



THE NEBRASKA MEDICAL CENTER  
FOSFOMYCIN: REVIEW AND USE CRITERIA

## BACKGROUND

Fosfomycin is a phosphonic acid derivative, which inhibits peptidoglycan assembly, thereby disrupting cell wall synthesis.<sup>1</sup> Its uptake into the bacterial cell occurs via active transport, by the L- $\alpha$ -glycerophosphate transport and hexose phosphate uptake systems. Once inside the bacteria, it competes with phosphoenolpyruvate to irreversibly inhibit the enzyme enolpyruvyl transferase that catalyzes the first step of peptidoglycan synthesis.<sup>1,2</sup> By irreversibly blocking this enzyme, cell wall synthesis is interrupted. Fosfomycin also decreases bacteria adherence to uroepithelial cells. Fosfomycin has been approved by the Food and Drug Administration (FDA) for the treatment of uncomplicated urinary tract infection (UTI) in adult women that is caused by *Escherichia coli* and *Enterococcus faecalis*.<sup>2</sup> Oral fosfomycin has also been used for non-FDA approved indication such as complicated UTI without bacteremia. Intravenous fosfomycin, which is not available in the US, has also been used for a variety of infections including meningitis, pneumonia, and pyelonephritis.<sup>2</sup> Fosfomycin does not have an indication for the treatment of pyelonephritis or perinephric abscess.<sup>2,3</sup>

Fosfomycin has broad spectrum of activity against aerobic gram positive and gram negative pathogens. It was shown in vitro and in clinical studies, to have activity against  $\geq 90\%$  of strains of *E. coli*, *Citrobacter diversus*, *C. freundii*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *P. vulgaris*, *Providencia rettgeri*, *Pseudomonas aeruginosa*, *E. faecalis* and *E. faecium* [including vancomycin resistant (VRE)] species, and *Staphylococcus aureus* [including Methicillin resistant *Staphylococcus aureus* (MRSA)] associated with UTI.<sup>2,3</sup> Currently, the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints exist only for *E. coli* and *E. faecalis*, with a fosfomycin MIC  $\leq 64$  mg/L considered susceptible for the treatment of UTIs.<sup>2,4</sup>

Fosfomycin is available only in the oral form in the US. Following oral administration, fosfomycin is rapidly absorbed with an oral bioavailability of 30-37% depending on fed state.<sup>2,5</sup> Fosfomycin does not undergo hepatic metabolism, and is primarily eliminated as unchanged drug by the kidneys through glomerular filtration. About 38% of the administered dose is eliminated in the kidneys.<sup>2</sup> Pharmacokinetic studies of fosfomycin show that peak serum concentration occurs within 4 hours of a 3g dose, with detectable levels (100mg/L) at 48 hours post dose.<sup>5,6</sup> Hence repeated dosing of fosfomycin is typically every 48 hours. Fosfomycin distributes into tissues (kidneys, bladder wall, prostate and seminal vesicles), although levels are generally lower than those in the urine. Renal dysfunction decreases excretion of fosfomycin.<sup>2</sup> In patients with varying renal dysfunction (CrCl 7-54ml/min) the recovery of fosfomycin in the urine decreased from 32% to 11%.<sup>7</sup> The clinical implication of this finding is unknown. Fosfomycin is eliminated by renal replacement therapy; therefore doses should be given after hemodialysis.<sup>3,6</sup> Fosfomycin exhibits time dependent killing. Thus optimal killing is achieved when the free drug concentration is above the organism's MIC (%fT>MIC) for 40-50% of the dosing interval.<sup>8</sup>

Resistance to fosfomycin is primarily chromosomal although cases of plasmid mediated resistance have been described.<sup>9,10</sup> Chromosomal resistance occurs as a result of mutations that interfere with the two transport systems required for fosfomycin uptake.<sup>2</sup> This mutation results in reduced intracellular concentrations of the drug. These mutations are uncommon and not associated with resistance to other agents. Two plasmid genes *fosA* and *fosB* have been described.<sup>9,10</sup> *FosA* gene has been detected in gram negatives including *S. marcescens*, *S. liquefaciens*, *K. oxytoca*, *K. pneumoniae* and *E. coli*. *FosA* is a glutathione S-transferase that adds glutathione to fosfomycin rendering it inactive.<sup>9</sup> *FosA* mediated resistance has not been described in gram positive bacteria. However, gram positive pathogens, mainly *Staphylococcus spp.* harbor a different plasmid gene, *FosB* and the mechanism of resistance has not been characterized.<sup>10</sup> Plasmid mediated resistance is quite rare.

## DEFINITIONS

Urinary tract infections (UTI) may be defined by their location (lower vs. upper) or whether they are complicated or uncomplicated. Typical symptoms of lower urinary tract infections include dysuria, frequency, urgency, suprapubic pain/tenderness, and/or hematuria usually in combination with pyuria and bacteriuria. Symptoms of upper urinary tract infections include fever, chills, nausea, vomiting, and flank pain or tenderness. Infections of the urinary tract can be categorized in 3 ways as well: uncomplicated, complicated, and pyelonephritis.<sup>11</sup> It is important to provide an overview of these terms for decision making regarding the use of fosfomycin.<sup>12</sup>

1. **Uncomplicated UTI** is defined as a UTI in someone with a structurally and neurologically normal urinary tract and usually only applies to premenopausal women.
2. **Complicated UTI** (cUTI) is characterized by UTI in the presence of functional or anatomical abnormalities of the urinary tract and usually includes UTIs in men, children, and pregnant women. One or more of the following conditions are usually present that increases the risk of developing an infection:

- Indwelling urinary catheter
  - Impaired bladder function due to neurologic or functional abnormalities (neurogenic bladder, obstructive uropathy, stones, etc.)
  - Azotemia due to intrinsic renal disease
3. **Pyelonephritis** is an infection involving the kidneys that manifests with upper symptoms as mentioned above. This infection may be associated with bacteremia with the same pathogen isolated in the urine. Symptoms of lower urinary tract infection may or may not be present. Although distinct disease states, the signs and symptoms often encountered in cUTI may be similar to those seen in acute pyelonephritis

## RECOMMENDATION

The newly released cystitis guidelines by IDSA recommend nitrofurantoin, trimethoprim-sulfamethoxazole or fosfomycin be used as first line agents for the empiric treatment of cystitis in adult patients.<sup>13</sup> They do not include fosfomycin as an agent for treatment of pyelonephritis. These guidelines and reported findings from clinical studies evaluating the efficacy of fosfomycin have been adapted for the proposed institutional fosfomycin dosing guidance.

As fosfomycin is unique in its mechanism of action and less likely to select for co-resistance it may have a place in the treatment of both simple cystitis and more complicated UTI although literature on the latter is less common. Based upon literature reviewed, the following recommendations regarding the use of fosfomycin are proposed:

### Criteria for use at TNMC:

1. Single dose fosfomycin for simple cystitis in uncomplicated UTIs can be used without restriction
2. Use for any other indication or duration **requires** documented sensitivity to the agent
  - a. Bacterial isolates are not routinely tested for susceptibility to fosfomycin but susceptibility testing is available by request in the microbiology laboratory (Please contact 552-2090 if this is desired)
  - b. The agent will not be dispensed for use until susceptibility has been documented
3. An ID consult is strongly recommended for all uses outside of simple cystitis

### Suggested Reasonable Uses:

1. Empiric treatment of simple cystitis (Nitrofurantoin and TMP-SMX are also potential options)
2. Complicated cystitis when other oral options are not available including:
  - a. ESBL producing and other multidrug resistant gram-negative pathogens
  - b. VRE resistant to usual first line options such as nitrofurantoin or tetracycline
3. Due to limited systemic absorption, fosfomycin should **not** be used for pyelonephritis
4. If persistence or reappearance of bacteriuria occurs after treatment with fosfomycin, repeat testing for sensitivity should be performed and another agents be considered as resistance can develop after treatment

**Table 1: Fosfomycin dosing guidance**<sup>14,15</sup>

Patients ≥15 years				Children <15 years (≥50ml/min) <sup>c</sup>	Children ≤1 year (CrCl ≥50ml/min) <sup>c</sup>
Infection (See definitions)	CrCl ≥50ml/min	CrCl 10-50ml/min <sup>a</sup>	CrCl <10ml/min <sup>ab</sup>		
Uncomplicated cystitis <sup>d</sup>	3g oral x 1 dose	3g sachet oral x 1 dose	3g sachet oral x 1 dose	2g sachet oral x 1 dose	1g sachet oral x 1 dose
Complicated cystitis <sup>d</sup>	3 g oral every 2 days for 7-21 days <sup>e</sup>	3g oral every 3 days for 7-21 days <sup>e</sup>	3g oral every 3 days for 7-21 days <sup>e</sup>	2g oral every 2 days for 7-21 days <sup>ef</sup>	1g oral every 2 days for 7-21 days <sup>e</sup>

<sup>a</sup>Renal dysfunction decreases renal excretion (concentration) and it is unknown if adequate levels are achieved in the urine. <sup>b</sup>In patients on HD, dose after HD session. <sup>c</sup>Adjust dosing interval for renal function as prescribed for ≥15 years. <sup>d</sup>Mix powder in 90-120 ml of **cool water** until it dissolves. <sup>e</sup>Duration of therapy should be based upon type of infection and pathogen. <sup>f</sup>Alternate dosing of 3g oral every 2 days for 7-14 days may be offered to children 12-14 years of age with CrCl ≥50ml/min.  
HD = hemodialysis

## JUSTIFICATION

### Internal Data

A report of urinary isolates of vancomycin resistant enterococci (VRE) and extended spectrum beta-lactamase (ESBL) producing organisms over the period January 2009 to December 2010 was generated. Clinical cases excluding duplicate urine cultures were reviewed for susceptibility to first line oral antibiotics and are presented in Table 2 below. VRE accounted for 1.45% (119/8213) and ESBL producing pathogens 0.62% (51/8213) of all urine cultures performed during this period.

Table 2: TNMC cases of VRE and ESBL pathogen Jan 2009-Dec 2010				
		Vancomycin-resistant Enterococci (cases=119; unique patients =95)		
		Nitrofurantoin resistant (%)	Tetracycline resistant (%)	
Vancomycin-resistant Enterococci (n=119)		70/119 (59)	87/119 (73)	
Resistant Both First Line Agents		54/119 (43.4)	54/119 (43.4)	
		Extended Spectrum Beta-Lactamases (ESBL) (cases= 51; unique patients = 46)		
		Ciprofloxacin resistant (%)	TMP/SMX resistant (%)	Nitrofurantoin resistant (%)
<i>E. coli</i> (n=28)		24/28 (86)	18/28 (64.3)	2/28 (7.1)
<i>Klebsiella oxytoca</i> (n=14)		13/14 (92.8)	0/14 (0)	1/14 (7.1)
<i>Klebsiella pneumoniae</i> (n=9)		4/9 (44.4)	5/9 (55.6)	5/9 (55.6)
Overall Resistance		41/51 (80.4)	23/51 (45.1)	8/51 (15.7)
Resistant to Three First Line Agents		5/51 (9.8)	5/51 (9.8)	5/51 (9.8)

VRE =Vancomycin resistant enterococci; ESBL=extended spectrum beta-lactamases; TMP/SMX =sulfamethoxazole/trimethoprim

As can be seen from Table 2, a majority of VRE isolates were *E. faecium*. Nitrofurantoin had lower resistance rate compared to tetracycline (63.1% vs. 73% respectively) for enterococci. *E. faecalis* was less likely to be resistant to nitrofurantoin compared to tetracycline. Fifty four of 119 (43.4%) clinical cases were resistant to both nitrofurantoin and tetracycline, hence annihilating first line oral agents for treating VRE UTI. This presents an area for the use of fosfomycin for the treatment of UTI. ESBL production was reported in *E. coli*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae*. *E. coli* was the predominant uropathogen. Ciprofloxacin was the least reliable agent for treating ESBL producing isolates particularly if the isolate is *Klebsiella oxytoca* or *E. coli*. Trimethoprim/Sulfamethoxazole (TMP/SMX) was less reliable for treating ESBL producing *E. coli* and greater resistance exist for nitrofurantoin among *Klebsiella pneumoniae* isolates. Overall, nitrofurantoin is a more reliable drug followed by TMP/SMX then ciprofloxacin (resistance rate 15.7% vs. 45.1% vs. 80.4% respectively). Resistance to all three agents was present 9.8% of the time, hence presenting an opportunity for the use of fosfomycin.

### Literature Review

Several studies have evaluated the use of fosfomycin for the treatment of UTIs due to susceptible and multidrug resistant pathogens. In these studies, clinical efficacy of fosfomycin ranged from 87.5-92.3% and microbiologic efficacy 81-98%.<sup>3</sup>

Evidence 1: *Fosfomycin versus nitrofurantoin*: Stein GE. *Clin Ther* 1999; 21:1864–72<sup>16</sup>

- Phase III multicenter (26 centers in US) double blind randomized trial of fosfomycin 3g po once compared with nitrofurantoin 100mg po q12hr for 7 days
- Study population included 749 ambulatory females aged ≥12 years with acute uncomplicated lower UTI (symptoms ≤96 hour)
- Patients with pyelonephritis, pregnant or lactating, structural or functional abnormalities, recurrent UTI (>3/year), renal or hepatic dysfunction, received antibiotic treatment 2 days prior to presentation were excluded
- Clinical (symptoms; dysuria, frequency, or urgency) and microbiologic (growth of ≥10<sup>5</sup> CFU/ml in urine) were pertinent diagnostic criteria
- Follow up visits occurred at 5-11 days (visit 2) after treatment initiation; 5-11 days (visit 3) and 4-6 weeks (visit 4) after the last day of treatment
- Outcomes of interest assessed at respective clinic visits were:
  - Bacteriologic response [as cure (urine culture with <10<sup>4</sup>CFU/mL of uropathogen) or failure (urine culture of ≥10<sup>4</sup> CFU/mL of uropathogen)]
  - Clinical response [cure (elimination of all pretherapy symptoms), improvement (most but not all symptoms improved or absent), or failure (not improved from initial assessment)].
- Results:

- 228 of 749 patients excluded from intent to treat (ITT) analysis because growth in urine  $\leq 10^5$  CFU/ml
  - 521 remaining patients (fosfomycin n=269 and nitrofurantoin n=252) constituted the modified ITT population
- Uropathogens included; *E. coli*, *Proteus mirabilis*, *Klebsiella pneumonia*, and *Staphylococcus saprophyticus*. *E. coli* represented the most common uropathogen
  - 94% of pretreatment isolates were susceptible to fosfomycin compared with 83% for nitrofurantoin

Visit	Clinical cure		P value	Bacteriologic cure		P value
	Fosfomycin n(%)	Nitrofurantoin n(%)		Fosfomycin n(%)	Nitrofurantoin n(%)	
Visit 2	216/263 (82.1)	206/245 (84.1)	0.3	192/246 (78.1)	189/219 (86.3)	0.02
Visit 3	207/229 (90.4)	193/217 (88.9)	0.3	146/168 (86.9)	127/157 (80.9)	0.17
Visit 4	184/202 (91.1)	165/180 (91.7)	0.91	120/125 (96)	102/112 (91.1)	0.18

Conclusion:

- Clinical and microbiologic cure rates were not different between fosfomycin and nitrofurantoin at 3<sup>rd</sup> and 4<sup>th</sup> visits. However early bacteriologic cure (visit 2) was higher for nitrofurantoin ( $p=0.02$ ) with no difference in clinical cure rates
- Adverse events were not different between the two treatment groups (5.3% for fosfomycin and 5.6% for nitrofurantoin)
- Fosfomycin presents a reasonable alternative particularly when antimicrobial resistance and patient's allergy precludes the use of first line agents for UTI.

Evidence 2: *Fosfomycin vs. TMP/SMX*: **Abstract:** Crocchiolo P. et al. *Chemotherapy* 1990; 36 Suppl 1:37-40<sup>17</sup>

- Randomized open label study of fosfomycin 3 g versus TMP/SMX 160/800 q12hr for 3 days
- Included 73 ambulatory non-pregnant women with uncomplicated UTIs
  - Patients excluded if they had complicated UTI, hypersensitivity to study drugs or renal insufficiency
- Result:
  - 36 were evaluable; 19 treated with fosfomycin and 17 with TMP/SMX
  - Bacteriological success after 4 weeks of follow-up was evaluated as such
    - Fosfomycin: cure in 17 (89%), and failure in 2 (11%).
    - TMP/SMX: cure in 13 (76%), and failure in 4 (24%).
  - Adverse events were reported in 3 patients on fosfomycin (2 diarrhea, 1 epigastralgia) and in 2 on TMP/SMX (1 rash, 1 asthenia)
- Conclusion: numerically fosfomycin had higher sustained bacteriologic cure compared to TMP/SMX at 4 weeks after treatment completion

Evidence 3: *Fosfomycin vs. ciprofloxacin*: **Abstract:** Bozkurt O, et al. *Turk Uroloji Dergisi* 2008; 34: 360–2<sup>18</sup>

- Efficacy of fosfomycin 3g x 1 dose was compared to ciprofloxacin 500mg po q12hr for 3 days in a double blind randomized controlled trial of 100 adult non-pregnant women with uncomplicated UTI
  - 50 received fosfomycin and 50 ciprofloxacin
  - Patients had to have symptoms of UTI (dysuria and frequency with pyuria) and bacteriuria ( $>10^5$  cfu/ml of urine)
  - Patients were excluded if they had significant leukocytosis, burning pain, high fever and upper UTI
  - Follow up assessment of treatment outcomes occurred at 10 days post treatment
- Results:
  - The mean age of study patients was  $36.2 \pm 4.53$  years
  - Isolated uropathogens included *E. coli*, *Staphylococcus aureus*, *Klebsiella oxytoca*. *E. coli* was the most predominant organism
  - Clinical cure among patients who received fosfomycin was 48 of 50 patients (96%) compared to 47 of 50 patients (94%) in the ciprofloxacin group

Conclusion: Single dose fosfomycin for the treatment of uncomplicated UTI in women was similar in efficacy and was more tolerable than ciprofloxacin

Evidence 4: *Fosfomycin vs. comparators*: Falagas ME, et al. *J Antimicrob Chemother.* 2010; 65: 1862-1877<sup>15</sup>

- Falagas and colleague conducted a meta-analysis of randomized controlled trials of fosfomycin versus comparators to evaluate its effectiveness and safety in the treatment of cystitis.
- 27 trials were included in the analysis
  - 8 were double blind
  - 16 involved exclusively non-pregnant female patients
  - 3 involved adult mixed populations of older age (non-pregnant female and male patients with acute/recurrent UTI).
  - 5 involved pregnant patients
  - 3 involved pediatric patients

- Comparative agents
  - Trials involving non-pregnant females: fosfomycin 3 g single dose (pediatric trials 1-2grams po x 1) was compared to
    - Quinolones (norfloxacin, ciprofloxacin and ofloxacin) in 9 trials
    - Trimethoprim in 2 trials
    - Trimethoprim/sulfamethoxazole in 1 trial
    - $\beta$ -lactams (cephalexin and amoxicillin) in 2 trials
    - Nitrofurantoin in 2 trials
  - In the mixed group studies (non-pregnant and male patients), fosfomycin was compared to
    - norfloxacin, netilmicin or amikacin, and amoxicillin/clavulanate
  - Studies of pregnant women, fosfomycin was compared to
    - $\beta$ -lactams in 3 trials (amoxicillin/clavulanate and ceftibuten)
    - Nitrofurantoin in 1 trial
  - In the three pediatric trials fosfomycin was compared with netilmicin and piperidic acid
- Outcomes
  - Primary effectiveness outcome was clinical success defined as the complete (cure) and/or non-complete (improvement) resolution of symptoms at the end of treatment
  - Secondary effectiveness outcomes included:
    - Microbiological success (eradication); presence of a negative urine culture at the end of treatment
    - Microbiological relapse: detection of the same treatment pathogen in urine at long-term follow-up evaluation, after the acquisition of sterile culture
    - Microbiological re-infection: detection of a pathogen at a long-term follow-up evaluation that is different from baseline isolate, after prior acquisition of a sterile culture
  - Safety outcomes included reports of any adverse event during the study period and study withdrawals due to adverse events
- Result:
  - Duration of treatment ranged from 3 to 7 days for comparators in 22 trials with the remainder involving single dose regimen as with fosfomycin

Composite Outcomes	Population Studied	Number of trials	Number of patients	Risk ratio (95% CI)
Clinical success	Non-pregnant females	10	1657	1.00 (0.98–1.03)
	Mixed studies	3	286	0.98 (0.87–1.11)
	Pregnant women	-	-	-
	Pediatrics	-	-	-
Microbiological success	Non-pregnant females	12	1602	1.02 (0.97–1.07)
	Mixed studies	3	218	1.01 (0.88–1.17)
	Pregnant women	4	505	1.00 (0.96–1.05)
	Pediatrics	2	209	0.98 (0.92–1.05)
Safety	Non-pregnant females	13	2388	1.25 (0.83–1.88)
	Mixed studies	3	297	0.76 (0.29–1.96)
	Pregnant women	4	507	0.35 (0.12–0.97)
	Pediatrics	None	None	None

- Data was not reported for pregnant women and pediatrics for clinical success due to limited data
- There was no difference in clinical success in separate analysis between fosfomycin and comparators in trials involving non-pregnant females and the mixed population
- There was also no difference in clinical cure in separate analyses, as well as in comprehensive analysis (7 RCTs, 1272 patients, RR=1.00, 95% CI=0.96–1.03)
- There was no difference observed between patients treated with fosfomycin versus comparator(s) in separate analyses, as well as in comprehensive analysis regarding microbiological relapse (8 RCTs, 828 patients, RR=0.84, 95% CI=0.50–1.39), and microbiological re-infection (7 RCTs, 748 patients, RR=1.26, 95% CI=0.77–2.02)
- No difference was observed with regards to occurrence of study withdrawals due to adverse events among studies of non-pregnant women (2 RCTs, 980 patients, RR=2.01, 95% CI=0.05–80.21); mixed studies (3 RCTs, 297 patients, RR=.33, 95% CI=0.03–3.08); none in pregnant and pediatric studies

Conclusion: fosfomycin showed comparable efficacy for the treatment of patients with cystitis and may provide a valuable alternative option for the treatment of cystitis in non-pregnant and pregnant women, elderly and pediatric patients

**Extended spectrum beta lactamase (ESBL) producers:**

Due to its unique mechanism of action fosfomycin has been evaluated *in-vitro* and *in-vivo* for the treatment of ESBL-producing pathogens and has been shown to be efficacious.<sup>19</sup>

Evidence 1: Auer S, et al. *Antimicrob Agents Chemother.* 2010;54(9):4006-8<sup>19</sup>

- Evaluated in vitro susceptibility of *E. coli* isolates to select treatment antibiotics
- 100 ESBL positive *E. coli* from ambulatory patients with confirmed UTI collected October 2004-January 2008
- Interest antibiotics were fosfomycin, pivmecillinam, nitrofurantoin and intravenous ertapenem
- Result:
  - Isolates were collected from females (78%) and males (22%); mean age 57.6 (2-97 years)

Susceptibility of ESBL-producing *E. coli* to test antibiotics

Yr	No. <i>E. coli</i> from urine	No of ESBL isolates (%)	Number (%) of ESBL-producing <i>E. coli</i> isolates susceptible to					
			FOS	ERT	NF	TMP/SMX	GM	CP
2005	1,809	18 (0.99)	17 (94.4)	18 (100)	16 (88.9)	6 (33.3)	13 (72.2)	5 (27.8)
2006	1,995	28 (1.40)	27 (96.4)	28 (100)	27 (96.4)	8 (28.6)	22 (78.6)	2 (7.14)
2007	2,262	44 (1.94)	44 (100)	44 (100)	41 (93.2)	10 (22.7)	35 (79.5)	13 (29.5)
<b>Total</b>	<b>6,076<sup>a</sup></b>	<b>100 (1.64)<sup>a</sup></b>	<b>97 (97)<sup>a</sup></b>	<b>66 (100)<sup>a</sup></b>	<b>94 (94)<sup>a</sup></b>	<b>27 (27)<sup>a</sup></b>	<b>78 (78)<sup>a</sup></b>	<b>22 (22)<sup>a</sup></b>

FOS= fosfomycin; ERT=ertapenem; NF= nitrofurantoin; TMP/SMX =trimethoprim/sulfamethoxazole; GM=gentamicin; CP= ciprofloxacin. <sup>a</sup>Includes 90 (from 2005 to 2007) plus 10 isolates from 2004 and 2008

Conclusion:

- Based on these in vitro susceptibility result, fosfomycin, nitrofurantoin and pivmecillinam could be considered treatment options
- Fosfomycin exhibited excellent in vitro susceptibility to ESBL-producing *E. coli*
- Other studies have also reported similar high susceptibilities of ESBL-producing *E. coli* to fosfomycin.<sup>20-22</sup> The study by Prakash and colleague involving 57 ESBL Enterobacteriaceae, predominantly *Escherichia coli* from USA reported a 95.6% susceptibility rate to fosfomycin.<sup>22</sup>

Evidence 2: Pullukcu H, et al. *Int J Antimicrob Agents.* 2007;29(1):62-5<sup>23</sup>

- Retrospective chart review to determine efficacy of fosfomycin for treatment of ESBL producing *E. coli* UTI
- Included inpatient and outpatient data between September 2004-July 2006
  - Patients aged >18 with dysuria, urinary frequency or urgency, pyuria (>20 leukocytes/mm<sup>3</sup>), and an ESBL-producing *E. coli* in urine culture (>10<sup>5</sup>cfu/mm<sup>3</sup>), without leukocytosis or fever were included
  - Patients had follow up culture 7-9 days post treatment
  - 52 patients (aged 55.0±18.3, range 19–85; 25 males and 27 males) treated with 3g po every other day x 3 doses
  - Outcomes were clinical success (resolution of symptoms on control visit), and microbiological success (sterile control urine cultures)
- Result:
  - All clinical isolates were resistant to ciprofloxacin and TMP/SMX, but susceptible to fosfomycin and carbapenems
  - Overall clinical and microbiological success with fosfomycin was 94.3% (49/52) and 78.5% (41/52), respectively
  - Analysis of patients who failed therapy was conducted to identify pertinent risk factors
    - Risk factors explored: presence of indwelling catheter, hemi/quadripareisis, malignancies of the urinary tract or other, diabetes mellitus, renal transplant, nephrolithiasis, and recent urological intervention
    - There were no statistically significant differences noted between failure rates in those with or without underlying risk factors
  - Relapse rate for the 28/52 urine cultures (performed 28 days after therapy) was 0% while re-infection rate was 10.7% (3/28)

Conclusion: fosfomycin is a suitable option for the treatment of lower UTI due to ESBL-producing *E. coli* although microbiologic success was low.

Evidence 3: Rodríguez-Baño J, et al. *Arch Intern Med.* 2008;168(17):1897-902<sup>24</sup>

- Multicenter (11 hospitals) case control study to investigate risk factors for all types of community acquired ESBL-producing *E. coli* infections
  - Among patients who had UTI, the goal was to delineate the efficacy of fosfomycin 3g single dose and amoxicillin/clavulanate 500 mg/125 mg every 8 hours, for 5-7 days
- 122 cases were included and 242 controls between February 2002-May 2003
  - Exclusion: case and controls hospitalized for >48 hours prior to sample collection; hospitalized >48 hours during the preceding month; prior ESBL-producing *E. coli* isolation in the previous year
- Risk factors explored: age > 60 years; female sex; diabetes mellitus; recurrent UTIs; previous invasive procedures of the urinary tract; follow-up in outpatient clinic; previous receipt of aminopenicillins, cephalosporins, and fluoroquinolones.
- Outcome of clinical cure defined as absence of symptomatic or recurrent UTI

Result:

- ESBL-producing *E. coli* were isolated from urine culture in 113 cases (93%) and blood culture in 6 (5%)

- Among patients with UTI, 73 had cystitis (60%), 33 asymptomatic bacteriuria (27%), 5 pyelonephritis (4%), and 2 prostatitis (2%)
- Seven patients (6%) were bacteremic and 3 of these patients had pyelonephritis
- 12 (10%) of patients with culture positive ESBL-producing *E. coli* required hospitalization
- All isolates were sensitive to fosfomycin but resistance to amoxicillin/clavulanate was reported in 35(29%) of 122 clinical isolates
  - Resistance to ciprofloxacin was 64% and 57% to TMP/SMX

Outcomes of patients with cystitis treated with fosfomycin or amoxicillin/clavulanate; n=65 <sup>a</sup>				
	Fosfomycin n(%) n=28	Amoxicillin/clavulanate n (%) n=37		
		Total n=37	MIC≤8mg/L <sup>b</sup> n=28	MIC≥16mg/L <sup>b</sup> n=9
Clinical cure rate	26 (93)	31 (84)	26 (93)	5 (56)

MIC= minimum inhibitory concentration; <sup>a</sup> information on treatment for remaining cases not reported <sup>b</sup>p value 0.02 for comparison between MIC≤8mg/L vs. MIC≥16mg/L

- Estimated population-based pool incidence of community-acquired ESBL-producing *E. coli* infections was 2.2 cases/100 000 population per year (1.5-3.9)
- Age > 60 years, female sex, certain underlying diseases (diabetes mellitus), recurrent UTI, healthcare associated infection, indwelling bladder catheter, invasive urinary tract procedure, and previous antimicrobial (aminopenicillins, cephalosporins, fluoroquinolones) were associated with ESBL-producing *E coli*
- Majority of cases [57 (47%)] had ≥3 risk factors

Conclusion: fosfomycin and amoxicillin/clavulanate are options for the treatment of UTI due to community acquired ESBL-producing *E coli*. However, isolates with higher MICs (≥16mg/L) may be less responsive to amoxicillin/clavulanate

Evidence 4: Falagas ME, et al. *Lancet Infect Dis.* 2010; 10: 43-50<sup>25</sup>

- Systematic analysis of studies evaluating antimicrobial susceptibility and clinical effectiveness of fosfomycin for the treatment of infections due to multidrug resistant Enterobacteriaceae
  - Included isolates that were multidrug resistance (per individual study definition), carbapenem resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases
- 5057 Enterobacteriaceae clinical isolates from 17 antimicrobial-susceptibility studies included in review
  - Isolates included: *E. coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Providencia stuartii*, *Morganella morganii*
  - 4448 (88%) were ESBL producers
- 4 clinical studies for a total of 21 studies were included in the analysis
- Result:
  - 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin using the CLSI susceptibility breakpoint of ≤64 mg/L

Fosfomycin Susceptibility In Different Pathogens	All Enterobacteriaceae <sup>a</sup> (%)	<i>Escherichia coli</i> <sup>a</sup> (%)	<i>Klebsiella pneumoniae</i> <sup>a</sup> (%)
Any multidrug-resistance <sup>b</sup>	3891/4478 (86.9)	1672/1725 (96.9)	608/748 (81.3)
ESBL-producer	3569/3911 (91.3)	1604/1657 (96.8)	608/748 (81.3)
Isolates from urinary tract	2061/2227 (92.5)	704/721 (97.6)	-
Isolates from outpatients	292/297 (98.3)	292/297 (98.3)	-
Isolates from hospitalized patients	1344/1519 (88.5)	864/909 (95)	480/610 (78.7)

<sup>a</sup>Cumulative susceptibility per CLSI criteria. <sup>b</sup>Multidrug resistance, carbapenem-resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases.

- Clinical effectiveness of fosfomycin was demonstrated in 2 studies that evaluated oral fosfomycin for lower UTIs with ESBL-producing *E coli*
  - Cumulative clinical cure was reported in 75 of the 80 (93.8%) patients included in these studies
  - Lower microbiologic cure rate reported in one study (41 of 52; 78.8%)

Conclusion:

- Fosfomycin showed excellent in vitro susceptibility to Enterobacteriaceae isolates with advanced resistance to antimicrobial drugs

- In contrast to outpatient isolates, in two studies of inpatient and nursing home patients, fewer than 50% of the isolates (involving *Enterobacter aerogenes* and *K pneumoniae*, respectively) were susceptible to fosfomycin
- AmpC producers also had lower susceptibility to fosfomycin compared to ESBL producers
- Achievable clinical success was high but microbiologic success is lower

### **Vancomycin resistance enterococcus:**

Fosfomycin has been used for the treatment of vancomycin resistance *Enterococcus faecium* and *Enterococcus faecalis*.<sup>26,27</sup> An extensive review of the treatment of vancomycin resistant enterococci (VRE) was summarized in the recently published article by Heintz and colleagues.<sup>12</sup> The publication outlines diagnostic criteria, risk factors, comparative susceptibility of fosfomycin to other agents active against VRE UTI, fosfomycin dosing, and algorithm for the management of a patient with VRE UTI.

Evidence 1: Allerberger F, et al. *J Antimicrob Chemother.* 1999; 43: 211-217<sup>27</sup>

- In vitro susceptibility testing of fosfomycin against 189 (majorly clinical) enterococci strains (with and without glycopeptides resistance)
  - *Enterococcus faecium* (VanA, n=69; VanB, n=5; glycopeptide-sensitive, n=8)
  - *Enterococcus faecalis* (VanA, n=11; VanB, n=3; glycopeptides sensitive, n=10)
  - *Enterococcus gallinarum* (VanC1, n=10)
  - *Enterococcus casseliflavus* (VanC2, n=2)
- MICs of fosfomycin were determined by agar dilution test and broth microdilution test and media supplemented with  $\alpha$ -D-glucose-6-phosphate
  - Also disc diffusion test [per then National Committee for Clinical Laboratory Standards (NCCLS) now CLSI method] performed
- MIC of  $\geq 128$  mg/L considered resistant, 32–64 mg/L intermediate, and  $\leq 16$  mg/L susceptible per study criteria
- Result:

Isolates		Susceptibility MIC mg/L n (%)				MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)
		$\leq 16$	32-64	$\geq 128$	CLSI $\leq 64$		
Agar dilution test	VRE <i>faecium</i> (n=74)	17 (23)	53 (71.6)	4 (5.4)	70 (94.6)	32	64
	VSE <i>faecium</i> (n=8)	3 (37.5)	5 (62.5)	-	8 (100)		
	VRE <i>faecalis</i> (n=14)	3 (21.4)	11 (78.6)	-	14 (100)		
	VSE <i>faecalis</i> (n=10)	1 (10)	9 (90)	-	10 (100)		
	VRE <i>gallinarum</i> (n=10)	-	10 (100)	-	10 (100)		
	VRE <i>casseliflavus</i> (n=2)	-	2 (100)	-	2 (100)		
	<b>Total (n=118)</b>	<b>24 (20.3)</b>	<b>90 (76.3)</b>	<b>4 (3.4)</b>	<b>114 (97)</b>		
Broth dilution test	VRE <i>faecium</i> (n=74)	4 (5.4)	63 (85)	7 (9.5)	67 (90.5)	64	64
	VSE <i>faecium</i> (n=8)	1 (12.5)	7 (87.5)	-	8 (100)	32	64
	VRE <i>faecalis</i> (n=14)	12 (85.7)	2 (14.3)	-	14 (100)	16	32
	VSE <i>faecalis</i> (n=10)	6 (60)	4 (40)	-	10 (100)	32	64
	VRE <i>gallinarum</i> (n=10)	1 (10)	9 (90)	-	10 (100)	32	64
	VRE <i>casseliflavus</i> (n=2)	-	2 (100)	-	2 (100)	32	64
	<b>Total (n=118)</b>	<b>24 (20.3)</b>	<b>87 (73.7)</b>	<b>7 (5.9)</b>	<b>111 (94.1)</b>	<b>32</b>	<b>64</b>

VRE= vancomycin resistant enterococci; VSE= vancomycin susceptible enterococci; MIC =minimum inhibitory concentration CLSI= Clinical and Laboratory Standards Institute

- By disc diffusion test, fosfomycin inhibited 96% of the VRE strains
- Conclusion:
- Resistance to fosfomycin was detected among VRE *faecium* isolates
    - There were occasional discordant test results between agar dilution (4 resistant isolate), disc diffusion (10 resistant isolate) and broth dilution (7 resistant isolate)
  - Overall, the three methods had good correlation in detecting fosfomycin resistance
  - Based on CLSI breakpoint susceptibility of  $\leq 64$ mg/L for vancomycin-susceptible *E. faecalis*, all the enterococci strains had excellent in vitro susceptibility to fosfomycin (97% vs. 94%)
  - However, if judging based on study susceptibility breakpoints, the MICs of fosfomycin for most VRE isolates were in the intermediate range, yielding a MIC<sub>50</sub> of 32 mg/L and an MIC<sub>90</sub> of 64 mg/L

Evidence 2: Perri MB, et al. *Diagn Microbiol Infect Dis* 2002;42:269–71<sup>28</sup>

- Evaluated in vitro activity of fosfomycin against 75 clinical isolates of VRE
  - All were clinical isolates from hospitalized patients from 1991 to 1998 from different U.S. hospitals
  - 52 isolates were *E. faecium* and 23 isolates were *E. faecalis*
  - 22 isolates were from urine and 16 isolates from blood
  - MIC determined by E-test, microtiter broth dilution, and according to then NCCLS now CLSI guidelines
  - Used NCCLS breakpoint susceptibility of fosfomycin for urinary tract isolates (MIC ≤ 64mg/L)
- Result:
  - 34 isolates had genotype available: 18 isolates were positive for vanA and 16 were vanB
    - For vanA isolates, fosfomycin MICs ranged from 8 to 128 mg/L. 4 isolates had MIC=128mg/L
    - For vanB isolates, fosfomycin MICs ranged from 16 to 128 mg/L. 3 isolates had MIC=128 mg/L

		No of strains	Susceptibilities of multidrug-resistant Enterococci to fosfomycin n(%)		
			MIC ≤64mg/L	MIC 128mg/L	MIC ≥256mg/L
Broth microdilution	<i>E. faecium</i>	52	35 (67.3)	16 (30.8)	1 (1.9)
	<i>E. faecalis</i>	23	23 (100)	0	0
	Total	75	58 (77.3)	16 (21.3)	1 (1.3)

Conclusion: All VRE *faecalis* tested were susceptible to fosfomycin and 35 out of 52 (67%) VRE *faecium* isolates were susceptible to fosfomycin and 16 (31%) were intermediate (MIC=128 mg/L)

Evidence 3: Shrestha NK, et al. *Scand J Infect Dis* 2003;35: 12–14<sup>29</sup>

- 75 consecutive clinical isolates of VRE *faecium* (40 blood and 35 urine isolates) over 1 year tested for susceptibility to linezolid, quinupristin/dalfopristin, fosfomycin and nitrofurantoin using the Etest
- NCCLS now CLSI breakpoint criteria for *E. faecalis* used to judge susceptibility

Result:

Susceptibility of the 75 isolates of vancomycin-resistant <i>Enterococcus faecium</i>					
Drugs	Susceptible n(%)	Intermediate n(%)	Resistant n (%)	MIC <sub>50</sub> (mg/L)	MIC <sub>90</sub> (mg/L)
Linezolid <sup>a</sup>	75 (100)	0 (0)	0(0)	1	1.5
Quinupristin/dalfopristin	74 (98.7)	0 (0)	1 (1.3)	0.5	0.75
Fosfomycin <sup>b</sup>	74 (98.7)	0 (0)	1 (1.3)	32	48
Nitrofurantoin	59 (78.7)	15 (2)	1 (1.3)	24	48

<sup>a</sup>Breakpoints used: ≤2 mg/L, susceptible; 4mg/L, intermediately susceptible; ≥8mg/L, resistant  
<sup>b</sup>Breakpoints used: ≤64mg/L, susceptible; 128mg/L, intermediately susceptible; ≥256mg/L, resistant

- All isolates were susceptible to linezolid. Fosfomycin and quinupristin/dalfopristin had good in vitro activity against VRE *faecium*, approaching 100%; susceptibility to nitrofurantoin was lower
  - The authors reported experiencing difficulty in reading Etest strips for nitrofurantoin, due to poorly demarcated zone of inhibition. This raises questions about the validity of the Etest method as a measure of VRE susceptibility to the drug and the presently reported susceptibility rate
  - However, nitrofurantoin susceptibility rate of 79% was comparable to 81% susceptibility of all enterococcal isolates in the USA based on SENTRY antimicrobial survey program

Conclusion:

- The result of this in vitro study is consistent with those previously reported for fosfomycin
- Fosfomycin is a useful alternative to linezolid and quinupristin/dalfopristin particularly in treating UTIs due to VRE strains in certain clinical situations, thus ameliorating resistance emergence among *Enterococcus spp.* to these agents

Evidence 4: Shrestha NK, et al. *Infect Dis Clin Pract* 2000; 9:368-71<sup>30</sup>

- Case report of complicated VRE UTI treated with fosfomycin
  - 85 year old with type 2 diabetes mellitus, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, obstructive prostatism from benign prostatic hypertrophy with intermittent catheterization, and chronic renal insufficiency (CrCl 25ml/min)
  - Had completed repeated courses of ciprofloxacin for suspected UTIs and for epididymo-orchitis at which time urine culture also grew VRE
  - He was again treated with ciprofloxacin for VRE UTI but failed to respond (with repeated; 4 emergency room visits over 6 weeks for symptomatic UTI)
    - During the 4<sup>th</sup> visit, prostatitis was suspected
  - Blood cultures were negative and leukocytosis was absent
  - Urine culture grew VRE *faecium* that was susceptible to nitrofurantoin (MIC=32mg/L) and intermediate to fosfomycin (MIC=64mg/L) per report criteria
  - Patient was treated with fosfomycin 3g po every 3 days for 21 days

- Repeat serial urinalysis and urine cultures remained negative at 3 months and clinical symptoms resolved after 2 doses of fosfomycin
- No adverse events were reported
- Conclusion: At the adjusted dose for renal function and duration for UTI with suspected prostate involvement complete clinical and bacteriologic cure was achieved with fosfomycin

Fosfomycin has also been used for the treatment of other gram positive pathogens including MRSA.<sup>26,31</sup> A meta-analysis by Falagas and colleague summarized findings of studies that evaluated the use of fosfomycin for the treatment of gram positive infections; MRSA, VRE, and penicillin-non-susceptible *S.pneumoniae*.<sup>31</sup> In 22 studies that evaluated MRSA isolates, 12 of them reported  $\geq 90\%$  of the isolates being susceptible, while 7/22 reported 50-90% susceptibility rate. The cumulative susceptibility by the individual authors' criteria was 87.9% (4240/4892 isolates), whereas applying the criteria of  $\leq 64\text{mg/L}$ , 95.3% were susceptible. Cumulative susceptibility rate of VRE to fosfomycin was 30.3% (183/604 isolates), and that of penicillin-non-susceptible pneumococci was 87.2% (191/219 isolates). Of note majority of isolates from these studies were of non-renal source and involved the use of intravenous fosfomycin in combination with other antibiotics. Yet these data provide evidence regarding the activity of fosfomycin against MRSA isolates.

**Pyelonephritis:** Ode B, et al. Chemioterapia. 1988;7(2):96-100<sup>32</sup>

- The IDSA guidelines do not recommend fosfomycin for the treatment of pyelonephritis due to less than optimal serum and renal tissue concentrations after oral dosing.<sup>13</sup>
- Ode and colleagues evaluated the efficacy of fosfomycin IV 8g twice daily compared to ampicillin IV 2g every 8 hours for 1 week in 38 patients with acute pyelonephritis.
  - The most common pathogen in the study was *E. coli* of which 17% was resistant to ampicillin
  - Result:
    - The treatment success rate was 44% for fosfomycin and 28% for ampicillin ( $p > 0.2$ )
    - The peak concentrations of fosfomycin in serum was 395 mg/l and 85mg/L in tissue fluid; however, urine concentrations ranged from 6990 -24,320 mg/L
- Conclusion: treatment with both fosfomycin and ampicillin achieved less than optimal success rate. Additionally, concentrations of fosfomycin achieved both in serum and tissue were significantly lower than those in the urine.

**PHARMACOECONOMICS<sup>3,7,23,33</sup>**

Medication	Cost (\$)	Cost per day(\$) <sup>^^</sup>	Comments
Meropenem	28.33 per gram	57	IV route only
Ertapenem	60 per gram	60	IV route only, once daily therapy
Tigecycline	63.74 for 50mg	191 (day 1) 127 (maintenance)	IV route only, urine = 33% (not indicated for UTIs)
Nitrofurantoin	0.64 for 100mg	1.27	Oral, CrCl rec to be $> 60\text{ml/min}$
Fosfomycin	38 for 3 grams	38	Oral

<sup>^^</sup>Estimated based on typical adult dose

- Single dose fosfomycin is cost effective compared to other antibiotics for the treatment of similar infections. However, cost may be increased with repeated dosing.

**CONCLUSION**

The convenience of a single-dose regimen, broad range of activity proven in vitro and in vivo, and minimal propensity for promoting resistant pathogens make fosfomycin an attractive regimen for the treatment of complicated and uncomplicated cystitis. Based on available evidence, the clinical efficacy of fosfomycin was comparable to first line agents for UTI; however bacterial efficacy was lower. It is important to note that majority of the studies centered on community acquired ESBL isolates, from ambulatory patients rather than healthcare acquired or hospitalized patients. Clinical evidence is still unavailable from well designed randomized trials for the use of fosfomycin in the treatment of multidrug resistant pathogens. However given increasing resistance and limited antibiotic choices, fosfomycin may be useful when first line agents are unavailable.

Summary efficacy of agents for UTI <sup>13</sup>			
Drug (dosage)	Estimated clinical efficacy <sup>a</sup> Mean % (range)	Estimated bacteriologic efficacy <sup>a</sup> Mean % (range)	Adverse effects
Nitrofurantoin 100mg q12hr x 5-7 days	93 (84-95)	88 (86-92)	Nausea, headache
Trimethoprim-sulfamethoxazole 160/800mg q12hr x 3 days	93 (90-100)	94 (91-100)	Rash, urticaria, nausea, vomiting, hematologic
Fosfomycin 3g once	91	80 (78-83)	Diarrhea, nausea, headache
Fluoroquinolones for 3 days	90 (85-98)	91 (81-98)	Nausea, vomiting, drowsiness
β-lactams for 3-5 days	89 (79-98)	82 (74-98)	Diarrhea, nausea, vomiting, rash, urticaria
<sup>a</sup> Based on data from follow up visit close to a 5–9-day period following treatment and are averages from several clinical trials			
<sup>b</sup> Includes data from studies of ofloxacin, norfloxacin, and ciprofloxacin.			
<sup>c</sup> Includes data from studies of second and third generation cephalosporins and amoxicillin/clavulanate			

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