Experience with Fosfomycin for the Treatment of Urinary Tract Infections due to Multi-Drug Resistant Organisms

Running Title: Fosfomycin for Resistant Urinary Tract Infections

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ABSTRACT

Fosfomycin has shown promising in vitro activity against multi-drug resistant (MDR) urinary pathogens however clinical data is lacking. We conducted a retrospective chart review to describe the microbiological & clinical outcomes of urinary tract infections (UTIs) with MDR pathogens treated with fosfomycin tromethamine. Charts from 41 hospitalized patients with a urine culture for a MDR pathogen who received fosfomycin tromethamine from 2006 to 2010 were reviewed. 41 patients had 44 urinary pathogens including 13 carbapenem-resistant Klebsiella pneumoniae (CR-Kp), 8 Pseudomonas aeruginosa, 7 vancomycin-resistant Enterococcus faecium (VRE), 7 extended-spectrum beta-lactamase (ESBL) producers and 9 others. In vitro fosfomycin susceptibility was 86% (median MIC 16 µg/mL, range 0.25-1024 µg/mL). Patients received an average of 2.9 fosfomycin doses per treatment course. Overall microbiological cure was 59%, failure was due to either relapse (24%) or reinfection UTI (17%). Microbiological cure rates by pathogen were 46% CR-Kp, 38% P. aeruginosa, 71% VRE, 57% ESBL producers, and 100% others. Microbiological cure (n=24) was compared to microbiological failure (n=17). There were significantly more solid organ transplant recipients in the microbiological failure group (59% vs 21%, p=0.02). None of the patients in the microbiological cure group had a ureteral stent compared to 24% of patients within the microbiological failure group (p=0.02). Fosfomycin demonstrated in vitro activity against UTIs due to MDR pathogens. For CR-KP, there was a divergence between in vitro susceptibility (92%) and microbiological cure (46%). Multiple confounding factors may have contributed to microbiological failures and further data regarding the use of fosfomycin for UTIs due to MDR pathogens are needed.
INTRODUCTION

An increasing proportion of urinary tract infections (UTIs) are due to multi-drug resistant (MDR) pathogens for which there are limited treatment options (8). Fosfomycin is a phosphonic acid derivative which is available in the United States as a powdered sachet approved by the Food and Drug Administration for the treatment of uncomplicated UTIs in women. Fosfomycin has a broad spectrum of activity against gram-positive and gram-negative bacteria. Recent reports show in vitro activity against MDR pathogens including carbapenem-resistant Klebsiella pneumoniae (CR-Kp), Pseudomonas aeruginosa, extended-spectrum β-lactamase (ESBL) producing bacteria and vancomycin-resistant enterococci (VRE) (5-6, 14, 20). However, clinical data for the use of fosfomycin for the treatment of UTIs due to MDR pathogens are limited (7). The aim of this study is to describe the microbiological outcomes of UTIs due to MDR pathogens treated with fosfomycin.

MATERIALS AND METHODS

Study Design and Patients. The study was conducted at Cleveland Clinic, a 1200-bed academic medical center in Cleveland, Ohio. This was a retrospective chart review of adult patients treated with fosfomycin for a MDR urinary pathogen from January 2006 to December 2010. This study was approved by the Cleveland Clinic Institutional Review Board.

Patients were included if they received at least one dose of fosfomycin in the hospital and had a urine culture with a MDR pathogen tested for fosfomycin susceptibility. Patients were determined to have a UTI if a corresponding urinalysis was abnormal (presence of leukocyte...
esterase or >5 white blood cells/high-powered field) and/or documentation of symptoms (dysuria, frequency, urgency, suprapubic tenderness, and/or hematuria). Data, including demographics, co-morbid conditions, and treatment were collected retrospectively from the electronic medical record. Medical records were reviewed for at least 90 days after discharge. Co-morbidities were measured using the Charlson co-morbidity index (2).

Definitions. Multi-drug resistance was defined as resistance to at least one agent in three or more antimicrobial classes (12). Immunosuppression was defined as having a solid organ or bone marrow transplant, receipt of chemotherapy in the previous 30 days, ≥ 30 mg prednisone or equivalent daily, or other immunosuppressive agents. Urinary complicating factors included the presence of a urinary foley catheter, suprapubic catheter, ureteral stent, percutaneous nephrostomy tube, umbilical stoma, or neurogenic bladder, history of recurrent UTIs, or urological surgery in the prior six months. Relapse was defined as the development of a UTI with the same pathogen within 30 days. A reinfection was defined as the development of a UTI with a different organism within 30 days. Microbiological failure was defined as the development of either relapse or reinfection (13). Microbiological cure was defined as the presence of a documented negative urine culture at completion of therapy and/or the absence of relapse or reinfection.

Microbiological Methods. Antimicrobial susceptibility testing was performed using the automated broth microdilution system VITEK® 2 (bioMérieux Inc., Durham, NC). Fosfomycin susceptibility was determined by the Etest (bioMérieux, Inc., Durham, NC) method. The Etest
was performed on Mueller-Hinton agar (BBL, Becton, Dickinson). Interpretive criteria from the Clinical and Laboratory Standards Institute for fosfomycin susceptibility are not available for *P. aeruginosa* and Enterobacteriaceae other than *Escherichia coli* (1). Therefore results were interpreted according to criteria for *E. coli* and *Enterococcus faecalis* (ie. susceptible ≤ MIC 64 µg/ml) as has been reported previously (1, 5, 14). A modified Hodge test, as described by Lee et al., was performed on *Klebsiella pneumoniae* isolates resistant to ertapenem (10).

**Statistical Analysis.** The primary outcome was the rate of microbiological cure. Patients with microbiological cure were compared to microbiological failure to evaluate for risk factors. All comparisons were unpaired and all tests of significance were 2-tailed. Continuous variables were compared using the Student t test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. The χ² or Fisher exact test was used to compare categorical variables.

**RESULTS**

During the study period, 41 patients were identified as receiving at least one dose of fosfomycin and having a UTI due to a MDR pathogen. The definition of UTI was met by the presence of a positive urine culture plus an abnormal urinalysis in 85% patients (35/41), urinary symptoms in 80% (33/41) or both 68% (28/41). 41 patients had 44 MDR urinary pathogens (Table 1). The MDR pathogens were CR-Kp (n=13), *P. aeruginosa* (n=8), ESBL producers (n=7 total, 4 *E. coli*, 3 *K. pneumoniae*), VRE (n=7), *E. coli* (n=5) and 4 others (*Acinetobacter baumannii*, *Enterobacter cloacae*, *E. faecalis*, *Proteus mirabilis*). Overall susceptibility to fosfomycin was high with 86%
(38/44) of all MDR isolates susceptible, 7% (3/44) intermediate, and 7% (3/44) resistant. No patients had a bloodstream infection associated with the UTI.

Microbiologic cure occurred in 59% (24/41) of patients with a UTI due to a MDR pathogen. Cure rates by pathogen are displayed in Figure 1. For CR-Kp, the microbiological cure rate was 46%. Overall, microbiological failure occurred in 41% (n=17) patients due to relapse (n=10) and reinfection (n=7) within 30 days. Microbiological cure rates varied by fosfomycin susceptibility, 60% (21/35) for isolates with MIC \( \leq 64 \) µg/ml, 100% (3/3) for isolates with MIC 128 µg/ml, and 0% (0/3) for MICs \( \geq 256 \) µg/ml.

Patients with microbiologic cure were compared to failures for determination of risk factors for failure. There were no differences between microbiological cure or failure groups in baseline characteristics including age, gender, or race (Table 2). The overall median hospital length of stay was 14 (range 3-166) days and was similar between microbiological cures and failures. The Charlson comorbidity index was not different between the two groups. The most frequent comorbid conditions were diabetes and chronic kidney disease. Solid organ transplant recipients made up a large subset of our patient population (n=15). The most frequent transplanted organ was kidney (n=10, 8 in the microbiological failure group and 2 in the microbiological cure group), followed by liver (n=3), lung (n=1), and heart (n=1). There were significantly more patients with solid organ transplants in the microbiological failure group, 59% compared to 21% in the microbiological cure group (p=0.02).
The number of patients with at least one urinary complicating factor was high overall (n=33, 80%); this was not statistically different between microbiologic cure (n=17, 71%) and failure (n=16, 94%) (Table 2). The most common urinary complicating factor was the presence of a foley catheter at time of urine culture (63% in microbiological cure and 65% in microbiological failure group). However, all patients in both groups had the urinary catheter removed or changed. Additional urinary complicating factors included history of recurrent UTI, urological surgery in the prior six months, and neurogenic bladder. All of the patients with ureteral stents were transplant recipients and all developed microbiological failure.

The 41 patients received a total of 120 doses of fosfomycin. The average number of doses per treatment course was 3.3±1.9 in the microbiological cure and 2.4±1.5 in the microbiological failure group (p=NS). Combination therapy was utilized in 27% (n=11) of the overall population. The most common agents utilized with fosfomycin were tigecycline (n=5), aminoglycosides (n=2), colistin (n=1), piperacillin/tazobactam (n=1), imipenem (n=1), and daptomycin (n=1). Combination therapy was more common in the microbiological failure group, 53% (9/17) compared to 8% (2/24) in the cure group (p=0.003).

Resistance to fosfomycin developed in three patients, all with kidney transplants and ureteral stents who were infected with CR-Kp and treated with a combination of tigecycline and fosfomycin. The first patient presented three months post-transplant with CR-Kp (fosfomycin MIC 32 µg/mL) UTI that was treated with two weeks of tigecycline and three doses of fosfomycin. The patient had urine cultures persistently positive for CR-Kp and susceptibilities...
performed on a urine culture three weeks after completion of therapy showed fosfomycin MIC > 256 µg/mL and tigecycline MIC > 4 µg/mL. The second patient had CR-Kp (fosfomycin MIC 16 µg/mL) transplant graft pyelonephritis and a suspected infected ureteral stent who was treated with combination tigecycline and fosfomycin for 14 days. At the end of therapy the urine cultures were positive for CR-Kp and the fosfomycin MIC was 256 µg/mL (tigecycline MIC ≤ 0.25 µg/mL). The third patient had a CR-Kp (fosfomycin MIC 8 µg/mL) UTI treated with a combination of tigecycline and fosfomycin for three weeks. The patient had persistently positive cultures until the ureteral stent was removed. Four months after the initial CR-Kp UTI the patient was admitted to the hospital with another CR-Kp UTI which was resistant to fosfomycin (MIC 256 µg/mL) but susceptible to tigecycline (MIC 0.5 µg/mL).

Two additional patients developed fosfomycin resistant superinfections. The first patient was a liver transplant recipient who was treated with 3 doses of fosfomycin for a *P. aeruginosa* UTI (fosfomycin MIC 8 µg/mL) who had a reinfection with fosfomycin-resistant (MIC > 1024 µg/mL) CR-Kp within 30 days. The second patient was started on fosfomycin for an ESBL-producing *E. coli* UTI (fosfomycin MIC 1 µg/mL) and then continued for chronic suppression due to a history of recurrent infections. Three months into the chronic suppression, the patient was readmitted to the hospital with a *K. pneumoniae* UTI with resistance to fosfomycin (MIC >1024 µg/mL).

Overall hospital mortality was 10% (n=4). All 4 patients were in the microbiological cure group; no patient died during the fosfomycin treatment course. Of the patients who survived to discharge, 39% were discharged home and 51% to a long-term care or skilled nursing facility (no
differences between groups). Readmission rate at 90 days was high overall 21/37 (57%) and not significant between groups (50% microbiological cure vs. 65% microbiological failure, p=0.51).

**DISCUSSION**

To our knowledge this is the largest series of MDR pathogen UTIs treated with fosfomycin to date. Patients received an average of 2.9 ± 1.8 doses (each dose = 3 grams fosfomycin tromethamine) per course of therapy. A microbiological cure occurred in 59% (24/41) of patients with a UTI due to a MDR pathogen. The most common MDR pathogens were CR-Kp, *P. aeruginosa*, ESBL producers, and VRE.

In this series we describe 13 CR-Kp UTIs treated with fosfomycin; 92% had in vitro susceptibility to fosfomycin (MIC$_{50/90}$ 32/64 µg/mL). Others have reported similar rates of susceptibility.

Endimiani and colleagues evaluated 68 bla$_{KPC}$-containing *K. pneumoniae* isolates, including those nonsusceptible to tigecycline and/or colistin and showed a 93% rate of susceptibility (5).

Another report by Falagas and colleagues reported MIC$_{50/90}$ 16/32 µg/mL for 30 clinical *K. pneumoniae* isolates which were both ESBL and metallo-β-lactamase producers (6). Maraki and colleagues reported slightly lower rates in their series with 15/25 (60%) carbapenemase-producing *K. pneumoniae* isolates susceptible to fosfomycin (14). The microbiological cure rate for CR-Kp isolates in our series was 46% (6/13). This is lower than the microbiological clearance rates reported by Satlin and colleagues for aminoglycosides (88%) and polymyxin (64%), but
similar to tigecycline (43%) and untreated controls (36%) with CR-Kp in the urine (18). Rationale for microbiological failure will be discussed in more detail, but could include high rates of immunocompromising conditions (9/13) and potentially infected ureteral stents (3/13) which were common cofactors in patients with CR-Kp isolates.

P. aeruginosa isolates generally demonstrate higher rates of resistance to fosfomycin in vitro compared to the Enterobacteriaceae (11). Our cohort consisted of eight P. aeruginosa isolates with a fosfomycin MIC$_{50}$ 8 µg/mL and MIC$_{90}$ 256 µg/mL. These isolates also had the lowest rate of microbiological cure (n=3/8, 38%) in our cohort. We hypothesize the higher MICs may have contributed to the lack of microbiological success. The fact that fosfomycin resistance occurs without a fitness cost in P. aeruginosa may also contribute (17).

It has previously been reported that fosfomycin has good in vitro activity against ESBL-producing E. coli and K. pneumoniae, as was also seen in our study (7, 14, 19). Clinical studies have shown fosfomycin to be effective for the treatment of lower UTIs due to ESBL-producing Enterobacteriaceae (7, 19). Fosfomycin may be a promising treatment option; however, increased usage has been shown to correlate with increasing resistance among ESBL-producing E. coli (16).

Previous work at our institution demonstrated 98.7% of VRE isolates were susceptible in vitro to fosfomycin (20). In this cohort we describe seven isolates, 86% were susceptible in vitro and
The microbiological cure rate was 71% (n=5/7). Further data is needed, but fosfomycin may have a role as a possible oral option for the treatment of VRE cystitis.

The overall microbiological failure rate was 41%. This could be explained by resistance development, immunocompromised hosts and the presence of prosthetic material (ureteral stents). Resistance developed in three patients and superinfection with a different fosfomycin-resistant organism occurred in two additional patients. It is interesting to note commonalities existed in these patients; four were transplant recipients and three had ureteral stents. The retained prosthetic material and immunocompromised status could have contributed to the development of resistance. In addition, one patient received fosfomycin for chronic suppression and it is possible that duration of exposure factors into the risk of developing resistance. Use of fosfomycin as a single agent may also contribute, as the development of resistance is known to occur in vitro when used as monotherapy (4, 21). In this cohort, combination therapy with tigecycline was used in all three patients who developed fosfomycin resistance. The lack of protective effect against resistance development may be due to the limited urinary excretion of tigecycline, however this was recently challenged (3, 15). An in vitro study showed the use of combination therapy with meropenem, colistin, or gentamicin reduced the development of resistance for KPC-producing *K. pneumoniae* (21). More data are needed to fully determine the role of combination therapy with fosfomycin for UTIs due to MDR pathogens, especially CR-Kp.
In addition to resistance development, immunocompromised hosts, including solid organ transplant recipients, and urinary complicating factors likely contributed to the rate of microbiological failure. There were significantly more transplant recipients in the microbiological failure group. Transplant recipients, especially kidney transplant patients, are at increased risk of developing UTIs which may lead to complications including allograft pyelonephritis(9). In addition, this cohort of patients had a high rate of urinary complicating factors. At least one complicating urinary factor was present in 94% of patients in the microbiological failure group and only 71% in the microbiological cure group. This was not statistically significant, but the small sample size of our study may be responsible for a type II error with regard to this outcome. Four patients had ureteral stents and all four patients developed microbiological failure; likely due to biofilm formation on the stent which highlights the importance of removal of prosthetic material whenever possible.

This study has important limitations revolving around the retrospective design, uncontrolled nature and single-center experience. The small sample size of our cohort may limit the ability to identify differences between groups and perform multivariate analysis. Defining UTI versus colonization can be challenging especially in patients with urinary foley catheters. Choice of therapy, including duration and decision to use combination therapy was at the discretion of the treating physicians. Other important variables were also not standardized due to the retrospective nature including timing of follow-up cultures to assess for relapse and reinfection; however 90% of patients had follow-up cultures within 21 days of initiating fosfomycin therapy.
The definitions of relapse and reinfection utilized were purely clinical in nature and are limited by the lack of clonal analysis.

In conclusion, in this cohort fosfomycin showed good in vitro activity against MDR urinary pathogens, including CR-Kp. Overall, the rate of microbiological cure (59%) was lower than in vitro susceptibility (86%). The largest divergence occurred in CR-KP, 92% in vitro susceptibility and 47% microbiological cure rate. Caution should be used in certain settings such as solid organ transplant recipients and patients with ureteral stents. Clinicians also need to be aware of possibility of resistance development. Additional data are needed to further define the role of fosfomycin in the treatment of UTIs due to MDR pathogens.
REFERENCES


Legend for Figure 1

CR-Kp = Carbapenem-resistant *K. pneumoniae*, VRE = Vancomycin-resistant *E. faecium*, ESBL = extended-spectrum beta lactamase producing *E. coli* and *K. pneumoniae*, Others = carbapenem-resistant *A. baumannii, E. cloacae, E. faecalis, P. mirabilis*
Figure 1. Microbiological Cure Rates by Pathogen

- CR-Kp (n=13)
- P. aeruginosa (n=8)
- VRE (n=7)
- ESBL (n=7)
- E. coli (n=5)
- Other (n=4)
Table 1. In Vitro Fosfomycin Susceptibility

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; µg/mL</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; µg/mL</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR-Kp (n=13)</td>
<td>32</td>
<td>64</td>
<td>92</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> (n=8)</td>
<td>8</td>
<td>256</td>
<td>75</td>
</tr>
<tr>
<td>VRE (n=7)</td>
<td>64</td>
<td>64</td>
<td>86</td>
</tr>
<tr>
<td>ESBL (n=7)</td>
<td>1</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td><em>E. coli</em> (n=5)</td>
<td>1</td>
<td>128</td>
<td>80</td>
</tr>
<tr>
<td>Other* (n=4)</td>
<td>*</td>
<td>*</td>
<td>75</td>
</tr>
</tbody>
</table>

CR-Kp = Carbapenem-resistant *K. pneumoniae*, VRE = Vancomycin-resistant *E. faecium*, ESBL = extended-spectrum beta lactamase producing *E. coli* and *K. pneumoniae*,

*Others = carbapenem-resistant *A. baumannii* (MIC= 128 µg/mL), *E. cloacae* (MIC=4 µg/mL), *E. faecalis* (MIC=64 µg/mL), *P. mirabilis* (MIC=1 µg/mL)
Table 2. Demographics and Co-morbidities

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total N=41</th>
<th>Microbiological Cure N = 24</th>
<th>Microbiological Failure N=17</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>62 ± 13</td>
<td>65 ± 13</td>
<td>59± 12</td>
<td>0.12</td>
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<tr>
<td>Gender, Male, (n,%)</td>
<td>19 (45%)</td>
<td>11 (46%)</td>
<td>8 (47%)</td>
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<tr>
<td>Race, Caucasian, (n,%)</td>
<td>22 (54%)</td>
<td>13 (54%)</td>
<td>9 (53%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hospital LOS, median (range)</td>
<td>14 (3-166)</td>
<td>14.5 (3-166)</td>
<td>12 (4-52)</td>
<td>0.97</td>
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<tr>
<td>Co-morbidities</td>
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<td></td>
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<tr>
<td>Diabetes</td>
<td>24</td>
<td>15 (63%)</td>
<td>9 (53%)</td>
<td>0.75</td>
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<tr>
<td>Chronic kidney disease</td>
<td>19</td>
<td>10 (42%)</td>
<td>9 (53%)</td>
<td>0.54</td>
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<td>Hematology/Oncology</td>
<td>6</td>
<td>2 (8%)</td>
<td>4 (24%)</td>
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<td>Solid Organ Transplant</td>
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<td>0.02</td>
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<td>Kidney</td>
<td>15</td>
<td>5 (21%)</td>
<td>10 (59%)</td>
<td>8</td>
</tr>
<tr>
<td>Liver</td>
<td>10</td>
<td>2</td>
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<td></td>
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<tr>
<td>Lung</td>
<td>3</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Heart</td>
<td>1</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>Immunosuppressed</td>
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<td>Charlson comorbidity index, median (range)</td>
<td>4 (0-8)</td>
<td>3.5 (0-8)</td>
<td>4 (0-7)</td>
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<tr>
<td>Urinary Complicating Factors</td>
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<tr>
<td>Foley catheter</td>
<td>26 (63%)</td>
<td>15 (63%)</td>
<td>11 (65%)</td>
<td>1.00</td>
</tr>
<tr>
<td>History of recurrent UTIs</td>
<td>10 (24%)</td>
<td>4 (17%)</td>
<td>6 (35%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Urological surgery*</td>
<td>6 (15%)</td>
<td>1 (4%)</td>
<td>5 (29%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>5 (12%)</td>
<td>2 (8%)</td>
<td>3 (18%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Ureteral stent</td>
<td>4 (10%)</td>
<td>0</td>
<td>4 (24%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other*</td>
<td>4 (10%)</td>
<td>1 (4%)</td>
<td>3 (18%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Patients with ≥ 1 complicating factor</td>
<td>33 (80%)</td>
<td>17 (71%)</td>
<td>16 (94%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Urological surgery within the prior 6 months
*Other = Percutaneous nephrostomy tube (2 microbiological failures), Umbilical stoma (1), and Suprapubic catheter (1)