

# Nitrofurantoin and Fosfomycin for Extended Spectrum Beta-lactamases Producing *Escherichia coli* and *Klebsiella pneumoniae*

Neeraj Kumar Tulara

Department of Infectious Disease, Dr L H Hiranandani Hospital, Mumbai, Maharashtra, India

## Abstract

Urinary tract infection (UTI) is a common and painful human illness that, unfortunately not responsive to commonly used antibiotics in current practice. The role of fosfomycin and nitrofurantoin in the era of growing bacteria resistance has been widely discussed. In this study, we aimed to know the local antimicrobial susceptibilities, fosfomycin and nitrofurantoin susceptibility in particular, for urinary extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Escherichia pneumoniae* (ESBL-EC and ESBL-KP) isolates in our hospital. We collected 464 urine isolates, including 384 ESBL-EC and 80 ESBL-KP isolates. Of 464 urine isolates culture positive ESBL-UTIs, EC caused 384 (82.75%), followed by *Klebsiella* in 80 (17.24%). Carbapenems and Colistin seems to remain as the first line therapy for the majority of ESBL-UTIs in the local setting. Colistin and fosfomycin remains the most sensitive antibiotic while nitrofurantoin still preserves the good sensitivity against ESBL and found to be an only oral sensitive antibiotic.

**Keywords:** Extended-spectrum beta-lactamase, *Escherichia coli*, fosfomycin, *Klebsiella pneumoniae*, nitrofurantoin

## INTRODUCTION

Urinary tract infection (UTI) is a common and painful human illness that, unfortunately not responsive to commonly used antibiotics in the current practice. *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KP) are the most common pathogens causing UTI. Extended-spectrum beta-lactamase produced by EC and KP (ESBL-EC and ESBL-KP) reduces the number of therapeutic options for the infection caused by these pathogens.<sup>[1,2]</sup> ESBL-EC and ESBL-KP are resistant to penicillins, cephalosporins, and monobactam. The ESBL producers can also develop co-resistance to other classes of antimicrobial agents, such as fluoroquinolones, co-trimoxazole, and aminoglycosides,<sup>[3]</sup> which are frequently used for UTI. Drug resistance among Gram-negative pathogens is a risk factor for inappropriate empiric treatment (IET), which in turn increases the risk for mortality. Carbapenems resistance is also growing concern which poses a severe threat to the health. Infection with carbapenems resistant enterococci was associated with a four-fold increased risk of receiving IET, which in turn increased mortality, length of stay and costs.<sup>[4]</sup>

Fosfomycin, which has bactericidal properties against various Gram-positive and Gram-negative bacteria, can inhibit UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), an enzyme catalyzing the early step in bacterial cell wall synthesis.<sup>[5,6]</sup> This antimicrobial agent has been used to treat UTI for nearly 40 years. Fosfomycin is increasingly important to treat UTI because the resistance rate of uropathogens to common antimicrobial agents is increasing. Although nitrofurantoin has been used for >60 years for the treatment of uncomplicated UTIs, its pharmacodynamic properties are not fully explored. Use is increasing because of increasing resistance to other antimicrobials due to ESBLs. In this study, we aimed to evaluate the antimicrobial activities of fosfomycin and nitrofurantoin and other common antimicrobials against the ESBL-EC and ESBL-KP isolates from urine.

**Address for correspondence:** Dr. Neeraj Kumar Tulara,  
Department of Infectious Disease, Dr L H Hiranandani Hospital, Central  
Avenue, Powai, Mumbai, Maharashtra, India.  
E-mail: drntulara@rediffmail.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Tulara NK. Nitrofurantoin and Fosfomycin for Extended Spectrum Beta-lactamases Producing *Escherichia coli* and *Klebsiella pneumoniae*. J Global Infect Dis 2018;10:19-21.

### Access this article online

#### Quick Response Code:



Website:  
www.jgid.org

DOI:  
10.4103/jgid.jgid\_72\_17

## MICROBIOLOGY REPORT

We collected 464 urine isolates, which includes 384 ESBL-EC and 80 ESBL-KP isolates between January 2015 to December 31, 2016. These samples constitute both indoor as well as outdoor patients. Their urine culture and antibiotic susceptibility reports were evaluated after obtaining informed written consent.

The identification of ESBL production was done using phenotypic testing based on the demonstration of synergy between clavulanic acid and broad-spectrum cephalosporins according to the Clinical and Laboratory Standards Institute (CLSI) guideline.<sup>[7]</sup>

The broth microdilution method was used to test the antimicrobial susceptibilities for the commonly used antibiotics, including ciprofloxacin, nitrofurantoin, amikacin, cotrimoxazole, and carbapenems. The breakpoints of these antimicrobial agents were using CLSI criteria.<sup>[7]</sup> Of 464 urine isolates culture positive ESBL-UTIs, EC caused 384 (82.75%), followed by *Klebsiella* in 80 (17.25%). 198 (42.67%) had a history of hospitalization within the past 3 months and included 53/80 (66.25%) of *Klebsiella* UTI and 145/384 (37.76%) of EC UTI. Antibiotic susceptibility of ESBL organisms is different between ESBL-EC and ESBL-KP [Table 1]. Carbapenems and Colistin remain most effective antimicrobial agents among both groups while nitrofurantoin and fosfomycin have got very good sensitivity for ESBL-EC group of organisms. Quinolones, monobactam, and cotrimoxazole have become widespread resistant in entire spectrum of ESBL whether it is ESBL-EC or ESBL-KP. We observed a higher percentage of EC over *Klebsiella* as ESBL producing organisms suggesting most ESBL-UTIs to be community acquired, Carbapenems and Colistin seems to remain as the first line therapy for the majority of ESBL-UTIs in the local setting in complicated UTIs. However, increasing resistance to Carbapenems and BL-BLI combination is a serious concern. Apart from carbapenems and colistin (ESBL-EC/KP), fosfomycin (ESBL-EC/KP), and nitrofurantoin s (ESBL-EC) found to be effective anti-microbial agents and holds good sensitivity and can be used as a first-line oral agents for non-complicated UTIs

**Table 1: Antimicrobial sensitivity for ESBL's**

Antibiotics	ESBL-EC (82.75%)	ESBL-KP (17.25%)
Meropenem	89.3	91.1
Imipenem	82.7	85.5
Colistin	95.7	97.7
Pip-Tazo	71.8	67.9
Monobactam	43.9	57.3
Aminoglycosides	47.8	53.8
Cotrimoxazole	37.9	28.8
Fosfomycin	99.6	87.7
Nitrofurantoin	93.7	57.7
Quinolones	24.3	45.3

ESBL: Extended-spectrum beta-lactamase, ESBL-EC: ESBL-producing *Escherichia coli*, ESBL-KP: ESBL-producing *Klebsiella pneumoniae*

which also can be continued as long-term treatment to avoid recurrence of UTI specially in old people, largely females. Another surprising finding which was noted as quinolones and cotrimoxazole has almost become resistant and can be avoided as a treatment for UTI which is the usual practice for non-complicated UTIs.

## DISCUSSION

Except among infants and the elderly, UTI occurs far more commonly in female than males. The acute uncomplicated cystitis in women is one of the most frequently diagnosed bacterial infection. For the antimicrobial therapy according to the European guidelines, the old oral antibiotics (fosfomycin trometamol, nitrofurantoin, pivmecillinam) should be prescribed, against which EC is still susceptible in over 90%.<sup>[8]</sup> The production of ESBLs by EC and *K. pneumoniae* is associated with the reducing susceptibility to fluoroquinolones, cotrimoxazole, and other antimicrobial agents.<sup>[9]</sup> The resistance rates of ESBL-EC and ESBL-KP to quinolones in this study [Table 1] were much higher than those reported from other countries. Carbapenems and colistin are the drugs of choice for treating severe complicated infections caused by ESBL-producing isolates. Aminoglycosides were inactive against both ESBL-EC and ESBL-KP isolates in this study [Table 1]. A study in New Zealand has reported zero resistance rate of ESBL-KP to amikacin.<sup>[10]</sup> In this study, another potential drug, fosfomycin was actively against ESBL-EC. Fosfomycin has been reported to have good potential in treating UTI caused by multidrug-resistant EC.<sup>[11-13]</sup> Fosfomycin is well tolerated in humans and causes little nephrotoxicity. Fosfomycin-tromethamine, an oral form of fosfomycin, is also indicated for uncomplicated UTI. In a systematic review, fosfomycin is found actively against *Enterobacteriaceae* producing ESBL, particularly EC.<sup>[14]</sup>

Our study showed the similar findings and the activity of fosfomycin against ESBL-EC isolates remained reliable. The role of fosfomycin against *K. pneumoniae* has been widely discussed. In the review by Falagas *et al.*<sup>[14]</sup> the susceptibilities of ESBL-KP isolates to fosfomycin were 76.7%–100%. In our study also, susceptibility rates for ESBL for fosfomycin is around 87%–99%. Hence, fosfomycin is a promising therapeutic option for treating inpatient and outpatient UTI caused by ESBL-EC (99.6%) as well as ESBL-KP (87.7%). Nitrofurantoin is an old drug used for uncomplicated UTI. Kashanian *et al.* has mentioned about the potential role of nitrofurantoin for uncomplicated UTI in the growing resistance era.<sup>[15]</sup> In this study, the susceptibility rate of ESBL-EC isolates for nitrofurantoin was near 90%, but ESBL-KP isolates have been reported to be associated with increased resistance to nitrofurantoin as the sensitivity was found to be around 57% only. Based on these findings, we suggest that nitrofurantoin may be another alternative option for treating uncomplicated UTI caused by ESBL-EC infection.<sup>[16]</sup> Cotrimoxazole and quinolones are one of few oral therapeutic options for ESBL-producing isolates.

However, in this study, it was the least active antimicrobial agent against ESBL-EC and ESBL-KP isolates [Table 1]. Hence, quinolones and cotrimoxazole can be avoided as a treatment for UTI.

In hospital-acquired, UTI caused by ESBL-EC and *K. pneumoniae*, initial inappropriate therapy is associated with higher mortality.<sup>[17]</sup> According to our data, carbapenems, colistin and fosfomycin, were reliable for hospital-acquired ESBL-EC and ESBL-KP. We suggest that fosfomycin has the potential to replace amikacin in treating hospital-acquired UTI when considering ESBL-producing isolates and less nephrotoxicity.

## CONCLUSIONS

Fosfomycin showed significantly higher activity against ESBL-EC than ESBL-KP in this study. Fosfomycin may be a potential therapeutic option for hospital- and community-acquired UTI caused by ESBL-EC and ESBL-KP. Nitrofurantoin was active against ESBL-EC but was less effective against ESBL-KP. Nitrofurantoin may be another alternative option for treating uncomplicated UTI caused by ESBL-EC in mainly outdoor settings or for uncomplicated UTI. Being a developing country, increasing resistance to high-end antibiotics is likely to add a significant burden to health budget. We feel that treatment of infections in general needs a careful approach adhering to recommended antibiotic guidelines to prevent the emergence of multidrug-resistant organisms. Antibiotic Stewardship program is an effective tool to fight with increasing resistance and save the community with growing resistance.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Gupta K. Emerging antibiotic resistance in urinary tract pathogens. *Infect Dis Clin North Am* 2003;17:243-59.
- Falagas ME, Polemis M, Alexiou VG, Marini-Mastrogiannaki A, Kremastinou J, Vatopoulos AC. Antimicrobial resistance of *Escherichia coli* urinary isolates from primary care patients in Greece. *Med Sci Monit* 2008;14:CR75-9.
- Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: A clinical update. *Clin Microbiol Rev* 2005;18:657-86.
- Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with *Enterobacteriaceae* urinary tract infection, pneumonia and sepsis. *BMC Infect Dis* 2017;17:279.
- Eschenburg S, Priestman M, Schönbrunn E. Evidence that the fosfomycin target Cys115 in UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) is essential for product release. *J Biol Chem* 2005;280:3757-63.
- Kahan FM, Kahan JS, Cassidy PJ, Kropp H. The mechanism of action of fosfomycin (phosphonomycin). *Ann N Y Acad Sci* 1974;235:364-86.
- Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. Supplement M100-S19. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
- Naber KG, Alidjanov JF. Are there alternatives to antimicrobial therapy and prophylaxis of uncomplicated urinary tract infections? *Urologia* 2016;(3 Suppl 3):37-44.
- Jean SS, Teng LJ, Hsueh PR, Ho SW, Luh KT. Antimicrobial susceptibilities among clinical isolates of extended-spectrum cephalosporin-resistant gram-negative bacteria in a Taiwanese University Hospital. *J Antimicrob Chemother* 2002;49:69-76.
- Heffernan HM, Woodhouse RE, Pope CE, Blackmore TK. Prevalence and types of extended-spectrum beta-lactamases among urinary *Escherichia coli* and *Klebsiella* spp. in New Zealand. *Int J Antimicrob Agents* 2009;34:544-9.
- Ko KS, Suh JY, Peck KR, Lee MY, Oh WS, Kwon KT, et al. *In vitro* activity of fosfomycin against ciprofloxacin-resistant or extended-spectrum beta-lactamase-producing *Escherichia coli* isolated from urine and blood. *Diagn Microbiol Infect Dis* 2007;58:111-5.
- Prakash V, Lewis JS 2<sup>nd</sup>, Herrera ML, Wickes BL, Jorgensen JH. Oral and parenteral therapeutic options for outpatient urinary infections caused by *Enterobacteriaceae* producing CTX-M extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2009;53:1278-80.
- Ho PL, Wong RC, Yip KS, Loke SL, Leung MS, Mak GC, et al. Antimicrobial resistance in *Escherichia coli* outpatient urinary isolates from women: Emerging multidrug resistance phenotypes. *Diagn Microbiol Infect Dis* 2007;59:439-45.
- Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, *Enterobacteriaceae* infections: A systematic review. *Lancet Infect Dis* 2010;10:43-50.
- Kashanian J, Hakimian P, Blute M Jr., Wong J, Khanna H, Wise G, et al. Nitrofurantoin: The return of an old friend in the wake of growing resistance. *BJU Int* 2008;102:1634-7.
- Cunha BA, Cunha CB, Lam B, Giuga J, Chin J, Zafonte VF, et al. Nitrofurantoin safety and effectiveness in treating acute uncomplicated cystitis (AUC) in hospitalized adults with renal insufficiency: Antibiotic stewardship implications. *Eur J Clin Microbiol Infect Dis* 2017;36:1213-6.
- Melzer M, Petersen I. Mortality following bacteraemic infection caused by extended spectrum beta-lactamase (ESBL) producing *E. coli* compared to non-ESBL producing *E. coli*. *J Infect* 2007;55:254-9.