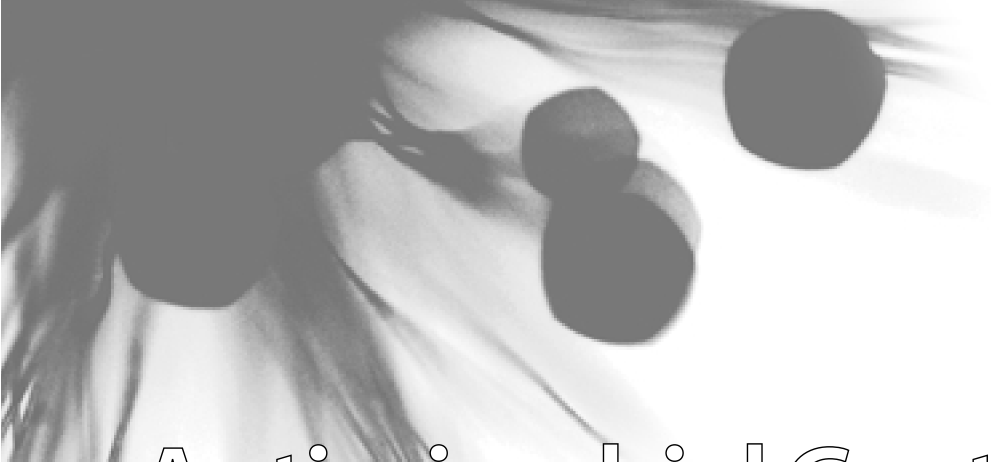


Antimicrobial Coatings: A Remedy for Medical Device-Related Infections

T.-L. Lin,* F.-M. Lu,* S. Conroy,* M.-S. Sheu,* S.-H. Su* and L. Tang**

* AST Products, Inc., Billerica, Massachusetts, USA ** The University of Texas at Arlington, Arlington, Texas, USA

This article discusses the mechanisms involved in the different approaches to antimicrobial coatings and reports on a new application that seems to offer an antimicrobial surface that is effective for long-term medical implants and suitable for a variety of drugs.

Lightening the costly burden

Although the tendency of foreign bodies to predispose patients to infection has been recognised since the fourteenth century, the mechanism(s) of device-related infection are still not completely understood. It is generally accepted that after a foreign body contacts blood or tissue fluid, a protein film adsorbs to its surface. Several adsorbed proteins, including fibronectin, vitronectin and fibrinogen (Fg),[1–3] have been shown to provide anchoring sites for bacteria. Bacterial adhesion, via the expressing of fibronectin-binding protein (FnBP), fibrinogen-binding protein (FBP) and other adhesion molecules,[4] occurs before, during or after implantation. After successive adhesion, bacterial proliferation gradually leads to the device-related infection.

Device-related infection is a heavy clinical and economic burden. For example, the management of catheter-related bacteraemia is likely to cost at least US$2836 per infection.[5] In an effort to prevent bacterial colonisation on implant surfaces, many industrial and academic institutions have explored surface modification technologies to mitigate these infections.

Both active and passive surface modifications can create a less infectious surface. The active approach targets the preadsorbed protein layer, in particular, adsorbed albumin, because surface albumin is documented to be a "comfort surface" for phagocytes that perform bactericidal functions. Thus, research efforts have been made to engineer surfaces with a high affinity to albumin. From a different angle, the passive approach directly targets bacteria. Specifically, surface coatings engineered to release antimicrobial and bactericidal agents in controlled fashion have prevented bacterial colonisation and infection.

Albumin-affinity surfaces

In-house experiments have recently identified that the spontaneously adsorbed Fg is responsible for the pathogenesis of device-related infection. In an in vivo system, different protein pre-coated polyethylene terepthalate (PET) discs were preseeded with bacteria and then implanted intraperitoneally for 16 h. The results showed that the percentage of residual bacteria on Fg-coated surfaces is almost 10-fold higher than that on albumin-coated surfaces.[6] These results indicate that albumin-rich surfaces provide an environment that allows peritoneal phagocytes to perform their bactericidal activity. In fact, these findings are supported by early observation that surfaces coated with crosslinked albumin have a much lower infection rate.[7]

Unfortunately, albumin pre-coated surfaces on medical devices are impractical from a manufacturing aspect because of packaging, sterilisation and storage requirements. An alternative technique based on high molecular weight Dextran:Cibacron blue, was developed to bind in a selective and reversible manner native albumin from blood and tissue fluid.[8] In addition to bulk incorporation of the blue dextran during device manufacture, surface modifica-

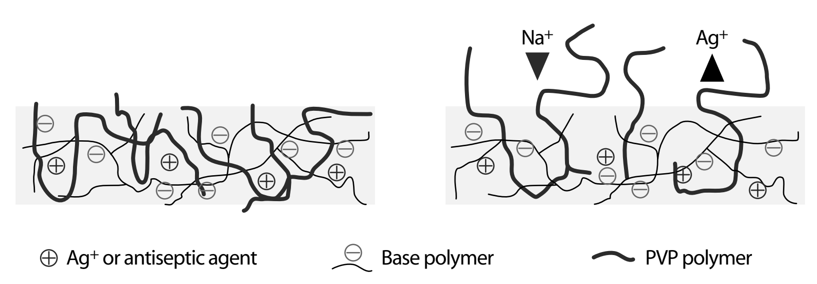


Figure 1: The mechanism of controlled, long-term release of silver ions from LubriLAST-K coating. LubriLAST-K coating is mainly composed of polyurethane with the addition of polyvinylpyrrolidone (PVP). PVP results in a swollen, gel-like watery layer. Silver ions or antiseptic agents first couple with negatively charged polyurethane matrix and later ion exchange between silver (Ag^+) and sodium (Na^+) ions occurs in the watery layer.

tion of the finished device with the dextran is also possible. Using a plasma polymerisation technique, amine groups are first generated on the biomaterial surface. The attachment of blue dextran is accomplished by incubating this amine-rich surface with oxidised blue dextran. After the attachment, reduction of oxidised blue dextran is required. Published data suggest that the blue dextran modified film has less adherent *Staphylococcus epidermidis*,[9] which may reduce the risk of infection.

The albumin affinity surfaces permit host defensive cells to function normally on medical device surfaces. This approach is advantageous in eliminating infections without releasing chemicals that are potentially toxic or incompatible to host tissues. However, for immunocompromised patients whose defensive cells show abnormal bactericidal activities, the efficacy of this albumin affinity surface remains to be proved.

Bacteria-inhibitory and bactericidal surfaces

To directly repel and eliminate adherent bacteria, significant research effort has been invested in the production of bacteria-inhibitory and bactericidal surfaces. These surfaces are relatively low cost, have long shelf-lives of more than two years, are easily sterilised and do not affect the overall mechanical properties of a device. Generally speaking, a bacteria-inhibitory surface discourages and/or prevents bacterial colonisation and proliferation and a bactericidal surface elutes bactericides. A notable bacteria-inhibitory surface, which is in clinical use, is a silver-deposited surface.[10] The possible working mechanism is that the silver surface precipitates membrane proteins of surface-associated bacteria to inhibit microorganism colonisation.

The bactericidal surfaces are in reality employing controlled release of antiseptics or disinfectants. A thin layer of polymer matrix that covers the biomaterial surfaces directs the controlled drug-release approach. This layer of polymers, either natural or synthetic, serves as a vehicle for loading and releasing drugs. The mechanisms of drug release include diffusion (molecular size), erosion of polymer matrix (polymer degradation) and dissociation of ionic coupling (bond dissociation). Every mechanism has advantages for various drug-release needs.

The diffusion mechanism is easy to practice in terms of ease of drug loading; however, the release time is relatively quick from a few hours to a few days. This makes it appropriate only for immediate and short term release profiles. The erosion mechanism takes advantage of polymer degradations and the drug-release rate is thus dependent on polymer-degradation rate. Adjustment of polymer molecular weight, manipulation of processing techniques and use of environment factors (including pH, hydophobicity and conductivity) can manipulate the drug-release rates. Thus, this mechanism can encompass a broad range of releasing times. However, for the use of implantable devices, the polymer debris resulting from the degradation process is a concern because the debris could potentially trigger inflammation.

The ionic coupling dissociation mechanism is relatively specific in target drugs. The anionic polymer matrix tends to trap cationic agents or vice versa. Because the release of drug depends on slow ion exchange at the surface (Figure 1), the efficacy of the drug is sustained for longer, from 4 to 8 weeks. The ionic coupling dissociating mechanism is thus preferred for long-term release profiles. One successful application of this mechanism is to create a bacteria-inhibitory surface by eluting silver ion from the polymer matrix.

As a test for this application, silver chloride of different concentrations (0.69, 1.38 and 2.1% by weight) was

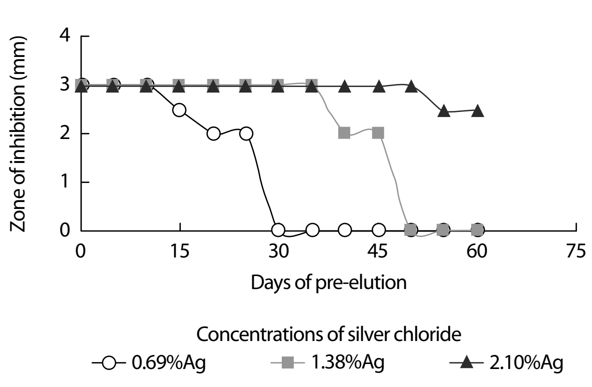
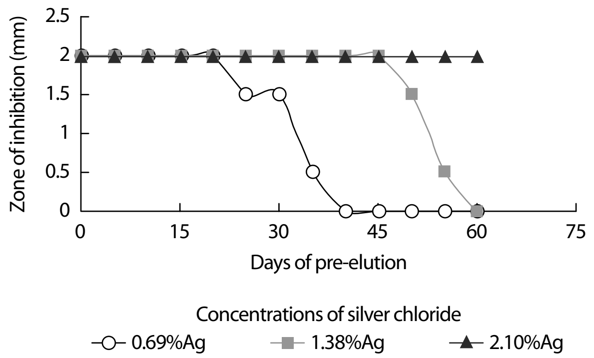


Figure 2: The relationship between the days of pre-elution and the zone of inhibition against *Staphylococcus epidermidis*. HDPE tubes (size 20 French) coated with LubriLAST-K containing different concentrations of silver chloride were incubated with phosphate buffer saline (50 mM, pH 7.4) for different periods of time. The antimicrobial properties of these tubings were then assayed via zone of inhibition tests.

premixed with an aqueous-based polymer coating matrix (mixture of polyurethane and polyvinylpyrrolidone).[11] The polymer mixture was then applied by dip coating onto high-density polyethylene (HDPE) tubing of size 20 French. Completely dried tubing specimens were first incubated in phosphate buffer for various times (up to 60 days). Then the antimicrobial properties of these tubings were assayed with the zone of inhibition tests.

Figures 2 and 3 illustrate the relationship between the days of pre-elution and the zone of pre-elution inhibition against *S. epidermidis* and *Escherichia coli*, respectively. A zone size greater than 1 mm was accepted as effective. With the lowest concentration of silver chloride (0.69%) after 3 weeks, the antimicrobial surfaces inhibited both strains of bacteria. Up to, but not limited to, 60 days of pre-elution, surfaces loaded with the highest initial concentration (2.1%) of silver chloride were also effective against both strains. These results demonstrate that the ionic antimicrobial surface coatings were effective for between 21 to 60 days, depending on the original silver-ion concentration. For the purpose of preventing device-related infections for chronic care, this long-lasting antimicrobial characteristic is an advantage.

Figure 3: The relationship between the days of pre-elution and the zone of inhibition against *Escherichia coli*. HDPE tubing (size 20 French) coated with LubriLAST-K containing different concentrations of silver chloride were incubated with phosphate buffer saline (50 mM, pH 7.4) for different periods of time. The antimicrobial properties of these tubings were then assayed via zone of inhibition tests.



Localised antibiotic release

For those patients with infected devices, replacement of the device and administration of antibiotics are frequently required to relieve the infections. It is generally believed that localised release of antibiotics from the device surface is more beneficial to patients, particularly to those who have low tolerance for the adverse effects resulting from the oral administration of antibiotics. The feasibility of localised release of antibiotics from the polymer matrix has also been demonstrated. Four types of antibiotics gentamicin, minocycline, vancomycin and doxycycline (0.3 g), were loaded into the surface coatings of 20-French HDPE tubes and were pre-eluted in phosphate buffer for predetermined times. Then zone of inhibition tests were carried out against *S. epidermidis*, *S. aureus*, *E. coli* and *Pseudomonas aeruginosa*. The results shown in Table I demonstrate that the surface coatings containing different types of antibiotics

Table I: Zone of inhibition against *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. HDPE tubings (size 20 French) coated with LubriLAST-K containing various antibiotics (initial weight of 0.3 g). Tubing was incubated with phosphate buffer for predetermined periods of time. The antimicrobial properties of these tubings were then assayed with the zone of inhibition tests.

		Zone of inhibition (mm)				
Bacteria strain	**Days of pre-elution**	**Gentamicin**	**Minocycline**	**Vancomycin**	**Doxycycline**	**Control**
Staphylococcus epidermidis	0	7	8.5	3.5	8	0
	2	3	7	1.2	6.5	0
	4	1.5	6.5	1	6	0
	7	1.5	6	1	5.5	0
Staphylococcus aureus	0	6.5	10	3.5	9	0
	2	3	8.5	1.5	7	0
	4	2	8	1.5	6.5	0
	7	1	7	1	6.5	0
Escherichia coli	0	5	7	0	5.5	0
	2	3.5	5	0	4.5	0
	4	2.5	4.5	0	4	0
	7	2.5	4.5	0	4	0
Pseudomonas aeruginosa	0	4	2	0	1.5	0
	2	2	0	0	0	0
	4	1.5	0	0	0	0
	7	1.5	0	0	0	0

(minocycline versus doxycycline) are equally effective in inhibiting the same strain of bacteria (*S. epidermidis*). It is thus concluded that the layer of polymer coating can be a universal vehicle for various drugs. It should be noted that this unique characteristic allows manufacturers to load different types of antibiotics (in order to deal with antibiotic-resistant strains) into the surface of devices and to treat the infected tissues surrounding devices.

Improving on nature

The clean up of microorganism on an albumin-affinity surface relies on the power of Mother Nature. This approach does not disturb the host's physiological conditions; however, it is theoretically less effective when used with immuno-compromised patients. In contrast, bacteria-inhibitory and bactericidal surfaces can be used with a broader range of patient population. The cytotoxicity of silver compounds[12] needs to be taken into consideration when preparing the surface coatings.

Antimicrobial surface modifications fulfil at least part of the need for anti-microbial devices. Their long-lasting effectiveness against a broad spectrum of microbes without compromising the efficacy of the device benefits patient care significantly. Equally important, the low cost, long shelf-life and easy sterilisation definitely soothe the economic burden of the medical care industry.

References

1. M. Paulsson et al., "Adhesion of Staphylococci to Chemically Modified and Native Polymers, and the Influence of Preadsorbed Fibronectin, Vitronectin and Fibrinogen," *Biomaterials,* **14,** 11, 845–53 (1993).
2. P. Francois et al., "Identification of Plasma Proteins Adsorbed on Haemodialysis Tubing that Promote Staphylococcus Aureus Adhesion," *J. Lab. Clin. Med.,* **135,** 1, 32–42 (2000).
3. P.E. Vaudaux et al., "Use of Adhesion-Defective Mutants of Staphylococcus Aureus to Define the Role of Specific Plasma Proteins in Promoting Bacterial Adhesion to Canine Arteriovenous Shunts," *Infect. Immun.,* **63,** 2, 585–90 (1995). Erratum appears in *Infect. Immun.,* **63,** 8, 3239 (1995).
4. T. Wadstrom, "Molecular Aspects of Bacterial Adhesion, Colonisation, and Development of Infections Associated with Biomaterials," *J. Invest. Surg.,* **2,** 4, 353–60 (1989).
5. S. Saint, "Clinical and Economic Consequences of Nosocomial Catheter-Related Bacteriuria," *Am. J. Infect. Control,* **28,** 1, 68–75 (2000).
6. L. Tang and Y. Sheng, "The Mechanism of Device-Centered Infection," *Trans. Soc. Biomater.,* **24,** 17 (1998).
7. Y.H. Bradley et al., "The Prevention of Prosthetic Infection Using a Cross-Linked Albumin Coating in a Rabbit Model," *J. Bone Joint Surg., Br.,* **79,** 5, 816–9 (1997).
8. J.R Keogh et al., "Albumin-Binding Surfaces for Implantable Devices," *J. Biomed. Mater. Res.,* **26,** 4, 441–56 (1992).
9. J.R Keogh and J.W. Eaton, "Albumin Binding Surfaces for Biomaterials," *J. Lab. Clin. Med.,* **124,** 4, 537–45 (1994).
10. T. Carrel et al., "Definitive Cure of Recurrent Prosthetic Endocarditis Using Silver-Coated St Jude Medical Heart Valves: A Preliminary Case Report," *J. Heart Valve Dis.,* **7,** 5, 531–3 (1998).
11. T.L. Lin and M.S. Sheu, Ionic Antimicrobial Coating, Lubrilast-K, AST Products, Inc. Patent pending.
12. E. Hidalgo and C. Dominguez, "Study of Cytotoxicity Mechanisms of Silver Nitrate in Human Dermal Fibroblasts," *Toxicol. Lett.,* **98,** 3, 169–79 (1998). mdt

Article Reprinted from the October 2001 issue of:

medical device technology

Tung-Liang Lin is Senior Scientist, **Fong-Ming Lu** is Research Scientist, **Suzanne Conroy** is Coating Manager, **Min-Shyan Sheu** is Director of R&D, and **Shih-Horng Su*** is Senior Scientist at AST Products, Inc., 9 Linnell Circle, Billerica, Massachusetts 01843-3902, USA, tel. +1 978 667 4500, fax +1 978 663 7746, e-mail: ssu@astp.com

Liping Tang is Associate Professor at the University of Texas at Arlington, Arlington, Texas, USA.