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NOTE

# Fosfomycin activity versus carbapenem-resistant *Enterobacteriaceae* and vancomycin-resistant *Enterococcus*, Detroit, 2008–10

Jason M Pogue[1,2], Dror Marchaim[2,3,4], Odaliz Abreu-Lanfranco[2], Bharath Sunkara[2], Ryan P Mynatt[1], Jing J Zhao[1], Suchitha Bheemreddy[2], Kayoko Hayakawa[2], Emily T Martin[1], Sorabh Dhar[2], Keith S Kaye[2] and Paul R Lephart[5]

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*Enterobacteriaceae* and enterococci are among the most common causes of urinary tract infections (UTI) in adults.[1] Carbapenem-resistant *Enterobacteriaceae* (CRE) and vancomycin-resistant *Enterococcus* (VRE) are multidrug-resistant (MDR) pathogens, which have become endemic in many locations worldwide.[2,3] These pathogens are associated with devastating outcomes among patients and their continued dissemination and spread pose a threat to public health.[4,5] According to the last report from the Centers for Disease Control and Prevention, in 2006–2007 10.1% of *Klebsiella pneumoniae* isolates associated with catheter-associated UTI (CAUTI) in the United States were carbapenem resistant, and 29.1% of *Enterococcus* species urinary isolates were resistant to vancomycin.[3] At Detroit Medical Center (DMC) in 2011, 6% of *K. pneumoniae* isolates were resistant to $\geqslant 1$ carbapenem and 40% of *Enterococcus* species were resistant to vancomycin. Treatment options for these pathogens are limited and often require the use of broad-spectrum agents, which further contribute to the development of resistance or agents that are more toxic. In addition, the treatment alternatives for CRE, notably colistin and tigecycline, are minimally renally excreted, making them less than ideal for the treatment of UTI.[6]

The prevalence of urinary catheterized patients is rising.[7,8] CAUTI is the most common infection acquired in the hospital or healthcare-associated settings.[1,9] Diagnosis of CAUTI remains challenging, and therefore many patients are prescribed with antibiotics when in fact they have asymptomatic bacteruria.[10,11] Neither CRE nor VRE asymptomatic bacteriuria should be treated with antibiotics.[1] However, there are patients who are not severely sick, their clinical condition does not necessitate hospitalization, but still a diagnosis of UTI cannot be completely ruled out in the presence of a positive urine culture coupled with potential clinical signs of infection such as mental status changes. In these scenarios, when CRE or VRE are the offending pathogens, often in elderly incontinent institutionalized individuals,[12,13] patients are hospitalized and treated with intravenous (IV) broad-spectrum and sometime toxic agents, owing to lack of oral regimens. If these patients could have been managed in the outpatient settings, both the patients and the acute-care facilities would have benefited.

Fosfomycin is a relatively safe antimicrobial agent approved in the United States as an oral formulation for the treatment of uncomplicated UTI.[14–16] Fosfomycin exerts its bactericidal activity by inhibiting uridine diphosphate-*N*-acetylglucosamine enolpyruvyl transferase (MurA), an enzyme that catalyzes the first step in bacterial cell-wall synthesis.[17] Recent data suggest that fosfomycin is active against various MDR pathogens, and that treatment with this agent was associated with a high rate of clinical cure.[17–20] We aimed to analyze the rates of fosfomycin susceptibility among CRE and VRE isolates from an endemic US location.

The DMC healthcare system consists of eight hospitals, has $>2200$ inpatient beds and serves as a tertiary referral hospital for metropolitan Detroit and Southeastern Michigan. Institutional review boards at Wayne State University and the DMC approved the study before its initiation. CRE isolates collected consecutively from 9 January 2008 to 8 December 2009 and VRE isolates collected consecutively from 6 January 2010 to 7 December 2010 were analyzed. Only patient's initial isolates were included for analysis as duplicates were excluded.

DMC has a single centralized clinical microbiology laboratory, which processes $\sim 500\,000$ samples annually. Bacteria were identified to the species level, and susceptibilities were determined to predefined

[1]Department of Pharmacy Services, Detroit Medical Center, Wayne State University, Detroit, MI, USA; [2]Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Detroit, MI, USA; [3]Division of Infectious Diseases, Assaf Harofeh Medical Center, Zerifin, Israel; [4]Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel and [5]Department of Clinical Microbiology, Detroit Medical Center, Wayne State University, Detroit, MI, USA
Correspondence: Dr D Marchaim, Division of Infectious Diseases, Detroit Medical Center, Wayne State University, 5 Hudson, Harper University Hospital, 3990 John R. Street, Detroit, MI 48201, USA.
Email: drormc@hotmail.com
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antimicrobials, based on an automated broth microdilution system (MicroScan; Siemens AG, Munich, Germany), in accordance with the Clinical and Laboratory Standard Institutions (CLSI) criteria.[21] All *Enterobacteriaceae* that were resistant to one or more 3rd generation cephalosporin and had a minimal inhibitory concentration (MIC) $\geqslant 2\,\mu g\,ml^{-1}$ to ertapenem were screened for carbapenemase production, with the modified Hodge test conducted according to CLSI criteria.[21] For the purposes of this analysis, only isolates with a positive Hodge test were considered CRE. The MICs to fosfomycin, colistin and tigecycline were determined by using E-tests strips (bioMérieux, Marcy l'Etoile, France) and using Mueller-Hinton media and quality-control strains, as indicated in the respective E-test product insert. Breakpoints to define nonsusceptibility were set to $>64\,mcg\,ml^{-1}$ for fosfomycin (extrapolated for all *Enterobacteriaceae* from CLSI breakpoint for *Escherichia coli* and for *Enterococcus faecium* and *E. faecalis* from CLSI breakpoints) and $>2\,mcg\,ml^{-1}$ for colistin and tigecycline, in accordance with CLSI guidelines (colistin breakpoint extrapolated from CLSI breakpoint for *Acinetobacter baumannii*, tigecycline breakpoint taken per FDA (Food and Drug Administration), as CLSI does not have formal breakpoints).

There were 93 CREs and 70 VREs that had susceptibility testing performed for fosfomycin. The majority of CRE cultures were obtained from the urine (35, 38%), followed by respiratory sources (29, 31%), blood (15, 16%), wounds (13, 14%) and cerebrospinal fluid (1, 1%). The majority of VRE cultures were also obtained from the urine (50, 72%), followed by blood (10, 14%) and wounds (10, 14%). The rate of fosfomycin susceptibility is displayed in Table 1. Overall, the rate of susceptibility of CREs to fosfomycin was 85%, and among urinary isolates the rate was 78%. Among VREs, the overall susceptibility rate was 86% and among urinary isolates 78%.

The susceptibility rates to other drugs commonly used for CREs and VREs were tested on the same group of pathogens. Among the CRE group, fosfomycin compared favorably both with colistin (82% susceptibility rate among all isolates and 74% among urinary isolates) and tigecycline (81% susceptibility rate among all isolates and 94% among urinary isolates). Interestingly, 14/20 (70%) of colistin-resistant *Enterobacteriaceae* isolates were susceptible to fosfomycin. Among VRE isolates, fosfomycin susceptibilities were lower compared with those for daptomycin (89% susceptibility rate among all isolates and 87% among urinary isolates) and linezolid (97% susceptibility rate among all isolates and 98% among urinary isolates).

Fosfomycin displayed good *in vitro* activity against both CRE and VRE isolates cultured from patients from an endemic US location. The drug is active versus isolates obtained from all body sites, including those obtained from the urine. Updated data pertaining to the clinical efficacy and the safety of the drug from recent years are lacking, but the drug had been reported to have been successfully used on small cohorts of patients with infections due to MDR Gram-negative and MDR Gram-positive infections in the past decade.[17] The drug is available in the United States in its oral formulation only, although in select overseas countries it has been used also in its IV formulation to treat systemic infections caused by MDR Gram-negative pathogens.[15,22] A single-dose regimen of fosfomycin is currently recommended and licensed for treatment of uncomplicated UTI.[23] Limited clinical data suggest that longer courses might be effective, where the drug is administered every 48 h for treatment of complicated UTIs.[24–26] If fosfomycin is considered for future use against UTI caused by MDR pathogens such as CRE or VRE, a three-dose regimen should be trialed and validated[24,25] because UTIs due to MDR pathogens are often catheter associated, and thus considered to be complicated by definition.[1]

There is an urgent need to broaden the available therapeutic armamentarium against CRE and VRE.[27] Fosfomycin seems to be a potential option, and because it is oral, is particularly attractive for outpatient management of UTIs. Fosfomycin can also be utilized in antimicrobial stewardship efforts to reduce utilization of broad-spectrum antimicrobials and to decrease antimicrobial costs. Although not specifically included in this analysis, there is a potential carbapenem-sparing effect that could be obtained with the use of fosfomycin against extended-spectrum β-lactamase-producing organisms. It is important to note that emergence of resistance with fosfomycin monotherapy is well described and warrants close monitoring.[28]

Our study has a few notable limitations: (1) it included only a convenience sampling of consecutively collected isolates. (2) MIC values were determined only by E-test, while variations are reported compared with broth dilution-based susceptibility testing methodologies. (3) The mechanisms of fosfomycin resistance were not determined and were beyond the scope of this investigation. (4) Patients with these isolates were not actually treated with fosfomycin, and therefore no clinical correlation can be made. (5) The epidemiology of CREs is evolving, and CRE isolates with negative Hodge test were excluded from our analysis. In addition, presences of carbapenemases were not conducted using a genotypic test. Nonetheless, this is an important first step for further investigating the use of fosfomycin for specific indications. Fosfomycin might prove to be an efficacious, safe and cheap alternative for the treatment

**Table 1 Susceptibility rates of carbapenem-resistant *Enterobacteriaceae* and vancomycin-resistant *Enterococcus* to fosfomycin, Detroit, 2008–2010**

| | | *Overall cultures* | | *Urinary cultures* | | | |
|---|---|---|---|---|---|---|---|
| | | *Number tested* | *Fosfomycin, number susceptible (%)* | *Number tested* | *Fosfomycin, number susceptible (%)* | *Fosfomycin $MIC_{50}$* | *Fosfomycin $MIC_{90}$* |
| Carbapenem-resistant *Enterobacteriaceae* | *Klebsiella* species | 79 | 67 (85%) | 29 | 23 (57%) | $32\,\mu g\,ml^{-1}$ | $96\,\mu g\,ml^{-1}$ |
| | *Enterobacter* species | 13 | 11 (72%) | 5 | 4 (80%) | | |
| | *Escherichia coli* | 1 | 1 (100%) | 1 | 1 (100%) | | |
| Vancomycin-resistant *Enterococcus* | *Enterococcus faecium* | 42 | 33 (76%) | 28 | 22 (60%) | $48\,\mu g\,ml^{-1}$ | $96\,\mu g\,ml^{-1}$ |
| | *Enterococcus faecalis* | 28 | 27 (96%) | 24 | 24 (100%) | | |

Abbreviation: MIC, minimal inhibitory concentration.

of lower-tract UTI caused by MDR pathogens. Controlled clinical data is needed, preferably directed toward treatment of CAUTI caused by MDR pathogens such as CRE and VRE.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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