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Experience with Fosfomycin for Treatment of Urinary Tract Infections Due to Multidrug-Resistant Organisms

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Fosfomycin has shown promising *in vitro* activity against multidrug-resistant (MDR) urinary pathogens; however, clinical data are lacking. We conducted a retrospective chart review to describe the microbiological and clinical outcomes of urinary tract infections (UTIs) with MDR pathogens treated with fosfomycin tromethamine. Charts for 41 hospitalized patients with a urine culture for an MDR pathogen who received fosfomycin tromethamine from 2006 to 2010 were reviewed. Forty-one patients had 44 urinary pathogens, including 13 carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp), 8 *Pseudomonas aeruginosa*, and 7 vancomycin-resistant *Enterococcus faecium* (VRE) isolates, 7 extended-spectrum beta-lactamase (ESBL) producers, and 9 others. *In vitro* fosfomycin susceptibility was 86% (median MIC, 16 μg/ml; range, 0.25 to 1,024 μg/ml). Patients received an average of 2.9 fosfomycin doses per treatment course. The overall microbiological cure was 59%; failure was due to either relapse (24%) or reinfection UTI (17%). Microbiological cure rates by pathogen were 46% for CR-Kp, 38% for *P. aeruginosa*, 71% for VRE, 57% for ESBL producers, and 100% for 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% versus 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.

An increasing proportion of urinary tract infections (UTIs) are due to multidrug-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 was 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 1,200-bed academic medical center in Cleveland, OH. This was a retrospective chart review of adult patients treated with fosfomycin for an 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 an 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, comorbid conditions, and treatment, were collected retrospectively from the electronic medical record. Medical records were reviewed for at least 90 days after discharge. Comorbidities were measured using the Charlson comorbidity index (1).

Definitions. Multidrug 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 6 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 with 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 the *Enterobacte-*

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TABLE 1 *In vitro* susceptibilities to fosfomycin

Organism (n^a)[b]	MIC (μg/ml)		% susceptible
	50%	90%	
CR-Kp (13)	32	64	92
P. aeruginosa (8)	8	256	75
VRE (7)	64	64	86
ESBL (7)	1	16	100
E. coli (5)	1	128	80
Other (4)			75

[a] *n*, no. of isolates.
[b] VRE, vancomycin-resistant *E. faecium;* ESBL, extended-spectrum beta-lactamase-producing *E. coli* and *K. pneumoniae*; Other, carbapenem-resistant *A. baumannii* (MIC = 128 μg/ml), *E. cloacae* (MIC = 4 μg/ml), *E. faecalis* (MIC = 64 μg/ml), and *P. mirabilis* (MIC = 1 μg/ml).

riaceae other than *Escherichia coli* (2). Therefore, results were interpreted according to criteria for *E. coli* and *Enterococcus faecalis* (i.e., susceptible at a MIC of ≤64 μg/ml), as has been reported previously (2, 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 those with 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 χ^2 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 an MDR pathogen. The definition of UTI was met by the presence of a positive urine culture plus an abnormal urinalysis in 85% of patients (35/41), urinary symptoms in 80% (33/41), or both in 68% (28/41). Forty-one patients had 44 MDR urinary pathogens (Table 1). The MDR pathogens were CR-Kp (n = 13 isolates), *P. aeruginosa* (n = 8), ESBL producers (n = 7 total: 4 *E. coli* and 3 *K. pneumoniae* isolates), VRE (n = 7), *E. coli* (n = 5), and 4 others (*Acinetobacter baumannii*, *Enterobacter cloacae*, *E. faecalis*, and *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.

Microbiological cure occurred in 59% (24/41) of patients with a UTI due to an MDR pathogen. Cure rates by pathogen are displayed in Fig. 1. For CR-Kp, the microbiological cure rate was 46%. Overall, microbiological failure occurred in 41% (n = 17) of 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 MICs of ≤64 μg/ml, 100% (3/3) for isolates with MICs of 128 μg/ml, and 0% (0/3) for isolates with MICs of ≥256 μg/ml.

Patients with microbiological cure were compared to treatment 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 days (range, 3 to 166) 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).

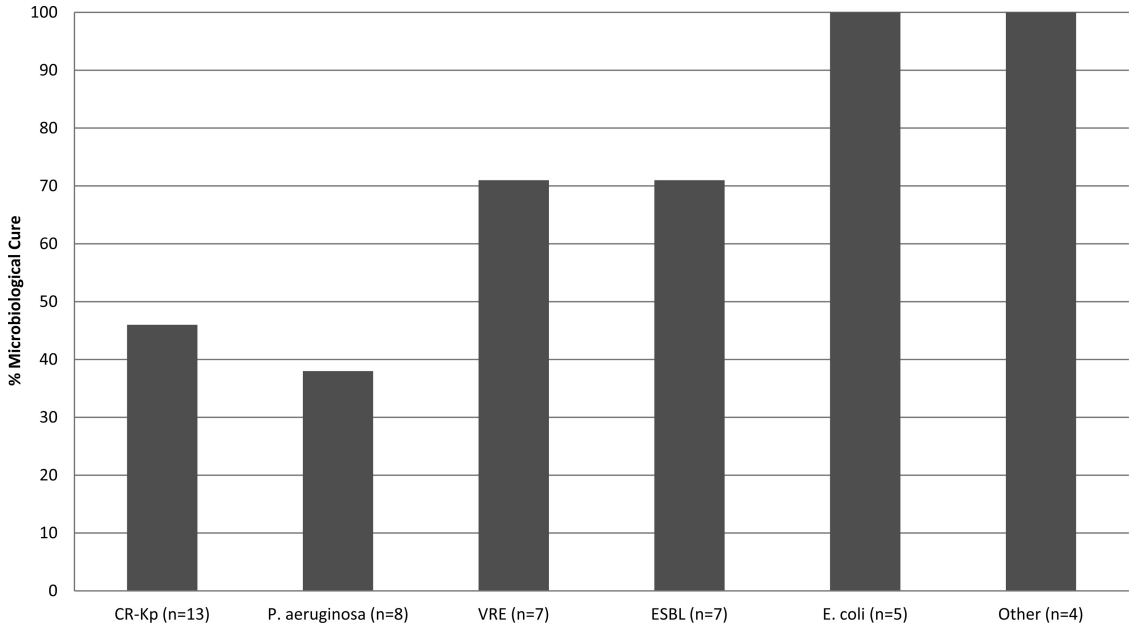

FIG 1 Microbiological cure rates by pathogen. VRE, vancomycin-resistant *E. faecium*; ESBL, extended-spectrum beta lactamase-producing *E. coli* and *K. pneumoniae*; Other, carbapenem-resistant *A. baumannii*, *E. cloacae*, *E. faecalis*, and *P. mirabilis*.

TABLE 2 Demographics and comorbidities

Demographic	Value for patient group (n^d)			*P* value
	Total (41)	Microbiological cure (24)	Microbiological failure (17)	
Age, mean ± SD	62 ± 13	65 ± 13	59 ± 12	0.12
No. (%) male	19 (45)	11 (46)	8 (47)	1.00
No. (%) Caucasian	22 (54)	13 (54)	9 (53)	1.00
Hospital LOS (days), median (range)[a]	14 (3–166)	14.5 (3–166)	12 (4–52)	0.97
Comorbidities				
No. (%) with:				
Diabetes	24	15 (63)	9 (53)	0.75
Chronic kidney disease	19	10 (42)	9 (53)	0.54
Hematology/oncology	6	2 (8)	4 (24)	0.22
Solid organ transplant	15	5 (21)	10 (59)	0.02
Kidney	10	2	8	
Liver	3	1	2	
Lung	1	1	0	
Heart	1	1	0	
Immunosuppression	21	9 (38)	12 (71)	0.06
Charlson comorbidity index, median no. (range)	4 (0–8)	3.5 (0–8)	4 (0–7)	0.73
No. (%) with urinary complicating factor				
Foley catheter	26 (63)	15 (63)	11 (65)	1.00
History of recurrent UTIs	10 (24)	4 (17)	6 (35)	0.27
Urological surgery[b]	6 (15)	1 (4)	5 (29)	0.07
Neurogenic bladder	5 (12)	2 (8)	3 (18)	0.63
Ureteral stent	4 (10)	0	4 (24)	0.02
Other[c]	4 (10)	1 (4)	3 (18)	0.29
≥1 complicating factor	33 (80)	17 (71)	16 (94)	0.11

[a] LOS, length of stay.
[b] Urological surgery within the prior 6 months.
[c] Other, percutaneous nephrostomy tube (2 patients, both microbiological failures), umbilical stoma (1 patient, microbiological failure), and suprapubic catheter (1 patient, microbiological cure).
[d] *n*, no. of patients.

The number of patients with at least one urinary complicating factor was high overall ($n = 33$; 80%); this was not statistically different between the microbiological cure ($n = 17$; 71%) and failure ($n = 16$; 94%) groups (Table 2). The most common urinary complicating factor was the presence of a Foley catheter at the time of urine culture (63% in the microbiological cure group and 65% in the microbiological failure group). However, for all patients in both groups, the urinary catheter was removed or changed. Additional urinary complicating factors included a history of recurrent UTI, urological surgery in the prior 6 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 numbers of doses per treatment course were not different between groups, 3.3 ± 1.9 in the microbiological cure group and 2.4 ± 1.5 in the microbiological failure group. 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 3 months posttransplant with a CR-Kp (fosfomycin MIC of 32 μg/ml) UTI that was treated with 2 weeks of tigecycline and three doses of fosfomycin. The patient had urine cultures persistently positive for CR-Kp, and susceptibility testing performed on a urine culture 3 weeks after completion of therapy showed a fosfomycin MIC of >256 μg/ml and a tigecycline MIC of >4 μg/ml. The second patient had CR-Kp (fosfomycin MIC of 16 μg/ml) transplant graft pyelonephritis and a suspected infected ureteral stent and 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 3 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) and had a reinfection with fosfomy-

cin-resistant (MIC > 1,024 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 > 1,024 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 (there were no differences between groups). The readmission rate at 90 days was high overall at 21/37 (57%) and was not significant between groups (50% for the microbiological cure group versus 65% for the microbiological failure group; $P = 0.51$).

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 g fosfomycin tromethamine) per course of therapy. A microbiological cure occurred in 59% (24/41) of patients with a UTI due to an 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% showed *in vitro* susceptibility to fosfomycin (MIC_{50} and MIC_{90} of 32 and 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 study, by Falagas and colleagues, found MIC_{50} and MIC_{90}s of 16 and 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 those for tigecycline (43%) and untreated controls (36%) with CR-Kp in the urine (18). The rationale for microbiological failure will be discussed in more detail, but it 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* than members of the *Enterobacteriaceae* (11). Our cohort consisted of eight *P. aeruginosa* isolates with a fosfomycin MIC_{50} of 8 μg/ml and MIC_{90} of 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 members of the *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* isolates (16).

Previous work at our institution demonstrated that 98.7% of VRE isolates were susceptible *in vitro* to fosfomycin (20). For this cohort, we describe seven isolates, 86% of which were susceptible *in vitro* and for which the microbiological cure rate was 71% ($n = 5/7$). Further data are 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 that 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 the duration of exposure factors into the risk of developing resistance. Use of fosfomycin as a single agent may also contribute, since the development of resistance is known to occur *in vitro* when it is used as monotherapy (4, 21). In this cohort, combination therapy with tigecycline was used for all three patients who developed fosfomycin resistance. The lack of a 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 that 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 an 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. The choice of therapy, including the duration and decision to use combination therapy, was at the discretion of the treating physicians. Other important variables also were 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 that of *in vitro* susceptibility (86%). The largest divergence occurred for CR-KP: 92% *in vitro* susceptibility and a 46% microbiological cure rate. Caution should be used in certain settings, such as with solid organ transplant recipients and patients with ureteral stents. Clinicians also need to be aware of the 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

1. **Charlson ME, Pompei P, Ales KL, MacKenzie CR.** 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. **40**:373–383.
2. **Clinical and Laboratory Standards Institute.** 2011. Performance standards for antimicrobial susceptibility testing: 21st informational supplement. CLSI document M100-S21. Clinical and Laboratory Standards Institute, Wayne, PA.
3. **Curcio D.** 2008. Treatment of recurrent urosepsis with tigecycline: a pharmacological perspective. J. Clin. Microbiol. **46**:1892–1893.
4. **Ellington MJ, Livermore DM, Pitt TL, Hall LM, Woodford N.** 2006. Mutators among CTX-M beta-lactamase-producing Escherichia coli and risk for the emergence of fosfomycin resistance. J. Antimicrob. Chemother. **58**:848–852.
5. **Endimiani A, et al.** 2010. In vitro activity of fosfomycin against blaKPC-containing Klebsiella pneumoniae isolates, including those nonsusceptible to tigecycline and/or colistin. Antimicrob. Agents Chemother. **54**: 526–529.
6. **Falagas ME, et al.** 2008. Antimicrobial susceptibility of multidrug-resistant Gram negative bacteria to fosfomycin. Eur. J. Clin. Microbiol. Infect. Dis. **27**:439–443.
7. **Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE.** 2010. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect. Dis. **10**:43–50.
8. **Hoban DJ, Nicolle LE, Hawser S, Bouchillon S, Badal R.** 2011. Antimicrobial susceptibility of global inpatient urinary tract isolates of Escherichia coli: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program: 2009-2010. Diagn. Microbiol. Infect. Dis. **70**:507–511.
9. **Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group.** 2009. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am. J. Transpl. **9**(Suppl 3):S1–S155.
10. **Lee K, et al.** 2001. Modified Hodge and EDTA-disk synergy tests to screen metallo-beta-lactamase-producing strains of Pseudomonas and Acinetobacter species. Clin. Microbiol. Infect. **7**:88–91.
11. **Lu CL, et al.** 2011. Antimicrobial susceptibilities of commonly encountered bacterial isolates to fosfomycin determined by agar dilution and disk diffusion methods. Antimicrob. Agents Chemother. **55**:4295–4301.
12. **Magiorakos AP, et al.** 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin. Microbiol. Infect. **18**:268–281.
13. **Mandell GL, Bennett JE, Dolin R.** 2010. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 7th ed. Churchill Livingstone/Elsevier, Philadelphia, PA.
14. **Maraki S, et al.** 2009. Susceptibility of urinary tract bacteria to fosfomycin. Antimicrob. Agents Chemother. **53**:4508–4510.
15. **Nix DE, Matthias KR.** 2010. Should tigecycline be considered for urinary tract infections? A pharmacokinetic re-evaluation. J. Antimicrob. Chemother. **65**:1311–1312.
16. **Oteo J, et al.** 2010. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli. J. Antimicrob. Chemother. **65**:2459–2463.
17. **Rodriguez-Rojas A, et al.** 2010. Assessing the emergence of resistance: the absence of biological cost in vivo may compromise fosfomycin treatments for P. aeruginosa infections. PLoS One **5**:e10193. doi:10.1371/journal.pone.0010193.
18. **Satlin MJ, et al.** 2011. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem-resistant Klebsiella pneumoniae from the Urine. Antimicrob. Agents Chemother. **55**: 5893–5899.
19. **Senol S, et al.** 2010. Carbapenem versus fosfomycin tromethanol in the treatment of extended-spectrum beta-lactamase-producing Escherichia coli-related complicated lower urinary tract infection. J. Chemother. **22**: 355–357.
20. **Shrestha NK, et al.** 2003. Antimicrobial susceptibility of vancomycin-resistant Enterococcus faecium: potential utility of fosfomycin. Scand. J. Infect. Dis. **35**:12–14.
21. **Souli M, et al.** 2011. In vitro interactions of antimicrobial combinations with fosfomycin against KPC-2-producing Klebsiella pneumoniae and protection of resistance development. Antimicrob. Agents Chemother. **55**:2395–2397.