The Role of Bacterial Biofilms in Device-Associated Infection

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Summary: There is increasing evidence that bacterial biofilm is responsible for the failure of medical devices, leading to device-associated infection. As plastic surgeons, we are among the leading users of prostheses in surgery, and it is important that we are kept informed of this growing problem. This article summarizes the pathogenesis of device-associated infection, outlines the evidence for such infection in a number of medical devices, and outlines operative strategies aimed at reducing the risk of bacterial contamination at the time of device deployment. It also outlines strategies under investigation to combat the development of device-associated infection. (*Plast. Reconstr. Surg.* 132: 1319, 2013.)

There is increasing evidence that the failure of many medical devices is a result of bacterial contamination.[1] Free-floating (planktonic) bacteria change when they come into contact with the surface of an alloplastic implant. Bacteria are able to form a three-dimensional matrix by excreting polymeric substances, which eventually bind firmly to the underlying surface. Over time, a biofilm, defined as bacteria encased within their own polymeric matrix, reaches a critical mass on the contaminated implant, induces a host inflammatory reaction, and can lead to ultimate failure of the implant.[2] It has been shown that bacteria within biofilms are significantly less susceptible to antibiotics, host defenses, and antiseptics, a characteristic making them difficult to treat.[3,4] Once a biofilm has led to implant failure, clinical options are limited and involve lifelong suppressive antibiotic therapy or revision surgery, which carries significant risk of morbidity and, in some cases, death. It is estimated that the cost of revision surgery from implant infection is approaching $1 billion a year in the United States alone.[2,5] The issue of device-associated infection will continue to grow as our Western population ages and demand for medical prosthetics increases. It is therefore imperative that strategies to reduce the risk of biofilm contamination of medical devices be developed and tested.

This article summarizes the pathogenesis of device-associated infection, outlines the evidence for device-associated infection, and outlines operative strategies for reducing the risk of biofilm contamination at the time of device deployment. It also outlines strategies under investigation for reducing the risk of device-associated infection.

FORMATION OF BACTERIAL BIOFILM

Biofilm formation follows a developmental progression involving four main stages (Fig. 1). These are reversible attachment, irreversible attachment, growth and differentiation, and dissemination.[6] Evidence from in vitro studies of biofilms suggests that this development is genetically regulated.[7] Initial contact of bacteria with a surface is mediated by van der Waals forces and may be determined by surface charge.[8] Once in contact, the bacteria undergo phenotypic change from a planktonic to a sessile (biofilm) state. The production of extracellular polymeric slime is then initiated. The combination of individual cells encased in their own extracellular polymeric
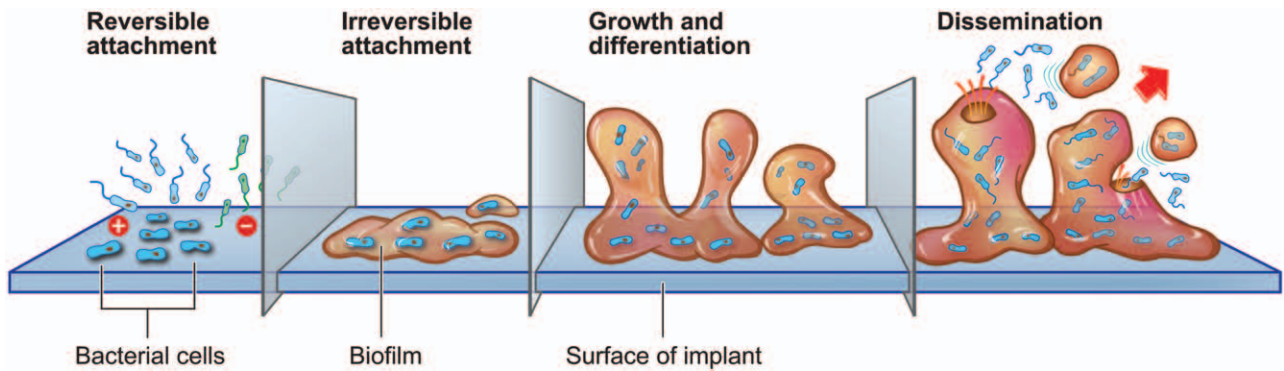
Fig. 1. Stages of biofilm growth: reversible attachment, irreversible attachment, growth and differentiation, and dissemination.

slime is defined as biofilm.[9] The biofilm becomes irreversibly attached to the underlying surface.

During growth and differentiation, the biofilm progressively spreads over the surface. Morphology of this biofilm varies according to environmental conditions. In a high-shear environment, for example, the biofilm is compact and densely cellular, with less extracellular polymeric slime. In a low-shear environment, flourishing extracellular polymeric slime "mushrooms" balloon out into the surrounding environment.[10–12] Within the matrix, a number of survival advantages are conferred upon the bacteria (Fig. 2). The extracellular polymeric slime provides a relative buffer against diffusion of antibiotics and antiseptics.[10,13–15] It also shields the bacteria from host immune access and may trigger a more intense inflammatory response.[3,16,17] There is some evidence that this inflammation may further provide advantage to the biofilm by promoting host cell lysis and subsequent release of nutrients for bacteria.[16] There are other, more subtle advantages, which include cooperative metabolism based on complex intercellular signaling[18] and the ability to use horizontal gene transfer to protect against unexpected environmental challenges.[19,20] Bacterial persister cells, which are metabolically inactive and highly resistant to antiinfective agents, have been shown to exist within
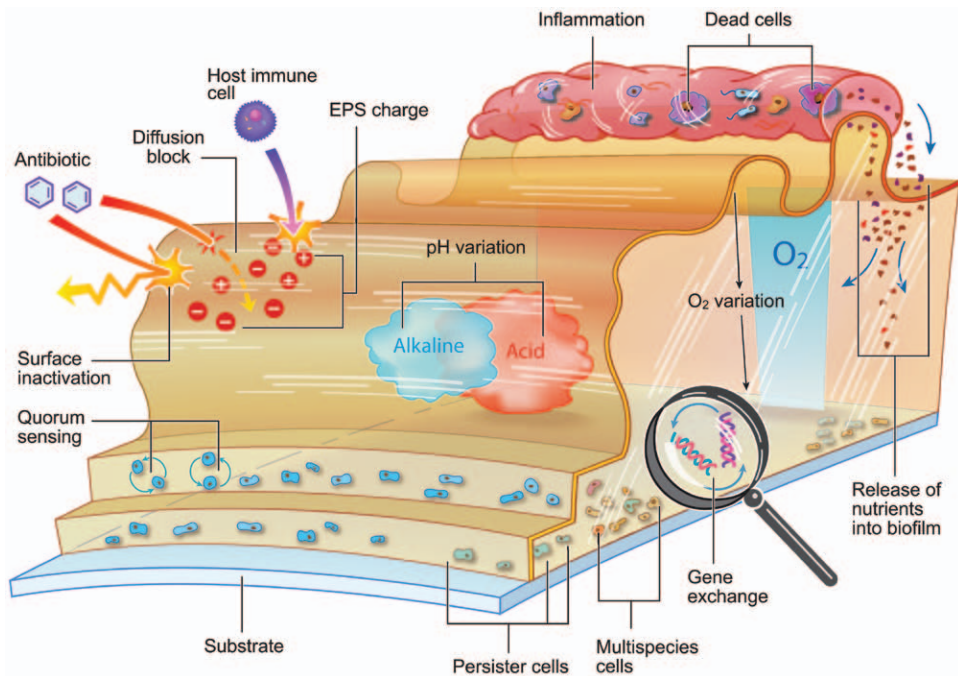

Fig. 2. Survival advantages of bacteria within biofilm include inactivation of antibiotics/antiseptics, prevention of host immune cell penetration, diffusion block, quorum sensing, gene exchange, variation in pH and oxygenation, and persister cells.

mature biofilms.[21] The environment within the biofilm is also heterogeneous, with significant variation in local pH and oxygenation.[22] Furthermore, evidence is emerging that the majority of biofilm is multispecies and in some cases can also harbor other prokaryotic cells and viruses.[6]

In the dissemination phase, cells from biofilm are released to colonize new surfaces. The method of dissemination can vary depending on whether the planktonic bacteria are motile or nonmotile.[10,11]

Surface biofilm has been visualized in the oldest detected fossils on earth, aged 3 billion years.[6,23,24] The mechanisms and strategies for surface attachment, proliferation, and dissemination have developed over millennia and effectively guarantee bacterial survival.

DETECTION OF BACTERIAL BIOFILM

Standard microbiological sampling is insufficient for detecting bacterial biofilm. Few bacteria are present on the surface of biofilm, and their release is prevented by their enclosed extracellular polymeric slime. In addition, their metabolic rate is low, making them difficult to culture.[3] The traditional approach to the detection of biofilm involves two steps: the recovery of live bacteria within the biofilm and subsequent identification and imaging of biofilm on the surface of the implant.[25–27]

For imaging biofilm, scanning electron microscopy offers the advantage of generating images of bacteria cells and the extracellular polymeric slime directly attached to the underlying surface (Fig. 3). However, because of the small visual window, the technique is open to sampling error.

For bacterial recovery, sonication serves to fracture the extracellular polymeric slime and release bacteria into the sample.[28,29] These bacteria are then cultured in enrichment media and are identified by means of traditional microbiological methods. This technique, while still remaining the standard, has been recently supplanted by more rapid and sensitive diagnostic techniques.

Bacterial DNA and RNA detection and sequencing have been used to detect bacteria within biofilm.[31,32] Polymerase chain reaction has the ability to detect and amplify low levels of bacterial nucleic acid for subsequent sequencing and molecular diagnosis. A number of authors have reported that polymerase chain reaction–based detection has identified microorganisms in samples when sonication culture techniques have failed.[33,34] However, polymerase chain reaction
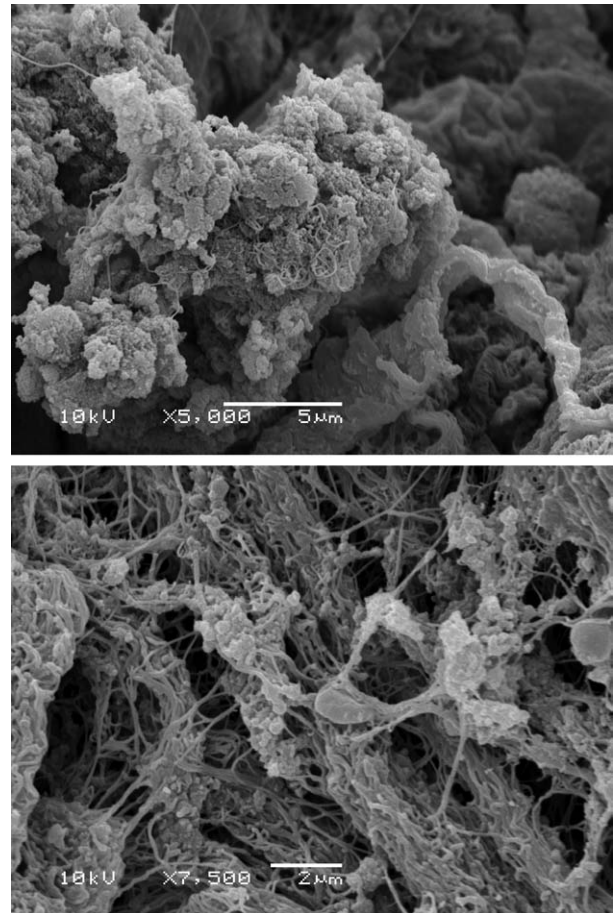

Fig. 3. Scanning electron microscopic images of biofilm on human breast implants. (*Above*) Staphylococcal biofilm on the surface of a breast prosthesis. (*Below*) Staphylococcal biofilm on the inner aspect of breast capsular contracture.

can detect only nucleic acid, not live organisms, and is open to false-positive reporting.

More recently, fluorescent in situ hybridization has been used. This technique utilizes a fluorescein-labeled probe, specific for the 16S ribosomal RNA of prokaryotic cells, to bind and detect biofilm on surface samples. Once bound, the biofilm can be detected with confocal laser scanning microscopy or fluorescent microscopy.[33] Confocal laser scanning microscopy can also be used in conjunction with live/dead DNA stains for nondestructive analysis and is used to characterize biofilm morphology in vitro (Fig. 4). The technique can be performed in real time to study the effect of treatment strategies on biofilm morphology.

The combination of multiple diagnostic techniques is the best strategy to detect biofilm in device-associated infection. These methods are not readily available commercially and are currently performed only in reference biofilm research laboratories. The quest continues for

a rapid, sensitive, specific diagnostic test for the presence of biofilm. A recent review has suggested that improvements in targeted radionuclide scanning may provide a novel approach for detection of device-associated infection.[34]

SCOPE OF DEVICE-ASSOCIATED INFECTION

Bacterial biofilm has been recovered from an increasing number of device-associated infections, including joint prostheses,[30] penile prostheses,[35] fracture fixation devices,[36,37] intravenous[38] and urinary catheters,[39] peritoneal dialysis catheters,[40] contact lenses,[41] breast prostheses,[42,43] endoscopes,[44] cardiovascular[45] and biliary[46] stents, pacemakers,[47] and cochlear implants.[48]

The evidence for biofilm as the leading cause of implant failure will be outlined for prosthetic joints, cardiovascular implants, and breast implants, as these have the most relevance to plastic and reconstructive surgeons.

Catheter Infection

Hematogenous spread from colonized central venous catheters is a long-recognized route of infection.[49,50] The traditional method for determining catheter colonization utilizes a semiquantitative culture technique in which a 5-cm segment of catheter is rolled across blood agar.[51] Sonication/enrichment culture has been shown to be equally sensitive.[52]

Prosthetic Joints

Up to 10 percent of joint prostheses will ultimately need revision surgery.[53–55] With

Fig. 4. Confocal live/dead stain of biofilm on prosthetic surface, with *green* representing live bacteria and *red* representing dead bacteria.

improvements in surgical technique and prosthesis design and biomaterials, the complications of heterotopic ossification, fracture, and dislocation are relatively uncommon. The two most common causes requiring revision surgery are aseptic or mechanical loosening and infection, which are estimated to occur in up to 25 percent of patients,[56] although not all of these require surgical revision. Although frank infection is uncommon, occurring in fewer than 1 percent of all joint replacements, there is increasing evidence that some proportion of "aseptic" loosening is in fact due to underlying biofilm infection.[34] Device-associated infection in relation to prosthetic joints is a serious complication of joint replacement surgery and carries significant morbidity, poor functional outcome, and a not-insignificant mortality rates.[53] This is more relevant when one considers the increasing number of prosthetics being placed in an aging population with higher prevalence of comorbidity and an increase in multidrug-resistant bacteria.

Identification rates for bacteria in implants removed for suspected infection range from 41 percent up to 86 percent with use of multiple standard culture techniques.[57] For implants not suspected of infection (i.e., aseptic loosening), sonication and enrichment culture of operative samples have shown that 22 percent of these implants grew bacteria.[28] The most common pathogens were *Staphylococcus epidermidis* and *Propionibacterium acnes.* Analysis of implants thought to have "aseptic" loosening have yielded positivity rates of up to 63 percent with fluorescent in situ hybridization and 72 percent with polymerase chain reaction to detect bacterial nucleic acid.[58,59] These data suggest that the role of biofilm in implant failure is greater than previously suspected.

Indirect evidence from analysis of cytokine profiles from periprosthetic fluid has also confirmed that inflammatory markers such as interleukin 6, tumor necrosis factor-α, tumor growth factor-ß, and interleukin 11 may be triggered by the presence of bacterial biofilm.[60] Researchers are investigating the potential for measuring serum antibody to staphylococcal slime polysaccharide antigens as a screening test for underlying device-associated infection.[61]

A recent study has identified the use of infection-specific radiotracers such as bacteriophages and thymidine kinase in conjunction with single-photon emission computed tomography and positron emission tomography scans to diagnose biofilm in orthopedic prostheses.[34] Further investigation of these modalities is warranted.
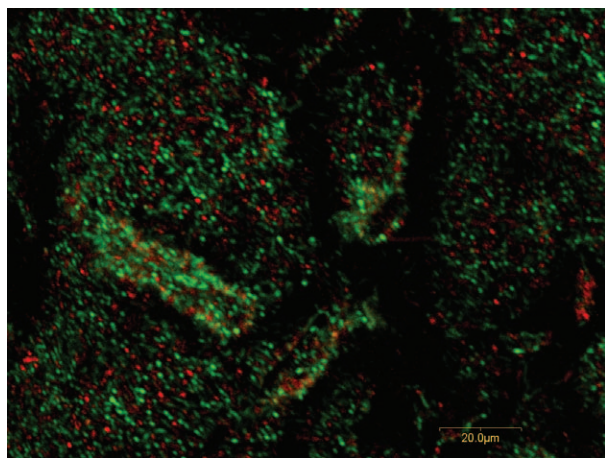
Cardiovascular Implantable Electronic Devices

Cardiovascular implantable electronic devices, which include implantable cardioverter-defibrillators and cardiac resynchronization therapy devices, are prone to develop biofilm infection.[45] Both enrichment culture and sonication have yielded skin commensals such as *Staphylococcus aureus, S. epidermidis,* and *P. acnes*. The incidence of clinical infection in these devices is increasing, most likely because of the complexity of the procedures involved and the associated comorbidities in the patient population receiving these prostheses.

Breast Implants

The presence of subclinical infection as a cause of capsular contracture around breast implants was first proposed by Burkhardt et al., who subsequently recommended betadine pocket irrigation to reduce the risk of bacterial contamination.[62] Breast implants are unique in that they are placed into a potentially contaminated pocket, with high levels of bacteria present in breast ducts and tissue.[63–65] Furthermore, the effects of subclinical infection are visibly and palpably evident as compared with other prostheses.[66]

Evidence has been accumulating that biofilm is the leading cause of contracture. Clinical studies have shown a higher rate of bacterial recovery in patients with high-grade contracture.[42,67] Pajkos et al. were the first to show a significant association with *S. epidermidis* biofilm in women with Baker grade III/IV contracture, as compared with Baker I/II.[43] Biofilm was identified with both sonication and culture, as well as scanning electron microscopy.

In vitro studies have shown that bacteria are able to bind to the surface of breast implants, regardless of surface texture.[68]

Animal models have now confirmed that seeding of bacteria onto breast implants can lead to biofilm formation and subsequent contracture. Shah et al., using a rat model, were the first to show that the thickness of the capsule was proportionate to the level of staphylococcal inoculation.[69] Tamboto et al. have shown with a porcine model that once biofilm is established on the surface of a breast implant from either direct inoculation or endogenous infection with porcine bacteria, 80 percent progress to high-grade capsular contracture[70] (Fig. 5). In the same study, the presence of biofilm was common in both contracted and noncontracted groups; however, the contracted groups demonstrated a significantly higher number of colony-forming units, again suggesting that critical bacterial mass is needed for progression to clinical device-associated infection. Marques et al. have shown with a rabbit model that the presence of coagulase-negative *Staphylococcus* species organisms results in thicker capsule and polymorphonuclear infiltrates than in controls.[71] Recent studies on the long-term effects of biofilm in breast implants in the porcine model have shown that Baker grade IV implant capsules had a significantly higher number of bacteria on quantitative analysis than did Baker I-II capsules.[72] Recent studies also have demonstrated a higher degree of biofilm formation in textured implants, likely due to an increase in surface area. Furthermore, a chronic T-cell inflammatory infiltrate was present in textured implants infected with biofilm.[72] This finding might point to chronic immune activation as a result of subclinical infection.

Strategies for Prevention of Device-Associated Infection in Breast Prostheses

On the basis of increasing evidence that bacterial access at the time of breast implant insertion is the leading cause of subsequent capsular contracture, we propose a number of clinical recommendations:

1. Use intravenous antibiotic prophylaxis at the time of anesthetic induction.
2. Avoid periareolar incisions; these have been shown in both laboratory and clinical studies to lead to a higher rate of contracture as the pocket dissection is contaminated directly by bacteria within the breast tissue.[64,73,74]
3. Use nipple shields to prevent spillage of bacteria into the pocket (Fig. 6).[64,73,75]
4. Perform careful atraumatic dissection to minimize devascularized tissue.
5. Perform careful hemostasis.
6. Avoid dissection into the breast parenchyma. The use of a dual-plane, subfascial pocket has anatomic advantages.
7. Perform pocket irrigation with triple antibiotic solution or betadine.[76–78]
8. Use an introduction sleeve.[79] We have recommended the use of a cut-off surgical glove to minimize skin contact (Fig. 6).
9. Use new instruments and drapes, and change surgical gloves prior to handling the implant.
10. Minimize the time of implant opening.
11. Minimize repositioning and replacement of the implant.
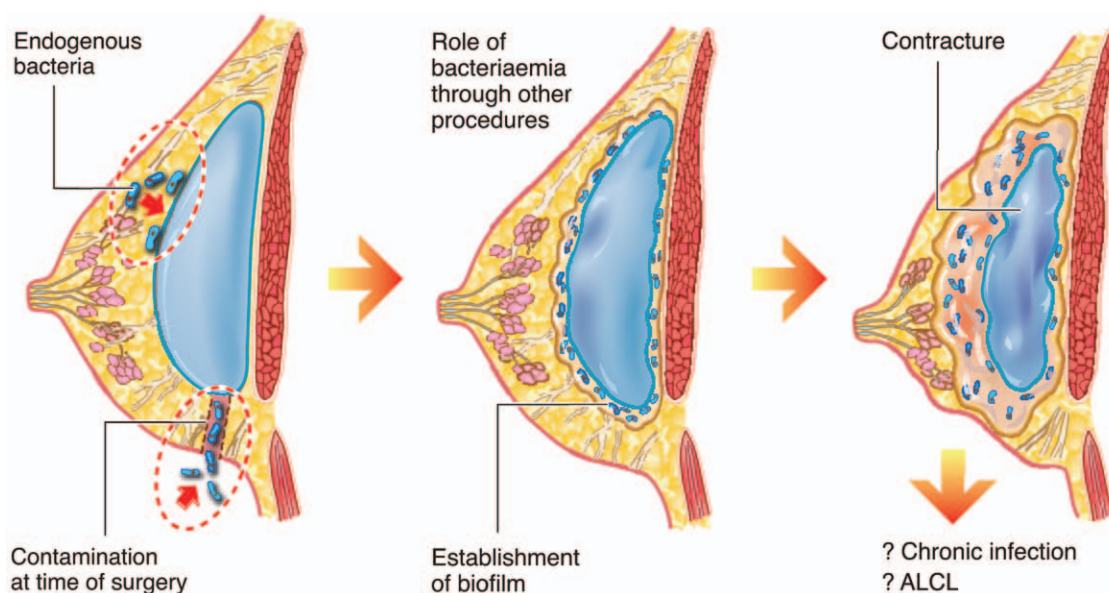12. Use a layered closure.

Fig. 5. The subclinical infection hypothesis for breast implants, showing initial contamination, biofilm formation, and subsequent inflammation and contracture. Chronic biofilm infection may lead to symptoms and potential malignant transformation of chronically activated lymphocytes.

13. Avoid using a drainage tube, which can be a potential site of entry for bacteria.
14. Use antibiotic prophylaxis to cover subsequent procedures that breach skin or mucosa.

PREVENTION

It is arguable that device-associated infections are best prevented. Most device-associated infections are likely to originate from implant contamination at the time of implantation. Perioperative intravenous antibiotic prophylaxis is recommended for all patients undergoing implant placement. This has been shown to be effective in decreasing the rate of infection of breast implants.[80]

Locally delivered antibiotics have also been utilized in both orthopedic and plastic surgery. The use of antibiotic-impregnated cement in primary arthroplasty, although not universally practiced, has been shown to result in the lowest rate of revision surgery.[81,82] In breast surgery, the use of triple antibiotic solution has been shown to significantly reduce the number of bacteria in the placement pocket.[76] A further clinical study has established that the use of antibiotic irrigation results in a significant reduction of capsular contracture.[78]

A recent animal study of breast implant contracture has shown that the concurrent use of antibiotic-impregnated absorbable mesh produced significantly less biofilm and contracture in a porcine model.[83] A similar mesh was also utilized in a clinical study of cardiovascular implantable electronic devices to produce a significantly lower infection rate at a 2-month follow-up.[84]

Antibacterial coatings have been used on catheters and drains to reduce the risk of device-associated infection. In prospective, randomized, controlled trials, the use of antibacterial coatings such as minocycline/rifampin, silver, platinum, and carbon has shown benefit in reducing the rate of catheter colonization and subsequent catheter-associated bloodstream infection.[85–87] The U.S. Food and Drug Administration has approved antimicrobial-coated catheters impregnated with minocycline and rifampin on their internal and external surfaces, on the basis of data showing a significant reduction in colonization and sepsis. In this study, no antimicrobial resistance emerged.[88]

The role of subsequent hematogenous seeding of prosthetics remains controversial.[89] Clinical cases of implant infection have been reported to occur after an invasive procedure.[90–92] The American Academy of Orthopedic Surgeons has issued a statement favoring the use of antimicrobial prophylaxis for patients with prosthetic joints undergoing dental, gastrointestinal, genitourinary, and other invasive procedures.[93] Further clinical study of these phenomena is required.

FUTURE DEVELOPMENTS

A number of potential strategies to reduce bacterial biofilm formation on prostheses are currently under investigation. Modifying the

Fig. 6. Surgical glove introduction sleeve to protect implant from contacting the skin and breast tissue during insertion. Note nipple shield in place. The sleeve is inspected after removal to ensure that it is complete.

surface of implants with antibacterial coatings, biologic membranes, and alterations of physical characteristics has had varying success.[85,94,95] The use of any drug-related coatings, however, would require regulatory scrutiny and approval, as the implant becomes a potential drug-delivery device. Anti-sense molecules and quorum sense inhibitors are compounds that disrupt bacterial communication. These have also been shown to have some effect on early biofilm formation and propagation.[96] Electric current and ultrasound as physical modalities have also shown some promise for removing established biofilm attached to prostheses.[97] Negative pressure in an in vitro model has also produced physical changes to the extracellular polymeric slime, resulting in increased susceptibility of biofilm bacteria to the action of anti-infective compounds.[98] Nanotechnology, especially the use of compounds such as zinc oxide, titanium dioxide, polymers, and

carbon nanotubes, is currently being investigated as potential surface disruptor to bacterial attachment.[99] Crossed single- and multi-walled carbon nanotubes arranged in a criss-cross pattern have been shown to prevent *Escherichia coli* biofilm.[100] The mechanism of action is thought to relate to direct toxicity and prevention of gene activation. Titanium dioxide nanoparticles have also been shown to produce antibiofilm activity when activated by ultraviolet light, leading to potential therapeutic applications.[101]

It is likely that in the next few years, a combination of chemical, physical, and as yet novel surface modifications may provide us with a truly intelligent medical device, able to repel planktonic bacteria and prevent the activation and attachment of biofilm bacteria. Furthermore, these devices may have the ability to self-clean by periodically examining their surface and actively shedding any attached bacterial biofilm. The ultimate goal

of providing a truly aseptic environment around medical devices may well translate into a reduction in device-associated infection and ultimately into better outcomes for our patients.

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