~39%)	*Klebsiella* spp. (~30%), (*K. pneumoniae*, *K. oxytoca*, *K. ornithinolytica*, *K. planticola*), *P. aeruginosa* (~27%), *E. faecium* (~17%), *P. mirabilis* (~12.5%), *S. epidermis* (~1–39%)	*Propionibacterium* spp. (~5%), *E. cloacae* (~3.4%), *M. morganii* (~3.3%), *E. aerogenes* (~3%), *S. aureus* (~2.8%), *A. baumannii* (~1.4%), *Pantoea agglomerans* (~1.3%), *P. vulgaris* (~1.1%), *Stenotrophomonas maltophilia* (~1.1%)	*B. bronchiseptica*, *B. cepacia*, *C. diversus*, *E. dissolvens*, *E. kobei*, *H. alvei*, *Kluyvera cryocrescens*, *Providencia stuartii*, *Providencia rettgeri*, *Ralstonia pickettii*, *Raoultella terrigena*, *S. marcescens*, *Yersinia rohdei*	*Candida* spp. (~8–26%) (*C. albicans*, *C. glabrata*, *C. tropicalis*)	135, 137, 141–143, 153

(Continued on next page)

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TABLE 1 (Continued)

Devices	Bacteria				Fungi	References
	Most frequently isolated	Frequently isolated	Less frequently isolated	Rarely isolated (all <1%)		
Intravascular devices	*S. aureus* (~>30%), *P. aeruginosa* (~>30%)	*S. epidermis* (~10–30%), *E. faecalis* (~10 to 30%), *P. aeruginosa* (~10–30%), *K. pneumoniae* (~10–30%)			*C. albicans* (~3–8%)	155, 160–162, 164
Breast implants (~1–2.5%)	*S. epidermis* (~19–41%), *C. acnes* (~12–25%)		*S. aureus* (~5%), *E. coli* (~1.5%), *Ralstonia* spp. (~1–7%)	*Corynebacterium* spp., *Lactobacillus* spp., *M. fortuitum*, *M. chelonae*, *M. abscessus*		174–176, 178, 184, 409, 410
Dental implants		*Fusobacterium* spp. (~5–9%)	*Campylobacter* spp. (~1–7%), *Porphyromonas gingivalis* (~1.8–5%), *Prevotella* spp. (*P. intermedia*) (~1–5%), *Tannerella forsythia* (~5%), *Eubacterium* spp. (~1–1.9%)	*E. corrodens*	*C. albicans* (~<1%)	197, 202, 207, 208, 245, 246
Contact lenses (~2.4–7%)	Coagulase-negative staphylococci (~39%)	*Cutibacterium* spp. (~25.8%), *Corynebacterium* spp.	*Corynebacterium* spp. (~4.6%), *Streptococcus* spp. (~2.8%), *Bacillus* spp. (~2.2%), *Pseudomonas* spp. (~2%), *Micrococcus* spp. (~1.9%), *S. aureus* (~1.6%), *Pseudomonas* spp. (~2%), *S. maltophilia* (~1.5%), *Serratia* spp. (~1.1%), *Acinetobacter* (~1.1%) spp.	*Stomatococcus* spp., *Planococcus* spp., *Nocardia* spp., *Listeria* spp., *Peptococcus* spp., *Moraxella* spp., *Flavobacterium* spp., *Commons* spp., *Neisseria* spp., *Achromobacter* spp., *Klebsiella* spp., *Alcaligenes* spp., *Haemophilus* spp., *Escherichia coli*, *Aggregatibacter* spp., *Sphingobacterium* spp., *Enterobacter* spp., *Moraxella* spp.	*Fusarium* spp. (~1–36%), *Aspergillus* spp. (~1–30%)	214, 411, 412
Other devices: IUDs (~62%), mechanical ventilation breathing machines (~2.7–10%), cochlear implants (~1.7–4.1%)	*S. aureus* (>30%), *Actinomyces* spp. (~10–66%), *Prevotella* spp. (~10–43%)	*E. faecalis* (~26%), *Streptococcus* spp. (~23%), *E. coli* (~17%), *Bacteroides* spp. (~36%), *Clostridium* spp. (~25%), *P. aeruginosa* (~30%), *Acinetobacter baumannii* (~13–26%)	*K. pneumoniae* (~3–9%)		*C. albicans* (~1–50%)	228–231, 234–238

[a]Microbes have been divided into four categories according to the relative isolation frequency reported in the literature. The "most frequently isolated" bacteria are found, according to the literature, more than 30% of the time, the "often isolated" are found between 10 and 30% of the time, the "less frequently isolated" correspond to a frequency between 1 and 10%, and the "rarely isolated" correspond to a frequency of <1%. Since fungi are rarely identified under the conditions considered, these microbes were grouped in a single column. Microbial percentages in intravascular devices were extrapolated from the reported literature. The first columns report also the percentages of infected devices versus the total of the devices used (only when data were available).

[b]Since many of the devices were analyzed after being removed because they were displaying signs of infections, the percentages of the device infected could be overestimated.

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implants, and contact lenses. *Candida* spp. are predominant among fungal colonizations, an observation that was already reported in 2004 by Kojic and Darouiche (247); among these, *C. albicans* is the most frequently isolated species. Only contact lenses have been reported to be infected by other fungi: *Fusarium* spp. and *Aspergillus* spp. Interestingly, fungal colonization has yet to be reported in breast implants (see Table 1 for details and relative references).

Much is known about the most frequently isolated microbes mentioned above. Indeed, recent outstanding works and reviews have focused on *Staphylococcus* spp. (in particular *S. aureus*) (248–256), *Acinetobacter* spp. (especially *A. baumannii*) (239–243, 256–259), *Enterobacteriaceae* such as *E. coli* and *K. pneumoniae* (243, 256, 260–263), *Pseudomonas* spp. (in particular *P. aeruginosa* and *P. fluorescens*) (256, 264–267), *Enterococcus* spp. (256, 268, 269), and *C. acnes* (270–273).

Some of the "less known" biofilm-forming microbial contaminants mentioned in Table 1 are considered emerging pathogens and much future work will be necessary to understand their biology. Among them, it is worth mentioning *Staphylococcus lugdunensis*, which is a newly recognized threat whose biofilm biomass has been recently investigated (274). *S. lugdunensis* is connected with hospital-acquired infections, especially in cases of orthopedic infections and aortic prosthetic valve endocarditis (96, 249, 275–277). *Cutibacterium avidum* is an "under-recognized" microbe (273), an opportunistic pathogen able to invade axillary regions and wet sites, where it is causing infections difficult to eradicate thanks to its capacity to form biofilms, particularly in total hip arthroplasty or breast implant surgeries (273, 278, 279). While much is known of *C. acnes*, very little is currently known regarding the biology of *C. avidum*, and many of its features must be better understood to treat *C. avidum* biofilm-related infections efficiently. *Stenotrophomonas maltophilia* is a Gram-negative bacillus and an opportunistic emergent pathogen isolated in gastrointestinal and urological implants (see Table 1) and can cause pneumonia in subjects mechanically ventilated, such as COVID-19 hospitalized patients (280). *S. maltophilia* can form biofilms that are clinically relevant and more resistant to antibiotic treatment than their planktonic counterparts (281, 282). Finally, special attention on *Corynebacterium striatum*, a strain usually found on human skin and nasal mucosa and able to cause nosocomial diseases, is needed. This organism can colonize orthopedic implants or catheters due to its strong capacity to adhere to surfaces and form biofilms. In addition, *C. striatum* is often isolated as a multidrug-resistant strain, so it is considered a concern within the scientific community (283–285).

ENVIRONMENTAL FEATURES

Fluid Flow

Many environmental factors can shape the development of biofilms on implanted medical devices. A nearly ubiquitous factor is fluid flow, along with the hydrodynamic forces and pressure variations that it generates (Fig. 2A). In many human body systems, including the gut, urinary tract, veins, artery, and eye, liquids are in motion. The shape and compliance of organs and their cyclic contraction movements make fluid flow in the human body complex and nonuniform; the typical range of values are given in Table 2. Medical implants placed in these systems are exposed to flow and are often placed to restore the physiological fluid motion through the systems after surgery or pathological obstructions. Urological catheters, biliary stents, and cerebrospinal fluid drainages are examples of implants placed to favor fluid flow (Fig. 2B), while contact lenses and dental implants are examples of devices exposed to liquids in motion. When considering flow-through medical devices, we must remember that their shape affects the flow and frequently adds complexity to the fluid flow path, as exemplified previously (286) using numerical simulations for the stented ureter. In all of these systems, flow can affect both the transport and the physiology of the small resident organisms, and these can respond to flow with phenotypic and behavioral changes, as extensively discussed earlier (287). Below, we describe some *in vitro* studies on bacterial-flow and biofilm-flow interactions, performed in different geometries and flow conditions (see Table 3 for details on geometry and flow conditions). These studies shed light on general biophysical phenomena triggered by flow in model systems. Given the wide range of flow velocities and shear stresses at play in the human body (Table 2), these phenomena probably play a role in human

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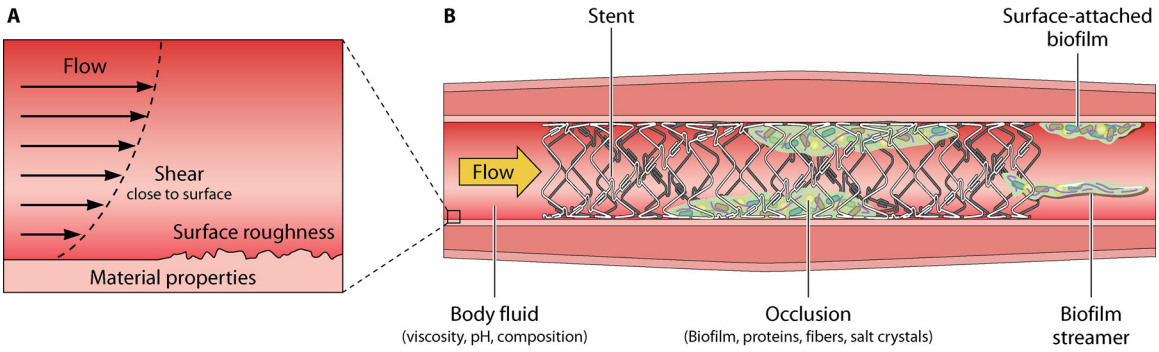

FIG 2 Nonmicrobiological factors affecting biofilm formation in a medical device. (A) When a moving fluid encounters a solid surface, its speed decreases gradually so that it becomes zero at the surface (i.e., no-slip boundary condition). This variation of the fluid speed in the layer close to the surface generates flow shear. Looking at the surface with a micrometric resolution, we can see the surface roughness, which is due to the material itself and the way material is processed. In addition, solid surfaces can have different material properties, as material mechanical properties and surface charge. Material properties, surface roughness, and flow shear close to the surface potentially influence the accumulation of bacteria or precipitates on the surface. (B) In conducts, fluid properties, such as viscosity and composition, can influence the flow regime within the conduct. When stents or catheters are inserted, occlusions can occur due both to biofilm growth and accumulation of substances transported by the fluid, such as fibers, proteins, and salt crystals. The nature of the precipitates depends on the type of body fluid and its chemical conditions. Biofilms inside the device can grow with different morphologies depending on the local flow conditions and geometrical constraints: surface-attached or as filament suspended in the flow, called streamers. The graphic work was done by modifying elements from Smart Servier Medical Art.

infections and colonization of medical devices. However, the complexity of the physical and physiological conditions in the human body and their variability makes it difficult to compare *in vitro* studies to their *in vivo* potential realization.

Bacteria in bulk fluid are transported by flow, which exerts hydrodynamic forces on their body and, under certain conditions, affects their spatial distribution. In narrow channels, fluid shear preferentially accumulates motile bacteria in the low-velocity, high-shear regions close to the sidewalls, creating a depletion in cell concentration by up to 70% in the central region of the channel and favoring bacterial surface colonization, as shown for both *B. subtilis* and *P. aeruginosa* (288). The same type of interaction promotes the formation of colonization hot spots on curved surfaces (such as pillars; Fig. 3A), creating a heterogeneous bacterial distribution on the surface, with potential effects on the subsequent biofilm development (289). These effects depend only on the morphology and motility of bacteria and are independent of other traits or physiological conditions.

Once bacteria are on a surface or located nearby, hydrodynamic interactions can trigger bacterial movement in the direction opposite to the flow: this behavior is observed in flagellated bacteria with an elongated body, swimming very close to a surface, and in bacteria moving on the surface thanks to type IV pili, the so-called "twitching motility." Upstream swimming has been studied in *E. coli* (290) and is a faster mechanism for surface colonization than colony spread by growth (291), with important implications for spreading infections in catheters and medical devices. Upstream twitching has been observed in *P.*

TABLE 2 Flow velocities and shear stresses measured in different body fluids and human organs[a]

Fluid	Organ/Device	Flow velocity (m s^{-1})	Shear stress (Pa)	Reference(s)
Urine	Bladder-urethra	0–0.3	0–0.4	413
	Ureter	0–0.48	0–0.5	414
Blood	Blood vessels		0.5–4.3	415
	Microcirculation	0.06–1.2	1.3–1.6	415, 416
Saliva	Unstimulated average flow	0.018–0.024		417
	Around orthodontic brackets	0.069–0.18		329
Bile	Bile duct	0–0.2		418, 419
Mucus	Airway surface	$(2–7) \times 10^{-5}$		420

[a]Several body fluids are considered, and the values characterizing their flow in different organs found in the literature are reported.

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TABLE 3 Flow velocities and shear stresses measured in *in vitro* studies of bacterial-flow and biofilm-flow interactions, performed using different geometries and flow conditions

Geometry	Effect(s) of flow	Bacterium/bacteria	Flow velocity (μm s^{-1})	Shear rate (s^{-1})	Reference(s)
Microfluidic straight channel	Cell accumulation in high shear	*B. subtilis*, *P. aeruginosa*	0–10^4	0–50	288
	Increased residence time	*P. aeruginosa*	750–10^5	50–10^4	297
	Upstream swimming motility	*E. coli*		0.1–60	290
				0–600	291
	Upstream twitching motility	*P. aeruginosa*		0.01–10	292
		X. fastidiosa	0–90		421
		M. mobile	0–700		294
	Catch bonds	*S. aureus*		2.5–10	298, 300
		E. coli		2.5–10	298
		S. epidermidis		1–10	299
	Increased virulence upon surface attachment	*P. aeruginosa*			301
	Mechanosensing	*P. aeruginosa*			302, 303
	Shape biofilm architecture	*E. coli*			306
		V. cholerae		2–2,000	307
Microfluidic curved surface	Preferential attachment to specific surface regions	*P. aeruginosa*, *E. coli*	150–2,000		289
	Biofilm streamer formation	*P. aeruginosa*	10^3		308, 309, 312
		S. aureus	6–2 $\times$ 10^4		313
	Interplay between flow and biofilm matrix composition	*P. aeruginosa*		150–200	314
Microfluidic flow network	Increased surface colonization capability	*P. aeruginosa*	16–250		295
		P. aeruginosa and *P. mirabilis*	2–2 $\times$ 10^4		296

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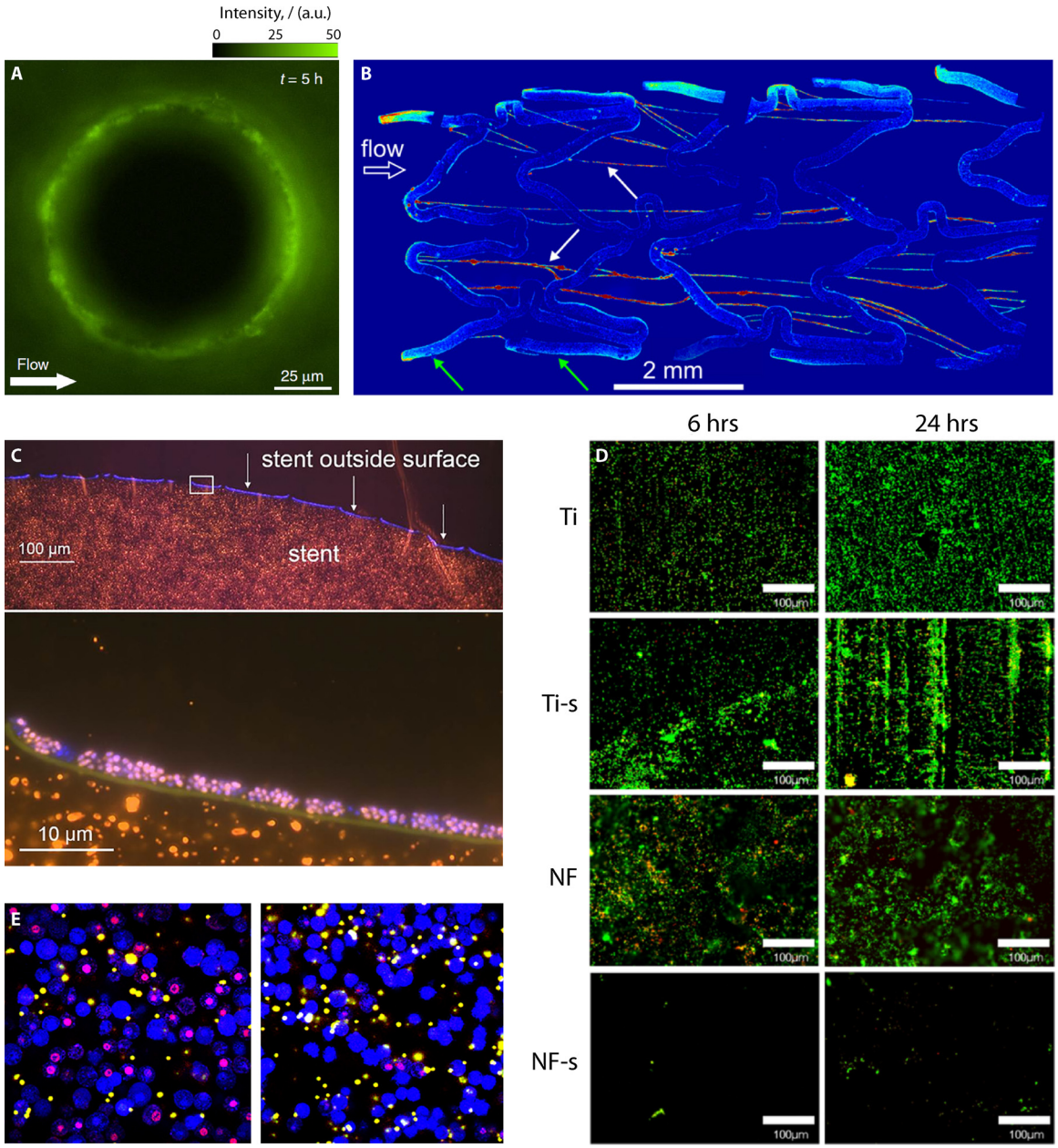

FIG 3 Mosaic of representative images. (A) Image of fluorescent *P. aeruginosa* bacteria attached to a 100-μm pillar in the presence of flow. Modified from Secchi et al. (289). (B) Maximum intensity projection image of biofilm streamers formed flowing a suspension of fluorescent *P. aeruginosa* in a bare-metal stent. Modified from Drescher et al. (312). (C) Bacterial colonization of a biliary polyethylene stent in a patient with bile duct stenosis, visualized by fluorescence in situ hybridization (FISH). Modified from Yan and Bassler (92). (D) Fluorescence images of *E. coli* on titanium (Ti), silanized titanium (Ti-s), nanoflower-coated (NF), and nanoflower-coated surfaces after silanization (NF-s). Modified from Montgomerie and Poat (333) with permission of Elsevier. (E) Confocal images (X63 magnification) of bone marrow-derived macrophage phagocytosis of fluorescent microspheres (yellow-white) and cell death with propidium iodide stain (red-purple) after exposure to *S. aureus* biofilm-conditioned medium (left-hand side) and *S. aureus* planktonic culture-conditioned medium (right-hand side). Modified from Torres et al. (383).

aeruginosa (292), *Xylella fastidiosa* (293), and *Mycoplasma mobile* (294). Despite being 100-fold slower than upstream swimming, twitching still confers *P. aeruginosa* advantages in the colonization of flow networks (295) and in the competition over its natural competitor *Proteus mirabilis* (296). Hydrodynamic interactions not only increase the surface exploration capabilities of *E. coli* and *P. aeruginosa* but also increase their residence time on surfaces (297) by activating, for example, in the case of *E. coli* specific catch-bonds between proteins present on type I pili and mannose adsorbed on the surface

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(298). Similar shear-enhanced adhesion mechanisms have been observed in *S. epidermis* (299) and *S. aureus* (300).

Surface colonization is the starting point for biofilm formation. Surface adhesion triggers virulence (301) and starts biofilm development in *P. aeruginosa* due to to hydrodynamic force-sensing mechanisms allowing bacteria to tune their adhesion strength (302). Mechanosensing has been recently recognized as an essential resource that bacteria have developed to optimize biofilm formation and pathogenicity, as discussed in a recent review (303). Once biofilm development has started, local flow can influence biofilm architecture, for example, determining the formation of a bacterial monolayer under high-flow conditions or multilayer structure under low flows (304, 305), affecting cell membrane permeability (306), determining the shape of the colony (307), or driving the formation of biofilm streamers when obstacles and constrictions are present (308–311).

Biofilm streamers, which are filamentous bacterial aggregates suspended in the middle of the flow, can have a more significant impact on the flow itself compared to classic biofilms, for example, by causing rapid clogging of artificial and natural conduits, porous media, and medical devices (Fig. 3B) (312, 313). An *in vitro* experiment conducted using a bare-metal stent has shown that streamers rapidly develop and span the gaps between metal wires (312). Given their potential impact on the clogging of medical devices, it is worth investigating their formation in *in vivo* scenarios. If biofilms are formed by several bacterial species, flow can affect population dynamics and biofilm morphology by segregating more-adhesive and less-adhesive cells (314). This interplay could also influence the evolution of biofilm multispecies infection in a medical context.

EPS is mainly constituted from polysaccharides, proteins, nucleic acids, and lipids (21, 316). Its composition can vary greatly depending on the microorganisms, nutrient availability, and environmental conditions, including the presence of fluid flow and the temperature (317–320). In biofilm formed in complex host environments, such as those in medical devices, extra-microbial-host-derived components may be incorporated in the biofilm. Examples of incorporation include fibronectin, a glycoprotein found in the matrix of eukaryotic cells, which plays a crucial role in the formation of *S. aureus* biofilm on devices, and calcium phosphate and magnesium phosphate crystals formed in urinary catheters due to urinary pH and incorporated in biofilms, resulting in a crystalline structure. However, despite the differences in EPS composition, its functions are universal: EPS forms the scaffold of the biofilm structure, is responsible for adhesion to surfaces and internal cohesion, and protects the microbial community from chemical and mechanical insults (21). In a medical context, surface adhesion is also influenced by the conditioning film formed by host-derived components attached to the surface and potentially interacting with the EPS. In addition, the viscoelastic nature of EPS confers biofilm mechanical resistance: when a force is applied, biofilms instantaneously undergo an elastic deformation as solids and then slowly flow as viscous fluids, further spreading on surfaces, while maintaining their structural integrity (321). The viscoelastic behavior increases the surface spreading and allows the formation of streamers (308, 309).

The number of studies focusing on the influence of local flow on biofilm growth in medical devices is still limited, despite the benefits of a better understanding of the role of fluid dynamics. Biliary stents are a primary example of devices subject to severe occlusion, requiring their removal and replacement. Studies have been conducted on removed stents (Fig. 3C) to shed light on the parameters affecting the clogging dynamics (89, 322, 323). The diameter has been shown to play a primary role since stents with a smaller diameter are more prone to occlusions, whereas stents with a larger lumen allow greater bile flow velocity (but lower shear rate) and, in turn, they are less prone to bile salt precipitation and protein accumulation (89). For this reason, metal stents, having a larger diameter, seem preferable to plastic stents (324) in this respect. Bile viscosity is another factor influencing the flow-pressure relation and consequently

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biofilm growth, since a higher viscosity implies a lower flow rate and consequently increases the probability of occlusion (28). When considering EPS composition, the flow has been shown to influence the ability to produce specific molecules in *S. epidermidis* strains isolated from high-shear and low-shear environments in the human body (325) and, in turn, the structure of the biofilm, as shown in an *in vitro* study (326).

Computational fluid dynamic simulations have been used to characterize the flow field within different configurations of an occluded and stented ureter, and it has been observed that bacterial attachment occurred preferentially near a ureteric occlusion (327). In this case, it has been recently recognized that UTIs should be studied in the context of the bladder's physical environment, which includes flow (328). For example, orthodontic appliances bonded to the tooth surface are exposed to salivary flow with a self-cleaning action. However, the shape of the appliances affects the flow pattern, potentially favoring the creation of vortexes and a resulting bacterial accumulation, as investigated using computational fluid dynamic simulations (329). *In vivo* studies focused primarily on the effect of the material, showing that plastic and stainless steel (330) and ceramic and metallic (331) brackets do not influence the composition of the bacterial population.

Surface Properties

Surface properties represent another critical factor that influences biofilm accumulation and the occlusion of implants. In blood-contacting medical devices, proteins contained in the blood, upon contact with the surface of the device, adhere to the surface, followed by platelets, and activate an immune response, resulting in the formation of a fibrin matrix that traps red blood cells and clogs the devices. Biofilm growth can contribute to speeding up this process. Central venous catheters are blood-contacting medical devices, subject to biofouling. *In vitro* experiments conducted with *S. epidermidis* using glass and polymer catheters have shown that these materials do not affect biofilm formation or morphology (332). However, very specific surface treatments can reduce biofouling: coating with superhydrophobic titania nanoflowers was shown to increase hemocompatibility and reduce protein deposition and consequently biofilm growth in an *in vitro* study (Fig. 3D) (333); similar results were obtained with a covalently attached layer of perfluorocarbon (334).

Studies on the influence of the implant material on biofilm formation have been conducted for biliary stents made of polyethylene and hydrophilic polymer-coated polyurethane (335). Inspection of the biofilms using SEM and confocal scanning microscopy (CSM) did not highlight any difference either in the type of biofilm or in the clogging dynamic. Although the type of material does not influence the fouling process, pilot studies have shown that gold coatings reduce the biofouling of different types of catheters (336–338). Furthermore, treatment of surface plasma with direct thrombin inhibitors has been shown to reduce staphylococcal binding, revealing the potential of these agents for implant surface coatings to prevent device-related infections (339). *In vitro* experiments have shown that biofilm formation on the surface of dental implant materials, such as titanium and zirconium, is comparable to that on hydroxyapatite, a typical tooth surface (340). These results have been obtained with six different bacterial species typically found in the human mouth. Not only were biofilms, imaged using CSM, structurally similar, but the composition of the bacterial community, analyzed by qPCR, also did not show appreciable differences. In another study of dental plaque formation in a flow chamber under anaerobic conditions (341), zirconia surfaces showed a statistically significant reduction in bacterial adhesion after 3 days of incubation compared to titanium surfaces. Nevertheless, differences between zirconia and titanium surfaces with regard to biofilm formation are still under debate.

Surface roughness is an important parameter when considering bacterial surface colonization. Roughness is a characterizing parameter of breast implants, in which the introduction of texture to the outer shell was aimed at increasing tissue incorporation. Based on their texture, breast implants can be divided into smooth (i.e., having a rugosity of <10 μm), microtextured (with rugosity ranging between 10 and 50 μm), and

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macrotextured (with a rugosity of >50 μm) (342). Several studies confirm that bacterial colonization on rough textures is generally favored (343), while the exact trend depends on the model of the implant and the bacterial species considered (343, 344). Differences in colonization have been recently attributed to different surface areas: rough textures offer a better surface area to which the bacteria can adhere. Plate counting, the methodology used to quantify surface colonization, normalized for the surface area did not show significant differences between textures and bacterial species (343). Similar results were obtained on typical surfaces of dental implants (345) and on biotic surfaces in general (346).

Material properties are essential parameters in controlling the colonization of soft contact lenses. Contact lenses are characterized by a different water content, which changes their comfort and long-term usability (347). A high water content (between 58 and 64%) results in softer lenses that are better suited for long-term use and also reduces biofilm formation (217, 225). Surface wettability is another parameter influencing bacterial adhesion on contact lenses: *in vitro* studies have shown that *P. aeruginosa*, *S. aureus*, or *S. epidermidis* adhere in greater numbers to the hydrophobic silicone hydrogel lenses compared to hydrophilic hydrogel lenses (217, 348). The same study revealed that a higher surface roughness increased the colonization by *S. epidermidis*, whereas no differences were reported for *P. aeruginosa* (217). When fungal biofilms are considered, they have been shown to have different structures on different types of lenses, but the differences have not been systematically analyzed in terms of surface properties (349). Finally, bacteria also respond to the mechanical properties of a surface, such as stiffness, which is positively correlated with the adhesion of different bacterial species, such as *S. epidermidis* and *E. coli*, independently of other surface properties (350). Conversely, another study showed that, when exposed to high-shear conditions, *E. coli* cells exhibit stronger adhesion properties on soft silicone substrates than on stiff ones, a difference that decreased when native silicone surfaces were coated with extracellular matrix molecules (351).

IMMUNOLOGICAL ASPECTS

Although the interplay between host immune response and biofilms has been investigated in the last decade (352, 353), very little is known about their crosstalk associated with medical devices. Most of the literature has focused on the immune response to biofilms formed by *P. aeruginosa* under specific pathological conditions, such as, for example, in cystic fibrosis patients (354, 355). *P. aeruginosa* biofilms stimulate the host immune response via extracellular polysaccharides (356), eDNA (357), outer membrane vesicles (OMVs) containing extracellular proteins (358), and small molecules, such as 3-oxo-C12-HSL (359, 360) or pyocyanin (361, 362). EPS components can impair complement activation (363), inhibit macrophage killing (364), and escape the action of neutrophil extracellular traps (NETs) (365). In general, it is known that some components of biofilms formed by *Salmonella enterica* serovar Typhi, *Burkholderia cepacia*, or other probiotic bacteria have displayed anti-inflammatory properties (366–368), whereas those formed by other bacteria, such as *Thermus aquaticus* and some *Lactobacillus* strains, seemed to be proinflammatory (369, 370). An overview of devices associated with biofilms and their induced host response mechanisms—which can result in either an immune response activation or its suppression—is provided in Table 4.

Bacteria belonging to the *Staphylococcus* genus, such as *S. aureus* and *S. epidermidis*, have been found to form biofilms on implanted medical devices. The immune system is less able to recognize bacteria belonging to the *Staphylococcus* genus when grown as biofilms, especially mature biofilms, compared to their planktonic growth (371, 372); in fact, biofilm bacteria can resist phagocytosis, the release of toxic granule components, and NET-mediated killing (373–375). One of the components of *Staphylococcus* biofilms, polysaccharide intercellular adhesin [also known as poly-*N*-acetyl-β-(1-6)-glucosamine (PIA/PNAG)], can protect against phagocytosis by neutrophils and macrophages (373, 376, 377), whereas *S. aureus* extracellular nuclease can destroy NETs (378, 379). In *S. aureus* biofilm, several proteins and toxins are highly expressed and are

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TABLE 4 Biofilms and human immune response

Biofilm component	Antigen	Organism involved	Effect	Immune response	Reference(s)
Exoproteins	β-Lactamase, lipoprotein, lipase, autolysin, and an ABC transporter lipoprotein	*S. aureus*	Induce antibody recognition and immune system activation	Activation	422
	Leukocidin, hemolysin, PG, LTA, Hla	*S. aureus*	Induce cell death in macrophages or in neutrophils via the secretion of leukocidins PVL and HlgAB	Evasion	375, 383
	Nuc1	*S. aureus*	Protects against NET formation by secreting LukAB and Hla	Evasion	382
EPS (exopolysaccharides)	Capsular EPS	*Streptococcus* spp.	Release of IL-1, IL-6, IL-8, and CCL2	Activation	423
	PIA/PNAG	*S. aureus*, *S. epidermidis*	Evasion from neutrophils killing NETs and the bacteria acquired the ability to resist to NET-mediated killing	Evasion	373, 376–379, 424
	Psl and alginate	*P. aeruginosa*	Elicit neutrophil aggressive response	Activation	356
	Alginate	*P. aeruginosa*	Inhibition of complement activation and macrophage killing	Evasion	363, 364
Extracellular DNA	EPS-eDNA	*P. aeruginosa*	Release of IL-8, IL-1β and Net induction	Activation	357, 425
Outer membrane vesicles (OMVs)	OMVs containing EPS proteins	*P. aeruginosa*	Have multiple PAMPs and are highly immunogenic	Activation	358
Small molecules	3-Oxo-C12-HSL	*P. aeruginosa*	Stimulation of neutrophils and IL-8 release	Activation	359, 360, 426–429
	Pyocyanin	*P. aeruginosa*	Induces ROS and NET production	Activation	361, 362, 430, 431
	High level of pyocyanin	*P. aeruginosa*	Create excessive level of NETosis that lead to host tissue damage and chronic infections	Evasion	432–434

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associated with immune response evasion, even at the early stage of biofilm formation (371, 380, 381). The release of Nuc1 protects against NET formation by neutrophils (382), the secretion of LukAB and Hla induces cell death in macrophages (Fig. 3E) (383), and the release of the leukocidins PVL and HlgAB allows the evasion of neutrophil-mediated killing (375).

Results from *S. aureus* biofilm secretome have demonstrated the presence of proteins with an immunogenic ability (384, 385); however, their presence is not sufficient to inhibit biofilm formation. *In vivo* studies on murine *S. aureus* infections and adaptive immune response found that inflammatory Th1/Th17 responses result in a link with biofilm formation; in contrast, protective Th2/Treg responses are associated with spontaneous clearance of infection without adjunctive therapy (386, 387). Also, the site of infection has an impact on the interaction between *S. aureus* and the host immune system (388); therefore, the insertion of a device should consider whether the site chosen for the surgery can be reached by the pathogens directly, such as through the blood flow, or indirectly, such as only after passing through the epithelial barrier and draining lymph nodes. Furthermore, the promotion of an anti-inflammatory and profibrotic environment derived from staphylococcal biofilm could occur via alternative macrophage activation (374) or via a distortion of the macrophage response to promote bacterial persistence (389). Between host mechanisms able to clear biofilm, both staphylococcal and that for *P. aeruginosa*, there is opsonization enhanced by ROS production (390) and the presence of polymorphonuclear neutrophils (PMN) at the site of infection, which have shown *in vitro* the ability to phagocytose bacteria (391, 392). Probiotic biofilms participate in the formation or destruction of pathological biofilm, depending on their anti-inflammatory ability (368, 369). For example, *L. plantarum* can help polymorphonuclear leukocytes (PMNs) destroy *P. aeruginosa in vitro* (393), whereas *L. rhamnosus*, when incubated with *S. aureus*, decreases ROS production and phagocytosis, helping *S. aureus* evasion to the host immune system (394).

In the study of biofilms associated with medical devices, the topography and the implant surface material must be considered as part of the crosstalk with the host immune system. Implants, also built with biodegradable biomaterials, generally induce a host reaction (395, 396) that can be recapitulated in four phases: (i) implantation, (ii) blood-biomaterial interaction, (iii) inflammation, and (iv) tissue remodeling (397). The foreign body reaction could be responsible for many aseptic device failures (398); for all the implants in contact with blood, it is necessary to consider the hemocompatibility of biomaterials (333). Indeed, to prevent thrombosis, an *in vitro* study using superhydrophobic titania nanoflowers recently improved hemocompatibility, as well as reduced bacterial adhesion compared to both nontextured and unmodified surfaces. A recent study by Doloff et al. demonstrated that breast implants with a roughness of $\sim$4 μm can induce a greater immune response compared less-rough implants (399).

A better understanding of the interplay between implants and the immune system may allow treatment of the surfaces of medical devices to trigger the host immune system to avoid biofilm formation or implant failure. As a proof of concept, Hanke et al. (400) targeted MΦ proinflammatory activity to reduce biofilm formation in a mouse model of MRSA catheter-associated infection, thus showing the possibility of using the host's endogenous innate immune cells to control device-associated biofilm infections. The role of IL-1β, in a mouse model of postarthroplasty *S. aureus* joint infection, has also been demonstrated (401) in controlling bacterial adhesion and biofilm formation through neutrophil recruitment to the site of infection. Based on this finding, Bernthal et al. speculate on the possibility of enhancing the early protective IL-1β response while minimizing any sustained inflammation as a therapeutic strategy to help prevent postarthroplasty infections.

CONCLUDING REMARKS

The recalcitrance to conventional antibiotic therapies of biofilms grown on medical devices usually requires revision operations and replacement of the implant, with

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increased morbidity, mortality, and a devastating impact on the patient's quality of life. In addition, the spread of multidrug-resistant bacteria is constantly growing, increasing public concern about the health risks for hospitalized patients due to device-associated microbial infections. Although much has been done to elucidate the mechanisms by which biofilm-forming microbes adhere to indwelling devices and interact with the host immune system, this has been primarily limited to selected pathogens and to a small number of medical implants. Efforts are needed to advance our knowledge of the different microbiota compositions that correlate with a particular device and with the presence of mechanical forces. Furthermore, studies on *in vivo* biofilms or under more physiological and clinically relevant conditions—such as, for example, in microfluidic systems—should be pursued to shed more light on the complex interplay between surface-attached bacteria and the peri-prosthetic microenvironment.

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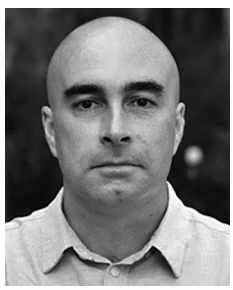

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