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Urinary tract infections due to extended-spectrum beta-lactamase-producing Gram-negative bacteria: identification of risk factors and outcome predictors in an Australian tertiary referral hospital

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SUMMARY

Objectives: Extended-spectrum beta-lactamase-expressing Gram-negative bacilli (ESBL-GNB) now commonly cause community-acquired infections, including urinary tract infections (UTI), and represent a challenge for practitioners in choosing empirical antibiotics. The aim of this study was to describe the epidemiology and clinical characteristics of UTIs/bacteriuria due to ESBL-GNB in Australia.
Methods: At a single-site tertiary referral hospital, 100 cases with UTIs/bacteriuria due to ESBL-GNB were matched to 100 cases where UTIs/bacteriuria were caused by organisms matching the ESBL bacterial species that had routine susceptibility to antibiotics. Potential risk factors for ESBL-GNB UTI/bacteriuria and differences in clinical outcomes were identified.
Results: Length of admission prior to positive sample (odds ratio (OR) 1.3, $p = 0.03$, per week), exposure to antibiotics (OR 5.7, $p < 0.001$), return from overseas travel (OR 6.5, $p = 0.002$), and nursing home residency (OR 4.2, $p = 0.03$) were identified as risk factors associated with ESBL-GNB UTI/bacteriuria in the multivariate analysis. In addition, ESBL-GNB-infected cases subsequently had a longer inpatient stay (median 6 vs. 2 days, $p = 0.002$) and were admitted to the intensive care unit more frequently (28/100 vs. 8/100, $p < 0.001$).
Conclusions: Our results emphasize the need for culture of a mid-stream urine specimen prior to commencing antibacterials, especially in patients with the risk factors identified herein associated with ESBL-GNB UTI/bacteriuria.

1. Introduction

Increasing resistance to antimicrobials among pathogens that cause common infections is a problem of great global proportions given the paucity of novel antibiotics in development. This is particularly the case for Gram-negative bacteria (GNB) where antibiotic development faces more substantial challenges than for Gram-positive organisms, yet antimicrobial resistance is readily acquired. The newest and gravest challenge among resistant Gram-negative bacteria is posed by New Delhi metallo-beta-lactamase 1 (NDM-1)-expressing organisms that are resistant to all but highly toxic antibiotics like colistin.[1] These organisms have been found infrequently in Australian patients.[2] While less attention grabbing, a much more prevalent current problem in Australia relates to the increasing frequency of resistant GNB expressing extended-spectrum beta-lactamases (ESBL) (http://www.agargroup.org/surveys). These organisms were first recognized as causing nosocomial infections in Europe in the 1980s[3], and in Australia, they have been associated with hospital outbreaks,[4] community infections,[5] and nursing home infections.[6] ESBL-expressing GNB (ESBL-GNB) now commonly cause community-acquired infections, including urinary tract infections (UTIs).[7] As they are frequently resistant to numerous antibiotic classes, including fluoroquinolones and aminoglycosides, these ESBL-GNB represent a challenge for practitioners in choosing empirical antibiotics where there is a reasonable likelihood of their presence.

The aim of this study was to highlight the presence of ESBL-GNB in patients presenting to Australian practitioners based both in

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community and hospital practice. A case–control study was performed to define the epidemiology and clinical outcomes of UTI/bacteriuria due to ESBL-GNB, concentrating on the recognized risk factors for the acquisition of these organisms. Recommendations for appropriate antimicrobials can be made in patients presenting with UTI who are at high risk of infection due to ESBL-GNB.

2. Methods

2.1. Patients and data collection

A retrospective case–control study was conducted to identify risk factors associated with community- or hospital-onset UTI/bacteriuria due to ESBL-producing GNB at the Royal Melbourne Hospital, a major primary and tertiary care service provider. Urine samples entered into the administrative database of the microbiology laboratory from January 1, 2003 to December 31, 2009 from patients aged 18 years or older were evaluated for culture results positive for urinary pathogens. These patients received either ambulatory or inpatient care. If multiple urine specimens from the same patient were available, only the first sample was selected for the analysis. The same patient was only included once as either a case or a control.

A comprehensive review of medical records and online hospital databases was performed to retrieve demographic, clinical, radiographic, and microbiological data. Data collection included gender, age, all medical diagnoses, hospitalization in the past 4 weeks, overseas travel within the last 12 months, exposure to antibiotics during the past 6 weeks, living in an aged care facility, type of urinary sample, antibiotic resistance profile, body temperature and blood pressure on the day of urine sampling, and type of urinary tract infection. Outcome variables included antimicrobial treatment, length of hospital stay and/or admission to the intensive care unit (ICU) after urine sampling, and all-cause inpatient mortality.

2.2. Microbiological methods

Gram-negative organisms with antibiotic resistance patterns indicative of the presence of ESBLs from automated susceptibility testing (resistance to amoxicillin but susceptibility to amoxicillin–clavulanate in the presence of resistance to third-generation cephalosporins using the time period-relevant Clinical and Laboratory Standards Institute breakpoints[8]), were confirmed as ESBL-expressing bacteria by applying a manual method using the 'keyhole test'. This test, in the past used routinely in Australia and internationally for this purpose, relies on identifying an increased zone of microbial inhibition around a third-generation cephalosporin disc in the locale of a clavulanic acid disc. As expected from previous experience at the Royal Melbourne Hospital and other centres, the microorganisms that carried ESBLs were *Escherichia coli*, *Klebsiella oxytoca*, or *Klebsiella pneumoniae*. A total of 316 ESBL-GNB from 178 patients were present among 15 142 positive urine cultures examined (Table 1). This analysis was confined to 100 cases that were selected randomly from urine samples with a significant growth of an ESBL-producing organism, taking into account the relative frequency of all cultured ESBL-producing bacteria (73 *E. coli*, 23 *K. pneumoniae*, and 4 *K. oxytoca*). We did not select patients for the presence of symptomatic UTI as we were interested in assessing the associations between ESBL urinary colonization in addition to infection. To allow the exploration of patient characteristics that may distinguish patients with ESBL-GNB UTI/bacteriuria from those without, controls were matched to cases in a 1:1 ratio only in relation to the bacterial species causing the UTI. Controls therefore consisted of randomly selected patients from the same study period displaying significant bacteriuria with a urinary pathogen matched to the ESBL-GNB-producing organism but that differed by maintaining susceptibility to third-generation cephalosporins.

Table 1
Distribution of *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella spp* cultured from urine specimens obtained between 2003 and 2009

Organism	Positive cultures, *n* (%)	% of total ESBL-positive
Escherichia coli	10 974 (72.5)	
ESBL-positive	232 (1.5)	73.4
Klebsiella oxytoca	572 (3.8)	
ESBL-positive	10 (0.1)	3.2
Klebsiella pneumoniae	1605 (10.5)	
ESBL-positive	74 (0.5)	23.4
Klebsiella spp	17 (0.1)	
Proteus mirabilis	1658 (11.0)	
Total	15 142 (100)	100

ESBL, extended-spectrum beta-lactamase.

2.3. Definitions

Asymptomatic bacteriuria, cystitis (complicated and uncomplicated), pyelonephritis, and urosepsis were defined according to published guidelines.[9] An ESBL-producing organism was considered multiresistant if it was additionally resistant to all three classes of the following antimicrobials: fluoroquinolones, trimethoprim–sulfamethoxazole, and aminoglycosides.[10]

2.4. Statistical analysis

Potential risk factors for ESBL-GNB UTI/bacteriuria were identified by univariate analysis. The Chi-square test or Fisher's exact test was used for categorical variables, and the Student *t*-test or the Mann–Whitney *U*-test for continuous variables, as appropriate. All variables that were associated with ESBL-GNB infection or ICU admission in the univariate analysis at the $p < 0.1$ level were included in the logistic regression using the forward conditional method. Variables were retained in the final model if they were significant at the $p < 0.05$ level. The final model included confounding variables significant at a two-tailed *p*-value of <0.05. SPSS version 18.0 software package was used for the analysis (SPSS Inc., Chicago, IL, USA).

3. Results

During the 7-year observation period, *E. coli*, *Proteus mirabilis*, or *Klebsiella* species were identified in 15 142 urine samples from 10 111 patients, including 316 (2.1%) specimens with an ESBL-GNB from 178 patients (Table 1). Samples were midstream specimens in 80% of controls and 57% of cases. Distinct clinical and microbiological features of UTI were only present in 40% of both cases and controls, with the remaining subjects being classified as suffering from asymptomatic bacteriuria. Among the patients who were treated, 50/58 cases and 53/54 controls (difference not significant) received appropriate directed antibiotic treatment.

Differences in risk factors and outcomes for cases and controls are displayed in Table 2 (univariate analysis). The length of hospital stay prior to the urine sampling episode analyzed here was significantly longer in cases than in controls ($p < 0.001$). In addition, exposure to antibiotics in the past 6 weeks and recent return from overseas travel, mainly to Asia, were identified as significant risk factors associated with UTI due to ESBL-GNB. Interestingly, the frequencies of major comorbidities such as diabetes or cancer and of past UTIs were not significantly different between cases and controls.

Table 2
Univariate analysis of risk factors and outcomes for ESBL-GNB UTI/bacteriuria[a]

Risk factors and outcomes	Cases $n=100$	Controls $n=100$	p-Value
Male, *n*	28	23	0.4
Age in years, mean (SD)	61.6 (22.4)	60 (20.9)	0.6
Hospitalization in previous month, *n*	17	12	0.4
Length of stay prior to positive sample in days, median (IQR)	5.5 (0–27)	0 (0–3)	<0.0001
Diabetes mellitus, *n*	22	23	0.9
Cancer/immunosuppression, *n*	23	24	0.8
Nursing home residency, *n*	10	4	0.1
Prostatism, *n*	7	8	1
Overseas travel in past 12 months	15	5	0.03
Asia	9	2	0.06
Other destinations	6	3	0.5
Exposure to antibiotics in past 6 weeks, *n*	70	27	<0.001
1 class	24	17	0.3
2 classes	20	8	0.02
>2 classes	26	2	<0.001
Third-generation cephalosporins	21	2	<0.001
Vancomycin	15	3	0.002
Previous UTI episodes, *n*	40	39	1
Duration of hospitalization after sampling in days, median (IQR)	6 (2–16)	2 (0–9)	0.002
Duration of treatment in days, median (IQR)	7 (0–10)	5 (0–7)	0.1
Admission to ICU, *n*	28	8	<0.001
All-cause mortality, *n*	8	4	0.4

ESBL-GNB, extended-spectrum beta-lactamase-expressing Gram-negative bacilli; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; UTI, urinary tract infection.
[a] Data are given as number of subjects which equals percentage.

Regarding outcomes after infection (Table 2), the median duration of stay after the diagnosis of UTI was three times longer in cases than in controls, as was the overall admission period (data not shown). This outcome was certainly influenced by the fact that almost 50% of cases were inpatients at the time of urine sampling compared to only 16% of controls. ESBL-GNB-infected cases were more likely to be admitted subsequently to the ICU for any reason than controls with a UTI due to the same organisms with routine susceptibility (Table 2). However, there was no difference in inpatient all-cause mortality between cases and controls, although there were few deaths overall.

As expected, ESBL-producing urinary pathogens were significantly more often resistant to non-beta-lactam antibiotics, and 27% of the isolates were classified as multidrug-resistant. However, susceptibility to carbapenems (100%) and nitrofurantoin (84%) was retained in the majority of ESBL-GNB isolates causing UTIs/bacteriuria (Table 3).

On multivariate analysis, previous overseas travel, recent exposure to antibiotics, residency in a nursing home, and longer hospitalization prior to positive sample were identified as independent risk factors in cases, with odds ratios between 1.2 and 6.5 (Table 4).

4. Discussion

Recent travel, previous exposure to antibiotics, residency in a nursing home, and length of hospital inpatient stay were found to be the factors associated with ESBL-GNB UTI at an Australian tertiary referral hospital during 2003 to 2009. Patients with ESBL-GNB were more likely to require ICU admission and had longer inpatient stays than those with organisms of the same species that had routine susceptibilities. Given the fact that only 40% of cases and controls suffered from a symptomatic UTI, these findings are even more remarkable. Asymptomatic urinary tract colonization might predispose to subsequent invasive infection with ESBL-GNB. Interestingly, previous studies that have described a significantly increased risk for invasive infection with an ESBL-GNB in patients with rectal colonization, did not screen for urinary tract colonization[11,12]. However, a recent study clearly showed that the urinary tract is actually a very frequent colonization site, and that more than 20% of patients will be missed if screening relies only on rectal swabs.[13] Australian data on rectal colonization with multidrug-resistant organisms in returning travelers[14] and aged care facility residents[6] have previously been reported, but the present study is the first to examine risk factors for ESBL-GNB UTI/colonization in Australian residents.

Table 3
Microbiological characteristics[a]

Number of isolates susceptible to:	All	Cases $n=100$	Controls $n=100$	p-Value
Ciprofloxacin, *n* (%)	140 (70)	40	100	<0.001
Trimethoprim, *n* (%)	99 (45.5)	20	79	<0.001
TMP–SMX, *n* (%)	106 (53)	24	82	<0.001
Gentamicin, *n* (%)	154 (77)	54	100	<0.001
Nitrofurantoin, *n* (%)	169 (84.5)	84	85	1
Meropenem, *n* (%)	200 (100)	100	100	1
Multidrug resistance[b], *n* (%)	27 (13.5)	27	0	<0.001

TMP–SMX, trimethoprim–sulfamethoxazole.
[a] Data are given as the number of subjects, which equals the percentage for cases and controls.
[b] Multidrug resistance was defined as combined resistance to fluoroquinolones, aminoglycosides, and trimethoprim–sulfamethoxazole.

Table 4
Multivariate analysis of risk factors associated with ESBL-GNB UTI/bacteriuria and with admission to the ICU

Variable	OR	95% CI	p-Value
ESBL-GNB UTI/bacteriuria			
Length of stay prior to positive sample	1.2[a]	1.0–1.3	0.03
Nursing home residency	4.2	1.1–15.7	0.03
Overseas travel in past 12 months	6.5	2.0–20.9	0.002
Exposure to antibiotics in past 6 weeks	5.7	2.8–11.6	<0.001
ICU admission			
Diabetes mellitus	0.3	0.1–0.9	0.03
ESBL-GNB UTI/bacteriuria	4.6	2.0–10.8	<0.001

CI, confidence interval; ESBL-GNB, extended-spectrum beta-lactamase-expressing Gram-negative bacilli; ICU, intensive care unit; OR, odds ratio; UTI, urinary tract infection.
[a] Per week of hospitalization.

Many of the risk factors identified herein have been associated with ESBL-GNB UTI in studies performed in European countries.[15,16] In these settings though, the effect of international travel is harder to quantify due to the widespread community prevalence of ESBL-GNB. Australian patients are clearly part of the global community, with the negative consequences of travel-associated acquisition of ESBL-GNB evident. Indeed, recent studies have shown prolonged enteric carriage of ESBL-GNB in returned Australian and Swedish travelers.[17,18] Whereas gastrointestinal colonization with multidrug-resistant organisms in repatriated patients is often anticipated and screened for,[19] clinicians are less vigilant about the possibility of multidrug-resistant organisms in patients presenting from the community who have not travelled in the past. Risk factors for ESBL-GNB UTI/bacteriuria identified in the present study will help to guide doctors in recognizing patients at high risk of infection/colonization due to these organisms.

Previous exposure to antibiotics has been identified as a risk factor for ESBL-GNB infection in multiple studies,[15,20] which clearly underscores the ongoing rationale for responsible use of antibiotics. Our findings of an increased length of stay and more frequent ICU admission in patients with ESBL-GNB compared to non-ESBL-GNB are consistent with evidence from previous studies[21,22] and highlight the increased burden of disease associated with resistant bacteria.

The frequency of resistance to antibiotics routinely used for UTI in this series of ESBL-GNB, emphasizes the need for culture of a mid-stream urine specimen prior to commencing antibiotics in patients with the risk factors identified herein. Studies such as these must be used to guide appropriate antibacterial therapy for patients at risk of ESBL-GNB. The majority (84%) of the ESBL-GNB organisms causing UTI at the Royal Melbourne Hospital during the period studied retained susceptibility to nitrofurantoin, which is among the choices for initial therapy of cystitis listed by the Australian Antimicrobial guidelines[23] and is clearly an appropriate initial therapy for a well patient with lower tract symptoms of UTI, even if they are at risk of ESBL-GNB infection. Where a patient has cystitis due to an ESBL-GNB that is resistant to nitrofurantoin, fluoroquinolones, and trimethoprim and where they remain well, the options for outpatient-based oral antibiotic therapy are limited to fosfomycin,[24] which is not licensed in Australia at the present and therefore is available only via a special access scheme. Thus these patients require hospital assessment and prescription of this antibiotic. Patients who are unwell with pyelonephritis due to ESBL-GNB require therapy with an intravenous meropenem, which, while thankfully retaining activity against all multi-resistant organisms in this study, is not an ideal agent due to its broad spectrum and relative instability that complicates hospital in the home (HITH) therapy.[25] Where the ESBL-GNB is susceptible, patients may be treated through HITH with the once-daily carbapenem drug ertapenem.[26]

Even more challenging are the patients with recurrent ESBL-GNB UTI. These patients are often prescribed long-term nitrofurantoin,[27] but the organism frequently develops resistance to this mainstay antibiotic, which has toxicity in long-term use[28] and must not be used where patients have renal impairment. Apart from investigating and correcting structural urological abnormalities, repeated courses of fosfomycin may be used, although there is little evidence to support this therapy. Falling back on old-fashioned approaches to urinary antisepsis using methenamine hippurate may be required, which has been shown to be useful for preventing UTI in patients without renal tract abnormalities in a recent Cochrane review.[29]

Our study has limitations, including the retrospective nature, the limited matching, and the inclusion of urine samples from both hospitalized and ambulatory patients, which might be associated with significant bias. The small sample size might have prevented the identification of additional risk factors for ESBL-GNB UTI/bacteriuria. In addition, the majority of cases and controls did not show evidence of infection but only colonization.

In summary, we have identified risk factors for UTI/colonization with ESBL-GNB in an Australian tertiary care centre to guide doctors in recognizing the patients at high risk of infections due to these organisms. Our results emphasize the need for culture of a mid-stream urine specimen prior to commencing antibiotics, especially in patients with the risk factors identified herein associated with ESBL-GNB UTI. Australia could never have hoped to be able to close its borders, so to speak, to the bacteria of the globe, and we have not been spared an increase in infections due to ESBL-GNB. Yet again, we are reminded of the need to carefully protect the antibiotics we currently have available and push for the discovery of new ones for the future.

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References

1. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009;**53**:5046–54.
2. Sheng WH, Badal RE, Hsueh PR, Program S. Distribution of extended-spectrum beta-lactamases, AmpC beta-lactamases, and carbapenemases among *Enterobacteriaceae* isolates causing intra-abdominal infections in the Asia-Pacific region: results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrob Agents Chemother* 2013;**57**:2981–8.
3. Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and *Serratia marcescens*. *Infection* 1983;**11**:315–7.
4. Eisen D, Russell EG, Tymms M, Roper EJ, Grayson ML, Turnidge J. Random amplified polymorphic DNA and plasmid analyses used in investigation of an outbreak of multiresistant *Klebsiella pneumoniae*. *J Clin Microbiol* 1995;**33**:713–7.
5. Denholm JT, Huysmans M, Spelman D. Community acquisition of ESBL-producing *Escherichia coli*: a growing concern. *Med J Aust* 2009;**190**:45–6.
6. Stuart RL, Kotsanas D, Webb B, Vandergraaf S, Gillespie EE, Hogg GG, et al. Prevalence of antimicrobial-resistant organisms in residential aged care facilities. *Med J Aust* 2011;**195**:530–3.
7. den Heijer CD, Donker GA, Maes J, Stobberingh EE. Antibiotic susceptibility of unselected uropathogenic *Escherichia coli* from female Dutch general practice patients: a comparison of two surveys with a 5 year interval. *J Antimicrob Chemother* 2010;**65**:2128–33.
8. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: nineteenth informational supplement. CLSI Document M100-S19. Wayne, PA: CLSI; 2009.
9. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005;**40**:643–54.
10. Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Fishman NO, Bilker WB, et al. Risk factors for increasing multidrug resistance among extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species. *Clin Infect Dis* 2005;**40**:1317–24.
11. Christiaens G, Ciccarella Y, Damas P, Hayette MP, Melin P, Nys M, et al. Prospective survey of digestive tract colonisation with *Enterobacteriaceae* that produce extended-spectrum beta-lactamases in intensive care units. *J Hosp Infect* 2006;**62**:386–8.
12. Reddy P, Malczynski M, Obias A, Reiner S, Jin N, Huang J, et al. Screening for extended-spectrum beta-lactamase-producing *Enterobacteriaceae* among high-risk patients and rates of subsequent bacteremia. *Clin Infect Dis* 2007;**45**:846–52.
13. Tschudin-Sutter S, Frei R, Dangel M, Stranden A, Widmer AF. Sites of colonisation with extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae*: the rationale for screening. *Infect Control Hosp Epidemiol* 2012;**33**:1170–1.
14. Kennedy K, Collignon P. Colonisation with *Escherichia coli* resistant to "critically important" antibiotics: a high risk for international travellers. *Eur J Clin Microbiol Infect Dis* 2010;**29**:1501–6.
15. Colodner R, Rock W, Chazan B, Keller N, Guy N, Sakran W, et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. *Eur J Clin Microbiol Infect Dis* 2004;**23**:163–7.

16. Ena J, Arjona F, Martinez-Peinado C, Lopez-Perezagua Mdel M, Amador C. Epidemiology of urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Urology* 2006;**68**:1169–74.
17. Rogers BA, Kennedy KJ, Sidjabat HE, Jones M, Collignon P, Paterson DL. Prolonged carriage of resistant *E. coli* by returned travellers: clonality, risk factors and bacterial characteristics. *Eur J Clin Microbiol Infect Dis* 2012;**31**:2413–20.
18. Tangden T, Cars O, Melhus A, Lowdin E. Foreign travel is a major risk factor for colonisation with *Escherichia coli* producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother* 2010;**54**:3564–8.
19. Chua KY, Grayson ML, Burgess AN, Lee JY, Howden BP. The growing burden of multidrug-resistant infections among returned Australian travellers. *Med J Aust* 2014;**200**:116–8.
20. Yilmaz E, Akalin H, Ozbey S, Kordan Y, Sinirtas M, Gurcuoglu E, et al. Risk factors in community-acquired/onset urinary tract infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. *J Chemother* 2008;**20**:581–5.
21. Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing *Escherichia coli* infections in Thailand: a case–case–control study. *Am J Infect Control* 2007;**35**:606–12.
22. Yang YS, Ku CH, Lin JC, Shang ST, Chiu CH, Yeh KM, et al. Impact of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* on the outcome of community-onset bacteremic urinary tract infections. *J Microbiol Immunol Infect* 2010;**43**:194–9.
23. Antibiotic Expert Group. Therapeutic guidelines: antibiotic. Version 14. Melbourne, Australia: Therapeutic Guidelines Limited; 2010.
24. Neuner EA, Sekeres J, Hall GS, van Duin D. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. *Antimicrob Agents Chemother* 2012;**56**:5744–8.
25. Viaene E, Chanteux H, Servais H, Mingeot-Leclercq MP, Tulkens PM. Comparative stability studies of antipseudomonal beta-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). *Antimicrob Agents Chemother* 2002;**46**:2327–32.
26. Bazaz R, Chapman AL, Winstanley TG. Ertapenem administered as outpatient parenteral antibiotic therapy for urinary tract infections caused by extended-spectrum-beta-lactamase-producing Gram-negative organisms. *J Antimicrob Chemother* 2010;**65**:1510–3.
27. Brumfitt W, Hamilton-Miller JM. Efficacy and safety profile of long-term nitrofurantoin in urinary infections: 18 years' experience. *J Antimicrob Chemother* 1998;**42**:363–71.
28. Hardak E, Berger G, Krivoy N, Solomonov A, Yigla M. Nitrofurantoin pulmonary toxicity: neglected threat. *Curr Drug Saf* 2010;**5**:125–8.
29. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev* 2012;**10**:CD003265.