Epidemiology of Ciprofloxacin Resistance and Its Relationship to Extended-Spectrum β-Lactamase Production in *Proteus mirabilis* Bacteremia

Kyung Mok Sohn[1,2], Cheol-In Kang[1], Eun-Jeong Joo[1], Young Eun Ha[1], Doo Ryeon Chung[1], Kyong Ran Peck[1], Nam Yong Lee[3], and Jae-Hoon Song[1]

[1]Division of Infectious Diseases, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [2]Division of Infectious Diseases, Department of Internal Medicine, Chungnam National University Hospital, Daejeon; [3]Department of Laboratory Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background/Aims: We evaluated the clinical features of ciprofloxacin-resistant *Proteus mirabilis* bacteremia and risk factors for ciprofloxacin resistance.

Methods: From October 2000 to July 2009, 37 patients with clinically significant *P. mirabilis* bacteremia were identified and data from patients with ciprofloxacin-resistant and ciprofloxacin-susceptible *P. mirabilis* bacteremia were compared.

Results: The most common underlying diseases were neurologic disease (37.8%) and solid tumors (29.7%). The most common site of infection was the urinary tract (35.1%). Ten of the 37 patients (27.0%) were infected with ciprofloxacin-resistant isolates, and univariate analysis revealed a significant relationship between ciprofloxacin-resistant *P. mirabilis* bacteremia and neurologic disease, recent operation, L-tube insertion, percutaneous tube use, and extended-spectrum β-lactamase (ESBL) production (all $p < 0.05$). ESBL was detected in six of 10 (60%) ciprofloxacin-resistant isolates, while only three of 27 (11%) ciprofloxacin-susceptible isolates produced ESBL ($p = 0.005$). In a logistic regression analysis, ESBL production remained a significant factor associated with ciprofloxacin resistance, after adjusting for other variables.

Conclusions: These data indicate a close association between ciprofloxacin resistance and ESBL-production in *P. mirabilis* bacteremia. This association is particularly troublesome because the therapeutic options for serious infections caused by ESBL-producing *P. mirabilis* are severely restricted. **(Korean J Intern Med 2011;26:89-93)**

Keywords: *Proteus mirabilis;* Ciprofloxacin; Drug resistance; Bacterial; Risk factors; Cephalosporin resistance

INTRODUCTION

Proteus mirabilis can cause a variety of community- or hospital-acquired infections, including urinary tract, intra-abdominal, and bloodstream infections [1,2]. Antimicrobial resistance has been reported increasingly for this species, and increased resistance to extended-spectrum cephalosporins due to the production of extended-spec-trum β-lactamases (ESBLs) has become of great concern [1,3,4]. Consequently, carbapenem has emerged as the agent of choice for the treatment of serious infections caused by ESBL-producing pathogens. Fluoroquinolones may be an effective alternative antimicrobial therapy. However, similar to *Escherichia coli* and *Klebsiella pneumoniae*, the incidence of ciprofloxacin resistance in *P. mirabilis* isolates is increasing [5,6].

Although the occurrence of ciprofloxacin resistance in *E. coli* and *K. pneumoniae* isolates is well-established, little is known of the epidemiology of *P. mirabilis* bacteremia caused by ciprofloxacin-resistant isolates. Thus, in this study, we evaluated the clinical features of ciprofloxacin-resistant *P. mirabilis* bacteremia to clarify the risk factors for ciprofloxacin resistance in *P. mirabilis* isolates causing bacteremia.

METHODS

The database in our clinical microbiology laboratory (Samsung Medical Center, Seoul, Korea; a 1,950-bed, tertiary-care university hospital and referral center) was reviewed to identify patients > 16 years of age diagnosed with *P. mirabilis* bacteremia from October 2000 to July 2009. Only the first episode for each patient was included in the analysis. Antibiotic susceptibility was tested using the VITEK II automated system (bioMérieux, Hazelwood, MO, USA) using the standard modified broth microdilution method. Minimum inhibitory concentration (MIC) breakpoints and quality control protocols were used according to standards established by the Clinical and Laboratory Standards Institute [7]. For the purposes of this study, isolates showing *in vitro* resistance to cefotaxime, ceftriaxone, or ceftazidime were classified as ESBL-producing organisms. Strains showing an 'intermediate' result to the tested antibiotics were considered resistant.

We compared the clinical features of patients with ciprofloxacin-resistant and ciprofloxacin-susceptible *P. mirabilis* bacteremia. The data collected included age, gender, underlying disease, primary site of infection, acquisition site, and antimicrobial regimen. The presence of the following comorbid conditions was also documented: recent operation, corticosteroid use, indwelling urinary catheter, L-tube insertion, percutaneous tube use, prior invasive procedure, and prior use of antibiotics. Nosocomial acquisition of infection was defined as an infection that occurred > 48 hours after hospital admission, while infections diagnosed within the first 48 hours of hospitalization were classified as community-onset infection, based on the time the culture samples were obtained. Because many cases of *Proteus* bacteremia that are present or incubating on admission to the hospital are nonetheless healthcare-associated, we refer to non-nosocomial bacteremia as community-onset rather than community-acquired. Community-onset infection was further classified as community-associated and healthcare-associated, as previously suggested [8]. The site of infection was determined by physicians, based on the isolation of *P. mirabilis* from the presumed portal of entry and clinical evaluation.

Student's *t* test was used to compare continuous variables, and χ^2 or Fisher's exact tests were used to compare categorical variables. A logistic regression analysis was performed to evaluate ESBL production as a factor associated with ciprofloxacin resistance. The odds ratio (OR) and 95% confidential interval (CI) were calculated. All *p* values were two-tailed, and $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Thirty-seven patients with *P. mirabilis* bacteremia were identified. Their demographic and clinical characteristics are shown in Table 1. The most common underlying diseases were neurologic diseases (38%) and solid tumors (30%). The most common site of infection was the urinary tract (35%). Ten (27%) of the 37 patients were infected with ciprofloxacin-resistant isolates and nine (24%) were infected with ESBL-producers. Among the 27 patients

Table 1. Clinical characteristics of 37 patients with *Proteus mirabilis* bacteremia

Characteristics	No. of patients (%)
Age, yr (mean ± SD)	62.4 ± 17.8
Female	22 (59.5)
Acquisition site	
Community-associated	17 (45.9)
Healthcare-associated	10 (27.0)
Nosocomial infection	10 (27.0)
Underlying disease	
Neurologic disease	14 (37.8)
Solid tumor	11 (29.7)
Diabetes mellitus	6 (16.2)
Cardiovascular disease	3 (8.1)
Renal disease	3 (8.1)
Primary site of infection	
Primary bacteremia	12 (32.4)
Urinary tract infection	13 (35.1)
Intra-abdominal infection	8 (21.6)
Pneumonia	4 (10.8)
Extended-spectrum β-lactamase production	9 (24.3)
Ciprofloxacin resistance	10 (27.0)

Table 2. Factors associated with ciprofloxacin resistance in *Proteus mirabilis* isolates causing bacteremia

	Ciprofloxacin-resistant (n = 10)	Ciprofloxacin-susceptible (n = 27)	p value
Male gender	6 (60.0)	9 (33.3)	0.258
Nosocomial infection	5 (50.0)	5 (18.5)	0.094
Underlying diseases			
Solid tumor	1 (10.0)	10 (37.0)	0.224
Neurologic disease	7 (70.0)	7 (25.9)	0.023
Renal disease	0 (0)	3 (11.1)	0.548
Diabetes mellitus	2 (20.0)	4 (14.8)	0.653
Comorbid conditions			
Recent operation	5 (50.0)	0 (0)	0.001
Corticosteroid use	3 (30.0)	3 (11.1)	0.166
Central venous catheterization	2/8 (25.0)	1/18 (5.6)	0.215
Indwelling urinary catheter	2 (20.0)	1 (3.7)	0.172
L-tube	3/8 (37.5)	0/18 (0)	0.022
Percutaneous tube	3/8 (37.5)	0/18 (0)	0.022
Prior invasive procedure	2/8 (25.0)	0/18 (0)	0.086
Prior use of antibiotics	3/8 (37.5)	1/18 (5.6)	0.072
ESBL production	6 (60.0)	3 (11.1)	0.005

Values are presented as number (%).

ESBL, extended-spectrum β-lactamase.

determined to have community-onset infections, five (19%) had ciprofloxacin-resistant bacteremia. Among the ten patients identified as having a nosocomial-acquired infection, five (50%) had ciprofloxacin-resistant bacteremia (p = 0.094).

Risk factors associated with ciprofloxacin-resistant *P. mirabilis* are listed in Table 2. Univariate analysis revealed a significant relationship between ciprofloxacin-resistant *P. mirabilis* bacteremia and neurologic disease, recent operation, L-tube insertion, percutaneous tube use, and ESBL production (all p < 0.05). ESBL was detected in six (60%) of ten ciprofloxacin-resistant *P. mirabilis* isolates. In comparison, only three (11%) of 27 ciprofloxacin-susceptible *P. mirabilis* isolates were ESBL producers. ESBL production was significantly associated with ciprofloxacin resistance among *P. mirabilis* isolates causing bacteremia (OR, 12.00; 95% CI, 2.10 to 68.6; p = 0.005). In a logistic regression analysis, ESBL production remained a significant factor associated with ciprofloxacin resistance, after adjusting for nosocomial infection, neurologic disease, or recent operation (OR, 13.93; 95% CI, 1.04 to 186.07; p = 0.046).

Four (40%) of ten patients with ciprofloxacin-resistant bacteremia received inappropriate initial antimicrobial therapy, while three (11%) of 27 patients with ciprofloxacin-susceptible bacteremia received inappropriate initial antimicrobial therapy (p = 0.069). Of 32 patients whose outcomes could be evaluated, eight (25%) died within 30 days; no significant difference was found between ciprofloxacin-resistant (1/9, 11%) and -susceptible (7/23, 30%) patients (p = 0.386). When factors associated with mortality were evaluated, solid tumor was found to be the only significant factor associated with mortality (p = 0.005).

DISCUSSION

This study revealed that neurologic disease, recent operation, L-tube insertion, and percutaneous tube were significant risk factors associated with the development of bacteremia caused by ciprofloxacin-resistant *P. mirabilis*. Ciprofloxacin resistance in *K. pneumoniae* has been reported to be closely associated with ESBL production [9]. Several studies have examined the relationship between quinolone resistance and ESBL production in *E. coli* and *K. pneumoniae* [10,11]. Ciprofloxacin-resistant Enterobacter bacteremia is closely associated with broad-spectrum cephalosporin resistance [12]. Consistent with the latter study, we also observed a close association of ciprofloxacin-resistant *P. mirabilis* bacteremia with broad-spectrum cephalosporin resistance conferred by ESBL.

This association is of great concern because ESBL-pro-

ducing *P. mirabilis* isolates are usually resistant to penicillins and cephalosporins. Thus, ciprofloxacin resistance severely limits already restricted treatment options. Additionally, the marked increase in the incidence of ESBL-producing *P. mirabilis* isolates in recent years is of great concern [1,3,13]. Although carbapenems remain the most effective option for treating serious infection caused by ESBL-producing *P. mirabilis*, the increasing use of carbapenems has been paralleled by the rapid emergence of carbapenem resistance in nosocomial pathogens [14,15].

What is the explanation for the coexistence of these two resistance mechanisms in Gram-negative bacilli? The relationship between ciprofloxacin resistance and ESBL production may be due to the interplay between prior heavy antibiotic use and conditions favoring patient-to-patient transfer of multidrug-resistant organisms, as described elsewhere [6,9,12]. Additionally, there are other potential explanations for the association between ciprofloxacin resistance and broad-spectrum cephalosporins resistance; these include active efflux and outer membrane protein alterations [16]. For ciprofloxacin resistance in *K. pneumoniae* and *E. coli*, transfer of the same plasmid has been suggested as a further possible explanation for the coexistence of the two resistance mechanisms [17,18]. Plasmid-mediated ciprofloxacin resistance has recently been reported in such strains [19,20]. Furthermore, a new plasmid-mediated quinolone resistance gene, *qnrC*, was reported in a clinical isolate of *P. mirabilis* [21]. However, the basis for the ciprofloxacin resistance combined with ESBL production is not yet fully understood. Further investigation of the possible mechanisms is needed.

Prior therapy with fluoroquinolones is an important risk factor for ciprofloxacin resistance in Gram-negative bacilli [22,23]. In this regard, we were unable to assess possible associations between ciprofloxacin resistance and prior use of antibiotics in this study because of the small number of cases. Additionally, we sought to delineate the clinical features of *Proteus* bacteremia, rather than focusing on microbiological analyses, and so did not characterize ESBL types. Thus, misclassification with regard to ESBL production may have been possible in several patients. Finally, because our study was conducted in a large tertiary-care hospital, the results may not necessarily be applicable to other institutions.

In conclusion, our investigation of risk factors for ciprofloxacin-resistant *P. mirabilis* bacteremia revealed a close association between ciprofloxacin resistance and

ESBL production. This association is particularly troublesome because the therapeutic options for serious infections caused by ESBL-producing *P. mirabilis* are severely restricted.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

REFERENCES

1. Endimiani A, Luzzaro F, Brigante G, et al. Proteus mirabilis bloodstream infections: risk factors and treatment outcome related to the expression of extended-spectrum beta-lactamases. Antimicrob Agents Chemother 2005;49:2598-2605.

2. O'Hara CM, Brenner FW, Miller JM. Classification, identification, and clinical significance of Proteus, Providencia, and Morganella. Clin Microbiol Rev 2000;13:534-546.

3. Wu JJ, Chen HM, Ko WC, Wu HM, Tsai SH, Yan JJ. Prevalence of extended-spectrum beta-lactamases in Proteus mirabilis in a Taiwanese university hospital, 1999 to 2005: identification of a novel CTX-M enzyme (CTX-M-66). Diagn Microbiol Infect Dis 2008;60:169-175.

4. Uh Y, Hwang GY, Kwon O, Yoon KJ, Kim HY. Isolation frequency of extended spectrum beta-lactamase producing Escherichia coli, Klebsiella species, and Proteus mirabilis. Korean J Clin Microbiol 2007;10:119-122.

5. Hernandez JR, Martinez-Martinez L, Pascual A, Suarez AI, Perea EJ. Trends in the susceptibilities of Proteus mirabilis isolates to quinolones. J Antimicrob Chemother 2000;45:407-408.

6. Saito R, Okugawa S, Kumita W, et al. Clinical epidemiology of ciprofloxacin-resistant Proteus mirabilis isolated from urine samples of hospitalised patients. Clin Microbiol Infect 2007;13:1204-1206.

7. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Seventeenth Informational Supplement (Document M100-S17). Wayne (PA): Clinical and Laboratory Standards Institute, 2007.

8. Friedman ND, Kaye KS, Stout JE, et al. Health care--associated bloodstream infections in adults: a reason to change the accepted

definition of community-acquired infections. Ann Intern Med 2002;137:791-797.

9. Paterson DL, Mulazimoglu L, Casellas JM, et al. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in Klebsiella pneumoniae isolates causing bacteremia. Clin Infect Dis 2000;30:473-478.

10. Kang CI, Kim SH, Kim DM, et al. Risk factors for ciprofloxacin resistance in bloodstream infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Microb Drug Resist 2004;10:71-76.

11. Lautenbach E, Strom BL, Bilker WB, Patel JB, Edelstein PH, Fishman NO. Epidemiological investigation of fluoroquinolone resistance in infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Clin Infect Dis 2001;33:1288-1294.

12. Kang CI, Kim SH, Park WB, et al. Clinical epidemiology of ciprofloxacin resistance and its relationship to broad-spectrum cephalosporin resistance in bloodstream infections caused by Enterobacter species. Infect Control Hosp Epidemiol 2005;26:88-92.

13. Kim JY, Park YJ, Kim SI, Kang MW, Lee SO, Lee KY. Nosocomial outbreak by Proteus mirabilis producing extended-spectrum beta-lactamase VEB-1 in a Korean university hospital. J Antimicrob Chemother 2004;54:1144-1147.

14. Eagye KJ, Kuti JL, Nicolau DP. Risk factors and outcomes associated with isolation of meropenem high-level-resistant Pseudomonas aeruginosa. Infect Control Hosp Epidemiol 2009;30:746-752.

15. Tacconelli E, De Angelis G, Cataldo MA, et al. Antibiotic usage and risk of colonization and infection with antibiotic-resistant bacteria: a hospital population-based study. Antimicrob Agents Chemother 2009;53:4264-4269.

16. Zavascki AP, Carvalhaes CG, Picão RC, Gales AC. Multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii: resistance mechanisms and implications for therapy. Expert Rev Anti Infect Ther 2010;8:71-93.

17. Jacoby G, Cattoir V, Hooper D, et al. qnr Gene nomenclature. Antimicrob Agents Chemother 2008;52:2297-2299.

18. Martinez-Martinez L, Pascual A, Jacoby GA. Quinolone resistance from a transferable plasmid. Lancet 1998;351:797-799.

19. Kim HB, Park CH, Kim CJ, Kim EC, Jacoby GA, Hooper DC. Prevalence of plasmid-mediated quinolone resistance determinants over a 9-year period. Antimicrob Agents Chemother 2009;53:639-645.

20. Wu JJ, Ko WC, Wu HM, Yan JJ. Prevalence of Qnr determinants among bloodstream isolates of Escherichia coli and Klebsiella pneumoniae in a Taiwanese hospital, 1999-2005. J Antimicrob Chemother 2008;61:1234-1239.

21. Wang M, Guo Q, Xu X, et al. New plasmid-mediated quinolone resistance gene, qnrC, found in a clinical isolate of Proteus mirabilis. Antimicrob Agents Chemother 2009;53:1892-1897.

22. Colodner R, Kometiani I, Chazan B, Raz R. Risk factors for community-acquired urinary tract infection due to quinolone-resistant E. coli. Infection 2008;36:41-45.

23. Levin PD, Fowler RA, Guest C, Sibbald WJ, Kiss A, Simor AE. Risk factors associated with resistance to ciprofloxacin in clinical bacterial isolates from intensive care unit patients. Infect Control Hosp Epidemiol 2007;28:331-336.