Modification of Polymer Surfaces of Medical Devices to Prevent Infections

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The extensive use of antibiotics to treat device-associated infections has contributed to the acceleration of the appearance of antibiotic-resistant bacteria by spreading them through contaminated hospital environments to patients (Shintani, 2003 and Shintani et al., 2004). Comprehensive research has had limited success in the reduction of device-associated infections, and usually the only therapy to treat the infections is the removal of the infected devices from patients. Recent strategies to minimize the risks of device-associated infections have focused on the following areas: good clinical practices, prudent selection of biomaterials used for device construction, and modification of device surfaces by increasing surface biocompatibility and decreasing bacterial adherence. This paper discusses from several aspects the elements of bacterial adhesion on indwelling device surfaces that may directly relate to infections and surface treatment technologies reducing the incidence of indwelling medical device-related infections.

Key words: Modification/Polymer surface/Medical device/Anti-infection.

INTRODUCTION

An ideal indwelling medical device would possess surfaces with the same properties as those inside the healthy human body, such as that of blood vessels. Surfaces of indwelling medical devices should be smooth, not only to allow healthy tissue cells to grow easily and resist bacterial adhesion, but also to destroy bacterial cells that come into contact with them. Therefore, strategies for manufacturing anti-infective devices should focus on developing the device surfaces that would not trigger the host defense system, that resist bacterial adhesion, and that promote the formation of a layer of living cells.

A smooth and uniform surface could be an important feature to resist bacterial adhesion. In a study on the bacterial adhesion on Dacron® fibers, it was reported that in a buffer solution containing human plasma protein, S. epidermidis adhered to the fiber surfaces (Wang et al., 1995). A conclusion that may be drawn from this evidence is that even if a surface inhibits bacterial adherence, bacteria can still find space to survive if the surface is rough enough.

Healthy integrated tissues are resistant to infections because the formation of a close, healthy homeostatic tissue integration provides a barrier against invading bacteria. Surface physiochemical properties of indwelling medical devices play an important role in the interfacial behavior of devices in contact with body fluids and tissues. If a medical device surface is designed and manufactured to favor integration by tissue cells, upon placing the device in a living body, the surface may either directly integrate with healthy tissue cells via chemical bonding or separate by an intervening layer of matrix proteins. This permits the surface to become inert to the body homeostasis as well as resistant to bacterial adherence.

Surface modification of the existing device is a relatively straight-forward strategy for creating...
indwelling medical devices with desirable surfaces. This review paper will consider the surface-treatment technologies that have been used to provide devices with anti-infective surfaces. The polymer surface modification procedures described in this paper are briefly summarized in the Table 1.

1. Modification of medical device surface without using anti-infective agents

Surface treatment to modify device properties has been used to increase the biocompatibility and decrease the susceptibility to bacterial adhesion.

The absorption of proteins on hydrophobic poly(perfluoroethylene-propylene) surfaces was found to increase surface hydrophilicity, which resulted in the reduction of bacterial adherence (Hogt et al., 1985). Device-surface properties such as hydrophilicity and surface free energy are, in part, determinants of the extent of bacterial adhesion (Table 2; Ista et al. 1996). It has been demonstrated that increased hydrophilicity of a solid surface decreases the adhesion of various bacterial species. Medical devices, made of both metals and plastics, are in general hydrophobic and have relatively high coefficients of friction that sometimes compound the infection problem. Surface treatment has been used to increase the hydrophilicity of those devices to reduce bacterial adhesion.

Modifying a hydrophobic surface to become more hydrophilic usually involves hydrogel technology, a process that applies biocompatible, water-absorbable polymer hydrogels to medical-device surfaces.

**TABLE 1.** Polymer surface modification procedure.

<table>
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<th>1. Modification without using anti-infective agents</th>
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Hydrogels are a class of hydrophilic polymers that can absorb water up to several times their own weight without dissolving. Hydrogel polymers are much softer after water absorption, providing a softer surface for tissue contact and, therefore, possibly reducing the stimulation of a foreign surface to living tissues and possibly increasing the biocompatibility of the medical device surface. In addition most microorganisms reduced adhesion on hydrogel-coated surfaces because of increased hydrophilicity (Brisset et al., 1996, Hogt et al., 1983, 1985, and 1986).

Polynvinylpyrrolidone and polyethylene glycol are typical examples of hydrogel polymers that have been used in indwelling medical device surface modifications. Hydrophilic polymer film formed by UV crosslinking derivatives of polynvinylpyrrolidone showed the reduction of bacterial adhesion in vitro on materials used to construct urinary catheters (Duran et al., 1995). A study on the bacterial attachment to a self-assembled monolayer of oligo (ethylene glycol) found that the surface resists the attachment of *D. marina* and *S. epidermidis* (Ista et al., 1996). Bridgett et al studied in vitro bacterial adherence of *S. epidermidis* on polystyrene surfaces modified by A-B-A copolymers, where A is poly (ethylene oxide) (PEO) and B is poly (propylene oxide) (PPO), and found substantial reductions in bacterial adhesion, up to 97 %, with all copolymers tested, and the reduction was independent of the PEO and PPO block length and copolymer molecular weight (Bridgett et al., 1992). The author suspects that copolymers absorb to the hydrophobic polystyrene via their hydrophobic PPO blocks, and the protruding hydrophilic PEO blocks may form a steric barrier to bacterial adhesion.

In a single-blind randomized clinical study, Bull et al compared the performance of a hydrogel-coated and a silicone-coated urinary catheter in 69 patients. They reported that the hydrogel catheters remained in place longer than those which were silicone-coated and caused less urine leakage problems. Eleven hydrogel-coated and nine silicone-coated catheters had to be changed because of encrustation during 16 weeks of the catheterization period (Bull et al.,

Citation from paper by Ista et al. (1996).

This result indicated bacteria attached onto more hydrophilic polymer surface.

**TABLE 2.** Comparison of degree of adhesion of *S. epidermidis* to polymer surfaces with different contact angle.

<table>
<thead>
<tr>
<th>Surface modification</th>
<th>Functional group</th>
<th>Contact angle</th>
<th>Attachment of <em>S. epidermidis</em> (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-S(CH₂)₉(CF₂)-CF₃</td>
<td>CF₃</td>
<td>120</td>
<td>27</td>
</tr>
<tr>
<td>-S(CH₂)₉CH₃</td>
<td>CH₃</td>
<td>107</td>
<td>57</td>
</tr>
<tr>
<td>-S(CH₂)₉COOH</td>
<td>COOH</td>
<td>&lt;5</td>
<td>100</td>
</tr>
</tbody>
</table>

This result indicated bacteria attached onto more hydrophilic polymer surface.
2. Modification of medical device surface by using anti-infective agents

Studies reveal that although surface properties such as surface energy, wettability, and uniformity, significantly influence the ability of bacteria to adhere to a medical device, changing bacterial strains and the physiological media with which the device is in contact will also alter the adhesion process. Modifying device surfaces to become more hydrophilic may reduce the adherence of some bacterial strains, but may also increase the adherence of some other strains (Hogt et al., 1983). No surface has been proven resistant to all important bacteria that cause device-related infections.

Incorporating non-toxic anti-infective agents, such as antimicrobials, antibiotics, and other pharmaceutical agents that kill bacteria, on the device surface would provide an alternate approach to assure a surface free of bacteria. Surface treatments to incorporate anti-infective agents onto the surfaces of medical devices have significant advantages. They can incorporate a large variety of anti-infective agents on the surface and modify the existing devices easily and inexpensively without changing the bulk properties of the device. Coatings with anti-infective agents have shown promising results and appear to increase biocompatibility and resist the adhesion of the bacteria on surfaces of indwelling medical devices (Pearson and Abrutyn, 1997).

Anti-infective agents that kill microorganisms can provide devices with a chemical barrier against the invading organisms. Device surfaces with such agents can provide a high concentration of anti-infective agents in a local environment, disinfec ting bacteria that enter together with the medical device or that encounter the device later through any other route before they have a chance to generate a biofilm to protect themselves.

The current surface-treatment technologies incorporating anti-infective agents can be classified into three categories and will discussed followings: the deposition of a thin film of anti-infective agents on the surface, the ionic bonding of anti-infective agents, and the entrapping of anti-infective agents in a polymer matrix.

2-1. Direct deposition method

The direct deposition method applies pure anti-infective agents directly onto a medical device surface. Silver and its compounds, as well as other antimicrobials, applied on a device surface by this method, have shown reductions of bacterial adherence.

The effectiveness of the silver ion as an antibacterial agent has long been known. Silver and its compounds have broad-spectrum antimicrobial activity and low toxicity to the human body. Recently, technologies have developed the use of silver and its compounds as anti-infective agents in reducing device-related infections after promising reports have shown that in vitro silver coatings prevent the adherence and growth of Escherichia coli and Pseudomonas aeruginosa without causing cell toxicity (Liedberg and Lundeborg, 1989).

Silver coatings were found to be effective in reducing the chances of infection caused by medical devices implanted or inserted into the body. A few small clinical trials of silver-coated urinary catheters in selected patients have found marked reductions in catheter-related bacteriuria (Lundeborg, 1986). In a randomized clinical study, silver alloy deposited on Foley catheters significantly reduced the incidence of catheter-related bacteriuria in comparison with Teflonized catheters after six days of catheterization. Ten% of the patients with silver-coated catheters developed bacteriuria compared with 37% of the patients who had the Teflonized latex catheters. The silver-impregnated Foley catheters showed promising results in reducing the incidence of catheter-associated urinary tract infection (Liedberg and Lundeborg, 1990).

Application of silver metal on the surface of orthopedic external fixation pins by ion beam assistant deposition was utilized to prevent pin tract infections, which were reported to have infection rates up to 40 percent (Ostermann et al., 1994). The silver film formed by this technology is minimally leachable and kills bacteria when they come into contact with it. In vitro colonization results indicate that the silver film-coated pins reduced the number of the colonies on the surface by more than 80% in three out of four bacteria tested: E. coli; P. aeruginosa; and K. pneumoniae. However, no reduction in the bacterium S. aureus was observed. In another study also using silver-coated pins, it was found that the reduction of colonization by four out of five different bacteria ranged from 67% to 95% as compared with uncoated pins (Wassall et al., 1997). With one test organism, S. haemolyticus, more bacterial cells adhered onto the silver-coated than onto the uncoated pins, presumably because of the unique cell-surface characteristics of this species (Wassall et al., 1997). After the pins were treated in human serum, similar patterns of bacterial adhesion were observed for both silver-coated and uncoated pins (Wassall et al., 1997). In an in vivo study where 12 uncoated and 36
silver-coated pins were implanted in the iliac crests of sheep and then followed by inoculation with *S. aureus* (Collinge et al., 1994), it was confirmed that after 18 days of implantation, 84% of the cases with uncoated pins showed infection, whereas the infection rate with silver-coated pins was 62%.

Benzalkonium (BAK) chloride is a known quaternary ammonium bactericide. Most Swan catheters have a complex of heparin-BAK deposited on the surface to reduce thrombosis. In addition, the heparin-BAK/coated catheters show anti-infective activity against a wide variety of potential catheter-related microbial pathogens. The rates of catheter-related bacteremia from the heparin-BAK catheters are three-fold lower than those of non-coated catheters. BAK on the surface confers some protection against surface colonization and catheter-related bacteremia. However, the anti-infective activity quickly diminished to undetectable amounts after the catheters come in contact with blood (Mermel et al., 1993). A silicone rubber surface modified by photochemical immobilization of an antimicrobial peptide, magainin, inhibited the growth of *S. epidermidis* in an *in vitro* study. The growth of the bacteria was reduced by 98% in the photoimmobilized samples as compared with only 5% reduction in the samples of simply absorbing magainin.

### 2-2. Ionic bonding method

Techniques of binding antibiotic molecules on a medical device surface via ionic bonding have been developed based on the fact that many antibiotic molecules possess either positive or negative charges. Surfactants can interact with both hydrophobic and hydrophilic functional groups. Surfactants are known to inhibit microbial adhesion to hydrophobic surfaces, to hydrocarbons by emulsan (Rosenberg et al., 1983), and to plastics by chlorhexidine gluconate (Tobgi et al., 1987) and Tween 20 (Klotz et al., 1985). A surfactant that has a positive or negative charge serves as an anchor for the subsequent binding of antibiotics with an opposite charge via ionic binding on the surfaces of indwelling medical devices.

Tridodecylmethylammonium chloride (TDMAC), one of the most widely used surfactants, has been used to bind antibiotics onto medical device surfaces. It is also a quaternary ammonium compound with three long hydrophobic hydrocarbon chains and a positively charged nitrogen (R-N⁺-R,R',R''-R⁴). Its chemical structure awards TDMAC a unique ability to bind negatively charged antibiotics via ionic binding on a device surface with antibiotics and a hydrophobic interaction with the device surface via van der Walls binding.

After exposure to body fluids, a medical device surface is in contact with the ions in body fluids. Negatively charged antibiotics on the surface are exchanged with anions in body fluids and are released slowly from the device surface. The release of antibiotics provides a high antibiotic concentration near the device surface, exceeding the amount that could be achieved by systemic administration to effectively kill the bacteria proximal to the medical device (Kamal et al., 1991).

An *in vivo* comparison study of polyethylene catheters, which were untreated, treated by being soaked in either penicillin or TDMAC solution, or treated with TDMAC-bonded penicillin, was performed using rats (Trooskin et al., 1985). The catheters were placed in a jugular vein of each rat and positioned in the right atrium. Before closure, the exit site was inoculated with 10⁵ CFU of *S. aureus*. Five days after inoculation, the catheters were removed, and the tips of catheters were cultured. High rates of catheter colonization, 60 to 80%, were found on the catheters that were either untreated or treated only by penicillin or TDMAC soaking. On the contrary, catheters with TDMAC-bonded penicillin did not show any colony formation (Trooskin et al., 1985).

Antibiotic susceptibility was studied and it was found that the combination of rifampin and minocycline was more effective in preventing the colonization of catheter surfaces than any other antibiotic or antibiotic combination tested (Raad et al., 1996). Treated surfaces displayed a broad-spectrum of inhibitory activity against major catheter-related organisms such as *S. epidermidis*, *S. aureus*, and *E. faecalis*. Clinical trials indicated that central venous catheters with TDMAC-bonded rifampin and minocycline on the surface had reduced the incidence of catheter-related bacterium and the infection rate (Raad et al., 1997).

TDMAC molecules are also shown to retain the neutral antibiotic vancomycin and proteins such as the tissue plasminogen activator on plastics, probably through the hydrophobic interaction (Harvey et al., 1989).

An aminoglycoside antibiotic, dibekacin sulfate (DBK), was bonded to the surface of urethral catheters via ionic bonds, and the prepared catheters were shown *in vitro* to provide a sustained release of DBK for more than 25 days (Sakamoto et al., 1985).

### 2-3. Entrapment

Entrapment of anti-infective agents in a polymer matrix applied on device surfaces has shown promising results *in vitro*, *in vivo*, and in clinical studies.
Polymer matrices can be formed either by in situ cross-linking of prepolymers or applying non-reactive polymer coatings. Application of non-reactive polymer matrices is widely used for indwelling medical devices and shows advantages of desired effectiveness and in the duration of protection. Polymer matrices with anti-infective agents could be used directly to construct a device or applied as a thin layer of coating on the medical device surface.

The manufacture of medical devices from anti-infective polymers presents problems in regards to selecting the anti-infective agents and matrix polymers as well as finding suitable processes of medical device construction, and has been more technically challenging than applying coating technology on device surfaces. A cuff, used as an attachment to a central venous catheter to block the potential bacterial entrance, was made of a biodegradable polymer, collagen, impregnated with silver. As the polymer slowly degrades during implantation, the impregnated silver is released to protect the catheter from bacterial invasion. A randomized, multi-center trial showed that the cuff attachment assisted the reduction of catheter-related infections (Maki et al., 1988).

The technology of non-reactive polymer coatings uses a coating liquid composed of specific polymers, anti-infective agents, and solvents. After a coating liquid is applied on a medical device surface, solvents are allowed to evaporate, leaving a thin film consisting of the polymers with a uniformly dispersed anti-infective agent. The thin film of polymer acts as a reservoir for a sustained release of anti-infective agents over an appropriate period at an effective concentration. Anti-infective agents in the matrices are not chemically bonded to the matrix polymers, however their activity still remains unaltered. After release from the matrix, the anti-infective agents can act immediately in a predictable manner in their biological effect: absorption, distribution, metabolism, and excretion.

The performance of prepared anti-infective coatings is influenced by the characteristics of both the anti-infective agents and the polymer matrix. Microbiological and physiochemical properties of both the anti-infective agent and polymer should be considered when selecting an anti-infective system. First, the choice of anti-infective agents should depend on the application of a device in order to be effective against the major microorganisms that cause infections on a particular device. The anti-infective agents must also keep their potency when entrapped in the polymer matrix. Broad-spectrum anti-infective agents with strong antibacterial effectiveness and low toxicity are preferred.

However, some clinical complications of the selected agents can only be found when a product is actually used in patients. An example is that after a number of years of application, hypersensitivity reactions to silver sulfadiazine chlorhexidine-coated central venous catheters were reported in Japan (USFDA, 1998). The loading of the anti-infective agents will influence the duration of the activity, the efficacy, and the toxicity of the coating. The solubility of a specific agent, the susceptibility of the targeted microorganisms, and its affinity to surrounding tissue all affect the performance of the coating. In addition, the hydrophilicity as well as the chemical structure of the polymer matrix play an important role in the performance of the coating. The elution rate of a given anti-infective agent is dominated by the polymer matrix in which the anti-infective agent is incorporated. The polymers for the matrices must be compatible with the substrates to which the coating is applied, as well as with the selected agent, and must not induce chemical reactions which might alter the chemical structure and potency of the anti-infective agent.

Although there is no chemical bonding between the matrix polymer and the molecules of anti-infective agent using entrapping method, intermolecular interactions exist in non-reactive polymer coatings. Dipole-dipole interactions and van der Waals forces are the intermolecular interactions involved in the system. Dipole-dipole interactions are the attraction between polar molecules, and the forces between molecules of non-polar compounds are van der Waals forces. Hydrogen bonding (RH - · · · HR') is an especially strong kind of dipole-dipole interaction that may be important in interactions after the device is placed in the body. A stronger interaction to a particular agent and a weaker interaction to others may be seen with some polymers. The difference in strength of intermolecular forces could be reflected in the release profile of the system.

Silver sulfadiazine and chlorhexidine in a polyurethane matrix applied to central venous catheters have been commercially available in past. In vitro and in vivo studies show that the coated catheters reduce the quantitative level and frequency of bacterial colonization (Bach et al., 1993). The rate of clinical infections was significantly reduced (Maki et al., 1997). A meta-analysis of published clinical studies comparing the silver sulfadiazine- and chlorhexidine-coated versus non-coated central venous catheters indicated that the coated catheters were effective in reducing catheter-related bloodstream infection by 40% in patients (Veenstra et al., 1999).

The water solubility and diffusivity of anti-infective agents through polymer materials determine the
changing the ratio of the two types of polymers, not irreversibly sequestered on the device surface. By infective agent are entrapped in the matrices and are drophilic and hydrophobic. Molecules of the anti-
devolved intermix two types of polymer chains, hy-
a controllable hydrophilicity. These coating matrices have been developed with
manner, coating matrices have been developed with anti-infective agents. The inferior results obtained from
in an in vitro study on the release profile of silver oxide from the silver-oxide-silicone-coated catheters are consistent with those obtained from the clinical studies (Johnson et al., 1990).
When fairly water soluble and silicone material diffusible antibiotics are used, the hydrophobic silici-
cone matrix can sustainedly release the antibiotics in effective concentrations against bacterial coloniza-
tion on the surface (Bayston et al., 1997; Schierholz et al., 1994).
It has been found that the hydrophilicity of the poly-
mer matrices can be crucial to the release of anti-
infective agents. The inferior results obtained from the silver oxide-coated catheters mentioned above have come from the low solubility of silver oxide in water as well as the matrix in which the silver oxide was incorporated. The very hydrophobic silicone ma-
trix restricts aqueous diffusion into and out of the sil-
ver oxide coatings, lowering the water solubility of the material coating, therefore limiting the ionic silver concentration near the device surface. On the other hand, hydrophilic coatings allow water molecules to diffuse easily into the polymer matrix and to diffuse out with anti-infective agents that will kill bacteria in the surrounding area after the coated device is ex-
posed to body fluids. Molecules of the anti-infective agent at the outer coating surface are released fairly easily, providing a bolus concentration to kill organ-
isms that entered with the device before they have a chance to generate biofilms. With more hydrophilic surfaces, poorly water-soluble compounds, such as silver salts, could be released in efficient concentra-
tions to protect the surface.
To release anti-infective agents in a controlled manner, coating matrices have been developed with a controllable hydrophilicity. These coating matrices developed intermix two types of polymer chains, hydrophilic and hydrophobic. Molecules of the anti-
infective agent are entrapped in the matrices and are not irreversibly sequestered on the device surface. By changing the ratio of the two types of polymers, matrices with a wide range of hydrophilicity can be formulated. By using polymer matrices with different hydrophilicity, one can control the release rate of anti-infective agents that have different solubilities in wa-
ter.

2-4. Application of anti-infective coatings

2-4-1. Antibiotic-resistant bacteria

The appearance rate of antibiotic-resistant bacteria is accelerating and is currently a great concern to the medical community. It is unclear how the release of antibiotics from the surfaces of the medical devices. It may contribute to the resistance of bacteria to anti-
biotics because the technology is new and little data is available. However, it still is an issue of concern in regard to using an antibiotic as an anti-infective agent in preventing device-related infections. Its contribu-
tion to the development of antibiotic-resistant bacte-
ria may be too small to be noticed because usually only a small amount of antibiotics is loaded onto each device compared to the amount delivered by sys-
temic administration.
Using combinations of antibiotics and antimicro-
bials or antimicrobials alone in the coating might ad-
dress the increasing concern of antibiotic-resistant bacteria efficiently, as there are few, if any, bacteria that have developed strains resistant to antimicro-
bials. Nevertheless, further investigation on antibiotic resistance is necessary to examine the impact from antibiotic-impregnated devices.

2-4-2. Leaching of anti-infective agents from medical device

There are two alternative approaches concerning surface treatments for indwelling medical devices that protect patients from device-related infections. One approach focuses on the technologies that pro-
vide the devices with a surface from which antimicrobials and/or antibiotics leach out to inhibit bacterial growth on and near the device surface. The other approach focuses on non-leachable technolo-
gies, by which bacteria are killed when they come into contact with a surface containing the tightly bound anti-infective agents. So far, neither way can definitively prevent the incidence of device-related in-
fecions.
Schierholz et al (Schierholz et al., 1994) studied the bacterial adhesion to the antibiotic-loaded silica,
cone shunt and the kinetics involved in killing the bac-
teria. They concluded from the results that an antibiotic release exceeding the minimal bactericidal concentration in the environment of the implant over a long period is a prerequisite for effectively prevent-
ing bacterial colonization. Only devices with this
spectrum of anti-infective properties are able to kill metabolic non-active subpopulations of adherent microorganisms and can prevent the bacterial colonization on polymeric device surfaces. Some antimicrobial-treated indwelling medical devices that show evidence of reducing the clinical incidence of bacterium on device surfaces have leachable surfaces. The examples are central venous catheters with antimicrobials (silver sulfadiazine and chlorhexidine), central venous catheters with an antibiotics (rifampin and minocycline), and Swan pulmonary-artery catheters with antimicrobial (benzalkonium).

Anti-infective agents released from devices will kill bacteria that not only are in direct contact with, but also float nearby, the surface. Although there is a sufficient amount of anti-infective agent released, devices usually do not exhibit observable signs of toxicity in the biocompatibility tests because the system is usually sophisticatedly designed: the dosage of anti-infective agent on each device is small, and the release is sustained. Typical loading of anti-infective agents per device (i.e., catheters) is in the milligram range, which is far less than a typical, systematically administered dosage. In addition, the small dosage is released over a period of time: as the agent diffuses from the vicinity of the device, it mixes with body fluids, which markedly decreases its concentration. The circulating levels of the agents are usually negligible, and the toxic potential from the agents is diminished.

On the other hand, products obtained by a surface treatment involving far less leaching, such as Foley catheters coated with a silver-oxide-silicone coating, showed poorer performance. The explanation for such a poor performance may be the following: after the devices are indwelled, their surfaces will encounter all species, such as bacteria, proteins, and salts, existing in the tissues and body fluids in direct contact. Layers of physiological deposition, which could be nutrients to bacteria, can be formed on the device surface quickly after the indwelling (Winters et al., 1995). Even dead bacteria that are killed by contact with the fresh anti-infective device could remain on the surface and shield newly entering bacteria from coming into contact with and being killed by the anti-infective surface (Morris et al., 1997). After the formation of physiological layers of deposition, the anti-infective activity on the surface will be partially deactivated, and the device may no longer be anti-infective if the agents are over-tightly bound to the surface.

The application of a non-leachable anti-infective surface may be well suited to cases where there is no biological deposition forming on the surface, or where a device is constructed in such a way that a thin layer of deposition will not shield its anti-infective activity, such as by use of long enough spacers between the surface and the anti-infective sites.

**CONCLUSION**

Discovery of anti-infective agents and biomaterials with long-lasting, highly active anti-infective properties to be used as surface treatment materials or to construct medical devices will add significant advantages when designing and developing indwelling medical devices that prevent device-related infections. Manufacturing processes which assure the production of uniform surfaces with desired porosity need to be improved. Successful manufacturing of medical devices with anti-infective surfaces that provide sustained resistance to bacterial adherence, enhance healthy tissue integration, and improve compatibility with host defense mechanisms will result in the prevention of medical device-related infections, thereby improving health care.

Anti-infective agent-impregnated medical devices have recently shown promising results in reducing device-related infections. However, in some applications the anti-infective activity still diminishes or disappears more quickly than desired after the device surfaces come into contact with body fluids or tissues, and bacterial colonization is still found on those devices. This may be due to either incorporating an insufficient amount of the anti-infective agent or binding the anti-infective agent too tightly to the coating to be effectively released. Optimization of the dosage and release rate of an anti-infective agent in the polymer matrix is certainly an important task.

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