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ORIGINAL ARTICLE

Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan

Hsin-Yi Liu [a], Hsiu-Chen Lin [b], Yi-Chun Lin [a,c], Shao-hua Yu [b,c], Wui-Hsiu Wu [a], Yuarn-Jang Lee [a,c,*]

[a] *Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan*
[b] *Department of Laboratory Medicine, Taipei Medical University Hospital, Taipei, Taiwan*
[c] *Department of Infection Control, Taipei Medical University Hospital, Taipei, Taiwan*

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Background: Urinary tract infections (UTIs) caused by extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* have become clinical problems because of limited therapeutic options. The role of fosfomycin in the era of growing bacteria resistance has been widely discussed recently. In this study, we aimed to know the local antimicrobial susceptibilities, fosfomycin susceptibility in particular, of urinary ESBL-producing *E coli* and *K pneumoniae* isolates in Taiwan.
Methods: We collected 200 urine isolates, including 134 ESBL-producing *E coli* (ESBL-*EC*) and 66 ESBL-producing *K pneumoniae* (ESBL-*KP*) isolates from July 2008 to December 2009 in a university-affiliated teaching hospital in Taiwan. We used disk diffusion method to determine susceptibility to fosfomycin. Fosfomycin may have lower susceptibility when using disk diffusion method compared with agar dilution method. Broth microdilution test was also used to determine minimal inhibitory concentrations (MICs) and susceptibilities to other antimicrobial agents.
Results: Imipenem was active against ESBL-*EC* and ESBL-*KP*. Fosfomycin had good susceptibility to ESBL-*EC* (95.5%), including in hospital-acquired isolates, but lower antimicrobial activity against ESBL-*KP* (57.6%). Trimethoprim-sulfamethoxazole had the highest resistance rate to ESBL-*EC* and ESBL-*KP*. Comparing with non-hospital-acquired isolates, hospital-acquired ESBL-KP was associated with significantly lower susceptibility of gentamicin (13.3% *vs.*

* Corresponding author. Department of Internal Medicine, Taipei Medical University Hospital, No. 252, Wu-Hsin Street, Taipei 110, Taiwan.
E-mail address: yuarn438@yahoo.com.tw (Y.-J. Lee).

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66.7%), trimethoprim-sulfamethoxazole (8.9% *vs.* 38.1%), ciprofloxacin (26.7% *vs.* 61.9%), and amikacin (46.1% *vs.* 81.0%) ($p < 0.05$). The resistance of some strains to ciprofloxacin was significantly associated with lower susceptibilities of gentamicin (32.6% in ESBL-*EC*), nitrofurantoin (2.4% in ESBL-*KP*) and trimethoprim-sulfamethoxazole (9.8% in ESBL-*KP*) ($p < 0.05$) but not accompanied with decreasing susceptibility of fosfomycin.

Conclusion: Fosfomycin had the excellent activity against ESBL-*EC* but not ESBL-*KP* in this study. Based on the study findings, we suggest that fosfomycin can be a therapeutic option for UTIs with ESBL-*EC*. Nitrofuranoin was actively against ESBL-*EC*. Nitrofurantoin may be an alternative option for uncomplicated UTIs with ESBL-*EC* in Taiwan.

Introduction

Escherichia coli and *Klebsiella pneumoniae* are the most common pathogens causing urinary tract infection (UTI). Extended-spectrum β-lactamase (ESBL) produced by *E coli* and *K pneumoniae* reduces the number of therapeutic options for the infection caused by these pathogens.[1,2] ESBL-producing *E coli* (ESBL-*EC*) and ESBL-producing *Kpneumoniae* (ESBL-*KP*) are resistant to penicillins, cephalosporins, and monobactams. The ESBL producers can also develop coresistance to other classes of antimicrobial agents, such as fluoroquinolones, co-trimoxazole, and aminoglycosides,[3] which are frequently used for UTI.

Fosfomycin, which has bactericidal properties against various gram-positive and gram-negative bacteria, can inhibit UDP-*N*-acetylflucoamine enolpyruvyl transferase (MurA), an enzyme catalyzing the early step in bacterial cell wall synthesis.[4,5] 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. But, as we know, the antimicrobial susceptibility of enterobacteriaceae to fosfomycin has not been assessed yet in Taiwan.

In this study, we aimed to evaluate the antimicrobial activities of fosfomycin and other common antimicrobials against the ESBL-*EC* and ESBL-*KP* isolates from urine.

Methods

Bacterial isolates

We chose urinary isolates of ESBL-*EC* and ESBL-*KP*, which were collected and identified between July 2008 and December 2009 in the microbiological laboratory of the Taipei Medical University Hospital, one of Taipei Medical University-affiliated teaching hospitals. We excluded duplicate isolates, which were defined as isolation of the same bacterial species from the same patient with the same antibiogram. We identified the species of *E coli* and *K pneumoniae* with the Phoenix automated system (Phoenix; Becton Dickinson, Sparks, MD, USA). Identification of ESBL production was done using phenotypic testing based on the demonstration of synergy between clavulanic acid and broad-spectrum cephalosporins according to Clinical and Laboratory Standards Institute (CLSI) guideline.[6] Hospital-acquired urinary isolates were collected 2 days after admission,[7,8] or collected from patients who were discharged within 30 days (either our facility or other facilities if recorded in chart).

Antimicrobial susceptibility testings

The broth microdilution method (Phoenix; Becton Dickinson, Sparks, MD, USA) was used to test the antimicrobial susceptibilities for the commonly used antibiotics, including ciprofloxacin, nitrofurantoin, gentamicin, amikacin, trimethoprin-sulfamethaxole, and imipenem. The breakpoints of these antimicrobial agents were using CLSI criteria.[6] With regard to the antimicrobial activity of fosfomycin, we used the CLSI-directed disk diffusion test for *E coli* and *K pneumoniae*, although the standard breakpoints of disk zone diameter were only issued for *E coli* but not for *K pneumoniae*.

Statistical analyses

We compared the differences in susceptibility or resistance between the groups with χ^2 test. The difference between groups were considered significantly different if *p*-values were smaller than 0.05. We analyzed the data with Statistical Package for the Social Sciences software for Windows Version 16.0 (SPSS, Inc., Chicago, IL, USA).

Result

We included 134 isolates of ESBL-*EC* and 66 isolates of ESBL-*KP* in the study. We tested seven antimicrobial agents (fosfomycin, nitrofurantoin, ciprofloxacin, gentamicin, trimethoprim-sulfamethoxazole, amikacin, and imipenem) for those 200 isolates. Table 1 is the comparison of antimicrobial susceptibilities in ESBL-*EC* and ESBL-*KP*. We found that imipenem was the most active antimicrobial agent against all the ESBL-*EC* and ESBL-*KP* isolates, with susceptibility rates of 99.3% and 90.9%, respectively. Only 57.6% of ESBL-*KP* isolates were susceptible to amikacin. Fosfomycin, showed significantly higher antimicrobial activity against ESBL-*EC* than ESBL-*KP*, with susceptibility of 95.5% and 57.6%, respectively ($p < 0.001$). The susceptibility rate of nitrofurantoin against ESBL-*EC* isolates was near 80% but was significantly decreased in ESBL-*KP* isolates ($p < 0.001$).

Among the 200 isolates of urinary ESBL-*EC* and ESBL-*KP*, 64 (47.8%) ESBL-*EC* isolates and 45 (68.2%) ESBL-*KP* isolates were compatible with definition of hospital-acquired isolates. Table 2 lists the antimicrobial susceptibilities of