Journal of Microbiology, Immunology and Infection (2015) xx, 1–7

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*

Ching-Lung Lo [a], Ching-Chi Lee [a,b], Chia-Wen Li [a,b], Ming-Chi Li [a,b], Po-Ren Hsueh [c,d], Nan-Yao Lee [a,b,e,*], Wen-Chien Ko [a,b,e,*]

[a] *Department of Internal Medicine, National Cheng Kung University Hospital, Tainin, Taiwan*
[b] *Center of Infection Control, National Cheng Kung University Hospital, Tainin, Taiwan*
[c] *Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[d] *Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*
[e] *Department of Medicine, National Cheng Kung University Medical College, Tainan, Taiwan*

Received 30 April 2015; received in revised form 16 July 2015; accepted 4 August 2015

Available online ■ ■ ■

KEYWORDS
bloodstream infections;
carbapenem;
Enterobacteriaceae;
ESBL;
fluoroquinolone

Abstract *Background/Purpose:* For extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* infections, carbapenems are recommended as first line therapy, and clinical data on the therapeutic efficacy of fluoroquinolones (FQs) is limited. This study compares the efficacy of FQs and carbapenems for bloodstream infections caused by ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae*.
Methods: Between 2008 and 2010, adults with ESBL-producing *E. coli* or *K. pneumoniae* bacteremia at two medical centers were reviewed. Adults receiving definitive FQ or carbapenem therapy were compared in a propensity score-matched analysis, and 30-day mortality was the primary endpoint.
Results: A total of 299 patients were eligible. Patients receiving a FQ ($n = 24$), either ciprofloxacin or levofloxacin, had a lower 30-day mortality rate than those with carbapenem therapy (8.3%, 2/24 vs. 23.3%, 64/275; $p = 0.12$). Multivariate regression analysis revealed that a critical illness [Pitt bacteremia score ≥ 4 points; odds ratio (OR), 7.09; $p < 0.001$], rapidly fatal

* Corresponding authors. Department of Internal Medicine, National Cheng Kung University Hospital, Number 138, Sheng Li Road, 704, Tainan, Taiwan.
E-mail addresses: nanyao@mail.ncku.edu.tw (N.-Y. Lee), winston3415@gmail.com (W.-C. Ko).

http://dx.doi.org/10.1016/j.jmii.2015.08.012

Please cite this article in press as: Lo C-L, et al., Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.08.012

underlying disease (OR, 5.73; $p < 0.001$), and hospital-associated infection (OR, 2.57; $p = 0.01$) were independently associated with 30-day mortality. By contrast, FQ definitive therapy was a protective factor compared with carbapenems (OR, 0.18; $p = 0.04$). There were 72 matched cases with carbapenem therapy in a propensity score-matched analysis, and a difference in the 30-day mortality rate of two groups was noted (8.3% vs. 29.2%; $p = 0.05$).
Conslusion: For ESBL-producing *E. coli* or *K. pneumoniae* bacteremia, ciprofloxacin or levofloxacin, if active *in vitro*, can be considered as a carbapenem-sparing alternative.

Introduction

In recent decades, nosocomial infections caused by extended spectrum beta-lactamase (ESBL)-producers became important issues,[1] because such infections were related to increased mortality and morbidity compared with infections caused by susceptible organisms.[2–4] A previous study demonstrated that third generation cephalosporins resulted in a higher mortality rate than carbapenems for treating ESBL-producing *Enterobacteriaceae* infections.[5] Therefore, carbapenems have been recommended as the drugs of choice for ESBL-producing pathogen infections.[6,7] However, increasing use of carbapenems has been accompanied by the emergence of carbapenem-resistant *Enterobacteriaceae*.[8–10] There are few studies reporting the role of carbapenem-sparing regimens, such as cephamycins,[11,12] beta-lactam/beta-lactamase inhibitiors,[13] or fluoroquinolones (FQs),[5] in treating ESBL-producing *Enterobacteriaceae* infections. Although, the antibacterial activity of ciprofloxacin or levofloxacin was not affected by ESBL production,[14] there was increasing resistance to FQs among ESBL-producing *Enterobacteriaceae* isolates,[15] arguing against empirical use of FQs for ESBL-producer infections. Therefore, the purpose of our study is to compare the therapeutic efficacy of FQs and carbapenems for definitively treating bloodstream infections caused by ESBL-producing *Enterobacteriaceae*.

Methods

Study designs and patients

The study was conducted in two hospitals, National Cheng Kung University Hospital in southern Taiwan and National Taiwan University Hospital in northern Taiwan. Adults (age >18 years) with ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* bacteremia between 2008 and 2010 were retrospectively reviewed. Eligible patients had to fulfill two criteria: (1) the isolation of an ESBL producer alone in blood culture(s), compatible with sepsis syndrome; and (2) parenteral therapy with a FQ or carbapenem as definitive therapy. Patients receiving more than one antibiotic as definitive therapy were excluded. If patients experienced more than one bacteremic episode, only the first episode was included. The study was approved by the Institutional Review Board of National Cheng Kung University Hospital (ER-100-182).

The clinical choice of antibiotics was at the discretion of the attending physicians. For patients with renal insufficiency, they received the following intravenous doses or adjusted equivalents: 1 g every 24 hours for ertapenem, 0.5 g every 6 hours for imipenem, 1 g every 8 hours for meropenem, 400 mg every 12 hours for ciprofloxacin, or 500 mg or 750 mg every 24 hours for levofloxacin. In both hospitals, the prescriptions of carbapenems and FQs were approved by infectious disease specialists and pharmacists for their indication and dosage.

In vitro susceptibility and ESBL detection

ESBL production was detected with the phenotypic confirmatory test recommended by the Clinical and Laboratory Standards Institute.[16] The minimum inhibitory concentrations of carbapenems and FQs were determined with agar dilution, and the interpretative breakpoints followed those recommended by Clinical and Laboratory Standards Institute in 2013.[16]

Clinical evaluation and outcomes

Clinical information was retrieved from medical charts and collected in a case record form. Bacteremia was defined as the isolation of organisms in one or more separately obtained blood culture with compatible clinical features. Patients receiving a FQ or a carbapenem for > 48 hours were included for assessment of outcome. The primary outcome was 30-day mortality. Immunosuppression was referred to as the receipt of corticosteroids (at least 10 mg or an equivalent dosage daily) for > 2 weeks or of antineoplastic or antirejection medication within 4 weeks before the onset of bacteremia. The severity of the underlying medical illness was stratified as being fatal, ultimately fatal, or nonfatal.[17] The severity of bacteremia on the day of bacteremia onset was graded with the Pitt bacteremia score.[18]

Statistical analysis

Data were analyzed with SPSS software for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean values ± standard deviation and compared with the Mann–Whitney *U* test or Student *t* test. Categorical variables expressed as percentages of case numbers were analyzed and compared with Fisher's exact test or Chi-square test. Independent predictors for

Please cite this article in press as: Lo C-L, et al., Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.08.012

30-day mortality were identified by means of the logistic regression analysis. Variables with $p \leq 0.1$, as determined using univariate analysis, were included in a multiple conditioning logistic regression analysis. A Cox proportional hazard model was used to compare survival in both groups, adjusted for confounding variables. A p value < 0.05 was considered statistically significant and all tests were two-tailed.

The factors related to 30-day mortality estimated in conditioning logistic regression analysis would be calculated as a propensity score for each case. Subsequently, each patient receiving definitive FQ therapy (the case group) was matched to three patients with definitive carbapenem therapy (the control group) with a similar propensity score. If there were more than three matches with an identical propensity score, the one with a similar immunosuppression condition (secondary matching variable) or a similar age (a backup secondary matching variable), would have a higher priority in the matching process.

Results

A total of 398 patients with bacteremia caused by ESBL-producing *E. coli* and *K. pneumoniae* were identified. Among them, 24 (6.0%) cases, including 13 cases of *E. coli* bacteremia and 11 of *K. pneumoniae* bacteremia, were treated with a FQ, either ciprofloxacin or levofloxacin, for $>$ 48 hours and designated as the FQ group. There were 275 (69.1%) cases, including 103 cases of *E. coli* bacteremia and 172 of *K. pneumoniae* bacteremia, receiving one of three carbapenems (ertapenem, imipenem, or meropenem) and referred to as the carbapenem group. The characteristics of the FQ group and carbapenem group are shown in Table 1. There was no difference between age, comorbidity, hospital onset, infection source, polymicrobial bacteremia, severity of underlying disease, or severity of bacteremia. However, there were more immunosuppressed patients in the carbapenem group (19.6% vs. 0%, $p = 0.01$). There was a shorter time from bacteremia onset to appropriate antimicrobial therapy in the FQ group than the carbapenem group (0.88 $\pm$ 1.4 days vs. 2.5 $\pm$ 2.3 days; $p = 0.001$).

Among these ESBL-producers, the susceptibility rate of ciprofloxacin and levofloxacin was 28.9% (115 isolates) and 34.7% (138 isolates), respectively. In 260 levofloxacin-nonsusceptible isolates, there was no isolate susceptible to ciprofloxacin, but in 283 ciprofloxacin-nonsusceptible isolates, there were 23 (8.1%) isolates susceptible to levofloxacin. To identify clinical variables predictive of susceptibility to ciprofloxacin and levofloxacin, a multivariate analysis showed that only underlying chronic obstructive pulmonary disease was significantly less likely to be susceptible to ciprofloxacin and levofloxacin [odds ratio (OR), 2.11; 95% confident interval (CI), 1.13—3.91; $p = 0.02$; Table 2].

While comparing the patients receiving appropriate therapy earlier or later than 72 hours after bacteremia onset, the 30-day mortality rate was similar (22.1% vs. 19.2%; $p = 0.53$). The 14-day mortality rate (OR, 2.39; 95% CI, 0.54—10.48; $p = 0.39$), 30-day mortality rate (OR, 3.34; 95% CI, 0.76—14.57; $p = 0.12$), or crude mortality rate (OR, 1.04; 95% CI, 0.44—2.47; $p = 1.0$), was not different in the carbapenem and FQ groups (Table 1). In a multivariate analysis, the presence of critical illness (a Pitt bacteremia score $\geq$ 4 points; OR, 7.09; 95% CI, 3.71—13.56; $p < 0.001$), and rapidly fatal underlying disease (OR, 5.73; 95% CI, 2.51—13.08; $p < 0.001$), and hospital onset infection (OR, 2.57; 95% CI, 1.22—5.45; $p = 0.01$), were independently associated with 30-day mortality, after adjustment of other confounding variables (Table 3). By contrast, definitive FQ therapy led to a better outcome while compared with definitive carbapenem therapy (OR, 0.18; 95% CI, 0.03—0.92; $p = 0.04$). Likewise, using the Cox regression model, the FQ group tended to have a better outcome than the carbapenem group (OR, 0.28; 95% CI, 0.07—1.14; $p = 0.08$; Figure 1). The survivors of the FQ group tended to have a shorter hospital stay after bacteremia onset (27.5 $\pm$ 26.9 days vs. 52.0 $\pm$ 77.5 days; $p = 0.14$).

Twenty-four patients receiving definitive FQ therapy were matched with the carbapenem group on the basis of propensity score. Seventy-two matched patients had $<$ 1% difference in their propensity score. After adjustment for confounding factors, including gender, condition of immunosuppression, hospital-onset infection, rapidly fatal underlying disease, and a Pitt bacteremia score $\geq$ 4 points, there was a lower 30-day mortality rate in the FQ group than that in the carbapenem group (OR, 4.53; 95% CI, 0.98—21.00; $p = 0.05$).

Discussion

ESBL-producing bacteria are typically associated with multidrug resistance, since multiple resistance genes often reside on the same plasmid.[19] According to previous studies, there was higher FQ minimum inhibitory concentrations in the ESBL-producer compared with those in non-ESBL producers.[15,20,21] In the present study, the susceptibility rate of ciprofloxacin or levofloxacin in ESBL-producing *E. coli* and *K. pneumoniae* bacteremia isolates was low, 29.1% and 34.7%, respectively. These figures were similar to that in the UK (ciprofloxacin susceptibility in 17.8—28.7% of *Enterobacteriaceae*),[22] but was lower in South Korea (ciprofloxacin susceptibility in 55.4% of *E. coli*).[23]

In the present study, adults receiving definitive FQ therapy had a better prognosis than those with carbapenem therapy. There were few studies about the treatment efficacy of FQs in the infections caused by ESBL-producers. The role of FQs in infections caused by ESBL-producers has been mentioned in an *in vitro* study[14] and a case series of urinary tract infection caused by ESBL-producers.[24] The series of Kang et al,[25] which included 117 cases comprising *E. coli* or *K. pneumoniae* bloodstream infections, observed that 30-day mortality rate of those receiving definitive ciprofloxacin and carbapenem therapy was similar (10.3% vs. 12.9%, respectively). This finding was compatible with our results, that patients with definitive FQ therapy have a noninferior or even better outcome compared with those with definitive carbapenem therapy. However, in literature there were contradictory data. Tumbarello et al[26] demonstrated ESBL-producing *Enterobacteriaceae* bacteremia treated with FQ would be associated with a remarkable high mortality rate, 50% in 16 cases, despite treated by ciprofloxacin that was active *in vitro*. Besides, Endimiani

Please cite this article in press as: Lo C-L, et al., Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.08.012

Table 1 Characteristics of patients with bacteremia caused by extended-spectrum beta-lactamase-producing organisms treated by a fluoroquinolone or a carbapenem.

Characteristics	FQ group $N = 24$	Carbapenem group $N = 275$	Matched group $N = 72$	p [a]	p [b]
Age (y)	70 (55–79)	70 (56–78)	71 (57–78)	0.86	0.65
Gender (male)	12 (50)	157 (57.1)	42 (58.3)	0.53	0.59
Hospital-onset bacteremia	16 (66.7)	194 (70.5)	49 (68.1)	0.65	1.0
Polymicrobial bacteremia	2 (8.3)	28 (10.2)	10 (13.9)	1.0	0.72
Source of bacteremia					
Urosepsis	7 (29.2)	67 (24.4)	23 (31.9)	0.62	1.0
Pneumonia	6 (25)	75 (27.3)	17 (23.6)	1.0	1.0
Vascular catheter-related infection	5 (20.8)	49 (17.8)	10 (13.9)	0.78	0.52
Primary	3 (12.5)	39 (14.2)	13 (18.1)	1.0	0.75
Skin & soft tissue infection	1 (4.2)	20 (7.3)	3 (4.2)	1.0	1.0
Intra-abdominal infection	2 (8.3)	34 (12.4)	8 (11.1)	0.75	1.0
Central nervous system infection	0 (0)	2 (0.7)	0 (0)	1.0	[c]
Bone & joint infection	0 (0)	2 (0.7)	0 (0)	1.0	
Comorbidity					
Malignancy	9 (37.5)	93 (33.8)	29 (40.3)	0.82	1.0
Diabetes mellitus	9 (37.5)	123 (44.7)	42 (58.3)	0.53	0.10
Chronic kidney disease	6 (25)	106 (38.5)	22 (30.6)	0.27	0.80
Chronic dialysis	3 (12.5)	65 (23.6)	14 (19.4)	0.31	0.55
Liver cirrhosis	3 (12.5)	32 (11.6)	9 (12.5)	0.75	1.0
Chronic obstructive pulmonary disease	2 (8.3)	51 (18.5)	16 (22.2)	0.27	0.23
Old cerebrovascular accident	0 (0)	20 (7.3)	7 (9.7)	0.39	0.19
Congestive heart failure	0 (0)	15 (5.5)	4 (5.6)	0.62	0.57
Immunosuppression	0 (0)	54 (19.6)	1 (1.4)	0.01	1.0
Severity of underlying disease (McCabe classification)					
Rapidly fatal	4 (16.7)	33 (12.0)	12 (16.7)	0.52	1.0
Pitt bacteremia score ≥ 4	8 (33.3)	89 (32.4)	25 (34.7)	1.0	1.0
Outcome					
14-d morality	2 (8.3)	49 (17.8)	16 (22.2)	0.39	0.23
30-d mortality	2 (8.3)	64 (23.3)	21 (29.2)	0.12	0.05
Crude mortality	9 (37.5)	106 (38.5)	31 (43.1)	1.0	0.81

Data are presented as *n* (%) or media (interquartile range).
FQ = fluoroquinolone.
[a] Crude analysis: fluoroquinolone group versus carbapenem group.
[b] Propensity score matched analysis: fluoroquinolone group versus matched carbapenem group.
[c] Ellipses indicate not available.

Table 2 Multivariate logistic regression analysis of the association among different variables and ciprofloxacin and levofloxacin susceptibility.

Variables	Susceptible to ciprofloxacin and levofloxacin		Univariate analysis		Multivariate analysis	
	Yes, $n = 115$	No, $n = 260$	OR (95% CI)	p	OR (95% CI)	p
Age (y)	66.4 ± 16.3	67.3 ± 16.2	[a]	0.65		
Male	64 (55.7)	150 (57.9)	1.10 (0.70–1.71)	0.73		
Diabetes mellitus	40 (34.8)	123 (47.3)	1.69 (1.07–2.66)	0.03	1.58 (1.00–2.50)	0.53
Chronic obstructive pulmonary disease	15 (13.0)	64 (24.6)	2.18 (1.18–4.01)	0.01	2.11 (1.13–3.91)	0.02
Liver cirrhosis	9 (7.8)	40 (15.4)	2.14 (1.00–4.58)	0.05	2.24 (1.04–4.82)	0.40
Old cerebrovascular accident	4 (3.5)	26 (10)	3.08 (1.05–9.05)	0.04	2.34 (0.77–7.09)	0.13

Data are presented as *n* (%) or mean ± standard deviation.
CI = confident interval; OR = odds ratio.
[a] Ellipses indicate not available.

Please cite this article in press as: Lo C-L, et al., Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.08.012

Table 3 Multivariate logistic regression analysis of the associations among different variables and 30-day mortality in the definitive therapy cohort.

Variables	Survivors $N = 233$	Nonsurvivors $N = 66$	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p	OR (95% CI)	p
Age (y)	67.0 ± 16.6	67.7 ± 16.4	[a]	0.46		
Male	128 (54.9)	41 (62.1)	1.35 (0.77–2.36)	0.33		
Hospital-onset bacteremia	157 (67.4)	53 (80.3)	1.97 (1.01–3.84)	0.05	2.57 (1.22–5.45)	0.01
Pneumonia	56 (24.0)	25 (37.9)	1.92 (1.08–3.45)	0.03	1.27 (0.65–2.48)	0.49
Urosepsis	68 (29.2)	6 (9.1)	0.24 (0.10–0.59)	0.001	0.47 (0.18–1.18)	0.12
Rapid fatal underlying disease	18 (7.7)	19 (28.8)	4.83 (2.36–9.90)	<0.001	5.73 (2.51–13.08)	<0.001
Pitt bacteremia score ≥ 4 points	55 (23.6)	42 (63.6)	5.67 (3.15–10.17)	<0.001	7.09 (3.71–13.56)	<0.001
Fluoroquinolone definitive therapy	22 (9.4)	2 (3.0)	0.30 (0.07–1.31)	0.12	0.18 (0.03–0.92)	0.04

Data are presented as *n* (%) or mean ± standard deviation.
CI = confident interval; OR = odds ratio.
[a] Ellipses indicate not available.

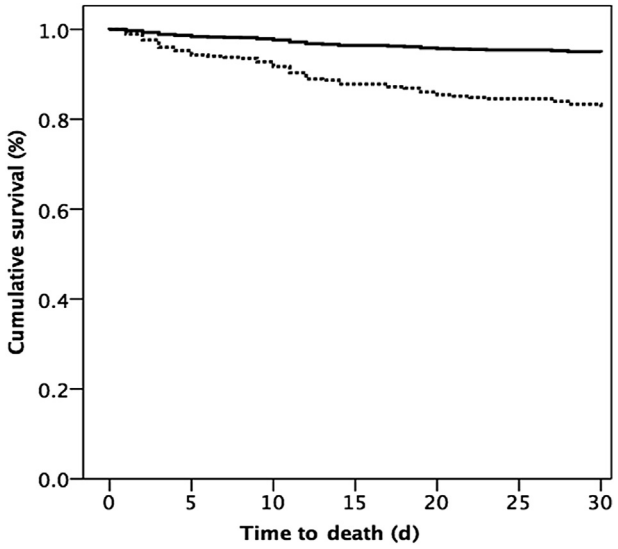

Figure 1. Cox proportional hazard model for survival analysis for patients with bacteremia due to extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*, categorized by definitive fluoroquinolone ($n = 24$, solid line) and carbapenem therapy ($n = 275$, dotted line; odds ratio, 0.28; 95% confidence interval, 0.07–1.14; $p = 0.08$).

et al[27] reported that 21 patients with ESBL-producing, ciprofloxacin-susceptible *K. pneumoniae* bacteremia, and found there was more treatment failure for patients receiving ciprofloxacin than those treated with imipenem (71.4% vs. 20%; $p = 0.03$).

Although a better outcome of FQ therapy favors their clinical use, our retrospective cohort remained to be inherently biased in two comparative groups. Those in the carbapenem group received appropriate antimicrobial therapy later than those in the FQ group. Previous studies showed that inadequate initial antimicrobial therapy was related to a poor outcome.[26,28] By contrast, Kang et al[25] showed that in patients receiving appropriate definitive carbapenem or ciprofloxacin therapy, no difference was noted in the 30-day mortality rate between those receiving inappropriate ($n = 37$) and appropriate ($n = 58$) empirical therapy (18.9% vs. 15.5%; $p = 0.66$). Similarly, Rodríguez-Baño et al[29] reported that those with empirical inappropriate and appropriate antimicrobial therapy had a similar 14-day (26% vs. 25%, respectively) or 30-day mortality rate (30% vs. 30%, respectively). These findings were consistent with our result, that a delay in prescribing appropriate therapy for 72 hours after bacteremia onset was not related to a poor outcome, suggestive of a therapeutic benefit of FQ treatment.

The nonsusceptible rate of ciprofloxacin (70.9%) was higher than that of levofloxacin (65.3%) in this study, and such a finding is compatible with the earlier concept that ciprofloxacin would be more easily affected by mutations in *GyrA*, a subunit of DNA gyrase, than levofloxacin.[30] Besides, ciprofloxacin resistance can be caused by other mechanisms, including modifying enzymes, DNA gyrase or topoisomerase, and plasmid-mediated efflux pump.[31] Host-related risk factors of FQ resistance, including residence in long-term care facilities, older age, and neurologic disease, were well recognized, and previous exposure to several classes of antibiotics, aminoglycosides, FQs, or third-generation cephalosporins, were often regarded as risk factors.[23,32,33] A novel host factor, chronic obstructive pulmonary disease, identified in the study, could be explained by more antibiotic exposure due to frequent hospitalizations for acute exacerbation of underlying pulmonary illness.

There were several limitations in our study. Firstly, we only included bloodstream infections due to *E. coli* and *K. pneumoniae*, two major *Enterobacteriaceae* pathogens. These results cannot be explored to the infections due to other species of the *Enterobacteriaceae* family. Secondly, although the case number of definitive FQ therapy is limited, that cannot make the difference in crude or sepsis-related mortality rate significant. The individuals in the FQ group and matched carbapenem group were comparable in terms of demographic characteristic and severity of illness. In addition, the primary outcome is better for the FQ group patients than the group receiving any carbapenem as the definitive therapy. Likewise, a similar finding was noted in the multivariate logistic regression analysis. More clinical data are warranted to verify the role of FQ therapy for ESBL-producer bacteremia. Thirdly, only hospitalization

Please cite this article in press as: Lo C-L, et al., Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.08.012

data were analyzed and the short-term outcome was available. It remains undetermined if there is no difference in long-term outcome between two study groups.

In conclusion, for adults with bacteremia due to ESBL-producing *E. coli* and *K. pneumoniae*, against which ciprofloxacin or levofloxacin is active *in vitro*, either can be regarded as one of the regimens of choice.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev* 2001;**14**:933–51.
2. Kang CI, Wi YM, Ko KS, Chung DR, Peck KR, Lee NY, et al. Outcomes and risk factors for mortality in community-onset bacteremia caused by extended-spectrum beta-lactamase-producing *Escherichia coli*, with a special emphasis on antimicrobial therapy. *Scand J Infect Dis* 2013;**45**:519–25.
3. Menashe G, Borer A, Yagupsky P, Peled N, Gilad J, Fraser D, et al. Clinical significance and impact on mortality of extended-spectrum beta-lactamase- producing *Enterobacteriaceae* isolates in nosocomial bacteremia. *Scand J Infect Dis* 2001;**33**:188–93.
4. Paterson DL, Ko WC, Gottberg AV, Mohapatra S, Casellas JM, Goossens H, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum β-lactamase production in nosocomial infections. *Ann Intern Med* 2004;**140**:26–32.
5. Paterson DL. Recommendation for treatment of severe infections caused by *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs). *Clin Microbiol Infect* 2000;**6**:460–3.
6. Ramphal R, Ambrose PG. Extended-spectrum beta-lactamases and clinical outcomes: current data. *Clin Infect Dis* 2006;**42**:S164–72.
7. Pitout JDD, Laupland KB. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. *Lancet Infect Dis* 2008;**8**:159–66.
8. Corbella X, Montero A, Pujol M, Domínguez MA, Ayats J, Argerich MJ, et al. Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant *Acinetobacter baumannii*. *J Clin Microbiol* 2000;**38**:4086–95.
9. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008;**29**:1099–106.
10. Hussein K, Sprecher H, Mashiach T, Oren I, Kassis I, Finkelstein R. Carbapenem resistance among *Klebsiella pneumoniae* isolates: risk factors, molecular characteristics, and susceptibility patterns. *Infect Control Hosp Epidemiol* 2009;**30**:666–71.
11. Doi A, Shimada T, Harada S, Iwata K, Kamiya T. The efficacy of cefmetazole against pyelonephritis caused by extended-spectrum beta-lactamase-producing *Enterobacteriaceae*. *Int J Infect Dis Infect Dis* 2013;**17**:e159–63.
12. Pilmis B, Parize P, Zahar JR, Lortholary O. Alternatives to carbapenems for infections caused by ESBL-producing *Enterobacteriaceae*. *Eur J Clin Microbiol Infect Dis* 2014;**33**:1263–5.
13. Tsai HY, Chen YH, Tang HJ, Huang CC, Liao CH, Chu FY, et al. Carbapenems and piperacillin/tazobactam for the treatment of bacteremia caused by extended-spectrum β-lactamase-producing *Proteus mirabilis*. *Diagn Microbiol Infect Dis* 2014;**80**:222–6.
14. Drago L, De Vecchi E, Mombelli B, Nicola L, Valli M, Gismondo MR. Activity of levofloxacin and ciprofloxacin against urinary pathogens. *J Antimicrob Chemother* 2001;**48**:37–45.
15. Bhusal Y, Mihu CN, Tarrand JJ, Rolston KV. Incidence of fluoroquinolone-resistant and extended-spectrum β-lactamase-producing *Escherichia coli* at a comprehensive cancer center in the United States. *Chemotherapy* 2011;**57**:335–8.
16. Clinical and Laboratory Standards Institute 2013. Performance standards for antimicrobial susceptibility testing. In: 23th informational supplement. Approved standard M100–S23. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
17. McCabe WR, Jackson G. Gram-negative bacteremia: I. etiology and ecology. *Arch Intern Med* 1962;**110**:847–55.
18. Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents* 1999;**11**:7–12.
19. Paterson DL. Resistance in gram-negative bacteria: Enterobacteriaceae. *Am J Infect Control* 2006;**34**:20–8.
20. Babini GS, Livermore DM. Antimicrobial resistance amongst *Klebsiella* spp. collected from intensive care units in Southern and Western Europe in 1997–1998. *J Antimicrob Chemother* 2000;**45**:183–9.
21. Raei F, Eftekhar F, Feizabadi MM. Prevalence of quinolone resistance among extended-spectrum β-lactamase producing uropathogenic *Klebsiella pneumoniae*. *Jundishapur J Microbiol* 2014;**7**:e10887.
22. Ben-Ami R, Rodríguez-Baño J, Arslan H, Pitout JDD, 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.
23. Lee DS, Choe HS, Lee SJ, Bae WJ, Cho HJ, Yoon BI, et al. Antimicrobial susceptibility pattern and epidemiology of female urinary tract infections in South Korea, 2010-2011. *Antimicrob Agents Chemother* 2013;**57**:5384–93.
24. De La Blanchardière A, Dargère S, Guérin F, Daurel C, Saint-Lorant G, Verdon R, et al. Non-carbapenem therapy of urinary tract infections caused by extended-spectrum β-lactamase-producing *Enterobacteriaceae*. *Med Mal Infect* 2015;**45**:169–72.
25. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, et al. Bloodstream infections due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. *Antimicrob Agents Chemother* 2004;**48**:4574–81.
26. Tumbarello M, Sanguinetti M, Montuori E, Trecarichi EM, Posteraro B, Fiori B, et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing *Enterobacteriaceae*: importance of inadequate initial antimicrobial treatment. *Antimicrob Agents Chemother* 2007;**51**:1987–94.
27. Endimiani A, Luzzaro F, Perilli M, Lombardi G, Colì 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.
28. Peralta G, Lamelo M, Alvarez-García P, Velasco M, Delgado A, Horcajada JP, et al. Impact of empirical treatment in extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* spp. bacteremia. A multicentric cohort study. *BMC Infect Dis* 2012;**12**:245.

Please cite this article in press as: Lo C-L, et al., Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.08.012

29. Rodríguez-Baño J, Picón E, Gijón P, Hernández JR, Cisneros JM, Peña C, et al. Risk factors and prognosis of nosocomial bloodstream infections caused by extended-spectrum-beta-lactamase-producing *Escherichia coli*. *J Clin Microbiol* 2010; **48**:1726—31.
30. Fu Y, Zhang W, Wang H, Zhao S, Chen Y, Meng F, et al. Specific patterns of gyrA mutations determine the resistance difference to ciprofloxacin and levofloxacin in *Klebsiella pneumoniae* and *Escherichia coli*. *BMC Infect Dis* 2013;**13**:8.
31. Redgrave LS, Sutton SB, Webber MA, Piddock LJ. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. *Trends Microbiol* 2014;**22**: 438—45.
32. Lautenbach E, Fishman NO, Bilker WB, Castiglioni A, Metlay JP, Edelstein PH, et al. Risk factors for fluoroquinolone resistance in nosocomial *Escherichia coli* and *Klebsiella pneumoniae* infections. *Arch Intern Med* 2002;**162**:2469—77.
33. Park KH, Oh WS, Kim ES, Park SW, Hur JA, Kim YK, et al. Factors associated with ciprofloxacin- and cefotaxime-resistant *Escherichia coli* in women with acute pyelonephritis in the emergency department. *Int J Infect Dis* 2014;**23**:8—13.

Please cite this article in press as: Lo C-L, et al., Fluoroquinolone therapy for bloodstream infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.08.012