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Profiles of the Bacterial Community in Short-Term Indwelling Urinary Catheters by Duration of Catheterization and subsequent Urinary Tract Infection

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Abstract

Objective: Urinary catheterization, even of short duration, increases risk of subsequent urinary tract infection (UTI). Whether the bacteria found on the surface of catheters placed for <3 days are associated with UTI risk is unknown.

Methods: We screened the biofilms found on the extraluminal surface of 127 catheters placed for <3 days from women undergoing elective gynecologic surgery, using targeted qPCR and an untargeted 16SrRNA taxonomic screen.

Results: Using qPCR, *Enterococcus spp.* were found on virtually all catheters and lactic acid bacteria in most catheters regardless of duration, but neither genus was associated with UTI development during follow-up. *Enterococcus*, *Streptococcus* and *Staphylococcus* were the most commonly identified genera in the taxonomic screen but were not associated with subsequent UTI. Although the most common cause of UTI following catheter removal was *E. coli*, detectable *E. coli* on the catheter surface was not associated with subsequent UTI.

Conclusions: Our analysis does not suggest that the composition of the bacteria growing on the catheter surface of catheters placed for <3 days are the reservoir for subsequent UTI. Other aspects of catheter care are likely more important than preventing bacterial colonization of the catheter surface for preventing UTI following short term catheter placement.

Introduction

Urinary catheterization is an essential component of many surgical procedures but increases risk of urinary tract infection (UTI). In the United States, as many as 79% of patients in adult critical care units have indwelling catheters(1); overall 23.6% of hospital patients are catheterized(2). Decreasing catheter duration significantly lowers UTI risk(3), but the risk is

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still substantial: as much as 38% in the 6 weeks following catheter removal among women undergoing short-term catheterization for elective gynecological surgery(4). Bacterial pathogens causing UTI during and following hospitalization are increasingly resistant to antibiotics, complicating treatment and increasing costs(5).

Presence of a urinary catheter enables movement of bacteria from the urethra into the bladder and the presence of a foreign body stimulates host immune response(6). Further, catheter insertion, removal or movement when in place can cause tissue trauma increasing risk of pathogen invasion(7). Using closed catheter systems, reducing catheter duration and minimizing catheter use decreases risk of UTI – both during catheterization and following removal(8). Improving catheter care and maintenance, antimicrobial stewardship and promoting team building and leadership engagement can further decrease catheter associated UTI (CAUTI)(9).

As catheter use cannot always be avoided, many investigators have focused on limiting biofilm growth on catheter surfaces, under the assumption that catheters are a reservoir for infection (10). Biofilm formation protects bacteria from flowing urine, host defenses, and antibiotics (11). A major gap in our current understanding is characterization of the biofilm found on the catheter surface, particularly those placed short-term. Bacterial culture of the material found on short-term catheters detects multiple bacterial species in significant numbers(12–14). However, whether these bacteria are associated with subsequent UTI is uncertain. Further, only three studies of urinary catheters to date have used untargeted non-culture techniques (15–17) but these focused on longer term catheterization.

Our study addresses these gaps by conducting an untargeted taxonomic screen (16SrRNA) and targeted qPCR for known catheter colonizers of 127 catheters placed for <3 days from women undergoing elective gynecologic surgery.

Methods

We screened the extraluminal surface of urinary catheters collected post-operatively from participants in a randomized, double-blinded, placebo-controlled trial of the therapeutic effect of cranberry juice capsules on preventing catheter-associated urinary tract infection post-catheterization supported by the National Institutes of Health (R21 DK085290)(4) ([ClinicalTrials.gov](https://clinicaltrials.gov)). All study participants from which a urinary catheter was obtained were eligible for this study regardless of treatment assignment. Briefly, non-pregnant women of at least 18 years of age without a history of nephrolithiasis, congenital urogenital anomaly or neurogenic bladder, or any known allergy to cranberry products were eligible. We excluded those whose surgery involved a fistula repair or a vaginal mesh removal and those who required therapeutic anticoagulant medicine during the six weeks post-surgery. Participants were followed for 8 weeks.

The participating medical units used two types of Foley catheters: Bardex All-Silicone Foley Catheter, 16 Fr./5cc ribbed balloon, Mfg. #: 165816 and Bard Foley Catheter, 16 Fr./5cc balloon, silicone coated, Mfg. #: 265716. Catheters were obtained from 130/160 (81%) of the women participating in the trial. For this analysis, we included only the 127 catheters

that were in place <3 days, were collected properly, and whose sequencing results met quality standards (See section on Sequencing Processing & Oligotyping Analysis below). All women were UTI-free at time of catheter removal. The 127 participants included in this subset were not significantly different from the 33 not included with regards to age (mean: 56.8 vs. 53.5 $p=0.22$), lifetime history of UTI (64% vs. 55%, $p=0.33$), or number of participants who experienced UTI in the previous 12 months (23 vs. 24%; $p=0.86$) but were more likely to develop a UTI in the 6 weeks following surgery (31.5% vs. 15.2%, $p=0.06$), and their reason for surgery was more likely to be organ prolapse (70.9% vs. 51.5%, $p=0.04$). The Institutional Review Board at the University of Michigan approved the study protocol and reviewed adverse events and outcomes (HUM00041108).

Catheter collection and processing:

The catheter was marked where it exited the body and removed from the patient by the nursing staff post-surgery. The part outside of the body, including the drainage tube, was discarded. The remaining portion of the catheter was placed in a sterile cup and transported to the lab on ice.

Upon arrival in the lab, the balloon portion of the catheter was cut off and discarded. The catheter length was measured and recorded. The catheter was cut vertically, leaving a segment proximal and distal to the urethra. This study includes data from the extraluminal (outside) of the proximal segment (segment closest to the urethra). This segment was scrubbed thoroughly using a sterile polystyrene swab dipped in 1 mL 1X PBS. If necessary, the swab was dipped into the 1 mL aliquot of PBS multiple times to ensure that all biomass material was sufficiently collected on the swab. The swab in 1x PBS was pulse vortexed to transfer material on the swab into the liquid. The Roche Swab Extraction Tube System was used to dislodge any extra material fixed to the swab. Any extracted volume was combined with the 1x PBS solution and frozen at -80°C until analysis.

DNA Extraction & qPCR:

The frozen samples were slowly brought to room temperature and when thawed, homogenized by pulse vortexing. 100 μL of sample were pre-treated with an enzyme cocktail and transferred to a Qiagen QIAcube for DNA extraction using the protocol “DNeasy Blood & Tissue – Bacteria or Yeast – Enzymatic Lysis”, previously described. (18)

Selecting microbes for qPCR analysis:

Using qPCR, extracted DNA was tested for the presence of *Enterococcus* spp., *Candida albicans*, *Staphylococcus aureus*, a primer for lactic acid bacteria (LAB) which identifies *Lactobacillus* spp., *Leuconostoc* spp., *Pediococcus* spp., and *Weissella* spp. (19), and *Escherichia coli*. These microbes were selected because either they were common colonizers on urinary catheters (*Enterococcus* spp. (17,20), *Candida* spp. (21–23), and *S. aureus*(24)), the vaginal cavity (LAB), or known uropathogens (*E. coli*(25)). qPCR was run in a CFX96 Thermocycler (Bio-Rad, CA) and performed and analyzed according to published protocol(4,18). We used previously published primer sequences and PCR conditions: *Enterococcus* spp. (26); Lactic acid producing bacteria (LAB) (19); *Escherichia coli* and *Candida albicans* (27); *Staphylococcus aureus* (28).

Sequencing the V4 Region:

MiSeq sequencing using the Kozich and Schloss dual indexing method(29) was performed on the extracted DNA by the University of Michigan Microbial Systems Laboratories using Illumina MiSeq V2 chemistry 2x250 (Illumina, San Diego, CA). A mock community and negative (water) samples were included as controls.

Sequencing Processing & Oligotyping Analysis:

Raw sequence files were analyzed using the Mothur 1.38.0 pipeline through quality filtering(30). Sequences were aligned to Silva reference alignment and classified using Greengenes 13.8. Two samples did not pass quality-filtering steps. Samples averaged 19,175 reads (range 5,345 to 41,578). Sequences from the remaining 127 samples were clustered into oligotypes using unsupervised minimum entropy decomposition (31) and default parameters.

Microbiome Analysis and Dirichlet Multinomial Modeling

We used Dirichlet multinomial mixture models to classify bacterial communities into community types [using the Dirichlet Multinomial package in R (32)]. The optimal number of community types was determined using the lowest Laplace approximation of model fit. Each sample was assigned a maximum probability score and misclassification set as a maximum probability score of less than 80% or a 10% probability of being classified as another community type. No samples in this dataset met these criteria; therefore, every sample was successfully assigned a community type.

Statistical Analysis:

Duration of catheterization was categorized based on natural breaks in the variable distribution: those in place for less than 14 hours, those in place between 14 and 30 hours, and those in place for over 30 hours. However, as there were only 3 individuals where the catheter was in place for over 30 hours, and the associated microbial communities did not cluster by time, for most analyses we present results for duration dichotomized into <14 and 14 hours or more. Age was categorized into less than 40 years, 40 to 69 years, and greater than or equal to 70 years of age. Smoking, estrogen use, vitamin C use, antibiotic use and UTI history within 12 months were dichotomized.

Alpha diversity was calculated using Shannon's diversity index. Beta diversity was measured using Bray-Curtis distances. The Kruskal-Wallis (KW) non-parametric test was used for testing for significance in both alpha and beta diversity.

For continuous variables, ANOVA was used as a test of significance. Oligotypes were collapsed to assigned taxonomic names at the genera level before the following analyses. We compared the relative abundance of specific genera by age (categorized), catheter type, duration of catheterization (categorized), estrogen use, smoking, UTI history in the past 12 months and ever, and whether the participant subsequently developed a UTI using ALDEx2(33) which takes sample variation into account for analyzing differential abundance and corrects for multiple testing.

We fit a logistic regression model to predict UTI by presence of individual microbes detected using qPCR and catheter duration after adjusting for risk factors identified in the analysis of clinical trial. As the microbes detected using qPCR are included in the sequencing results, we fit a second model using the community state types. Analyses were performed using R 3.3.2 and SAS 9.5.

Results

Catheters were obtained from 127/160 (79.3%) of participants in a cranberry pill clinical trial (4). These participants averaged 57 years of age, and the majority were white (85% white, 4% black, 11% other). Slightly more catheters were obtained from participants assigned to placebo (67/80 (83.8%)) than those assigned to cranberry (60/80 (75.0%)). In this trial, women assigned to cranberry were half as likely to have a UTI as those assigned placebo.

Treatment started at time of discharge (after catheters were removed). Catheters were generally removed at the end of the surgery or first thing in the morning the day following surgery: for categorical analysis we used natural breaks in the distribution (<14 hours (n=23), 14 to <30 hours (n=101), and ≥30 hours (n=3)). On average, catheters were in place for 23 hours.

We sequenced and screened using qPCR the DNA extracted from the extraluminal surface of the half of the catheter that was inside the body and proximal to the urethral opening. The mean length of the sequenced catheter segment was 2.61 cm (SD=1.10). Six of the catheters were silicone; the remainder were latex. Forty of the 127 participants whose catheters we tested developed UTI within 6 weeks after surgery (31.5%); 14 among participants assigned to cranberry. Results of urine culture at time of UTI identified *E. coli* as the leading cause of UTI (14/40), followed by *Enterococcus* (7/40), *Enterobacter spp.* (3/40), *Klebsiella pneumoniae* (2/40), *Group B Streptococcus* (2/40), and others including unidentified bacteria (12/40).

Using qPCR, we detected *Enterococcus spp.* (99%) in almost all catheters, and LAB (81%) and *Escherichia coli* (57%) in most (Table 1). However, the 73 women whose catheters had *E. coli* were no more likely to have a UTI caused by *E. coli* during follow-up (8/73 or 11%) than those whose catheters did not have *E. coli* (6/54 or 11%) ($p=0.97$). *Candida albicans* was detected less frequently (14%) and *Staphylococcus aureus* not at all. Sixty-one catheters had *Enterococcus spp.*, LAB and *Escherichia coli*; seven of these had *Candida albicans*. LAB were detected more frequently in catheters from women using estrogens (96% vs 77%; $p<0.05$) and/or Vitamin C (89% vs 72%; $p<0.05$). By contrast there was no *Candida albicans* detected in catheters from women using estrogens (0% vs 17.3%; $p<0.05$). *E. coli* was found in the catheters of all 10 women who smoked compared to 54% of catheters from nonsmokers ($p<0.05$). There was no association between prevalence of detected species and UTI history ($p=0.97$) or development of UTI within the 6 weeks following enrollment ($p=0.80$).

Sequencing Results:

Analysis of the 16S rRNA from catheter material found no differences in the alpha diversity by whether the participant subsequently developed a UTI. Alpha diversity varied only slightly by duration of catheter placement: the average Shannon diversity among those catheterized for <14, 14 to 29, or 30 or more hours was similar (<14 hours average = 2.34, >=14 but <=30 average=2.20, >30 average=2.36, KW=1.46, p=0.48), but the beta diversity decreased with duration: at <14, average within category Bray Curtis distance was 0.85, at >=14 and <=30 the average within category Bray Curtis distance was 0.83 (KW =8.11, p=0.004). At >30 hours, the average within category Bray Curtis distance was 0.91, however, only 3 catheters were in place for >30 hours, and this was not statistically significantly different. Clustering of microbial communities using Dirichlet Multinomial Modeling identified three community state types. There was no association between community state type and UTI development or duration of catheterization.

When the communities of each catheter were clustered using Euclidean distance in a heat map, there were no apparent associations with duration of catheterization, developing a UTI during follow-up or community state type (Figure 1). Principle components also showed no clear differences in catheter community structure by age (dichotomized), catheter type, duration of catheterization (categorized), estrogen use, smoking, UTI history in the past 12 months and ever, and whether the participant subsequently developed a UTI (data not shown).

We used ALDEx2 to compare the relative abundance of genera detected by selected demographic and medical history variables. ALDEx2 accounts for the compositional data structure and corrects for multiple comparison (there were 159 genera tested). Only those with a corrected p value less than or equal to 0.1 are noted here. Consistent with our graphical analysis, duration of catheterization was positively associated with increased relative abundance of *Enterococcus* (p=0.005). No genera were associated at an alpha of 0.2 with subsequently developing a UTI.

After adjustment for duration of catheter placement, treatment assignment, intermittent catheterization (variable transformed using the natural log as highly skewed) and presence of an indwelling catheter in a logistic regression model, neither presence of individual microbes on the catheter surface detected using qPCR nor the structure of the catheter bacterial community (community state type) were associated with subsequent development of UTI (Table 2).

Discussion

We characterized the extraluminal microbial communities found on 127 urinary catheters placed for less than 3 days in women undergoing elective gynecological surgery using targeted qPCR and an untargeted taxonomic screen of the 16SrRNA. Bacteria were detected on all catheters – including species known to cause UTI, but neither the presence of specific species nor the overall composition of the catheter bacterial community was associated with UTI risk. Although the most common cause of UTI following catheter removal was *E. coli*,

women whose catheter had detectable *E. coli* on the surface were no more likely to have a UTI during follow-up than those whose catheters had no *E. coli*.

The prevalence of selected species and genera found in this study are consistent with our understanding of the sources of catheter bacteria. The catheter is inoculated during insertion by bacteria colonizing the urethra; bacteria colonizing the urethral opening colonize the catheter exterior and ascend. Bacteria already present in the urinary microbiome also may colonize the catheter surface. LAB, *Streptococcus*, *Staphylococcus* and *Enterococcus* are common inhabitants of the urinary microbiome [Reviewed in Aragón, et al.(34)]. Further, *E. faecalis* is known to adhere to urinary catheters and form biofilms [Reviewed in Kline and Lewis(35)], and *Enterococcus* cause 15% to 30% of all catheter-associated UTIs (here, 18% of the UTI were caused by *Enterococcus*). Estrogen use is known to enrich the vaginal cavity for LAB leading to a decrease in prevalence of *C. albicans* (36), however hormonal replacement therapy among post-menopausal women is associated with an increased risk of vaginal yeast infections(37). While *E. coli* was the cause of most UTI in the 6 weeks following catheter removal (14/40 (35%)), there was no association with qPCR detection of *E. coli* on the catheter surface and subsequent development of UTI.

The biofilm growing on the surface of a catheter has been previously considered a reservoir for UTI (10). At least for catheters placed for <3 day, this does not seem to be the case: we found no evidence that the composition of the bacteria growing on the catheter surface of catheters was associated with subsequent UTI. Other aspects of catheter care, such as proper aseptic technique(38) are likely more important than preventing bacterial colonization of the catheter surface for preventing UTI following short term catheter placement (39).

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Highlights

- We characterized the extraluminal microbial communities found on 127 urinary catheters placed for <3 days in women undergoing elective gynecological surgery
- *Enterococcus*, *Streptococcus* and *Staphylococcus* were the most commonly identified genera in the taxonomic screen but were not associated with UTI during follow-up
- There was no association between detection of *E. coli* on the catheter surface using qPCR and subsequent development of UTI

Table 1:

Prevalence of selected bacteria found on urinary catheters, and diversity of catheter microbial communities by development of UTI during 60 days of follow-up. 127 urinary catheters placed for <3 days collected from women undergoing elective gynecologic surgery 2011 – 2013.

	All N=127 N (%)	No UTI N=87 N(%)	UTI N=40 N(%)	p value
Enterococcus: Positive	126 (99.2%)	86 (98.9%)	40 (100%)	1.00
Lactic Acid Bacteria (LAB): Positive	103 (81.1%)	68 (78.2%)	35 (87.5%)	0.32
<i>E. coli</i>: Positive	73 (57.5%)	49 (56.3%)	24 (60.0%)	0.84
<i>C. albicans</i>: Positive	18 (14.2%)	14 (16.1%)	4 (10.0%)	0.52
Shannon Index Tertiles:				0.42
Tertile 1 (<=1.95)	43 (33.9%)	28 (32.2%)	15 (37.5%)	
Tertile 2 (>1.05, <=2.47)	42 (33.1%)	32 (36.8%)	10 (25.0%)	
Tertile 3 (>2.47, <=3.72)	42 (33.1%)	27 (31.0%)	15 (37.5%)	
Chao Index Tertiles:				0.95
Tertile 1 (<=59.3)	43 (33.9%)	30 (34.5%)	13 (32.5%)	
Tertile 2 (>59.3, <=75.1)	42 (33.1%)	28 (32.2%)	14 (35.0%)	
Tertile 3 (>75.1, <=131)	42 (33.1%)	29 (33.3%)	13 (32.5%)	
Community State Types (CST):				1.00
CST 1	70 (55.1%)	48 (55.2%)	22 (55.0%)	
CST 2	38 (29.9%)	26 (29.9%)	12 (30.0%)	
CST 3	19 (15.0%)	13 (14.9%)	6 (15.0%)	
Treatment:				0.09
Placebo	67 (52.8%)	41 (47.1%)	26 (65.0%)	
Cranberry	60 (47.2%)	46 (52.9%)	14 (35.0%)	
Self-Catheterization:				<0.001
No	70 (55.1%)	61 (70.1%)	9 (22.5%)	
Yes	57 (44.9%)	26 (29.9%)	31 (77.5%)	
Catheter Type:				0.40
Silicone	103 (81.1%)	73 (83.9%)	30 (75.0%)	
Latex	6 (4.72%)	3 (3.45%)	3 (7.50%)	
‘Missing’	18 (14.2%)	11 (12.6%)	7 (17.5%)	
Duration of Catheterization				0.08
< 14 Hours	23 (18.1%)	20 (23.0%)	3 (7.50%)	
14 hours, 30 hours	101 (79.5%)	65 (74.7%)	36 (90.0%)	
>30 hours	3 (2.36%)	2 (2.30%)	1 (2.50%)	
Age Category:				0.77
<40	12 (9.45%)	9 (10.3%)	3 (7.50%)	
40 to 69	92 (72.4%)	61 (70.1%)	31 (77.5%)	

	All N=127 N (%)	No UTI N=87 N(%)	UTI N=40 N(%)	p value
>70	23 (18.1%)	17 (19.5%)	6 (15.0%)	
Antibiotics:				0.57
Yes	98 (77.2%)	68 (78.2%)	30 (75.0%)	
‘Missing’	15 (11.8%)	11 (12.6%)	4 (10.0%)	
Estrogen Use:				0.56
Yes	99 (78.0%)	70 (80.5%)	29 (72.5%)	
‘Missing’	1 (0.79%)	1 (1.15%)	0 (0.00%)	
Smoker:				0.51
Yes	10 (7.87%)	7 (8.05%)	3 (7.50%)	
‘Missing’	1 (0.79%)	0 (0.00%)	1 (2.50%)	
UTI in the past 12 months:				1.00
Yes	29 (22.8%)	20 (23.0%)	9 (22.5%)	
Vitamin C use:				0.39
Yes	60 (47.2%)	42 (48.3%)	18 (45.0%)	
‘Missing’	1 (0.79%)	0 (0.00%)	1 (2.50%)	
Indwelling catheter *				0.21
No	120 (94.5%)	84 (96.6%)	36 (90.0%)	
Yes	7 (5.51%)	3 (3.45%)	4 (10.0%)	

* Seven women failed their voiding trial, and a new catheter was inserted at time of discharge.

Table 2:

Logistic models predicting UTI within 8 weeks post-procedure by duration of catheterization; presence or microbes detected from qPCR or Community State Types (CST) of catheter microbes, treatment with cranberry pills, and log-transform of self-catheterization count as independent variables. 127 urinary catheters placed for <3 days collected from women undergoing elective gynecologic surgery 2011 – 2013.

	Unadjusted OR (95%CI)	Including microbes detected using qPCR Adjusted OR (95% CI)	p-value (Walds t-test)	Including CSTs Adjusted OR (95% CI)	p-value (Walds t-test)
Catheter Duration (<14 hours)	1.0 (Reference)	1.0 (Reference)			
14 hours, 30 hours	3.69 (1.03,13.28)	2.28 (0.51,10.17)	0.28	2.19 (0.52,9.27)	0.29
Greater than 30 hours	3.33 (0.23,49.09)	2.57 (0.1,65.99)	0.57	3.5 (0.17,71.75)	0.43
<i>E. coli</i>: Positive	1.16 (0.54,2.49)	0.61 (0.24,1.57)	0.31	--	--
Lactic Acid Bacteria: Positive	1.96 (0.67,5.68)	2.92 (0.79,10.74)	0.11	--	--
Enterococcus: Positive	2678052.48 (0,Inf)	7329278.77 (0,Inf)	0.99	--	--
<i>C. albicans</i>: Positive	0.58 (0.18,1.89)	0.81 (0.21,3.15)	0.76	--	--
Community State Types (Reference CST 1)		--	--		
CST 2	1.01 (0.43,2.36)	--	--	0.89 (0.31,2.51)	0.82
CST 3	1.01 (0.34,3.00)	--	--	0.52 (0.14,1.89)	0.32
Treatment (Cranberry vs placebo)	0.48 (0.22,1.04)	0.61 (0.24,1.53)	0.29	0.56(0.23,1.37)	0.22
Log frequency self-catheterization *	1.91 (1.44,2.54)	1.99 (1.46,2.73)	<0.001	2.00 (1.46,2.73)	<0.001
Indwelling catheter	3.11 (1066,14.61)	10.45 (1.38,78.84)	0.023	4.43 (0.82,23.91)	0.083

* Transformed using the natural log because variable was highly skewed.