PROTECTION THAT LIVES ON
MICROBAN®

The Use of Incorporated Silver-Based Antimicrobials in Silicone Medical Devices

Gina Sloan, Ph.D., Burke Nelson, Ph.D., Ivan Ong, Ph.D.

Biographical Note

Ivan is the V.P. of R&D at Microban International, Ltd., a global leader in providing customized antimicrobial solutions for consumer and commercial products. For the past sixteen years, he has participated in active research in profiling numerous antimicrobial systems for microbiological activity and suitability for application in polymers, textiles and ceramics to satisfy specific performance and durability needs. In the last three years, his research teams have taken their investigation into the area of medical devices where robust levels of antimicrobial efficacy are expected. Ivan obtained his B.S.E. at Duke University in Mechanical Engineering in Durham, North Carolina, and a M.S. and Ph.D. at the Johns Hopkins University in Materials Science and Engineering in Baltimore, Maryland. He currently resides in Charlotte, North Carolina.

Abstract

The traditional approach to introducing antimicrobial attributes to silicone-based medical devices such as catheter tubing involves coating the surfaces with silver-releasing compounds. Manufacture involving a coating process is time consuming, with difficult quality control and may not serve to control the release of silver well over the duration of device usage in patients.

Our research shows that by incorporating appropriate silver antimicrobials directly into the silicone matrix during processing, it is possible to offer as good as or better antimicrobial efficacy compared to silver-based coatings. Direct incorporation of Microban's silver-based additives into the silicone matrix during extrusion allows a high degree of consistency as it is a controllable and highly reproducible process. The antimicrobial attributes of incorporated silver technologies in silicone have been shown to be impressive with significant reductions in planktonic bacteria and biofilm.

Medical Devices and the Need for Antimicrobial Protection

The incidence of hospital acquired infections (HAIs) is increasing around the world, driving the need for better preventative techniques and technologies to reduce infection rates. Developing effective solutions will involve efforts by both healthcare providers and medical device manufacturers. In the United States, due to changing health insurance policies, hospitals are increasingly made to bear the cost of treating HAIs. Many healthcare institutions are therefore attempting to reduce infection rates by modifying their infection control protocols to improve aseptic techniques and compliance. In addition, manufacturers of medical devices are an important part of the solution as they seek out new and better technologies to help reduce the growth of microorganisms on their devices.

There is a particularly high prevalence of HAIs in temporary in-dwelling medical devices such as urinary Foley catheters. In fact, urinary tract infections are the highest category of HAIs and the majority of cases are traceable back to in-dwelling devices (1, 2). Once acquired, HAIs are extremely difficult to treat, especially for weaker, immune-compromised patients, and can extend post-surgery recovery period or result in costly re-admissions.

Current urinary Foley catheters in the market include silicone offerings with a silver-containing coating as a means of inhibiting the growth of bacteria growth. For this reason, silicone Foley catheters have been chosen for study. The following sections outline the organisms of interest, the test protocols used to study antimicrobial performance and the results generated in the two major types of medical-grade silicone used for catheters.

Silver-Based Antimicrobials

Silver-based antimicrobials have long being employed for creating antimicrobial attributes in medical devices. Silver is able to express wide-spectrum antimicrobial efficacy against both Gram-positive and negative bacteria, and in some cases, yeast organisms such as Candida albicans. In addition, silver is noted for having negligible toxicity effects when interacted with human tissue and fluids.

Typical silver antimicrobial technologies available include:

Pure silver: These include silver sols impregnated into bandages and dressings and silver fibers that are woven into a fabric.
Elementary silver compounds: The use of silver chloride is especially prevalent in textiles for odor and antibacterial

control.
Silver cation ion exchange systems. These systems consist of a host structure capable of “housing” silver cations. Silver cations are released through interaction with moisture and counter ions. These include:

Silver-zirconium hydrogen phosphate
Silver-zeolites
Silver-glass

The key to antimicrobial action in silver-based systems is dependent on its ability to generate silver cations. As such, a number of silver based systems are available, and all derive their activity on the ability to supply, under the right circumstances, a critical concentration of silver cations necessary for antimicrobial effect. Microban silver-glass technology has very efficient silver cation release mechanisms, good control over release rates and can be incorporated into silicone without affecting the mechanical properties of the base material for greatly simplified manufacture.

Microbial Growth

Microorganisms are able capable of altering growth patterns in response to environmental signals. These signals can include but are not limited to; nutrient concentrations, surface availability and the number of microorganisms present. Without environmental signals microbes exist as single-celled organisms not associated or interacting with other microorganisms and are termed planktonic cells. Planktonic cells have been studied since the discovery of microorganisms by Leeuwenhook and the founding of the “germ theory of disease” by Koch (3).

Recently it has been determined that planktonic cells are not the most common growth state for microbes. Instead microorganisms exist in multicellular and sometimes multi-species communities called biofilms. These communities are typically surface associated, encased in a biologically derived polymeric matrix, and inherently resistant to antibiotic treatment regimens (4). Biofilms can be found throughout nature, industry and hospital settings. Within the hospital setting biofilms are highly recalcitrant to antibiotic treatment, demonstrating up to 1000 fold increase in antibiotic resistance over planktonic cells (5). In order to provide an efficient and effective antimicrobial device, the ability of the antimicrobial device to control biofilm formation must be assessed alongside the ability to control planktonic cells. Biofilm buildup leads to encrustation and early removal of devices for patient safety reasons(6); any device that reduces or retards such build-up increases patient quality of life and extends the lifespan of the protected product.

Materials and Methods

Initial studies using Microban silver technology in silicone were conducted in vitro to mimic a urinary tract infection that would occur on the seventh day of catheterization. To determine durability out to the seventh day of catheterization, antimicrobial testing incorporated a seven day soak in artificial urine. In addition, since antimicrobials are inherently susceptible to inactivation by biological compounds samples were exposed to heat inactivated serum.

Strains and Growth Media

Three different gram negative organisms were evaluated, Escherichia coli (ATCC 8739), Proteus mirabilis (ATCC 7002), and Pseudomonas aeruginosa(ATCC 13388). All gram negative organisms were grown in the presence of a 1:500 dilution of Brain Heart Infusion Broth (3M) during testing conditions. Two gram positive organisms were utilized through testing,

Staphylococcus aureus (ATCC 6538), and Enterococcus faecalis (ATCC 29212). For these organisms an increased nutrient concentration of 1:100 BHIB was utilized to allow for optimal biofilm formation on control surfaces. Candida albicans (ATCC 18806), a yeast species, was also included for testing purposes and was tested using a 1:50 dilution of Sabouraud Dextrose Broth (BD). All media for antimicrobial testing were made in artificial urine (7, 8) and optimized for biofilm formation on control polymer plaques.

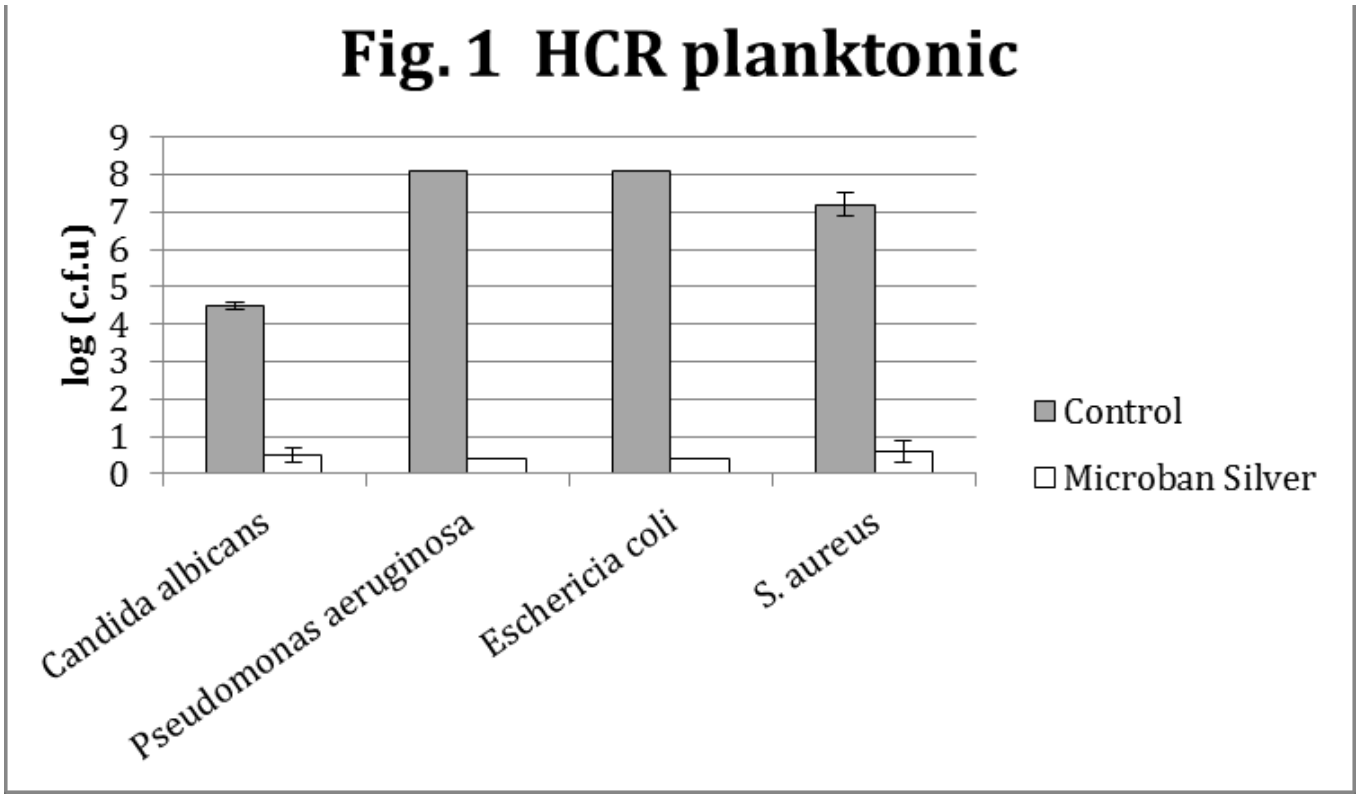
Determining the Effectiveness of Treated Silicones Against Planktonic and Biofilm Microorganisms

The microtiter biofilm minimum inhibitory concentration determination assay, as described by Harrison et.al., was modified to allow for the detection of efficacy of a treated silicone product (9). Testing was conducted to mimic a urinary tract infection occurring on the 7th day of catheterization. Briefly, sterile 2.25 in2 samples are placed into individual wells of a 24 well dish. Samples were covered with 2.5 ml of heat inactivated human sera and incubated at ambient temperature for 30 minutes. After incubation, the serum was removed and the samples were washed 3 times with 3ml of sterile diH2O. Samples were placed into 2.5ml of artificial urine and incubated at 37°C for 7 days to simulate use for that time period. Following the soak in artificial urine, the liquid was removed from the wells, and replaced with artificial urine supplemented with growth media containing 104 cfu/ml of the appropriate organism. For slow growing organisms, samples were incubated at 37°C for 48 hours to allow for optimal biofilm formation (S. aureus, C. albicans, and E. faecalis). For all other organisms, samples were incubated at 37°C for 24 hours and then enumerated. Log reductions were calculated by:

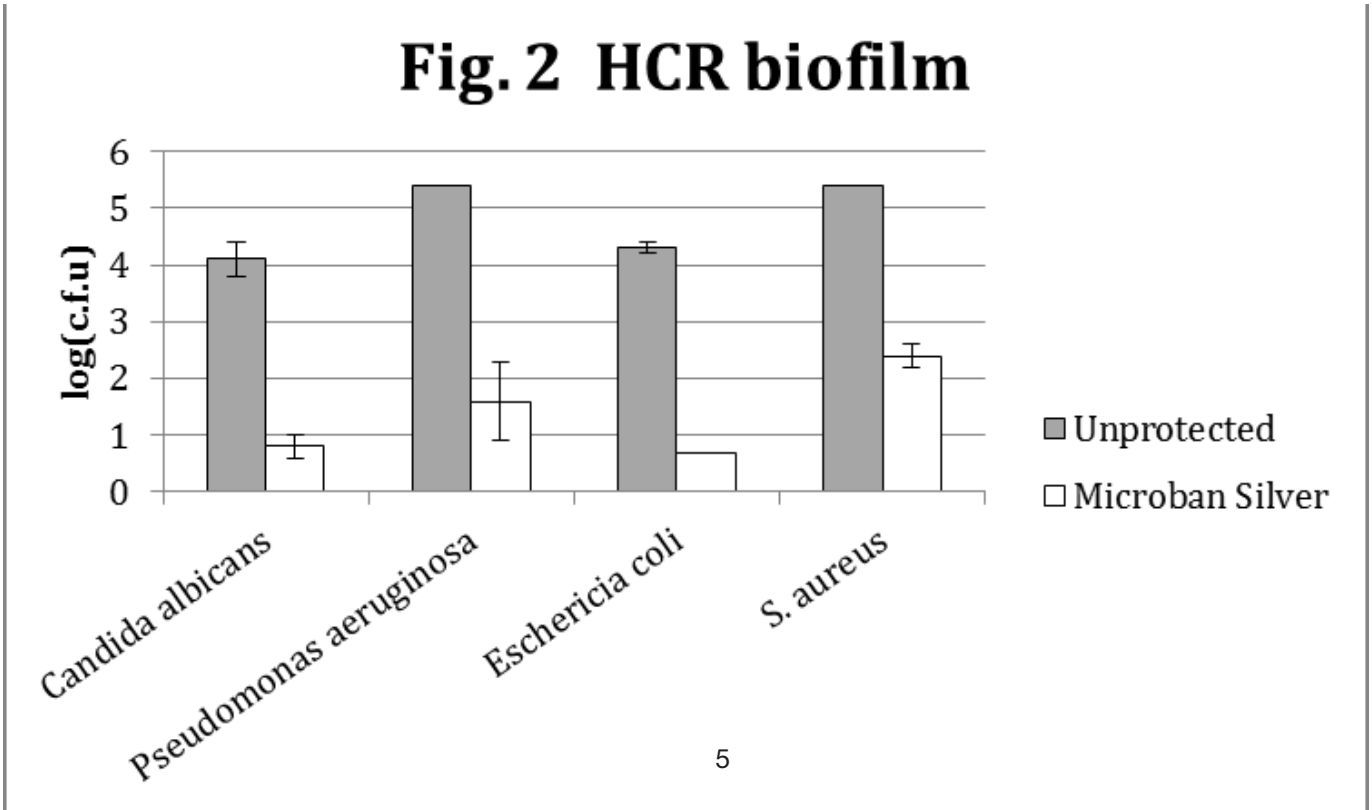
Log Reduction= Log (average c.f.u. recovered from controls) - Log (recovered c.f.u. from a treated sample). Controls and samples were repeated in triplicate.

Results
Evaluation of HCR silicone.

Microban antimicrobial silver technology was incorporated into a two-part HCR (High Consistency Rubber) silicone material at a 5% level and tested against multiple organisms selected based on clinical relevance (10) . Antimicrobial efficacy of silicone with Microban technology was then assessed against planktonic and biofilm borne bacteria. Current FDA antimicrobial guidance indicates that a 4 log planktonic reduction is required to make antimicrobial claims on products (11). Microban antimicrobial silver technologies surpassed FDA required log reductions delivering greater than a 7-log reduction for bacteria and a 4-log reduction on the yeast species, C. albicans (Figure 1).



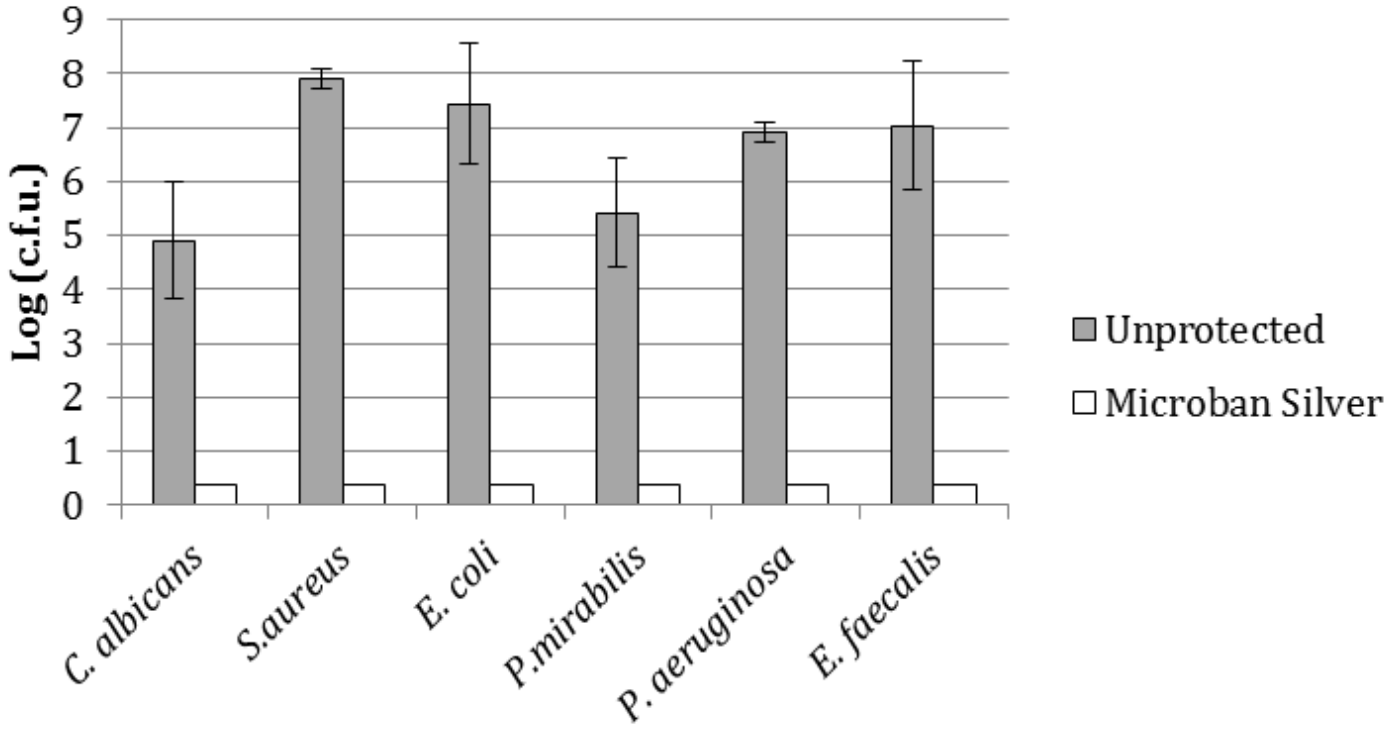
The Microban silver incorporated HCR was subjected to testing that allowed for biofilm formation on control test specimens. As shown in Figure 2, significant biofilm reductions were obtained for every organism tested. In addition, for all species tested, the Microban silver-treated HCR suppressed bacterial colonization to less than 500 c.f.u over the entirety of the sample surface. While additional experiments are needed to determine the bacterial state of growth, this indicates that Microban silver technology has the capacity to prevent the early stages of biofilm development on the surface of the polymer.



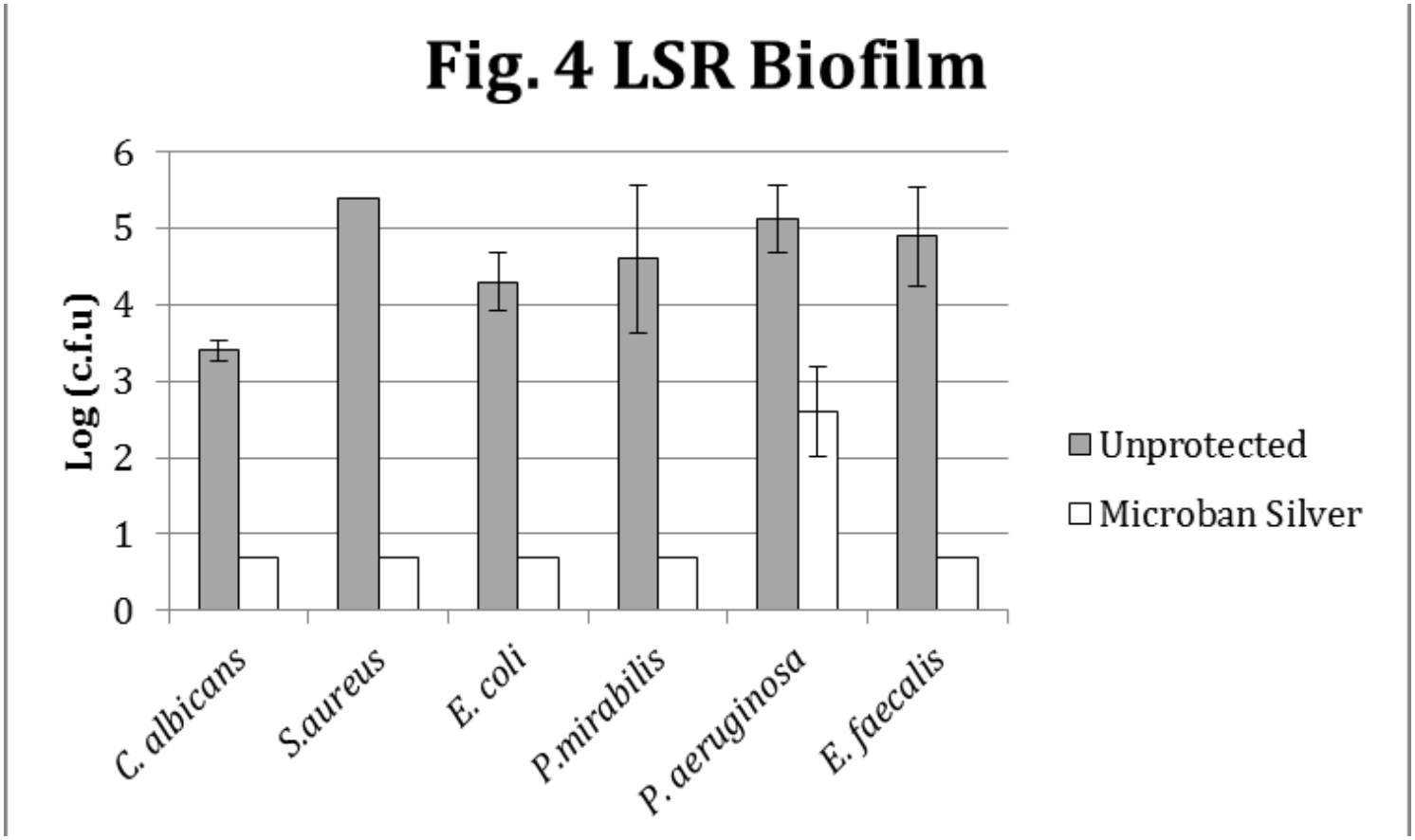
Evaluation of silver treated LSR

Unlike HCR silicones, LSR (Liquid Silicone Rubber) silicones represent a more challenging incorporation for silver antimicrobial treatment. This is due to differences in silicone grade and catalysts used. Improper pairings and conflicts can lead to strong substrate discoloration and quenched antimicrobial effect. Microban's silver technology was incorporated in a LSR system at a 10% addition rate. The subsequent treated LSR was evaluated using the same procedure utilized for HCR. Due to the prevalence of LSR in the medical setting, a wider array of organisms was evaluated. For all species tested the treated LSR was able to reduce the planktonic population by a minimum of 5-logs compared to the control untreated sample (Figure 3). Once again, this meets and exceeds the current FDA guidance for antimicrobial-treated medical devices.

Fig. 3 LSR Planktonic



Similar to treated HCR, the Microban silver-treated LSR was capable of reducing surface-associated, biofilm microorganisms to below the lower limit of detection, with the exception of P. aeruginosa (Figure 4). Growth of P. aeruginosa was suppressed in comparison to the control, untreated LSR but there was not a complete reduction of adhered bacterial cells. The observed variance in log reductions between organisms is strictly due to the proclivity of the microorganism to form biofilms. As such, organisms that preferentially exist as biofilms, such as P. aeruginosa, exhibited higher log reductions than organisms with increased motility such as P. vulgaris.



Conclusions

Approximately two-thirds of preventable HAIs are device associated and can be classified into three main groups; central line-associated bloodstream infections, catheter-associated urinary tract infections, and ventilator-associated pneumonia. The work presented herein focused on testing that would mimic a urinary tract infection. While testing was designed to mimic a UTI, the organisms selected to test against are the organisms most commonly associated with device-related HAI. As HCR and LSR are common silicones throughout the medical field, these results are broadly applicable to multiple end-use scenarios. With the increased scrutiny being given to HAIs, the utilization of antimicrobial treated products has the propensity to reduce HAI infections. The ability of incorporated Microban's antimicrobials to deliver strong antimicrobial attributes at the surface of HCR and LSR silicone is demonstrated by the above examples. This is evidenced by multi-log reductions in various microbes between silver-treated and untreated materials in planktonic bacterial and biofilm evaluation tests.

References

1. Weinstein JWMD, Dorothy Mazon RN, Pantelick ERN, Reagan‐Cirincione PP, Dembry LMMD, Hierholzer WJJMD. A Decade of Prevalence Surveys in a Tertiary‐Care Center: Trends in Nosocomial Infection Rates, Device Utilization, and Patient Acuity • Infection Control and Hospital Epidemiology. 1999;20(8):543-8. doi: 10.1086/501675.
2. Richards MJMF, Edwards JRMS, Culver DHP, Robert P. Gaynes MD, the, System NNIS. Nosocomial Infections in Combined Medical‐Surgical Intensive Care Units in the United States • Infection Control and Hospital Epidemiology. 2000;21(8):510-5. doi: 10.1086/501795.

4. Parsek MR. Microbiology: Bilingual bacteria. Nature. 2007;450(7171):805-7.
5. Mishra M, Parise G, Jackson KD, Wozniak DJ, Deora R. The BvgAS Signal Transduction System Regulates Biofilm Development in Bordetella. Journal of Bacteriology. 2005;187(4):1474-84. doi: 10.1128/jb.187.4.1474-1484.2005.
6. SM J, DJ S, HLT M, ME S. Complicated Catheter-Associated urinary Tract Infections Due to Escherichia coli and Proteus mirabilis. Clinical Microbiology Reviews. 2008;21(1):34.
7. Putnam D. Composition and concentrative properties of human urine. National Aeronautics and Space Administration. 1971:1-112.
8. Yang B. Urea and urine concentrating ability: new insights from studies in mice2005;288(5):F881-F96. doi: 10.1152/ajprenal.00367.2004.
9. Harrison JJ, Stremick CA, Turner RJ, Allan ND, Olson ME, Ceri H. Microtiter susceptibility testing of microbes growing on peg lids: a miniaturized biofilm model for high-throughput screening. Nat Protocols. 2010;5(7):1236-54. doi: http://www.nature.com/nprot/jo...
10. Alicia I. Hidron MD, Jonathan R. Edwards MS, Jean Patel P, Teresa C. Horan MPH, Dawn M. Sievert P, Daniel A. Pollock MD, et al. NHSN Annual Update: Antimicrobial‐Resistant Pathogens Associated With Healthcare‐Associated Infections: Annual Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007 • Infection Control and Hospital Epidemiology. 2008;29(11):996-1011. doi: 10.1086/591861.
11. Health CfDaR. Draft Guidance for Industry and FDA Staff: Premarket Notification[510(k)] Submissions for Medical Devices that include Antimicrobial Agents2007.