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Biofilms in device-related infections

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The use of various medical devices including indwelling vascular catheters, cardiac pacemakers, prosthetic heart valves, chronic ambulatory peritoneal dialysis catheters and prosthetic joints has greatly facilitated the management of serious medical and surgical illness. However, the successful development of synthetic materials and introduction of these artificial devices into various body systems has been accompanied by the ability of microorganisms to adhere to these devices in the environment of biofilms that protect them from the activity of antimicrobial agents and from host defense mechanisms. A number of host, biomaterial and microbial factors are unique to the initiation, persistence and treatment failures of device-related infections. Intravascular catheters are the most common devices used in clinical practice and interactions associated with these devices are the leading cause of nosocomial bacteremias. The infections associated with these devices include insertion site infection, septic thrombophlebitis, septicemia, endocarditis and metastatic abscesses. Other important device-related infections include infections of vascular prostheses, intracardiac prostheses, total artificial hearts, indwelling urinary catheters, orthopedic prostheses, endotracheal tubes and extended wear lenses. The diagnosis and management of biofilm-associated infections remain difficult but critical issues. Appropriate antimicrobial therapy is often not effective in eradicating these infections and the removal of the device becomes necessary. Several improved diagnostic and therapeutic modalities have been reported in recent experimental studies. The clinical usefulness of these strategies remains to be determined.

Keywords: biofilms; glycocalyx; biomaterials; prosthetic devices

The formation of thick biofilms in natural environments is dependent on extensive glycocalyxes produced by the bacteria that mediate their attachment to surfaces, and the formation of microcolonies [15,19,39]. The microcolonial (biofilm) mode of bacterial growth has been demonstrated in a number of chronic bacterial diseases such as cystic fibrosis and osteomyelitis [46] and in device-related colonization and infections [44,45,47]. The tissues involved in chronic infections and the surface of medical devices are acellular or inanimate and therefore resemble surfaces in nature. The exposed outer surface of bacterial cells plays an important role in the survival and pathogenesis of the microorganisms. Most bacteria prefer, during growth in liquid medium, attaching to surfaces rather than growing in the aqueous phase. The mechanism of adhesion depends on the bacterial inhabitant and the nature of the surface. Physical forces, the charged surfaces, Brownian motion, or chemical bonding all may have a role in attracting the bacteria to the surfaces. Many bacterial strains have the ability to produce exopolysaccharides, known as glycocalyx, that play an important role in bacterial adherence and colonization of the surfaces. Once bacteria attach and adhere to the surface, the cells surround themselves with additional glycocalyx and replicate within the biofilm matrix to form adherent microcolonies. The microcolony formed acts as a nucleus for attracting other cells of the same or different bacterial strains. The bacterial inhabitant and the nature of the surrounding medium determine the composition and properties of the formed biofilm matrix. The biofilm matrix may act as a reservoir from which bacteria can detach and release causing contamination of the surrounding medium. Adherent or sessile bacteria differ markedly from floating planktonic cells in the same ecosystem as well as from those grown in laboratory media. These differences include growth rate, composition and structure of cell walls, immunogenicity, enzyme activities and susceptibility to antimicrobial agents and host defense mechanisms [16].

Colonization of implanted medical devices such as indwelling vascular catheters, cardiac pacemakers, prosthetic heart valves, chronic ambulatory peritoneal dialysis catheters, prosthetic joints and the subsequent transformation into invasive infection contribute significantly to morbidity and complications associated with the underlying illnesses for which these devices are used. In addition, every one of the more than 20 million surgical procedures of all types performed in the United States involves the temporary or permanent use of biomaterials [32]. The prosthetic devices are made of synthetic materials and are truly foreign bodies. The host's reaction to the foreign body starts by coating the device with ionic and glycoproteinaceous constituents from the host environment including fibrin, fibronectin, albumin, laminin, and vitronectin which may act as receptors for adherence of bacteria. *Staphylococcus aureus* and *Candida* species have been shown to adhere tightly to fibrin and fibronectin [34,74]. Both of these organisms produce coagulase and benefit from the process of thrombogenesis in adhering to the fibrin-rich layer of the biofilm. Coagulase-negative staphylococci adhere to fibronectin but not to fibrin [74]. The adherent organisms begin to excrete the exopolysaccharides forming a thick

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biofilm matrix within which the bacteria replicate and form microcolonies. The concentrated nutrients and free energy derived from the surface stimulate microbial proliferation and the formation of polysaccharide slime [32]. The initial microcolonies act as a nucleus for attracting other cells of the same or different bacterial strains. The factors that determine if and when these biofilm-associated bacteria will lead to a local or systemic infectious process are not clearly understood.

Characteristics of device-related infections

A number of host, biomaterial and microbial factors are involved in the initiation and persistence of device-related infections and consequent treatment failures.

Host factors

The presence of tissue damage, leading to loss of local immunity and absence of tissue integration at the biomaterial–tissue interface resulting in chronic inflammation, are the most important factors for the initiation of an infectious process related to a device. The presence of biomaterial may also cause alterations in host defense mechanisms. The coating by host proteins such as albumin and fibrin forms the conditioning glycoproteinaceous film on the biomaterial. The pattern of protein deposition is directed by the surface properties of the biomaterial and these adhesive protein films are discontinuous. Uncoated areas may also provide attractive sites for bacterial adhesion [10,11].

Biomaterial factors

The biomaterials are physico-chemically active and may directly modulate molecular events at their surfaces, such as cellular adhesion and inflammatory and immunological response [12,23,25,28,29,37,54,55]. The surface binding sites of the polymers and metals are further modified by topography, texture, manufacturing processes, trace chemicals and debris. Polymer surfaces are more hydrophobic than metals. In general, tissue cells adhere to less hydrophobic materials such as clean metal alloy [2,3]. On the other hand, hydrophobic bacterial cell surfaces adhere better to hydrophobic biomaterial surfaces [36,61].

Microbial factors

Adhesion to surfaces is a general property of almost all bacteria. The exposed outer surface of bacterial cells plays an important role in survival and pathogenesis of the microorganisms [1]. The physical force, charged surfaces, Brownian motion or chemical bonding may have a role in attracting the bacteria to the surface. Many bacterial species have the ability to produce exopolysaccharide glycocalyx that plays an important role in the bacterial adherence and colonization of the surfaces of medical devices [16].

Bacteria in biofilms are resistant to host defense mechanisms and antibiotic therapy. The optimal management of these infections often requires removal of the device. Routine antibiotic susceptibility testing done in the liquid phase may not be predictive of therapeutic outcomes in the presence of persistent biofilm-associated bacteria. The presence of a biomaterial stratum transforms nonpathogens or opportunistic pathogens such as *Staphylococcus epidermidis* into virulent organisms. The device-related infectious episodes may be polymicrobial due to heterogeneity of the biofilms.

Important device-related infections

Intravascular catheters

Intravascular catheters are the most common medical devices used in medical and surgical patients. In the acute care setting they are used for hemodynamic monitoring, and administration of fluids, nutrition and chemotherapeutic agents. They are also used for home infusion therapy for patients requiring long-term treatment with intravenous feeding or antibiotics. Except for the totally implanted catheters with a subcutaneous reservoir or port, these devices all transect the skin and provide an opportunity for microorganisms from the skin surface to colonize the external surface of the catheter. Contamination of the catheter hub leading to colonization of the luminal surface of the catheter is the second most important cause of infections related to these devices. Less common etiologies include contamination of the infusate and seeding of the intravascular component of the catheter during a bloodstream infection.

Infections associated with catheters include insertion site infection causing local inflammation and purulence, septic thrombophlebitis, seeding of the blood stream by detached sessile bacteria leading to septicemia, and rarely, distant infections eg metastatic abscesses and endocarditis. The septicemias are related to catheters only by association, as it is not possible to obtain a definitive diagnosis with the catheter still in place, and currently available methods of culture of catheter tips after removal lack sensitivity and specificity. The incidence of bacteremia related to central venous catheters is reported to be 4–14% [27,49,59,60]. Moreover, 82% of 2073 nosocomial bacteremias reported in the National Nosocomial Infection Surveillance (NNIS) study were associated with intravascular catheters [17]. It has been estimated from recent data that 3 million central venous catheters (CVC) are inserted annually in the United States and, assuming only a 4% rate of septicemia, one would expect at least 120 000 cases of CVC-related septicemia each year [27]. The three most common types of organisms causing vascular catheter-related infections are coagulase-negative staphylococci, particularly *S. epidermidis* and *S. aureus*, and *Candida* species [7,9,13,14,33,51,64,66,69]. *Candida albicans* is the most common candida species causing vascular catheter-related infections, followed by *C. parapsilosis*. Table 1 shows the organisms grown from a prospective study of vascular catheters at our institution. In this study all catheter tips were cultured in the research laboratory irrespective of their possible or definite role in an infectious episode. A total of 781 catheter tips were cultured. Of these, 207 showed growth, with 162 tips growing one and 45 growing multiple organisms. The total number of isolates from 207 catheter tips was 264, of which only four could not be identified.

S. aureus and coagulase-negative staphylococci are introduced from the skin insertion site and the hands of medical personnel leading to contamination of the hub. *Candida* species are thought to seed hemotogenously from the gastrointestinal tract and adhere to the fibrin and fibronectin

Table 1 Organisms grown from vascular catheters in a prospective study of catheter-related infections

Organisms	Number (total = 260)	Percentage
Gram-positive organisms		
Staphylococcus epidermidis	149	57.3
Other coagulase-negative staphylococci	62	23.8
Staphylococcus aureus	8	3.1
Enterococci	6	2.3
Other Gram-positive cocci	3	1.2
Gram-negative organisms		
Enterobacteriaceae	17	6.5
Pseudomonas species	6	2.3
Yeast		
Candida species	9	3.5

on the catheter surface in about 50% of the catheter-related candidemias [42,43]. Pre-colonization of the catheters by *S. epidermidis* enhances the amount and frequency of colonization by *Candida albicans* [38]. *Bacillus* species and corynebacteria, especially JK strains, introduced from the skin or catheter hub can cause catheter-related infections. Enteric organisms such as enterococci, *Escherichia coli* and *Klebsiella pneumoniae* rarely cause catheter-related infections. Nosocomially acquired Gram-negative bacilli such as *Acinetobacter* species, *Pseudomonas* species and *Xanthomonas maltophilia* have also been reported to cause catheter-related septicemia [6,21,22].

Management of vascular catheter-associated infections includes appropriate antibiotic therapy and removal of the catheter. Surgical incision of the vein is often required for septic thrombophlebitis induced by a catheter. The type of antibiotic and the duration of therapy is based on the type of organisms cultured from the blood, catheter tip or both. More than one blood culture growing out of the same species of coagulase-negative staphylococci such as *S. epidermidis* is required to make the diagnosis of a true bacteremia and rule out skin contamination [26]. Since most of the coagulase-negative staphylococci are resistant to the antistaphylococcal penicillins, intravenous vancomycin is the treatment choice prior to the availability of the *in vitro* antimicrobial susceptibility results. If the patient responds within 48–72 h, a 5 to 7-day course of treatment is considered adequate [33]. Recent studies have shown that catheter-related bacteremia due to coagulase-negative staphylococci can be treated successfully without catheter removal [6,35,75]. However, there is a 3% risk of recurrence if the catheter is removed compared to 20% if it is not removed [62]. Serious infectious complications such as septic thrombosis, fatal septicemia and deep-seated infections such as endocarditis, osteomyelitis, septic emboli and abscesses are commonly associated with catheter-related *S. aureus* bacteremia; the incidence ranges from 19% to 46% in various patient populations [20,41,50,52,63,78]. An uncomplicated bacteremia with *S. aureus* should be treated for 10–14 days with an antistaphylococcal antibiotic, eg oxacillin or vancomycin. The duration of intravenous therapy for bacteremia complicated by deep-seated infections or septic thrombosis should be at least 4 weeks. The removal of the catheter in *S. aureus* bacteremia decreases the rate of relapse and sepsis-related deaths [20]. Antibiotics that can be used for the treatment of catheter-related infections due to Gram-negative bacilli include third generation cephalosporins, carbopenems, monobactams, aminoglycosides and quinolones. For *X. maltophilia* bacteremia, TMP/SMX is the antibiotic treatment of choice. Duration of therapy should be 1–2 weeks. Antibiotic therapy alone does not generally cure catheter-related infections caused by *Pseudomonas* species and the CVC must be removed [6]. Vancomycin remains the antibiotic of choice for treatment of catheter-related infections due to Gram-positive bacilli such as *Corynebacterium, Jeikeium* and *Bacillus* species. Because of serious complications such as endocarditis associated with these infections, removal of the catheter has been recommended [5,48,65]. Uncomplicated catheter-related candidemia can be treated with a short course of amphotericin B (0.5 mg kg^{-1} day^{-1} for 10–14 days). A thorough evaluation to rule out complications such as endocarditis and venous thrombosis, and fundoscopic examination to rule out retinitis is necessary [73]. The CVC should be removed when a patient fails to respond to antifungal therapy within 96 h or when the candidemia persists for >48 h after the patient has been started on appropriate antifungal therapy [24]. The role of newer azole antifungal agents in the treatment of candidemia is being evaluated. Several recent studies have focused on the role of antimicrobial combinations, combinations of antimicrobial agents and enzymes, and combinations of antimicrobial agents with agents that eradicate the glycocalyx matrix of biofilms and increase the rate of penetration of antibiotic through biofilms [79]. Blenkinsopp *et al* [8] showed that three common industrial biocides have enhanced activity against *P. aeruginosa* biofilms within a low strength electric field of a low current density. If this bioelectric effect holds true for a wide variety of biofilms, surfaces and antimicrobial agents, this technology has promise as a therapeutic modality. However, the clinical usefulness of these experimentally effective strategies remains to be determined.

Vascular prostheses

Vascular grafts made of Dacron are commonly used for treatment of atherosclerotic vascular disease. The indolent nature and microbiologic characteristics of bacterial biofilm infections versus the morbidity of graft excision and extra-anatomic bypass grafting are an important consideration in the use of these protheses. Late prosthetic graft infections are commonly caused by coagulase-negative staphylococci that survive within the biofilm on the surface of these devices [4]. *Staphylococcus aureus* and Gram-negative bacteria also cause infections of these devices. Occult graft infection by coagulase-negative staphylococci has been shown to be responsible for two-thirds of anastomotic femoral pseudoneurysms that develop after aortofemoral bypass grafting. *S. epidermidis* is by far the most common species implicated in late graft infections. Infection of a vascular prosthesis by *S. epidermidis* tends to manifest months to years after graft implantation or revision. The infection presents as a graft-healing complication such as anastoaortic false aneurysm, perigraft cavity abscess, graft

enteric fistula or graft cutaneous sinus tract. Diagnosis of infection is made by pre-operative imaging findings of perigraft inflammation and the presence of purulence surrounding the prosthesis at the time of graft excision. Significant systemic symptoms and signs of infection are not usually present. Treatment requires graft excision and extra-anatomic bypass grafting in addition to appropriate antimicrobial therapy. Recently, *in situ* replacement of vascular prostheses infected by bacterial biofilms has been shown to be successful [4].

Intracardiac prostheses

Prosthetic valve endocarditis is most often due to implantation of microorganisms either at the time of surgery or in the perioperative period. The sources of such contamination include breaks in aseptic surgical technique, contaminated cardiac bypass equipment, infection of indwelling intravascular catheters and, rarely, contamination of the valves themselves. Porcine valves have been reported to be contaminated with *Mycobacterium chelonei* [40]. The most common organisms involved in early onset prosthetic valve endocarditis are coagulase-negative staphylococci. Less commonly, diptheroids, fungi (eg *Candida* and *Aspergillus*) and a variety of other organisms have been implicated. Patients with prosthetic valves remain at definite though decreased risk of endocarditis in the years following implantation. The bacteriology of late onset prosthetic valve endocarditis resembles that of native valve endocarditis and *Streptococcus viridans* strains are the most frequent etiological agents. These endocardial infections result from transient bacteremias which may be spontaneous or may occur during a procedure such as dental cleaning. Other organisms that can cause late onset prosthetic valve endocarditis include enterococci, coagulase-negative staphylococci, *Staphylococcus aureus* and fastidious Gram-negative coccobacilli (*Hemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingea*). Eradication of infection from a prosthetic valve is very difficult even with prolonged bactericidal antimicrobial therapy. Removal and replacement of the infected prosthesis along with antimicrobial therapy is often needed to cure prosthetic valve endocarditis.

Total artificial hearts

The total artificial heart is a composite of many materials including metals and polymers and requires compatibility not only between materials but also between the materials and adjacent tissues (solid tissues and blood elements). An air hose from the pneumatic power source usually transverses organ space, body cavities and skin, representing a pathway for microbial colonization. Ultrastructural studies of these devices have shown a failure of true tissue integration and diffuse, adhesive bacterial colonization of biomaterial surfaces [31]. The biomaterials, damaged vascular endothelium and blood elements provide an extensive surface area for microbial colonization and biofilm formation. The clinical course of these infections is characterized by a failure to eradicate infection, with intermittent septicemia and distant abscess formation. The infections are polymicrobial involving nonpathogens or uncommon organisms and are only partially suppressed by antibiotics. Removal of the device is necessary for adequate treatment.

Indwelling urinary catheters

Catheterization of the urinary tract is the most common cause of nosocomial infection [53,58,71,76,77]. Bacteriuria associated with substantial morbidity and mortality will eventually develop in the majority of patients with long term catheterization. Bacteriuria develops in almost 100% of patients if the catheter remains in place for more than 30 days. Systemically-administered antibiotics either fail to eradicate the infection, or the bacteriuria quickly recurs after the antibiotics are discontinued. Thick adherent bacterial biofilms have been demonstrated on the surface of urinary catheters. The resistance of urinary catheter-associated infections to systemic antimicrobial therapy is due to the presence of sessile adherent bacteria surrounded by an extensive exopolysaccharide glycocalyx. Antibiotics usually fail to eradicate the infection or cause substitution by a more resistant organism.

Orthopedic prostheses

Replacement of joints destroyed by injury or arthritis has become a routine procedure. An estimated 400 000 joint replacements are performed each year in the United States [18]. Patients receiving orthopedic prostheses are at risk for bacterial infections such as septic arthritis, deep infections involving implants and bacteremia [30].

Infection remains the major cause of failure of these devices. Microorganisms are usually introduced at the time of implantation. Occasionally, the devices may get infected secondary to a bacteremia. The organisms eventually form a thick adherent biofilm over the device and are refractory to eradication by antibiotics. Polymethylmethacrylate cement used to affix the artificial device to the adjacent bone enhances the risk of infection. The heat generated during the polymerization process, damaging the adjacent tissue, or a direct inhibitory effect on host responses may be responsible for this increased risk of infection [56,57]. These infections can manifest as an acute inflammatory process associated with fever, swelling and suppurative drainage, or as indolent infections with pain and dysfunction of the prosthesis. Successful treatment of prosthetic joint infections requires removal of the device in addition to prolonged administration of an appropriate antibiotic. In addition, the patient is left with a physical disability which may be worse than that caused by the underlying process. The operative field needs to be sterilized effectively before a replacement of the prosthesis can be attempted.

Endotracheal tubes

Nosocomial pulmonary infections are common in patients requiring mechanical ventilation and result in significant morbidity and mortality [70]. These infections start as oropharyngeal colonization followed by aspiration of the organisms. With improved sterilization techniques, the role of respiratory therapy equipment in these infections has become less important. Unlike most other devices, endotracheal tubes are placed in an environment that has a resident flora that normally produces large amounts of mucus. Adherent colonization of the endotracheal tube is the most

significant risk factor for nosocomial pneumonia. Polyvinylchloride is commonly used for the manufacture of endotracheal tubes. Vascular catheters composed of polyvinylchloride become colonized more easily compared to those made of polyurethane and Teflon [67]. Using electron microscopy and qualitative culture techniques, 84% of endotracheal tubes were shown to be completely covered by an amorphous bacteria-containing matrix and 16% were partially covered by the matrix [70]. Some bacterial aggregates enclosed in the biofilms projected from the matrix to the lumen of the tube. The dislodgement of these aggregates by suction apparatus may be responsible for the repeated inoculations of the lungs in intubated patients. The treatment of endotracheal tube-associated pneumonias is difficult because of the persistence of the biofilm and polymicrobial nature of infections.

Extended-wear lenses

The risk factors for eye infections associated with contact lenses include contaminated cleaning solutions, improper handling techniques, corneal compromise from hypoxia, tear deprivation and diabetes mellitus [68]. However, normal corneal epithelium is resistant to bacterial colonization by virtue of its intact cell membranes and their surface polymers. Bacterial adhesion to corneal cell membranes occurs only when these cells have been damaged or exposed [72]. Contact lenses can serve as a passive but constant substratum for bacterial colonization and as a nidus for bacterial shedding with subsequent adhesions to damaged corneal basal epithelial cells [68]. The most frequently isolated organism in contact lens-associated infections are *Pseudomonas aeruginosa* and *S. epidermidis*. Using cytochemistry and scanning and transmission electron microscopy techniques, Slusher *et al* [67] demonstrated biofilm mediated adhesion of *P. aeruginosa* and *S. epidermidis* to the surface of a typical extended-wear contact lens.

Other devices

Other biomaterial-associated infections involve adherent biofilms on the surface of devices such as urinary stents, biliary stents and catheters; internal and external fixation devices used in the management of various types of bone injuries and diseases; tracheal plugs in patients with tracheostomy; cardiac pacemakers, chronic ambulatory peritoneal dialysis catheters, dental implants and sutures.

A large number of devices have become an integral part of management of medical and surgical problems. A common and disturbing complication of the use of many of these devices is persistent, recurrent, frequently catastrophic and always costly infection [68]. The adherent mode of growth is ubiquitous and is the natural state of bacterial existence in biomaterial-related infections. These infections persist until removal of the foreign body nidus. Strategies for prevention of these infections include: i) minimizing tissue destruction and removal of all extraneous biomaterial and devitalized tissue during surgery; ii) development of biomaterials that resist the initial adherence of bacteria by surface characteristic or by promoting bactericidal, bacteriostatic or phagocytic activity at their surfaces; iii) further study of the microstructure and chemical nature of the adherence mechanism and development of analogs and enzymes that might block the initial adherence by modification of receptors and ligands. Efforts to improve the outcome of device-related infections should include: i) optimal sampling and culture methods for early identification of the infecting organisms; ii) better methods of *in vitro* antimicrobial susceptibility testing with results relevant to the adherent biofilm-associated bacteria rather than the organism in suspension and; iii) development of antimicrobial agents with improved activity within the microenvironment of the biofilm.

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