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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

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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.*

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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

Table 1 Comparison of antimicrobial susceptibilities between ESBL-producing *E coli* and ESBL-producing *K pneumoniae*

Antibiotic	ESBL-EC ($n = 134$)		ESBL-KP ($n = 66$)		p
	S (%)	MIC_{90} (mg/L)	S(%)	MIC_{90} (mg/L)	
Fosfomycin	95.5		57.6		<0.001
Nitrofurantoin	79.1	>128	13.6	>128	<0.001
Ciprofloxacin	29.1	>4	37.9	>4	0.276
Gentamicin	44.8	>16	30.3	>16	0.049
Trimethoprim-sulfamethoxazole	22.4	>4	18.2	>4	0.492
Amikacin	97.0	8	57.6	>64	<0.001
Imipenem	99.3	1	90.9	4	0.003

ESBL-*EC* = extended-spectrum β-lactamase producing *Escherichia coli*; ESBL-*KP* = extended-spectrum β-lactamase producing *Klebsiella pneumoniae*; MIC = minimal inhibition concentration; S = susceptibility.
Significantly different if $p < 0.05$.

the hospital-acquired and non-hospital-acquired ESBL-*EC* and ESBL-*KP* isolates. None of the antimicrobials tested had significant difference in activity against the hospital-acquired or non-hospital-acquired ESBL-*EC* isolates. Imipenem (susceptibility rate 91.1%) was still actively against the hospital-acquired ESBL-*KP*, followed by fosfomycin (susceptibility rate 55.6%), and amikacin (susceptibility rate 46.7%). Amikacin (susceptible rate 81%) was still actively against non-hospital-acquired ESBL-*KP* isolates. Less than 30% hospital-acquired urinary ESBL-producing isolates were susceptible to ciprofloxacin.

Table 3 characterizes the antimicrobial susceptibilities of the ESBL-*EC* and ESBL-*KP* isolates with respect to ciprofloxacin resistance. Imipenem, fosfomycin, and amikacin had good activity against both ciprofloxacin- susceptible and ciprofloxacin nonsusceptible ESBL-*EC* isolates. The susceptible rate of gentamicin was significantly lower in ciprofloxacin nonsusceptible ESBL-*EC* isolates comparing with ciprofloxacin-susceptible isolates (32.6% *vs.* 74.4% isolates, $p < 0.001$). Among ESBL-*KP* isolates, imipenem still showed high activity in both groups. Fosfomycin has higher activity against ciprofloxacin-sensitive group but without statistical significance comparing with ciprofloxacin non-susceptible group ($p = 0.181$). Comparing with ciprofloxacin-susceptible group, the susceptible rates of ESBL-*KP* isolates for nitrofurantoin and trimethoprim-sulfamethoxazole were significantly decreased in the ciprofloxacin nonsusceptible isolates (32.0% *vs.* 2.4%, $p = 0.001$; 32% *vs.* 9.8%, $p = 0.023$; respectively).

Discussion

E coli and *K pneumoniae* play important roles in UTI, which is one of the most frequently encountered infectious diseases. Cephalosporins and trimethoprim-sulfamethoxazole are widely used in treating UTI. Because of the rising resistance of *E coli* to trimethoprim-sulfamethoxazole, fluoroquinolones has been used more frequently. But the production of ESBLs by *E coli* and *K pneumoniae* is associated with the reducing susceptibility to fluoroquinolones and other antimicrobial agents.[9–13] Ciprofloxacin has commonly been used as oral therapeutic option for ESBL-producing isolates. The resistance rates of ESBL-*EC* and ESBL-*KP* to ciprofloxacin in this study (Table 1) were higher than those reported from other countries. In the last two decades, ESBL-producing enterobacteriaceae have emerged in both the community and hospital settings in most countries, including Taiwan.[9,13–18] Carbapenems are the drugs of choice for treating severe infections caused by the ESBL-producing isolates. In our study, imipenem was most actively against ESBL-*EC* and ESBL-*KP* isolates.

Aminoglycosides are therapeutic alternatives to ESBL-producing enterobacteriaceae. Gentamicin was inactive

Table 2 Antimicrobial susceptibilities of hospital-acquired and non-hospital-acquired ESBL-producing *E. coli* and ESBL-producing *K. pneumoniae* isolates

Antibiotic	ESBL-EC		p	ESBL-KP		p
	HA ($n = 64$)	Non-HA ($n = 70$)		HA ($n = 45$)	Non-HA ($n = 21$)	
Fosfomycin	96.9	94.3	0.469	55.6	61.9	0.627
Nitrofurantoin	76.6	81.4	0.489	11.1	19.0	0.382
Ciprofloxacin	25.0	32.9	0.317	26.7	61.9	0.006
Gentamicin	42.2	47.1	0.564	13.3	66.7	<0.001
Trimethoprim-sulfamethoxazole	20.3	24.3	0.582	8.9	38.1	0.004
Amikacin	95.3	98.6	0.268	46.7	81.0	0.009
Imipenem	100	98.6	0.337	91.1	90.5	0.933

ESBL-*EC* = extended-spectrum β-lactamase producing *Escherichia coli*; ESBL-*KP* = extended-spectrum β-lactamase producing *Klebsiella pneumoniae*; HA = hospital acquired.
Significantly different if $p < 0.05$.

Table 3 Antimicrobial susceptibilities of ESBL-producing *E coli* and ESBL-producing *K pneumoniae* isolates with respect to ciprofloxacin resistance

Antibiotic	ESBL-EC		*p*	ESBL-KP		*p*
	CIP-S ($n = 39$)	CIP-NS ($n = 95$)		CIP-S ($n = 25$)	CIP-NS ($n = 41$)	
Fosfomycin	92.3	96.8	0.249	68.0	51.2	0.181
Nitrofurantoin	84.6	76.8	0.315	32.0	2.4	0.001
Gentamicin	74.4	32.6	<0.001	44.0	22.0	0.059
Trimethoprim-sulfamethoxazole	33.3	17.9	0.051	32.0	9.8	0.023
Amikacin	97.4	96.8	0.854	72.0	48.8	0.064
Imipenem	97.4	100	0.117	96.0	87.8	0.261

CIP-S = ciprofloxacin-susceptible (MIC $\leq$ 1 mg/L); CIP-NS = ciprofloxacin-resistant or intermediate (MIC $\geq$ 2 mg/L); ESBL-*EC* = extended-spectrum β-lactamase producing *Escherichia coli*; ESBL-*KP* = extended-spectrum β-lactamase producing *Klebsiella pneumoniae*. Significantly different if $p < 0.05$.

against both ESBL-*EC* and EBL-*KP* isolates in this study (Table 1), and amikacin exhibited similar activity to imipenem against ESBL-*EC*. The activities of amikacin against ESBL-KP are various in previous studies.[12,13,19] According to SMART 2005–2007, Hawser et al.[13] showed that 75.4% ESBL-*KP* related to intraabdominal infection is susceptible to amikacin. A study in New Zealand has reported zero resistance rate of ESBL-KP to amikacin.[19] The amikacin susceptibility rate in this study is lower than that in previous published data in Taiwan.[12]

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 *E coli*.[14,20,21] 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 *E coli*.[22] Our study showed the similar finding, and the activity of fosfomycin against ESBL-*EC* isolates remained reliable even in ciprofloxacin-nonsusceptible isolates. Ko et al.[14] has shown that fosfomycin does not have cross-resistance with other antimicrobial agents. This finding may be because of the unique antibacterial mechanism of fosfomycin. The CLSI criteria of fosfomycin have been issued for urinary *E coli* isolates. Other national organizations, such as British Society for Antimicrobial Chemotherapy and Antimicrobial Committee of the French Microbiology Society, recommend fosfomycin for other enterobacteriaceae, but with more conservative criteria.[23] But, the role of fosfomycin against *K pneumoniae* has been widely discussed. In the review by Falagas et al.,[22] the susceptibilities of ESBL-*KP* isolates to fosfomycin were 76.7% to 100%. But, in this study, ESBL-*KP* exhibited high resistance rate to fosfomycin (42.4%) according to CLSI criteria (Table 1). Hence, fosfomycin is a promising therapeutic option for treating inpatient and outpatient UTI caused by ESBL-*EC* rather than ESBL-*KP*.

Nitrofurantoin is an old drug used for uncomplicated UTI, but its use is limited because of its nephrotoxicity. Recently, the potential role of nitrofurantoin for uncomplicated UTI in the growing resistance era has been mentioned.[24] In this study, the susceptibility rate of ESBL-*EC* isolates for nitrofurantoin was near 80%, which was not significantly changed in the presence of ciprofloxacin resistance (Table 3). *K pneumoniae* isolates producing ESBL has been reported to be associated with increased resistance to nitrofurantoin.[25] As shown in Table 3, our study finding showed that the resistance rate was also increased significantly in ciprofloxacin nonsusceptible ESBL-*KP*. Based on those findings, we suggest that nitrofurantoin may be another alternative option for treating uncomplicated UTI caused by ESBL-*EC* infection.

Trimethoprim-sulfamethoxazole is one of few oral therapeutic options for ESBL-producing isolates. But in this study, it was the least active antimicrobial agent against ESBL-*EC* and ESBL-*KP* isolates (Table 1). Ko et al.[14] showed that the resistance rates for trimethoprim-sulfamethoxazole among *E coli* are rising accompanied with ciprofloxacin resistance and ESBL production.

In hospital-acquired UTI caused by ESBL-producing *E coli* and *K pneumoniae*, it is easy to use an inappropriate antibiotic as empiric therapy. The initial inappropriate therapy for hospital-acquired infection is associated with higher mortality.[26] According to our data, imipenem, fosfomycin, and amikacin were reliable for hospital-acquired ESBL-*EC* (Table 2). None of ESBL-*EC* was resistant to imipenem, and only two of three isolates were resistant to fosfomycin and amikacin, respectively. With regard to hospital-acquired ESBL-*KP* isolates, the activity was significantly lower in amikacin, ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole ($p < 0.05$). Fosfomycin showed similarly activity in the two groups. Amikacin was frequently used for hospital-acquired UTI as combination therapy for broad-spectrum covering. Patients with hospital-acquired infection have higher risk for nephrotoxicity, which is probably related to amikacin because of comorbidity and unstable hemodynamic status. Fosfomycin had similar activity as amikacin against hospital-acquired ESBL isolates (Table 2). We suggest that fosfomycin has the potential to replace amikacin in treating hospital-acquired UTI when considering ESBL-producing isolates and less nephrotoxicity.

This study has two limitations. First, only disk diffusion method was used to determine the fosfomycin susceptibility. We did not keep all isolates for further MIC. de Cueto et al.[15] showed discrepancy between different methods testing the susceptibility of ESBL-*KP* to fosfomycin, whereas no significant difference has been found for *E coli*. Disk diffusion method reported greater resistance to fosfomycin for *K pneumoniae* than agar dilution method. Second, the non-hospital-acquired group may include health

care-associated isolates from other health care institutions or other hospital if not recorded in chart. It may decrease the susceptible rates of antimicrobials in the non-hospital-acquired group.

In conclusion, fosfomycin showed significantly higher activity against ESBL-*EC* than ESBL-*KP* in this study. The susceptibility to fosfomycin was also kept for hospital-acquired ESBL-*EC* isolates. Fosfomycin may be a potential therapeutic option for hospital- and community-acquired UTI caused by ESBL-*EC*. Nitrofurantoin was actively against ESBL-*EC* only. Nitrofurantoin may be another alternative option for treating uncomplicated UTI caused by ESBL-*EC* in Taiwan.

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Reference

1. Gupta K. Emerging antibiotic resistance in urinary tract pathogens. *Infect Dis Clin North Am* 2003;**17**:243—59.
2. Falagas ME, Polemis M, Alexiou VG, Marini-Mastrogiannaki A, Kremastinou J, Vatopoulos AC. Antimicrobial resistance of *Esherichia coli* urinary isolates from primary care patients in Greece. *Med Sci Monit* 2008;**14**:CR75—9.
3. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. *Clin Microbiol Rev* 2005;**18**:657—86.
4. Eschenburg S, Priestman M, Schonbrunn 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.
5. Kahan F, Kahan J, Cassidy P, Kropp H. The mechanism of action of fosfomycin (phosphonomycin). *Ann N Y Acad Sci* 1974;**235**: 364—86.
6. Clinical and Laboratory Standards Institue. *Performance standards for antimicrobial susceptibility testing*. Supplement M100-S19. Wayne, PA: Clinical and Laboratory Standards Institue; 2009.
7. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;**16**:28—40.
8. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting; 2008. *Am J Infect Control* 2008;**36**:309—32.
9. Jean SS, Teng LJ, Hsueh PR, Ho SW, Luh KT. Antimicrobial susceptibilities among cilinical isolates of extended-spectrum cephalosporin-resistant Gram-negative bacteria in a Taiwanese University Hospital. *J Antimicrob Chemother* 2002;**49**: 69—76.
10. Paterson DL, Mulazimoglu L, Casellas JM, Ko WC, Goossens H, Von Gottberg AV, et al. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum β—lactamase production in *Klebsiella pneumoniae* isolates causing bacteremia. *Clin Infect Dis* 2000;**30**:473—8.
11. Lautenbach E, Strom BL, Bilker WB, Patel JB, Edelstein PH, Fishman NO. Epidemiology investigation of fluoroquinolone resistance in infections due to extended-spectrumβ—lactamase—producing *Escherichia coli* and *Klebsiella pneumoniae*. *Clin Infect Dis* 2001;**33**:1288—94.
12. Liao CH, Sheng WH, Wang JT, Sun HY, Wang HK, Hsueh PR, et al. In vitro activities of 16 antimicrobial agents against clinical isolates of extended-spectrumβ—lactamase—producing *Escherichia coli* and *Klebsiella pneumoniae* in two regional hospitals in Taiwan. *J Microbiol Immunol Infect* 2006;**39**:59—66.
13. Hawser SP, Bouchillon SK, Hoban DJ, Badal RE. In vitro susceptibilities of aerobic and facultative anaerobic Gram-negative bacilli from patients with intra-abdominal infections worldwide from 2005-2007: results from the SMART study. *Int J Antimicrob Agents* 2009;**34**:585—8.
14. 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 β-lactamase-producing *Escherichia coli* isolated from urine and blood. *Diagn Microbiol Infect Dis* 2007; **58**:111—5.
15. de Cueto M, Lopez L, Hernandez JR, Morillo C, Pascual A. In vitro activity of fosfomycin against extended-spectrum-β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*: comparison of susceptibility testing procedures. *Antimicrob Agents Chemother* 2006;**50**:368—70.
16. Canton R, Coque TM. The CTX-M β-lactamase pandemic. *Curr Opin Microbiol* 2006;**9**:466—75.
17. Yu WL, Jones RN, Hollis RJ, Messer SA, Biedenbach DJ, Deshpande LM, et al. Molecular epidemiology of extended-spectrum-β-lactamase—producing, fluoroquinolone-resistant isolates of *Klebsiella pneumoniae* in Taiwan. *J Clin Microbiol* 2002;**40**:4666—9.
18. Yan JJ, Ko WC, Tsai SH, Wu HM, Jin YT, Wu JJ. Dissemination of CTX-M-3 and CMY-2 β-lactamases among clinical isolates of *Escherichia coli* in southern Taiwan. *J Clin Microbiol* 2000;**38**: 4320—5.
19. Heffernan HM, Woodhouse RE, Pope CE, Blackmore TK. Prevalence and types of extended-spectrum-β-lactamase among urinary *Escherichia coli* and *Klebsiella spp*. in New Zealand. *Int J Antimicrob Agents* 2009;**34**:544—9.
20. Prakash V, Lewis II JS, Herrera ML, Wickes BL, Jorgensen JH. Oral and parenteral therapeutic options for outpatient urinary infections caused by Enterobacteriaceae producing CTX-M extended-spectrum β-lactamases. *Antimicrob Agents Chemother* 2009;**53**:1278—80.
21. 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.
22. Falagas ME, Kastoris AC, Kapaskelis AM, Karageogropoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis* 2010;**10**:43—50.
23. Falagas ME, Kanellopoulou MD, Karageorgopoulos DE, Dimopoulos G, Rafailidis PI, Skarmoutsou ND, et al. Antimicrobial susceptibility of multidrug-resistant Gram negative bacteria to fosfomycin. *Eur J Clin Microbiol Infect Dis* 2008;**27**: 439—43.
24. Kashanian J, Hakimian P, Blute Jr M, 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.
25. Procop GW, Tuohy MJ, Wilson DA, Williams D, Hadziyannis E, Hall GS. Cross-class resistance to non-β-lactam antimicrobials in extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*. *Am J Clin Pathol* 2003;**120**:265—7.
26. Melzer M, Peterson 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.