Catheter associated urinary tract infection (CAUTI) is the most common nosocomial infection, accounting for more than 1 million patients annually in United States acute-care hospitals and extended-care facilities. Infected urinary catheters are covered by a thick biofilm that contain the infecting organisms. These organisms are embedded in a matrix of host proteins and microbial slime. This biofilm provides a “home” for the organisms and promotes increased drug resistance. These biofilm bacteria are notably resistant to antibiotics, and CAUTI infections cannot normally be cleared without the removal of this most common of medical devices. Novel anti-infective impregnated urinary catheters with anti-infective surfaces have been clinically proven to significantly reduce short term CAUTI (less than 2 weeks).

Traditional microbiological methods used to evaluate anti-infective medical devices are not necessarily indicative of their performance in-vivo.

Using confocal scanning laser microscopy (CSLM), we have devised a dynamic in-vitro model utilizing CSLM and a flow cell bioreactor to examine biofilm development and assess the efficacy of anti-infective coatings on indwelling medical devices. This study explored the application of this technology on three different Foley catheters.

In an in-vitro biofilm assay comparison study of a new, novel silver-based hydrogel coated all-silicone Foley catheter against a silver-based hydrogel coated latex Foley catheter and an uncoated all-silicone control Foley catheter. The in-vitro biofilm assay detected significant differences among anti-infective properties for each catheter tested.
Introduction and Pathogenesis

Indwelling urology catheters are implicated in ~90% of the 1 million episodes of nosocomial infection that occur each year in U.S. hospitals (1-4). A prospective study showed that even 3-4 colony-forming units (CFU/ml) cultured from an intraluminal specimen is highly predictive of CAUTI (5). Despite increased awareness about device-associated infection, nosocomial infections are increasing (6).

Anti-infective coated or impregnated catheters, which reduce adherence of microorganisms on the catheter surface and provide inhibitory elution profiles, may confer the greatest benefit for preventing CAUTI’s. The pathogenesis of intraluminal and extraluminal CAUTI is hypothesized to be an initial conditioning film of urinary proteins that allow for subsequent bacterial attachment and biofilm formation. Colonizing bacteria are then presumed to ascend the catheter surface and infect the bladder, resulting in urosepsis and potential subsequent bloodstream infection.

Microorganisms are presumed to gain initial access to the catheters by the patient’s own colonic and perineal microbiota or from the hands of health care workers upon insertion (7).

We have devised a novel in-vitro model to study bacterial attachment, growth, and colonization in a dynamic or biofilm model. All aspects of the biofilm model have been optimized to be clinically relevant and account for the assumed pathogenesis of CAUTI’s.

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Methods and Procedures

Six clinical isolates of relevant urinary tract infection (UTI) pathogens were maintained in a static environment throughout the trial period to insure a consistent challenge.

We tested a Dover* Silver, a silver-based hydrogel coated all-silicone Foley catheter, (The Kendall Company, a division of Tyco Healthcare Group LP, Mansfield, MA) and the Bardex I.C. silver-based hydrogel coated latex Foley catheter (Bard Medical, Covington, GA). We used the Kendall Dover all-silicone Foley catheter as the reference catheter.

In order to understand bacterial suppression, catheter samples conditioned in human urine, were continually exposed to microorganisms and evaluated every 24 hours over a 7-day period. Six clinically relevant UTI pathogens were utilized with a constant daily challenge of ~10³ CFU/ml to simulate bacteriuria (7) (see graphs). The biofilm was developed in a one-pass flow cell bioreactor under standardized, laminar flow conditions. In addition to traditional scraping and plating techniques, samples were observed in-situ for bacterial adherence and viability utilizing Molecular Probes BacLight™ Live/Dead stain. Measurement parameters were evaluated for percent area of biofilm coverage and percent of live cells vs. dead cells within the biofilm. In accordance with standards traceable to NIST standards, 20 random fields were examined.
The results of the experiments show daily viability and adherence rates for the following clinically important UTI pathogens; *C. albicans, Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae,* and *Proteus mirabilis.*

**Discussion and Comments**

**Escherichia coli** (gram negative organism) After 7 days (168 hrs), the Kendall Dover Silver all-silicone catheter exhibited over 2 logs less colony forming units (CFUs) ($2.99 \times 10^2$) than the Bardex I.C. latex catheter with anti-infective coating($2.30 \times 10^5$). Using the confocal scanning laser microscope (CSLM), the Kendall Dover Silver all-silicone catheter sample had 25% bacterial attachment of which 10% were shown to be viable. The Bardex I.C. latex catheter was found to have 90% bacterial attachment of which 90% were shown to be viable. (reference graphs)

**Klebsiella pneumoniae** (gram negative organism) After 7 days (168 hrs), the Kendall Dover Silver all-silicone catheter exhibited over 2 logs less CFUs ($7.60 \times 10^2$) than the Bardex I.C. latex catheter with anti-infective coating($1.26 \times 10^5$). Using CSLM, the Kendall Dover Silver all-silicone catheter sample had 35% bacterial attachment of which 10% were shown to be viable. The Bardex I.C. latex catheter was found to have 90% bacterial attachment of which 90% were shown to be viable. (reference graphs)

**Pseudomonas aeruginosa** (gram negative organism) After 5 days (120 hrs), the Kendall Dover Silver all-silicone catheter exhibited over 2 logs less CFUs ($5.90 \times 10^3$) than the Bardex I.C latex catheter with anti-infective coating($2.00 \times 10^5$). Using CSLM, the Kendall Dover Silver all-silicone catheter sample had 35% bacterial attachment of which 50% were shown to be viable. The Bardex I.C. latex catheter was found to have 90% bacterial attachment of which 90% were shown to be viable. (reference graphs)
Enterococcus faecalis (gram positive organism) After 7 days (168 hrs), all three catheters tested demonstrated resistance at or below the daily challenge with this organism. (reference graphs)

Candida albicans (fungi classified as a yeast) After 7 days (168 hrs), all three catheters tested demonstrated resistance at or below the daily challenge with this organism. (reference graphs)

Proteus mirabilis (gram negative organism) After 3 days (72 hrs), the Kendall Dover Silver all-silicone catheter exhibited over 2 logs less CFUs (4.50E+03) than the Bardex I.C. latex catheter with anti-infective coating (5.80E+05). Using CSLM, the Kendall Dover Silver all-silicone catheter sample had 40% bacterial attachment of which 65% were shown to be viable. The Bardex I.C. latex catheter was found to have 50% bacterial attachment of which 80% were shown to be viable. (reference graphs)

Conclusions:

CSLM offers a reliable alternative to traditional microbiological techniques. The in-vitro biofilm assay detected significant differences among anti-infective properties for each catheter tested. Clinical trials are encouraged to confirm the results of this in-vitro assay.

Under the conditions of this study, the three catheters outlined were challenged by six clinical isolates for a seven-day period in triplicate. This resulted in 378 catheter samples being evaluated at 42 time points. A bacterial suppression summary graph has been provided below which compares the results of the three catheters tested in this in-vitro assay. A catheter sample will have suppressed bacterial growth if the plate counts were at or below the daily inoculum challenge levels at these time points.
The daily challenge population verifications confirmed all test articles and controls were continuously challenged with $10^{1-4}$ CFU’s/ml over a 7 day time period.


*Dover Silver is a trademark of Sherwood Services AG.*