International Journal of Infectious Diseases 17 (2013) e159–e163

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae*

Asako Doi [a,*], Toshihiko Shimada [b], Sohei Harada [c], Kentaro Iwata [d], Toru Kamiya [a,e]

[a] Department of Infectious Diseases, Rakuwakai Otowa Hospital, Otowachinji-cho 2, Yamashina-ku, Kyoto, Japan
[b] Department of General Internal Medicine, Nara City Hospital, Nara, Japan
[c] Department of Microbiology and Infectious Diseases, Toho University School of Medicine, Ota-ku, Tokyo, Japan
[d] Division of Infectious Diseases, Kobe University Hospital, Chuo-ku, Kobe, Hyogo, Japan
[e] Department of General Internal Medicine, Rakuwakai Otowa Hospital, Otowachinji-cho 2, Yamashina-ku, Kyoto, Japan

ARTICLE INFO

Article history:
Received 3 April 2012
Accepted 26 September 2012

Corresponding Editor: William Cameron, Ottawa, Canada

Keywords:
Extended-spectrum beta-lactamase (ESBL)
Cefmetazole
Cephamycin
Carbapenem
Urinary tract infections

SUMMARY

Objectives: Urinary tract infections (UTIs) caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* are on the increase. Although cefmetazole is stable in vitro against the hydrolyzing activity of ESBLs, no clinical study has ever evaluated its role in infections caused by these organisms. We therefore evaluated the efficacy of cefmetazole compared to carbapenems against pyelonephritis caused by ESBL-producing *Enterobacteriaceae*.
Methods: A retrospective chart review was conducted at a tertiary care hospital from August 2008 to July 2010. Chart reviews were done for patients with ESBL-producing organisms in urine identified in the microbiology database. Patients who were treated with cefmetazole were compared to those treated with carbapenems. The clinical and bacteriological cure rates at 4 weeks after completion of therapy were evaluated.
Results: Two hundred and fifty-six urine cultures growing ESBL-producing organisms were identified during the study period. Ten patients treated with cefmetazole and 12 patients treated with carbapenems were evaluated. There was no difference in clinical (9/10 vs. 12/12, $p = 0.46$) or bacteriological cure rate (5/7 vs. 6/7, $p = 1.00$) at 4 weeks after the completion of therapy. There was no difference in the incidence of adverse effects (2/10 vs. 2/12, $p = 1.00$).
Conclusions: Cefmetazole may be a useful option for the treatment of UTIs caused by ESBL-producing organisms. Prospective and larger sized studies are needed to confirm our findings.

1. Introduction

The frequency of urinary tract infections (UTIs) caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs) is increasing worldwide, even in community settings.[1] Although there are few nationwide reports on ESBL-producing organisms in Japan,[2] data have shown that CTX-M (particularly CTX-M-9) in *Escherichia coli* is prevalent in Japan;[3,4] the prevalence of ESBL-producing organisms in our hospital has also been increasing (unpublished data). In 2010, the Clinical and Laboratory Standards Institute (CLSI) changed the susceptibility breakpoint of *Enterobacteriaceae* against cephalosporins and aztreonam, and the routine detection of ESBLs in regular bacterial culture was not recommended for therapeutic purposes;[5] however their detection in routine culture has continued in many microbiology laboratories in Japan.

It is recommended that infections caused by ESBL-producing organisms, especially serious ones such as bacteremia, should be treated with carbapenems.[1,6] Carbapenems are the drug of choice for the treatment of infections caused by highly-resistant Gram-negative bacteria, however the increase in their use could lead to the selection of carbapenem-resistant organisms and have undesirable effects on hospitals and in the community with regard to microbial resistance.

Although there are few published reports on clinical efficacy, cephamycins are known to be stable against the hydrolytic activity of ESBLs.[6–8] However, a decrease in the expression of outer membrane protein can occur and the production of inducible or constitutive AmpC beta-lactamase during treatment may result in treatment failure.[9,10] Because of this, cephamycins are not recommended as first-line therapy for serious infections caused by ESBL-producing organisms, despite their good in vitro activity. If acquired AmpC beta-lactamases co-exist with ESBLs, the efficacy of cephamycins is disrupted; however, a report has shown that plasmid-mediated AmpC beta-lactamases are rare in Kinki region where our hospital is located.[11] To date, flomoxef is the only

* Corresponding author. Tel.: +81 75 593 4111; fax: +81 75 581 6935.
E-mail address: asakodoi@gmail.com (A. Doi).

1201-9712/$36.00 – see front matter
http://dx.doi.org/10.1016/j.ijid.2012.09.010

cephamycin to have been evaluated retrospectively,[9,12] and no clinical study has ever evaluated the role of cefmetazole – the only cephamycin available in Japan with a CLSI breakpoint for *Enterobacteriaceae* – for infections caused by ESBL-producing bacteria.

The purpose of the current study was to evaluate the efficacy of cefmetazole against pyelonephritis caused by ESBL-producing *Enterobacteriaceae* in comparison to carbapenems, which are considered the standard therapeutic agents for infections caused by these organisms.

2. Materials and methods

2.1. Hospital setting and study design

This retrospective study was conducted at a 588-bed tertiary care teaching hospital from August 2008 to July 2010. In our hospital, the proportion of ESBL-producing *Enterobacteriaceae* during the study period was 15.6% in *E. coli*, 3.4% in *Klebsiella pneumoniae*, 1.9% in *Klebsiella oxytoca*, and 37.2% in *Proteus mirabilis*.

This study compared the efficacy of cefmetazole and carbapenems given empirically or as definitive therapy, which was defined as antimicrobials given after the susceptibility results were obtained. A chart review was done for patients with ESBL-producing organisms such as *E. coli*, *Klebsiella spp*, and *P. mirabilis* in urine as identified from the microbiology database for the period August 2008–July 2010.

Inclusion criteria were: (1) patient age $\geq$15 years and a diagnosis of pyelonephritis by clinicians based on bacteriuria with $>10^4$ CFU/ml and pyuria; (2) no foci other than the urinary tract were found; and (3) patient empirically treated with cefmetazole or carbapenem from the beginning to the end of treatment, or treated first with other antimicrobials then changed to cefmetazole or carbapenem based on culture results (definitive therapy). Patients with complicated UTIs such as infections with a neurogenic bladder, urinary stones, and anatomical abnormalities (i.e., bladder cancer or prostatic problems) were also included. Cases with positive blood cultures in addition to urine cultures at the onset of fever were not excluded. Exclusion criteria included: (1) the occurrence of a case of new different illness during the treatment of pyelonephritis; (2) treatment with both cefmetazole and carbapenem; (3) an entire duration of treatment of less than 5 days with a drug to which there was in vitro susceptibility; (4) empirical treatment for more than 7 days with other antimicrobials to which there was in vitro susceptibility; and (5) empirical treatment with carbapenem or cefmetazole changed to another antimicrobial to which there was in vitro susceptibility. Diabetes mellitus was defined when patients were treated with oral or injection anti-diabetic medications. Renal failure was defined in the case of a serum creatinine >1.5 mg/dl at entry; immunosuppression was defined in the case of HIV infection, neutropenia, cancer, or the consumption of steroids or other immunosuppressive agents. The activities of daily living (ADL) score was estimated based on whether patients were able to move from the wheelchair by themselves or not. The Pitt bacteremia score is a scoring system for the prediction of mortality originally used in intensive care unit (ICU) patients with sepsis, using four factors: mental status, vital signs, need for mechanical ventilation, and recent cardiac arrest; this was used for our analysis.[13]

The primary outcome was the rate of clinical cure at 4 weeks after the completion of therapy. The secondary outcome was the rate of bacterial cure at the same point or thereafter if culture results were not available. Because of the retrospective nature of the current study, the approval of the ethics committee at Rakuwakai Otowa Hospital was not required.

2.2. Bacterial isolates

Identification of the isolates and susceptibility testing were performed using the MicroScan Walkaway 96 SI system (Siemens Healthcare Diagnostics, Tokyo, Japan), and the minimum inhibitory concentrations (MICs) were interpreted using the CLSI criteria.[14] The presence of ESBLs was evaluated by the procedure described in the CLSI guidelines.[14] Isolates positive by initial screen test according to the MIC criteria were tested with a phenotypic confirmatory test by disk diffusion method in the hospital laboratory.

2.3. Statistical analysis

Variables from each group were compared using R version 2.12.2.[15] The *t*-test was used to assess differences in continuous variables, while Fisher's exact test was used to assess differences in dichotomous variables. A two-tailed $p < 0.05$ was considered statistically significant.

3. Results

Two hundred and fifty-five urine cultures with ESBL-producing organisms were identified. Susceptibilities to cefmetazole and meropenem for all *Enterobacteriaceae* from urine specimens identified during the study period were 99.6% and 100%, respectively. We excluded 131 patients who were considered to have colonization only, 10 patients with insufficient data, six patients under 15 years of age, 12 patients who were considered to have cystitis, 12 patients who developed comorbid conditions during treatment such as pneumonia, eight patients who were treated with both cefmetazole and meropenem, five patients who were administered other antimicrobials to which there was susceptibility after cefmetazole and carbapenems, 48 patients treated with other antimicrobials, and one patient whose treatment duration was less than 5 days (Figure 1). As a result, 22 eligible patients were included. Ten patients were treated with cefmetazole and 12 patients were treated with carbapenems, and all the relevant isolates were susceptible to cefmetazole or carbapenems. Meropenem or imipenem/cilastatin was used in the carbapenem group.

Patient characteristics are shown in Table 1. There was no difference between the groups in patient characteristics except for the presence of diabetes mellitus (5/10 vs. 0/12, $p = 0.010$), concurrent bacteremia (0/7 vs. 8/12, $p = 0.013$), and the use of antimicrobials other than cefmetazole or carbapenems initially as empirical treatment (9/10 vs. 5/12, $p = 0.031$). Other complications found in the cefmetazole group were cerebral infarction (two patients) and fracture without urinary incontinence (one patient), and in the carbapenem group one patient had a spinal cord injury. There was no significant difference in age, gender, ADL score, complicated UTI, immunosuppression, other comorbidities, inpatient treatment for UTI, change of antimicrobials, or treatment duration between the groups.

There was no difference in clinical cure rate at 4 weeks (9/10 vs. 12/12, $p = 0.46$) or bacteriological cure rate (5/7 vs. 6/7, $p = 1.00$). One patient in the cefmetazole group had recurrence of pyelonephritis concurrent with pneumonia after incomplete treatment. The urine culture grew ESBL-producing *E. coli* which had the same sensitivity results as that recovered from the urine before treatment. There was no difference in the incidence of adverse effects (2/10 vs. 2/12, $p = 1.00$) (Table 2).

Table 1
Comparison of patient characteristics between the cefmetazole group and the carbapenem group

	Cefmetazole	Carbapenem	*p*-Value
Number of patients	10	12	
Sex	3/10 (30)	7/12 (58.3)	0.231
Age, mean years	77.0	78.75	0.603
ADL[a]	1/10 (10)	5/12 (41.7)	0.162
Bacteremia	0/7 (0)	8/12 (66.7)	0.013
Pitt bacteremia score	NA	1.92	
Urine culture	*E. coli* 9/10 (90)	*E. coli* 12/12 (100)	0.455
	K. pneumoniae 1/10 (10)	*Klebsiella sp* 0/12 (0)	0.455
	P. mirabilis 0/10 (0)	*P. mirabilis* 1/12 (8.3)	1.000
Inpatient	9/10 (90)	8/12 (66.7)	0.323
Complicated UTI	5/10 (50)	10/12 (83.3)	0.172
Urinary catheter inserted	5/10 (50)	6/12 (50)	1.000
Diabetes mellitus	5/10 (50)	0/12 (0)	0.010
Renal failure	1/10 (10)	4/12 (33.3)	0.323
Immunosuppression	0/10 (0)	2/12 (16.7)	0.481
Other complications	3/10 (30)	1/12 (8.3)	0.293
Prior antibiotic use within 3 months	7/10 (70)	7/12 (58.3)	0.675
Change of antimicrobials	9/10 (90)	5/12 (41.7)	0.031
Duration, mean days	11.9	12.5	0.771

NA, data not available; UTI, urinary tract infection.
[a] Activities of daily living, based on whether patients were able to move from a wheelchair by themselves (=1) or not (=0).

4. Discussion

We are now practicing in an aging population, and the majority of infections in elderly patients from nursing-care facilities are pneumonia and UTIs. Risk factors for ESBL-producing organisms are recent antibiotic use, residence in a long-term care facility, recent hospitalization, age ≥65 years, and male sex.[1,16–19] Elderly patients who are repeatedly hospitalized often acquire multidrug-resistant organisms, such as those producing ESBLs. Infections caused by CTX-M ESBL-producing *E. coli* in the community setting are on the increase.[1,16,20] While this may warrant the choice of a carbapenem as empiric therapy for the treatment of serious community-acquired infections due to the lack of any other convincing antimicrobials,[21,22] we have to spare these as much as

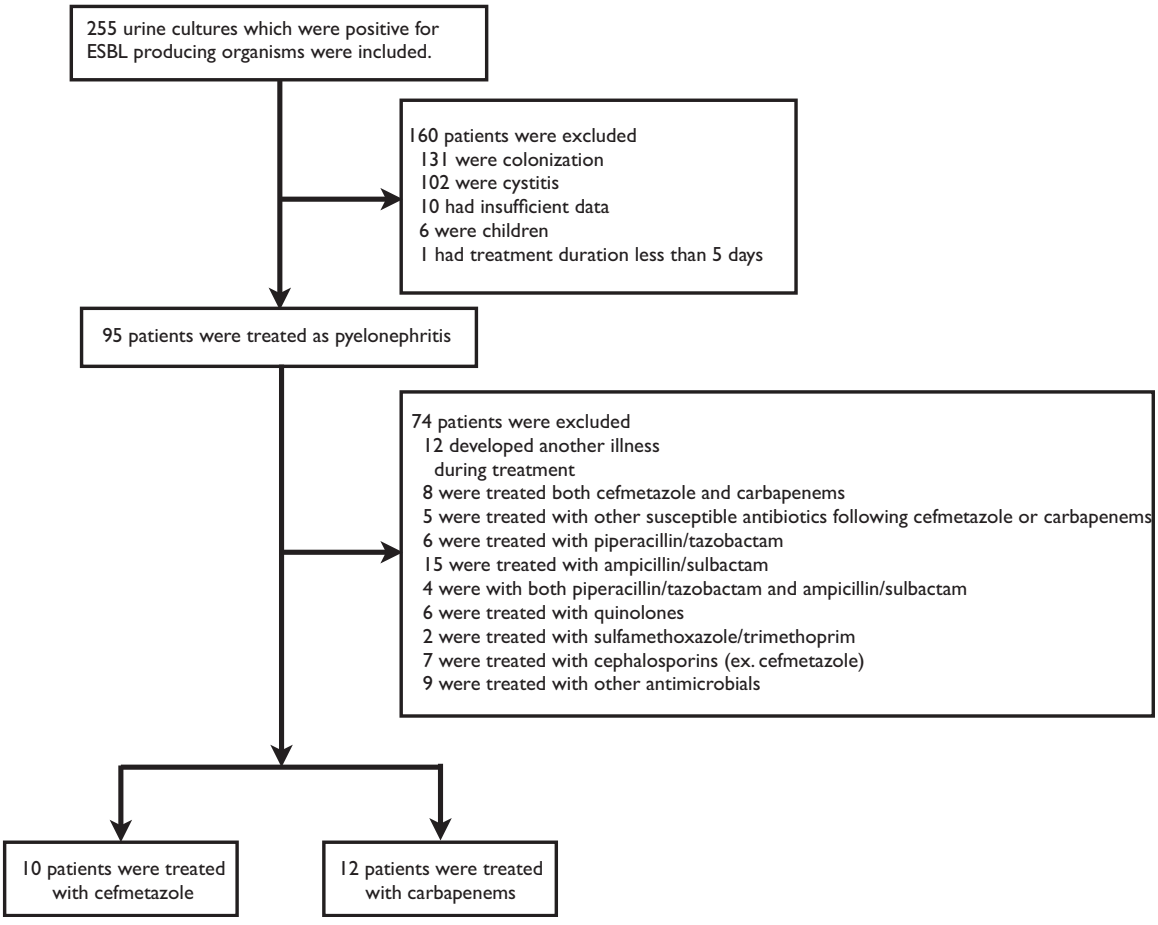

Figure 1. Enrollment of the patients.

Table 2
Comparison of the outcome between the two treatment groups

	Cefmetazole	Carbapenem	*p*-Value
Clinical cure rate at 4 weeks after treatment	9/10 (90)	12/12 (100)	0.46
Microbiological cure rate at 4 weeks after treatment	5/7 (71.4)	6/7 (85.7)	1.00
Adverse effects	2/10 (20)	2/12 (16.7)	1.00

possible because only a few new antimicrobials have been added to the market.

Drugs other than carbapenems such as fluoroquinolones and amoxicillin/clavulanate have been recommended for the treatment of UTIs if the organisms are susceptible in vitro.[1,5] The efficacy of fosfomycin and nitrofurantoin has recently been evaluated for community-acquired UTIs caused by ESBL-producing organisms[23–27] and they have been added to the current armamentarium for first-line empirical therapy of uncomplicated lower UTIs.[16,28] beta-Lactam/beta-lactamase inhibitors (BLBLIs)[29,30] and flomoxef[9,12] have also been evaluated in clinical studies of infections caused by ESBL-producing organisms and BLBLIs have been used for the treatment of UTIs due to such organisms.[8] A recent post-hoc analysis comparing BLBLIs with carbapenems for the treatment of blood stream infections showed there was no difference in mortality or duration of hospital stay between the groups.[31] However, piperacillin–tazobactam is affected by the inoculum effect in vitro,[32] and inhibitor-resistant CTX-M beta-lactamases might evolve under exposure to BLBLIs;[30] there is a case report of treatment failure in prosthetic valve endocarditis due to the development of resistance during therapy.[33] Because of these mixed results, the use of BLBLIs in the treatment of infections caused by ESBL-producing bacteria remains controversial.

In this study, there was no difference between the efficacy of cefmetazole and that of meropenem in terms of clinical and bacteriological cure rates at 4 weeks after the completion of therapy.

There were several limitations to this study. First, more patients with a low ADL were included in the cefmetazole group, and more complicated UTIs were seen in the carbapenem group. Also, more bacteremia was seen in the latter group. This may have resulted from the use of cefmetazole in aged patients with a low ADL in order to avoid the injudicious use of broad-spectrum antibiotics. In addition, the tendency to use a carbapenem in bacteremic cases might have affected the outcome, because more serious cases might have been included in the carbapenem group than in the cefmetazole group. Likewise, there was a significant difference in initial empirical treatment. More patients in the cefmetazole group received antimicrobials other than either cefmetazole or carbapenems. This may be because cefmetazole was not as likely to be chosen as the initial empiric therapeutic agent before susceptibility test results became available, since its spectrum is not broad enough. Furthermore, significantly more diabetic patients were included in the cefmetazole group; the reason for this is unclear. Selection bias might have caused these differences in the two groups. To overcome these limitations, prospective and larger sized studies are needed.

In conclusion, cefmetazole was successfully used for the treatment of UTIs caused by ESBL-producing organisms. Cefmetazole may be an option to spare carbapenem use and this may aid in better antimicrobial stewardship.

Conflict of interest: No conflict of interest to declare.

References

1. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. *Lancet Infect Dis* 2008;**8**:159–66.
2. Yamaguchi K, Ohno A, Ishii Y, Tateda K, Iwata M, Kanda M, et al. In vitro susceptibilities to levofloxacin and various antibacterial agents of 12,919 clinical isolates obtained from 72 centers in 2007 (in Japanese). *Jpn J Antibiot* 2009;**62**:346–70.
3. Suzuki S, Shibata N, Yamane K, Wachino J, Ito K, Arakawa Y. Change in the prevalence of extended-spectrum-beta-lactamase-producing *Escherichia coli* in Japan by clonal spread. *J Antimicrob Chemother* 2009;**63**:72–9.
4. Chong Y, Yakushiji H, Ito Y, Kamimura T. Clinical and molecular epidemiology of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a long-term study from Japan. *Eur J Clin Microbiol Infect Dis* 2011;**30**:83–7.
5. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twentieth informational supplement. M100-S20. Wayne, PA: CLSI; 2010.
6. Harada S, Ishii Y, Yamaguchi K. Extended-spectrum beta-lactamases: implications for the clinical laboratory and therapy. *Korean J Lab Med* 2008;**28**:401–12.
7. Paterson DL, Daveson K. Cefoxitin, cefotetan and other cephamycins (cefmetazole and flomoxef). In: Grayson ML, editor. *Kucers' The use of antibiotics*. London: Edward Arnold; 2010. p. 301–10.
8. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev* 2005;**18**:657–86.
9. Lee CH, Chu C, Liu JW, Chen YS, Chiu CJ, Su LH. Collateral damage of flomoxef therapy: in vivo development of porin deficiency and acquisition of bla_{DHA-1} leading to ertapenem resistance in a clinical isolate of *Klebsiella pneumoniae* producing CTX-M-3 and SHV-5 beta-lactamases. *J Antimicrob Chemother* 2007;**60**:410–3.
10. Bradford PA, Urban C, Mariano N, Projan SJ, Rahal JJ, Bush K. Imipenem resistance in *Klebsiella pneumoniae* is associated with the combination of ACT-1, a plasmid-mediated AmpC beta-lactamase, and the loss of an outer membrane protein. *Antimicrob Agents Chemother* 1997;**41**:563–9.
11. Yamasaki K, Komatsu M, Abe N, Fukuda S, Miyamoto Y, Higuchi T, et al. Laboratory surveillance for prospective plasmid-mediated AmpC beta-lactamases in the Kinki region of Japan. *J Clin Microbiol* 2010;**48**:3267–73.
12. Lee CH, Su LH, Tang YF, Liu JW. Treatment of ESBL-producing *Klebsiella pneumoniae* bacteraemia with carbapenems or flomoxef: a retrospective study and laboratory analysis of the isolates. *J Antimicrob Chemother* 2006;**58**:1074–7.
13. Rhee JY, Kwon KT, Ki HK, Shin SY, Jung DS, Chung DR, et al. Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: a comparison of the Pitt bacteremia score and the acute physiology and chronic health evaluation II scoring systems. *Shock* 2009;**31**:146–50.
14. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twenty-first informational supplement. M100-S21. Wayne, PA: CLSI; 2011.
15. R foundation for Statistical Computing. Available at: http://www.r-project.org (accessed January 11, 2012).
16. Rodríguez-Baño J, Alcala JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008;**168**:1897–902.
17. Ben-Ami R, Rodríguez-Baño J, Arslan H, Pitout JD, Quentin C, Calbo ES, et al. A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in nonhospitalized patients. *Clin Infect Dis* 2009;**49**:682–90.
18. Pitout JD, Nordmann P, Laupland KB, Poirel L. Emergence of *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs) in the community. *J Antimicrob Chemother* 2005;**56**:52–9.
19. Marchaim D, Gottesman T, Schwartz O, Korem M, Maor Y, Rahav G, et al. National multicenter study of predictors and outcomes of bacteremia upon hospital admission caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamases. *Antimicrob Agents Chemother* 2010;**54**:5099–104.
20. Cantón R, Coque TM. The CTX-M beta-lactamase pandemic. *Curr Opin Microbiol* 2006;**9**:466–75.
21. Endimiani A, Luzzaro F, Perilli M, Lombardi G, Coll A, Tamborini A, et al. Bacteremia due to *Klebsiella pneumoniae* isolates producing the TEM-52 extended-spectrum beta-lactamase: treatment outcome of patients receiving imipenem or ciprofloxacin. *Clin Infect Dis* 2004;**38**:243–51.
22. Paterson DL, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. *Clin Infect Dis* 2004;**39**:31–7.
23. 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.
24. Senol S, Tasbakan M, Pullukcu H, Sipahi OR, Sipahi H, Yamazhan T, et al. Carbapenem versus fosfomycin tromethanol in the treatment of extended-spectrum beta-lactamase-producing *Escherichia coli*-related complicated lower urinary tract infection. *J Chemother* 2010;**22**:355–7.

25. Pitout JD. Infections with extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: changing epidemiology and drug treatment choices. *Drugs* 2010;**70**:313–23.
26. Oteo J, Bautista V, Lara N, Cuevas O, Arroyo M, Fernández S, et al. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*. *J Antimicrob Chemother* 2010;**65**:2459–63.
27. Schultsz C, Geerlings S. Plasmid-mediated resistance in *Enterobacteriaceae*: changing landscape and implications for therapy. *Drugs* 2012;**72**:1–16.
28. Auer S, Wojna A, Hell M. Oral treatment options for ambulatory patients with urinary tract infections caused by extended-spectrum-beta-lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2010;**54**:4006–8.
29. Rodríguez-Baño J, Navarro MD, Retamar P, Picón E, Pascual A. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. *Clin Infect Dis* 2012;**54**:167–74.
30. Ripoll A, Baquero F, Novais Â, Rodríguez-Domínguez MJ, Turrient MC, Cantón R, et al. In vitro selection of variants resistant to beta-lactams plus beta-lactamase inhibitors in CTX-M beta-lactamases: predicting the in vivo scenario? *Antimicrob Agents Chemother* 2011;**55**:4530–6.
31. Owens RC. An overview of harms associated with beta-lactam antimicrobials: where do the carbapenems fit in? *Crit Care* 2008;**12**(Suppl 4):S3.
32. Thomson KS, Moland ES. Cefepime, piperacillin–tazobactam, and the inoculum effect in tests with extended-spectrum beta-lactamase-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother* 2001;**45**:3548–54.
33. Zimhony O, Chmelnitsky I, Bardenstein R, Goland S, Hammer Muntz O, Navon Venezia S, et al. Endocarditis caused by extended-spectrum-beta-lactamase-producing *Klebsiella pneumoniae*: emergence of resistance to ciprofloxacin and piperacillin–tazobactam during treatment despite initial susceptibility. *Antimicrob Agents Chemother* 2006;**50**:3179–82.