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Original Article

# Activity of ertapenem, ciprofloxacin, ceftriaxone, piperacillin-tazobactam, and ampicillin-sulbactam against 12 common clinical isolates of community-acquired bacteremia

**Kao-Pin Hwang[1,2], Ya-Fen Tang[2], Yea-Huei Shen[3]**

*[1]Department of Pediatrics, and [2]Infection Control Committee, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Chang Gung University College of Medicine; and [3]Infection Control Committee, Yuan General Hospital, Kaohsiung, Taiwan*

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**Background and purpose:** To compare the antimicrobial activities of ertapenem, ciprofloxacin, ceftriaxone, piperacillin-tazobactam, and ampicillin-sulbactam against 12 common organisms that cause community-acquired bacteremia and to identify the most active agents for the treatment of extended-spectrum β-lactamase (ESBL)–producing *Escherichia coli* and *Klebsiella pneumoniae*.

**Methods:** 1200 blood specimens from patients with community-acquired bacteremia were collected at Chang Gung Memorial Hospital, Kaohsiung, Taiwan. All isolates were identified by the API system, and each culture's antimicrobial susceptibility was determined by the standard disk-diffusion method. The minimal inhibitory concentrations of the antibiotics were detected by the Epsilimeter test.

**Results:** The in vitro susceptibilities of 11 of the 12 common pathogens to ertapenem were 100%. The frequency of ESBL-producing *E. coli* and *K. pneumoniae* was 6.2% and 9.5%, respectively. Only 48% and 50% of *E. coli* and *K. pneumoniae*, respectively, were susceptible to ciprofloxacin. These data infer that ciprofloxacin should not be given for ESBL-producing *E. coli* and *K. pneumoniae*. Ceftriaxone and piperacillin-tazobactam had high activity against the most common pathogens isolated.

**Conclusions:** ESBL *E. coli* and *K. pneumoniae* are highly resistant to ciprofloxacin, so this antibiotic should be avoided for patients with community-acquired bacteremia. ESBL *E. coli* and *K. pneumoniae* are highly susceptible to ertapenem.

**Key words:** Anti-infective agents; beta-Lactamases; Community-acquired infections; Microbial sensitivity tests

## Introduction

Community-acquired bacteremia is a serious consequence of localized infections, which may originate from the urinary tract, gastrointestinal tract, respiratory tract, surgical sites, and indwelling catheters. Community-acquired bacteremia is responsible for approximately 7 to 12/1000 hospital admissions in the United States [1]. The incidence is 0.2/1000 in children and 26/1000 in patients older than 85 years [1]. In the early 1960s, Gram-negative bacteria were identified as the predominant cause of septic shock [2]. However, there has been a shift in the etiology of nosocomial infections, with an increased frequency of Gram-positive bacteria [3]. Staphylococci, streptococci, *Escherichia coli,* and enterococci remain the most commonly isolated pathogens in community-acquired bacteremia. Treatment with inappropriate empiric antibiotics is associated with a higher mortality rate [4].

Ampicillin-sulbactam, ceftriaxone, piperacillin-tazobactam, ciprofloxacin, and ertapenem have been used against community-acquired bacteremia at the Chang Gung Memorial Hospital, Kaohsiung, Taiwan. This study was conducted to compare the antimicrobial activities of ertapenem with ampicillin-sulbactam, ceftriaxone, piperacillin-tazobactam, and ciprofloxacin

*Corresponding author: Dr. Yea-Huei Shen, Infection Control Committee, Yuan General Hospital, 162 Cheng-Kung 1st Rd., Kaohsiung, Taiwan.*
*E-mail: shen7291@yahoo.com.tw*

against 12 common organisms that cause community-acquired bacteremia, including extended-spectrum β-lactamase (ESBL)–producing *E. coli* and *Klebsiella pneumoniae*.

## Methods

1200 clinical isolates were cultured from blood specimens obtained from patients with community-acquired bacteremia during a 2-year period from January 2005 to December 2006. The patients had been admitted to the Chang Gung Memorial Hospital, a tertiary care medical center in Kaohsiung, Taiwan. The first 50 isolates from patients with community-aquired bacteremia were collected each month to ascertain the normal seasonal distribution. Permission for the study from the Institutional Review Board of Chang Gung Memorial Hospital was obtained.

To exclude nosocomial infections, community-acquired bacteremia was defined as clinical infection with positive blood culture within 48 h of admission and no hospital admission within the previous 3 months. There were 2 species of Gram-positive organisms and 37 species of Gram-negative bacteria isolated. All pathogens were identified by the API system. Bacterial strains that were cultured from at least 25 isolates included 2 Gram-positive cocci and 12 Gram-negative bacilli. The antimicrobial susceptibility of these isolates was investigated in vitro by the standard disk-diffusion method, as described by the Clinical and Laboratory Standards Institute (CLSI) [5]. Susceptibility and resistance were based on CLSI breakpoints [5]. ESBL production was suspected if the inhibition zone of ceftriaxone was ≤25 mm or of ceftazidime was ≤22 mm by disk-diffusion susceptibility test. The isolates were subjected to cefotaxime 30 μg, cefotaxime-clavulanate 30/10 μg, ceftazidime 30 μg, and ceftazidime-clavulanate 30/10 μg disk testing. An increase of ≥5 mm in the diameter of the inhibition zone when either of the oxyminocephalosporins were combined with clavulanate was considered evidence of ESBL production [6]. The reference strains were *E. coli* American Type Culture Collection (ATCC) 25922 and *K. pneumoniae* ATCC 700603.

The minimal inhibitory concentrations (MICs) of the antibiotics were detected by Epsilimeter test (E-test). The E-test strips of the 5 antibiotics, ertapenem, ciprofloxacin, ceftriaxone, piperacillin-tazobactam, and ampicillin-sulbactam, were supplied by AB Biodisk (Solna, Sweden).

## Results

1200 patients had bloodstream infections. Ninety three percent of the isolates (1119/1200) were Gram-negative bacilli. The most common pathogen was *E. coli*, which accounted for 35.3% of the strains (n = 423). The second most common pathogen was *K. pneumoniae*, which accounted for 20.8% of strains (n = 249). ESBL strains of *E. coli* and *K. pneumoniae* occurred at a rate of 6.2% (n = 28) and 9.5% (n = 26), respectively.

Table 1 shows the in vitro activities of the 5 antibiotics against Gram-positive bacteria. *Streptococcus pneumoniae* were 100% susceptible to ertapenem, piperacillin-tazobactam, and ampicillin-sulbactam. Based on the concentrations for inhibition of 50% ($MIC_{50}$) and 90% ($MIC_{90}$) of the isolates, ertapenem had the most potent activity. In comparison, the susceptibility of *S. pneumoniae* to ceftriaxone and ciprofloxacin was 74%. *Streptococcus pyogenes* were also 100% susceptible to ertapenem, ceftriaxone,

**Table 1.** Comparative in vitro activities of ertapenem, ciprofloxacin, ceftriaxone, piperacillin-tazobactam, and ampicillin-sulbactam against Gram-positive pathogens from patients with bloodstream infection.

| Organism (no. of isolates) | Antibiotic | Minimal inhibitory concentrations (mg/L) | | | |
|---|---|---|---|---|---|
| | | 50% | 90% | Range | Susceptibility (%) |
| *Streptococcus pneumoniae* (53) | Ertapenem | 0.190 | 0.500 | 0.006-1.000 | 100 |
| | Ciprofloxacin | 1.000 | 2.000 | 0.380->32 | 74 |
| | Ceftriaxone | 0.750 | 1.500 | 0.016-2.000 | 74 |
| | Piperacillin-tazobactam | 1.000 | 3.000 | <0.016-4.000 | 100 |
| | Ampicillin-sulbactam | 0.500 | 2.000 | <0.016-4.000 | 100 |
| *Streptococcus pyogenes* (28) | Ertapenem | 0.008 | 0.016 | 0.006-0.032 | 100 |
| | Ciprofloxacin | 0.500 | 1.000 | 0.380-4.000 | 93 |
| | Ceftriaxone | 0.047 | 0.094 | 0.023-0.250 | 100 |
| | Piperacillin-tazobactam | 0.094 | 0.125 | 0.047-0.380 | 100 |
| | Ampicillin-sulbactam | 0.032 | 0.064 | 0.016-0.500 | 100 |

piperacillin-tazobactam, and ampicillin-sulbactam, and 93% susceptible to ciprofloxacin.

For community-acquired Gram-negative bacteremia, the susceptibility of *Aeromonas hydrophila* to ciprofloxacin, ertapenem, and ceftriaxone was 92%, 88%, and 88%, respectively. The susceptibility of community-acquired *E. coli* ranged from 100% for ertapenem to 77% for ampicillin-sulbactam. The ESBL phenotype was detected in 6.2% of 451 *E. coli* isolates. *E. coli*, including the ESBL strain, was highly susceptible to ertapenem (100%) and piperacillin-tazobactam (90%). More than 90% of *E. coli* were susceptible to ceftriaxone (93%) and piperacillin-tazobactam (98%). Only 48% of ESBL strains were susceptible to ciprofloxacin. Similar results were noted for *K. pneumoniae* (Table 2). The ESBL strain was detected in 9.5% of 275 *K. pneumoniae* isolates. Ciprofloxacin was active in vitro against only 50% of ESBL-producing *K. pneumoniae*.

Ertapenem and ciprofloxacin were all active against *Enterobacter cloacae*. The susceptibilities of *Morganella morganii* to ertapenem, piperacillin-tazobactam, ceftriaxone, and ciprofloxacin were 100%, 97%, 95%, and 92%, respectively. Ertapenem and piperacillin-tazobactam exhibited excellent antimicrobial activity against *Proteus mirabilis* (100%). *Salmonella enterica* serogroup B were highly susceptible to 4 of the 5 antibiotics, excluding ampicillin-sulbactam. All 5 antibiotics were 100% active against *S. enterica* serogroup D (Table 2).

Table 3 shows the geometric mean MICs of the 5 antibiotics against the 12 pathogens. The geometric mean MIC values of ertapenem against 11 of the 12 pathogens were lower than for the other 4 antibiotics, especially for ESBL-producing *E. coli* and *K. pneumoniae*. The geometric mean MIC values of ciprofloxacin against ESBL-producing *E. coli* and *K. pneumoniae* and *S. pneumoniae* were 8- to 50-fold higher than those for the other organisms. Ceftriaxone had high geometric mean MIC values against the ESBL-producing strains. Piperacillin-tazobactam was not active against *A. hydrophila*, *E. cloacae*, and the ESBL-producing *E. coli* and *K. pneumoniae* according to the geometric mean MIC values.

## Discussion

Ciprofloxacin showed excellent in vitro activity against a wide range of Gram-negative bacteria such as *Enterobacteriaceae, Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Moraxella catarrhalis*. Ciprofloxacin also exhibited in vitro activity against methicillin-susceptible *Staphylococcus aureus* and *Staphylococcus epidermidis*, but was less active against streptococcal species, including *S. pyogenes*, *S. pneumoniae*, and viridans streptococci [7-9]. Similarly, the results of this study showed that, overall, ciprofloxacin sensitivity was 74% for *S. pneumoniae* ($MIC_{50}$, 1.0 mg/L) and 93% for *S. pyogenes* ($MIC_{50}$, 0.5 mg/L). The newer quinolones, moxifloxacin, levofloxacin, and gatifloxacin have exhibited more potent activity against streptococcal species than ciprofloxacin [10]. Ertapenem, a parenteral broad-spectrum 1-β-methyl-carbapenem, has exhibited potent in vitro activity against many common aerobic and anaerobic Gram-positive and Gram-negative bacteria. The in vitro activity of ertapenem against *Enterobacteriaceae* carrying plasmid- or chromosomal-mediated β-lactamases, including AmpC-and ESBLs, was clinically significant [11-15]. Ertapenem also had excellent in vitro activity against *S. pneumoniae* and *S. pyogenes* [16] with $MIC_{90}$ values for 90% of strains tested of 0.5 mg/L and 0.016 mg/L, respectively.

*Enterobacteriaceae*, especially *E. coli* and *K. pneumoniae*, are major community and nosocomial pathogens. ESBL-producing *E. coli* and *K. pneumoniae* were first described in 1983 and 1987, respectively [17,18]. Ciprofloxacin-resistant strains of *E. coli* and *K. pneumoniae* have been more frequently detected in patients with bacteremia, which correlates with an upward trend of quinolone treatment in the community and in hospitals [19-21]. The susceptibility rates of ESBL-producing *E. coli* and *K. pneumoniae* to ciprofloxacin in this study were 48% and 50%, respectively. Ciprofloxacin resistance emerged in *E. coli* and *K. pneumoniae* contingent on multiple mutations that diminish the affinity of its topoisomerase II and IV targets, reduce permeability, and upregulate efflux [22]. Plasmid-mediated resistance has also been reported [23]. In contrast, ertapenem has demonstrated high stability against nearly all β-lactamases, including ESBLs and AmpC [24], with the exception of metallo-β-lactamases. Ertapenem may be an alternative to other carbapenems for the treatment of ESBL-producing *E. coli* and *K. pneumoniae* infections [25].

*M. morganii* was highly sensitive to ertapenem, with an $MIC_{90}$ of 0.125 mg/L, and mildly resistant to piperacillin-tazobactam, ceftriaxone, and ciprofloxacin. The high susceptibility rate of *M. morganii* to ceftriaxone (95%) inferred that the prevalence of

**Table 2.** Comparative in vitro activities of ertapenem, ciprofloxacin, ceftriaxone, piperacillin-tazobactam, and ampicillin-sulbactam against Gram-negative pathogens from patients with bloodstream infection.

| Organism (no. of isolates) | Antibiotic | Minimal inhibitory concentrations (mg/L) | | | |
|---|---|---|---|---|---|
| | | 50% | 90% | Range | Susceptibility (%) |
| *Aeromonas hydrophila* (26) | Ertapenem | 0.500 | 6.000 | 0.125->32.000 | 88 |
| | Ciprofloxacin | 0.012 | 0.750 | 0.004-4.000 | 92 |
| | Ceftriaxone | 1.500 | 8.000 | 0.064->256.000 | 88 |
| | Piperacillin-tazobactam | 12.000 | >256.000 | 1.000->256.000 | 50 |
| | Ampicillin-sulbactam | >256.000 | >256.000 | >256.000 | 0 |
| *Escherichia coli* | Ertapenem | 0.080 | 0.023 | 0.004-0.750 | 100 |
| (non-ESBL) [423] | Ciprofloxacin | 0.064 | >32.000 | 0.003->32.000 | 86 |
| | Ceftriaxone | 0.064 | 0.190 | <0.016->256.000 | 93 |
| | Piperacillin-tazobactam | 1.500 | 3.000 | 0.032->256.000 | 98 |
| | Ampicillin-sulbactam | 6.000 | 24.000 | 0.38->256.000 | 77 |
| *E. coli* (ESBL) [28] | Ertapenem | 0.932 | 0.380 | 0.012-2.000 | 100 |
| | Ciprofloxacin | >32.000 | >32.000 | 0.008->32.000 | 48 |
| | Ceftriaxone | >256.000 | >256.000 | 4.000->256.000 | 0 |
| | Piperacillin-tazobactam | 2.000 | 16.000 | 1.000->256.000 | 90 |
| | Ampicillin-sulbactam | 24.000 | 128.000 | 6.000->256.000 | 8 |
| *Enterobacter cloacae* (36) | Ertapenem | 0.094 | 0.750 | 0.023-1.500 | 100 |
| | Ciprofloxacin | 0.023 | 0.190 | 0.008-1.000 | 100 |
| | Ceftriaxone | 0.250 | 64.000 | 0.094->256.000 | 89 |
| | Piperacillin-tazobactam | 2.000 | 32.000 | 0.500->256.000 | 87 |
| | Ampicillin-sulbactam | 24.000 | >256.000 | 3.000->256.000 | 28 |
| *Klebsiella pneumoniae* | Ertapenem | 0.012 | 0.016 | 0.006-1.500 | 100 |
| (non-ESBL) [249] | Ciprofloxacin | 0.032 | 0.094 | 0.004->32.000 | 96 |
| | Ceftriaxone | 0.064 | 0.094 | <0.016->256.000 | 99 |
| | Piperacillin-tazobactam | 2.000 | 3.000 | 0.094->256.000 | 99 |
| | Ampicillin-sulbactam | 4.000 | 12.000 | 1.000->256.000 | 90 |
| *K. pneumoniae* (ESBL) [26] | Ertapenem | 0.094 | 0.500 | 0.012-1.500 | 100 |
| | Ciprofloxacin | 0.380 | >32.000 | 0.016->32.000 | 50 |
| | Ceftriaxone | >256.000 | >256.000 | 0.094->256.000 | 0 |
| | Piperacillin-tazobactam | 6.000 | >256.000 | 0.75->256.000 | 73 |
| | Ampicillin-sulbactam | 32.000 | >256.000 | 1.5->256.000 | 12 |
| *Morganella morganii* (34) | Ertapenem | 0.032 | 0.125 | 0.012-0.250 | 100 |
| | Ciprofloxacin | 0.023 | 1.000 | 0.004->32.000 | 92 |
| | Ceftriaxone | 0.023 | 2.000 | <0.016->256.000 | 95 |
| | Piperacillin-tazobactam | 0.500 | 1.500 | 0.125-24.000 | 97 |
| | Ampicillin-sulbactam | 16.000 | 48.000 | 0.25->256.000 | 27 |
| *Proteus mirabilis* (75) | Ertapenem | 0.023 | 0.047 | 0.004-0.230 | 100 |
| | Ciprofloxacin | 0.125 | 16.000 | 0.008->32.000 | 83 |
| | Ceftriaxone | 0.016 | 0.064 | <0.016->256.000 | 92 |
| | Piperacillin-tazobactam | 0.500 | 1.500 | 0.125-8.000 | 100 |
| | Ampicillin-sulbactam | 3.000 | 16.000 | 0.190->256.000 | 80 |
| *Salmonella enterica* | Ertapenem | 0.012 | 0.016 | 0.008-0.023 | 100 |
| serogroup B (29) | Ciprofloxacin | 0.016 | 0.125 | 0.008-0.750 | 100 |
| | Ceftriaxone | 0.094 | 0.094 | 0.047-0.190 | 100 |
| | Piperacillin-tazobactam | 2.000 | 4.000 | 1.500-4.000 | 100 |
| | Ampicillin-sulbactam | 1.500 | 32.000 | 0.75-64.000 | 66 |
| *S. enterica* | Ertapenem | 0.012 | 0.016 | 0.006-0.047 | 100 |
| serogroup D (25) | Ciprofloxacin | 0.023 | 0.200 | 0.008-0.200 | 100 |
| | Ceftriaxone | 0.094 | 0.125 | 0.047-0.380 | 100 |
| | Piperacillin-tazobactam | 2.000 | 3.000 | 0.750-4.000 | 100 |
| | Ampicillin-sulbactam | 1.500 | 2.000 | 0.500-4.000 | 100 |

Abbreviation: ESBL = extended-spectrum β-lactamase.

**Table 3.** Geometric mean minimal inhibitory concentrations of ertapenem, ciprofloxacin, ceftriaxone, piperacillin-tazobactam, and ampicillin-sulbactam against pathogens from patients with bloodstream infections.

| Organism (no. of isolates) | Geometric mean minimal inhibitory concentrations (mg/L) | | | | |
|---|---|---|---|---|---|
| | Ertapenem | Ciprofloxacin | Ceftriaxone | Piperacillin-tazobactam | Ampicillin-sulbactam |
| *Streptococcus pneumoniae* (53) | 0.092 | 1.099 | 0.324 | 0.446 | 0.327 |
| *Streptococcus pyogenes* (28) | 0.009 | 0.638 | 0.051 | 0.087 | 0.033 |
| *Aeromonas hydrophila* (26) | 0.908 | 0.046 | 1.980 | 19.205 | >256.000 |
| *Escherichia coli* (non-ESBL) [423] | 0.011 | 0.118 | 0.102 | 1.544 | 6.872 |
| *E. coli* (ESBL) [28] | 0.059 | 1.882 | 179.924 | 3.500 | 27.314 |
| *Enterobacter cloacae* (36) | 0.104 | 0.033 | 0.859 | 3.729 | 29.652 |
| *Klebsiella pneumoniae* (non-ESBL) [249] | 0.046 | 0.046 | 0.080 | 2.337 | 4.618 |
| *K. pneumoniae* (ESBL) [26] | 0.095 | 0.885 | 82.850 | 10.402 | 37.400 |
| *Morganella morganii* (34) | 0.032 | 0.070 | 0.065 | 0.567 | 15.707 |
| *Proteus mirabilis* (75) | 0.023 | 0.205 | 0.070 | 0.542 | 3.279 |
| *Salmonella enterica* serogroup B (29) | 0.011 | 0.025 | 0.008 | 2.246 | 3.652 |
| *S. enterica* serogroup D (25) | 0.012 | 0.023 | 0.093 | 2.064 | 1.507 |

Abbreviation: ESBL = extended-spectrum β-lactamase.

ESBL was low or none. Similarly, *P. mirabilis* was sensitive (92%) to ceftriaxone, which suggested a low prevalence of ESBL. However, ESBL production should continue to be monitored closely in view of the frequent multiple resistances found among *P. mirabilis* and *M. morganii* [26].

*S. enterica,* including serogroup B and D, was highly susceptible to ertapenem, ciprofloxacin, ceftriaxone, and piperacillin-tazobactam with low $MIC_{90}$ values. The MICs of the antibiotics against pathogens from patients with bacteremia in this study may differ from other reports [27]; ESBL production may play a major role in resistance. The ESBL phenotype was detected in 6.2% of *E. coli* isolates, which was lower than the rate reported in Northern Taiwan (10.5%) [28] and in 9.5% of *K. pneumoniae* isolates, which was lower than previously reported (28.4%) [29].

In conclusion, ertapenem demonstrated high antimicrobial activity against major bloodstream pathogens, especially ESBL-producing *E. coli* and *K. pneumoniae*. In contrast, ciprofloxacin required high $MIC_{90}$ values (>32 mg/L) for susceptibility rates of ESBL-producing *E. coli* and *K. pneumoniae* of 48% and 50%, respectively. Thus, carbapenems, including ertapenem, are the drug of choice for the empirical treatment of bacteremia caused by ESBL-producing *E. coli* and *K. pneumoniae.* Antimicrobial resistance among bloodstream pathogens should be monitored continuously.

## References


1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303-10.
2. McCabe WR, Jackson GG. Gram-negative bacteremia 1. Etiology and ecology. Arch Intern Med. 1962;10:847-55.
3. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. JAMA. 1995;274:639-44.
4. Bochud PY, Glauser MP, Calandra T. Antibiotics in sepsis. Intensive Care Med. 2001;27(Suppl 1):S33-48.
5. Performance standards for antimicrobial susceptibility testing. Fifteenth informational supplement. Approved standard, M100-S15. Wayne: Clinical and Laboratory Standards Institute; 2005.
6. Performance standards for antimicrobial susceptibility testing. Eleventh informational supplement. NCCLS document, M100-S11. Wayne: National Committee for Clinical Laboratory Standards; 2001.
7. Bauernfeind A, Petermuller C. In vitro activity of ciprofloxacin, norfloxacin and nalidixic acid. Eur J Clin Microbiol. 1983;2:11-5.
8. Karas JA, Pillay DG, Muckart D. Treatment failure due to extended-spectrum β-lactamase. J Antimicrob Chemother. 1996;37:203-4.
9. Paterson DL. Recommendation for treatment of severe infection caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs). Clin Microbiol Infect. 2000;6:460-3.
10. Niederman MS. Challenges in the management of community-acquired pneumonia: the role of quinolones and moxifloxacin. Clin Infect Dis. 2005;41(Suppl 2):S158-66.
11. Burkhardt O, Derendorf H, Welte T. Ertapenem 5 years

after first FDA licensing for clinical practice. Expert Opin Pharmacother. 2007;8:237-56.
12. Gesser RM, McCarroll K, Teppler H, Woods GL. Efficacy of ertapenem in the treatment of serious infections caused by *Enterobacteriaceae*: analysis of pooled clinical trial data. J Antimicrob Chemother. 2003;51:1253-60.
13. Livermore DM, Sefton AM, Scott GM. Properties and potential of ertapenem. J Antimicrob Chemother. 2003;52:331-44.
14. Mody RM, Erwin DP, Summers AM, Carrero HA, Selby EB, Ewell AJ, et al. Ertapenem susceptibility of extended spectrum beta-lactamase-producing organisms. Ann Clin Microb Antimicrob. 2007;6:6-10.
15. Hernandez JR, Velasco C, Romero L, Martinez-Martinez L, Pascual A. Comparative in vitro activity of ertapenem against extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated in Spain. Int Antimicrob Agents. 2006;28:457-9.
16. Reynolds R, Potz N, Colman M, Williams A, Livermore D, MacGowan A, et al. Antimicrobial susceptibility of the pathogens of bacteremia in the UK and Ireland 2001-2002: the BSAC Bacteraemia Resistance Surveillance Programme. J Antimicrob Chemother. 2004;53:1018-32.
17. Knothe H, Shah P, Kremery 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.
18. Pena C, Albareda JM, Pallares R, Pujol M, Tubau F, Ariza J. Relationship between quinolone use and emergence of ciprofloxacin-resistant *Escherichia coli* in bloodstream infections. Antimicrob Agents Chemother. 1995;39:520-4.
19. Paterson DL, Mulazimoglu L, Casellas JM, Ko WC, Goossens H, 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.
20. Livermore DM, Nichols T, Lamagni TL, Potz N, Reynolds R, Duckworth G. Ciprofloxacin-resistant *Escherichia coli* from bacteraemias in England; increasingly prevalent and mostly from men. J Antimicrob Chemother. 2003;52:1040-2.
21. Livermore DM, James D, Reacher M, Graham C, Nichols T, Stephens P, et al. Trends in fluoroquinolone (ciprofloxacin) resistance in *Enterobacteriaceae* from bacteremias, England and Wales, 1990-1999. Emerg Infect Dis. 2002;8:473-8.
22. Everett MJ, Jin YF, Ricci V, Piddock LT. Contributions of individual mechanisms to fluoroquinolone resistance in 36 *Escherichia coli* strains isolated from humans and animals. Antimicrob Agents Chemother. 1996;40:2380-6.
23. Bell JM, Chitsaz M, Turnidge JD, Barton M, Walters LJ, Jones RN. Prevalence and significance of a negative extended-spectrum β-lactamase (ESBL) confirmation test result after a positive ESBL screening test result for isolates of *Escherichia coli* and *Klebsiella pneumoniae*: result from the SENTRY Asia-Pacific surveillance program. J Antimicrob Chemother. 2007;45:1478-82.
24. Jacoby G, Han P, Tran J. Comparative in vitro activities of carbapenem L-749,345 and other antimicrobials against multiresistant Gram-negative clinical pathogens. Antimicrob Agents Chemother. 1997;41:1830-1.
25. Jacoby GA, Mills DM, Chow N. Role of β-lactamases and porins in resistance to ertapenem and other β-lactams in *Klebsiella pneumoniae*. Antimicrob Agents Chemother. 2004;48:3203-6.
26. Tsakris A, Ikonomidis A, Poulou A, Spanakis N, Pournaras S, Markou F. Transmission in the community of clonal *Proteus mirabilis* carrying VIM-1 metallo-β-lactamase. J Antimicrob Chemother. 2007;60:136-9.
27. Miriagou V, Tassios PT, Legakis NJ, Tzouvelekis LS. Extended-spectrum cephalosporin resistance in non-typhoid *Salmonella*. Int J Antimicrob Agents. 2004;23:547-55.
28. Lee SC, Huang SS, Lee CW, Fung CP, Lee N, Shieh WB, et al. Comparative antimicrobial susceptibility of aerobic and facultative bacteria from community-acquired bacteremia to ertapenem in Taiwan. BMC Infect Dis. 2007;7:79-83.
29. Kuo KC, Shen YH, Hwang KP. Clinical implications and risk factors of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* infection in children: a case-control retrospective study in a medical center in southern Taiwan. J Microbiol Immunol Infect. 2007;40:248-54.