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A Real Word Perspective on the Efficacy of Fosfomycin for the Treatment of Multidrug Resistant Pathogens Causing Urinary Tract Infections

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BACKGROUND

- Urinary tract infections (UTI) are the most common health care associated infection in the United States. Over the past decade there has been an increase in rates of UTI caused by resistant organisms (1).
- These are associated with poorer outcomes, increased length of stay and healthcare costs as therapeutics options are limited and often associated with toxicity or substantial cost (2).
- Fosfomycin is a phosphonic acid derivative (cis-1,2-eposypropyl-phosphonic acid) that exerts bactericidal antimicrobial activity by blocking the early stage of bacterial cell wall synthesis (3) It has a broad range of activity and is generally well-tolerated.
- In vitro studies have demonstrate promising activity against MDR organisms However, clinical data is limited.
- In this study we aimed to examine the clinical outcomes of hospitalized patients within MDR UTIs treated with Fosfomycin.

METHODOLOGY

- Retrospective cohort study of patients with Carbapenem resistant (CRE) or extended spectrum β-Lactamase producing (ESBL) Enterobacteriaceae or vancomycin resistant Enterococcus (VRE) UTIs treated with at least one dose of Fosfomycin.
- UTI was defined as:
  - Positive urine culture growing ≥1,000 CFU/ml of bacteria
  - ≥1 of the following symptoms: dysuria, increased urinary frequency, flank pain or tenderness, fevers, and/or altered mental status without an alternative etiology
- CRE, ESBL and VRE were defined as per CLSI guidelines (4)
- Bacterial identification and routine antimicrobial susceptibility testing was performed with Microscan WalkAwayTM (Siemens Healthcare Diagnostics).

Definitions:

- Empiric therapy: prescription of Fosfomycin prior to knowledge of susceptibility results
- Definitive therapy: prescription of Fosfomycin after the results of susceptibility testing were available
- 14 day clinical cure: resolution of UTI signs and symptoms within 14 days of treatment or discharge in stable condition
- Overall clinical cure: resolution of UTI signs and symptoms or discharge in stable condition without relapse within 30 days
- Relapse: reoccurrence of symptoms with a positive urine culture for the same organism within 30 days of treatment
- Microbiological failure: positive repeat culture within 14 days of therapy

RESULTS

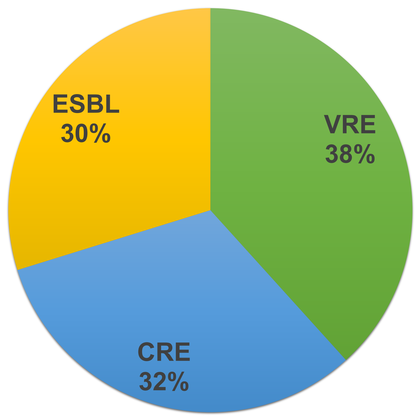
Table 1: Patient and Diseases Characteristics

Variable	N= 47
Demographics n (%)	
Age [median (range)]	65 (95- 20)
Male Gender	9 (19.1)
Non- Caucasian Race	0 (0)
Co-morbidity Charleston score [median (range)]	5 (12-0)
Risk factors n (%)	
Prior infection with same MDR organism	17 (36.2)
Indwelling Foley catheter/intermittent catheterization	12 (25.5)
Neurogenic bladder	4 (8.5)
Recurrent/persistent renal calculi	4 (8.5)
Urological procedure within the past 180 days	3 (6.4)
Ureteral Stent	3 (6.4)
Nephrostomy Tube	2 (4.3)
BPH	2 (4.3)
UPJ Obstruction	1 (2.1)
Diabetes Mellitus	21 (44.7)
Solid Organ Transplant	4 (8.5)
Hematological Malignancy	4 (8.5)
Neutropenia	4 (8.5)
Other immunosuppression[1]	3 (6.4)
Met CDC/NSHN definition of UTI, n (%)	30 (63.8)
Type of UTI, n (%)	
Cystitis	45 (95.7)
Pyelonephritis	2 (4.3)
Place of acquisition, n (%)	
Community	22 (46.8)
Hospital	18 (38.3)
Health Care Facility	8 (17.0)
Clinical features, n (%)	
Fever	13 (27.7)
Increased Frequency	13 (27.7)
Alerted mental status	12 (25.5)
Suprapubic pain/tenderness	10 (21.3)
Dysuria	9 (19.1)
Urgency	5 (10.6)
CVA pain/tenderness	3 (6.4)
New incontinence	3 (6.4)
Concomitant infection, n (%)	7 (14.9)
Culture/Serology confirmed [2]	5 (10.6)
Primary bacteremia	3 (6.4)
Intra-abdominal	2 (4.3)
Bone and/or Joint	2 (4.3)
SSTI	1 (2.1)
UA/Laboratory findings, n (%)	
Serum Creatinine (median)	1.1
Serum WBC (median)	8.4
Positive Leukocyte Esterase	40 (85.1)
Urine Pyuria[3]	38 (80.9)
Positive Urine Nitrite	11 (23.4)
Colony count, n (%)	
=>100,000	39 (83.0)
=50,000-100,000	1 (2.1)
=<50,000	7 (14.9)
Polymicrobial Urine Culture	11 (23.4)
Indication, n (%)	
Resistance profile, n (%)	20 (42.6)
Convenience, n (%)	7 (14.9)
Empiric therapy, n (%)	16 (34.0)
Side effect profile/Antibiotic allergies n (%)	4 (8.5)
ID consulted, n (%)	23 (48.9)
Days, [median(range)]	1(1-6)
Fosfomycin Doses, [median (range)]	1 (1-3)
Received >1 dose of Fosfomycin, n (%)	8 (17)
Received 2 doses of Fosfomycin	5 (10.6)
Received 3 doses of Fosfomycin	3 (6.3)
Prior active therapy [4], n (%)	3 (6.4)

1- Other causes of immunosuppression included chemotherapy and immunosuppression for autoimmune disease
2- 2 patients had concomitant *Staphylococcus aureus* bacteremia. 2 patients had PCR confirmed *Clostridium difficle.* 1 patient had a *Staphylococcus aureus* septic arthritis, 1 patient had *Serratia marcescens* bacteremia,
3- Pyuria was defined as >5 white blood cells/high powered field
4- Receipt of an agent for more than 3 days with in vitro activity against CRE.

BPH= benign prostatic hyperplasia, CDC= Centers of Disease Control, ID= Infectious Diseases, MDR: Multidrug resistant, NHSN= National Healthcare Safety Network CVA = Costovertebral angle UPJ= uteropelvic junction UTI= Urinary Tract Infection, WBC= white blood cell count

Figure 1: MDR UTI Pathogens Treated with Fosfomycin



Outcomes of Patients With MDR UTIs Treated with Fosfomycin

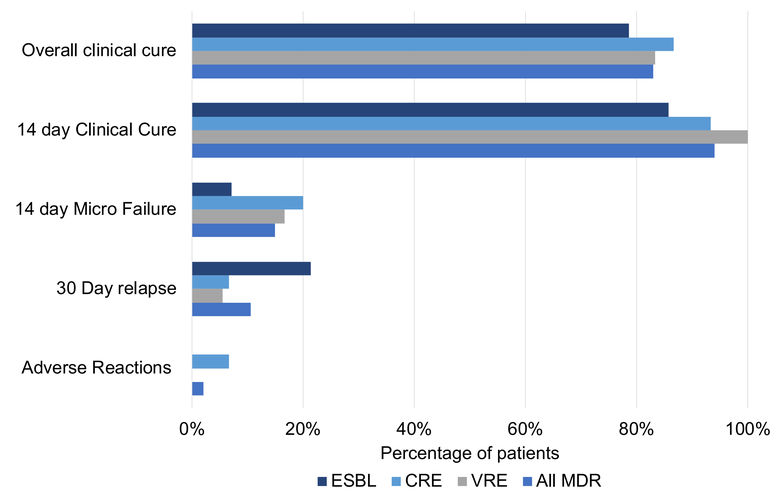


Table 2: Patient Outcomes

Outcome	All MDR n= 47	VRE n= 18	CRE n=15	ESBL n=14	Pvalue
Overall clinical cure, n (%)	39 (83)	15 (83.3)	13 (86.7)	11 (78.6)	0.5482
14 day clinical cure, n (%)	44 (94)	18 (100)	14 (93.3)	12 (85.7)	0.3069
14 day microbiological failure, n (%)	7 (14.9)	3 (16.7)	3 (20)	1 (7.1)	0.6924
Documented 30 day relapse, n (%)	5 (10.6)	1 (5.5)	1 (6.7)	3 (21.4)	0.2934
In hospital mortality/discharge to hospice, n (%)	4 (8.5)	2 (11.1)	1 (6.7)	1 (7.1)	0.8801
Adverse reactions, n (%)	1 (2.1)	0 (0)	1 (6.7)	0 (0)	0.3363

CONCLUSION

- Clinical cure at 14 days was 94% and overall clinical cure at 30 days was 83%.
- Microbiological failure was 15%, however only a limited number of patients had repeat urine cultures for evaluation
- Further studies to evaluate dosing strategies and effectiveness of Fosfomycin compared to alternative agents for treatment of MDR UTIs are needed

REFRENCES

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