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## The Clinical Impact of Fluoroquinolone Resistance in Patients with *E. coli* Bacteremia

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### Abstract

**Background**—There are limited data on fluoroquinolone resistance and its impact on mortality in cases of *E. coli* bloodstream infection (BSI).

**Objective**—To determine risk factors for in-hospital mortality among patients with *E. coli* BSIs.

**Design**—A retrospective case-control study

**Setting**—A 1250-bed tertiary academic medical center

**Patients**—Patients with fluoroquinolone-resistant *E. coli* BSI from January 1, 2000 through December 31, 2005 with 1:1 matched control patients with fluoro-quinolone sensitive *E. coli* BSI.

**Independent Outcome**—In-hospital mortality

**Results**—A total of 93 cases and 93 control patients were included. Compared to control patients, cases were more likely to be admitted from a long term care facility (35% vs. 9%;  $p < 0.001$ ) and to have a hospital-acquired bacteremia (54% vs. 33%;  $p = 0.008$ ). Crude mortality was 26% for cases and 8% for controls ( $p = 0.002$ ). On univariate analysis, predictors for in-hospital mortality included female gender, admission from a long term care facility, APACHE II score  $> 10$ , Charlson comorbidity score  $> 4$ , cardiac dysfunction, cirrhosis, renal dysfunction, treatment with corticosteroids, and a fluoroquinolone-resistant *E. coli* bacteremia. On multivariate analysis, independent risk factors for in-hospital mortality were cirrhosis [adjusted Odds Ratio (aOR) 7.2; CI (1.7, 29.8);  $p = 0.007$ ], cardiac dysfunction [aOR 3.9; CI (1.6, 9.4);  $p = 0.003$ ], and infection with a fluoroquinolone-resistant *E. coli* isolate [aOR 3.9; CI (1.5, 10.2);  $p = 0.005$ ].

**Conclusions**—After controlling for severity of illness and multiple comorbidities only fluoroquinolone resistance, cirrhosis, and cardiac dysfunction independently predicted mortality in patients with *E. coli* bacteremia.

### Keywords

*Escherichia coli*; bacteremia; fluoroquinolone; resistance; mortality

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## Introduction

Among Gram-negative pathogens, *E. coli* is one of the most common causes of both community-acquired and nosocomial bloodstream infections<sup>1, 2</sup>. Fluoroquinolone resistance among *E. coli* clinical isolates was first observed in patients with hematologic malignancies<sup>3, 4</sup> but is no longer restricted to this population<sup>5</sup> and has spread in the community<sup>6</sup>. Multiple studies have examined potential risk factors for fluoroquinolone resistance in *E. coli* infections.<sup>7-9</sup> Prior fluoroquinolone use stands out as a repeatedly documented risk factor<sup>10</sup>. In *E. coli* bacteremias, data on the impact of fluoroquinolone resistance on mortality are limited<sup>9, 11, 12</sup>. Ortega and colleagues performed a landmark analysis of a large dataset stemming from bacteremia surveillance data collected over 17 years<sup>9</sup>. They found that mortality was associated with both shock and inappropriate empirical treatment, and that inappropriate empirical treatment in turn was linked to fluoroquinolone resistance. Laupland et al. reported results from a population-based study in Canada, and could elicit age, comorbidities, ciprofloxacin resistance, and a non-urinary focus of infection as risk factors for mortality<sup>11</sup>. Lastly, a smaller study by Cheong et al. found a high APACHE II score (i.e., high severity of illness) but not fluoroquinolone resistance ( $p=0.08$ ) to be associated with poor outcomes<sup>12</sup>.

The prevalence of fluoroquinolone resistance among *E. coli* isolates in our hospital has surpassed 20%. In this setting, an adjustment of recommendations for empirical treatment may become necessary. This is particularly important since some studies have demonstrated that inappropriate empiric therapy in patients with bloodstream infection results in higher mortality<sup>13</sup>. The aim of this case-control study was to determine the impact of fluoroquinolone resistance on in-hospital mortality among patients with *E. coli* bacteremia.

## Methods

### Study design, setting and patients

This case-control study was conducted at Barnes-Jewish Hospital, a 1250-bed academic medical center in St. Louis, Missouri. A case was defined as any adult patient with a positive blood culture for fluoroquinolone-resistant *E. coli* between January 1, 2000, and December 31, 2005. Cases were identified from Medical Informatics database. Patients who were found to be bacteremic but were not admitted (e.g., emergency room visit without admission) were excluded. One control patient with a blood culture positive for fluoroquinolone-sensitive *E. coli* was randomly matched to each case by year of infection. Demographic data such as age, race, gender and clinical data such as severity-of-illness and comorbidity scores and processes of care such as timing of antibiotic administration and appropriateness of empiric therapy were collected from paper and electronic medical records..

### Definitions

*Appropriate empiric therapy* was defined as receipt of an antimicrobial with *in vitro* activity against the *E. coli* isolate before or within 48 hours of the blood culture being drawn. No antimicrobial therapy while the blood cultures were under incubation was considered inappropriate empiric therapy<sup>13</sup>. *Cardiac dysfunction* was defined as having a history of atrial fibrillation or congestive heart failure. *Central venous catheter (CVC)* was defined as the presence of central venous catheter for at least 48 hours at the time of the positive culture was drawn. *Clinical cure* was achieved if the patient was discharged from the hospital or survived 30 days after the bacteremia without a recurrent *E. coli* infection and no positive blood cultures for *E. coli* were recovered within 14 days after initiation of treatment. *History of fluoroquinolone use* was defined as receipt of any fluoroquinolone within 90 days prior to

the bacteremia. A *history of C. difficile* disease was defined as having been diagnosed with *C. difficile* disease in the past 6 months prior to the bacteremia. *History of surgery* was defined as having had a surgical procedure in the previous 30 days. A *history of urinary tract infection* (UTI) was defined as a UTI 90 days prior to the bacteremia. *Hospital-acquired infections* were defined as infections which were not active or present at admission and the positive blood cultures were obtained 48 hours or greater after admission. *In-hospital mortality* was defined as death in the hospital within 30 days after the positive blood culture. *MRSA colonization* was defined as a history of colonization with methicillin-resistant *Staphylococcus aureus* any time prior to the bacteremia. *Prior antibiotic use* was defined as receipt of any antibiotic within 90 days prior to the bacteremia. *Previous hospital admission* was defined as admission to a hospital in the last 90 days. *Renal dysfunction* was defined as acute renal failure (serum creatinine level at the time blood cultures were drawn was twice that of the last available creatinine level), chronic renal insufficiency (creatinine >1.6 mg/dL), or renal failure requiring dialysis. *VRE colonization* was defined as a history of infection or stool colonization with vancomycin-resistant enterococci (VRE) any time prior to the bacteremia.

### Statistical analysis

Univariate analysis of categorical variables in this case-control study was performed using Mantel-Haenszel chi-square or Fisher's exact test as appropriate. Continuous variables were compared using the student's t test or the Mann Whitney U test depending on the normality assumptions of the variable. Multivariate analysis was performed using backward stepwise conditional logistic regression. Variables that were found to have a p-value of  $\leq 0.10$  on univariate analysis along with age, gender, and race were included in the conditional logistic regression model. Variables which were associated with fewer than five patients were not included in the multivariate analysis despite having a p-value of  $\leq 0.10$  on univariate analysis. Goodness-of-fit of the logistic regression model was determined by Hosmer-Lemeshow test and the model with the best fit was retained as the final model. A two-sided p-value of  $\leq 0.05$  was considered statistically significant. Data analysis was performed using SPSS version 17 (SPSS, Chicago, Illinois).

The study was approved by the Washington University Human Research Protection Office.

### Results

#### Differences among patients with fluoroquinolone-resistant and fluoroquinolone-sensitive *E. coli* bacteremia

Nine-hundred and thirty patients had *E. coli* bacteremia during the study period. Ninety-eight patients had fluoroquinolone-resistant *E. coli* but blood cultures from 5 patients were collected in the outpatient setting and no follow-up information was available; these patients were excluded from the analysis. Ninety-three patients met the definition of a case and were matched with 93 patients with fluoroquinolone-sensitive *E. coli* bacteremias by year of infection for each of the cases. A comparison of the baseline demographic data and comorbid illnesses is shown in Table 1. When compared to control patients, cases were more likely to be admitted from a long term care facility (35% vs. 9%;  $p < 0.001$ ) and to have a hospital-acquired bacteremia (54% vs. 33%;  $p = 0.008$ ). Cases were also more likely to have been admitted to a hospital in the previous 30 days ( $p < 0.001$ ), colonized with vancomycin-resistant enterococci ( $p = 0.006$ ), have a central venous catheter in place ( $p = 0.04$ ), and have been treated with antibiotics including fluoroquinolones ( $p < 0.001$ ). The clinical cure rate was higher among controls (91% vs. 72%;  $p = 0.001$ ). Crude mortality was 26% for cases and 8% for controls ( $p = 0.002$ ). Although there was no difference in the mean

severity-of-illness score between cases and controls, cases had a longer mean length of stay (see Table 1).

### Risk factors for mortality from *E. coli* bacteremia

On univariate analysis, predictors for in-hospital mortality included female gender, admission from a nursing home or other long-term care facility, APACHE II score of >10, Charlson comorbidity score >4, a previous diagnosis of cardiac dysfunction, cirrhosis, renal dysfunction, and treatment with corticosteroids (see Table 2). Fluoroquinolone resistance was also associated with increased mortality [unadjusted Odds Ratio (*u*OR) 4.27; 95% Confidence Interval (CI) (1.7, 10.5)]. On multivariate analysis (see Table 3), independent risk factors for in-hospital mortality were cirrhosis [adjusted Odds Ratio (*a*OR) 7.2; 95% CI (1.7, 29.8); *p*=0.007], a history of cardiac dysfunction [*a*OR 3.9; 95% CI (1.6, 9.4); *p*=0.003], and infection with a fluoroquinolone-resistant *E. coli* isolate [*a*OR 3.9; 95% CI (1.5, 10.2); *p*=0.005]. The Hosmer-Lemeshow test revealed a *p*-value of 0.54. Both severity-of-illness indices were found not to be independent predictors of in-hospital mortality.

### Discussion

This case-control study represents one of the larger studies on fluoroquinolone-resistant *E. coli* bacteremia and adds to the growing body of literature on the impact of fluoroquinolone resistance and other factors predictive of mortality. In multivariate analysis, fluoroquinolone resistance was associated with in-hospital mortality from *E. coli* bacteremia, as were the comorbid illnesses cirrhosis and cardiac dysfunction.

Among the risk factors for fluoroquinolone-resistant *E. coli* bacteremia described in the literature are previous fluoroquinolone exposure<sup>9, 10, 12</sup>, nosocomial acquisition<sup>9</sup>, presence of a urinary catheter<sup>9</sup>, urinary source of bacteremia, previous surgery, and comorbid illnesses<sup>10</sup>. If the scope of infections was not limited to the bloodstream, other factors like structural changes in the urinary tract<sup>7</sup>, recurrent urinary tract infections<sup>14</sup>, residence in a long-term care facility, age, and prior exposure to aminoglycosides<sup>8</sup> were also reported. In our study, previous fluoroquinolone exposure, residence in a long-term care facility, recent hospitalization, nosocomial acquisition of infection, were associated with cases with fluoroquinolone-resistant isolates. We also found that a larger proportion of the cases received corticosteroids prior to the episode of bacteremia; to our knowledge, this finding has not been reported before.

In contrast to results on fluoroquinolone resistance in both *E. coli* and *K. pneumoniae* infections reported by Lautenbach et al.<sup>13</sup>, those patients in our study who were infected with the fluoroquinolone-resistant phenotype were not more likely to receive inappropriate empiric therapy than control patients (52% vs. 55%; *p*=0.8). This finding may be explained by the relatively low level of appropriate treatment even in the patients with fluoroquinolone-susceptible *E. coli*. For comparison, Lautenbach and colleagues saw a much higher percentage, 90%, of the patients with the susceptible phenotype received appropriate therapy<sup>13</sup>. The high proportion of inappropriate empiric therapy in our study may have played a role in the relatively high overall mortality rate (17%) that we observed. This is in contrast to a recent retrospective study on appropriateness of therapy for *E. coli* bacteremia which found that only 16% of bacteremia episodes (106 out of 663) were inadequately treated<sup>15</sup>, and the overall mortality was as low as 5%. A significant number of patients in our study however did not receive any antimicrobial therapy until blood cultures results were reported as positive and these situations did not meet the definition for appropriate empiric therapy. These same patients did not have all the signs and symptoms associated with sepsis syndrome and so were not treated with any antimicrobials until blood cultures were reported to be positive. Eventually, Lautenbach et al. stated that – after adjusting for

inadequate treatment – there was no longer an association between fluoroquinolone resistance and mortality in their population<sup>13</sup>. On the other hand, a recently published landmark Spanish study on factors influencing the outcome of 4,758 *E. coli* bacteremias reported that inappropriate treatment and shock were the two independent predictors of mortality; however, inappropriate treatment was significantly associated with fluoroquinolone resistance<sup>9</sup>. Laupland et al. who performed a population-based study of *E. coli* bacteremias in Canada elicited ciprofloxacin resistance as an independent predictor of mortality but the authors did not adjust for appropriateness of treatment<sup>11</sup>. In that study, a urinary source of the bacteremia and younger age turned out to be protective. We studied both variables in our study but failed to confirm their findings.

Previous studies have reported that fluoroquinolone-resistant clinical isolates collected from urine samples contain less virulence factors compared to the fluoroquinolone-susceptible *E. coli*<sup>16–18</sup>. Although no data are available specifically for bloodstream isolates, our finding of increased mortality in fluoroquinolone-resistant isolates is not consistent with these conceptual findings among *E. coli* isolates from the urinary tract. A delay in delivering the appropriate therapy cannot account for this since the proportion of patients who did not receive appropriate therapy within 48 hours of the blood cultures being drawn was similar among the cases and control patients. Nevertheless, it would be interesting to assess virulence factor profiles in *E. coli* bloodstream isolates that are stratified by their susceptibility to fluoroquinolones. The pathogens in our cohort may possess unidentified virulence mechanisms as well as resistance mechanisms towards fluoroquinolones. Since only patients with bacteremia were included in this study, it is possible that we have selected for a more virulent subpopulation of *E. coli* strains capable of more invasive disease than uropathogenic isolates. In the past, a number of small studies have indeed demonstrated differences in virulence factor profiles when comparing *E. coli* isolates strictly from urinary tract infections with those urinary tract isolates causing bacteremia<sup>19, 20</sup>. Another potential explanation for the observed association between fluoroquinolone-resistance and increased mortality may be unmeasured severity of illness among the cases. The cases were more likely to have a health-care associated infection, more likely to come from a long-term care facility or have been previously admitted, or associated with a longer length of stay. We did account for severity of illness using both the APACHE II score and the Charlson Index of Co-Morbidity but it is still possible these indices may not be adequate to account for the differences between the cases and controls.

We found a higher crude mortality among patients with fluoroquinolone-resistant *E. coli* bacteremia than in patients with fluoroquinolone-susceptible *E. coli* (26% vs. 8%;  $p=0.002$ ). This is similar to the crude mortality rate for fluoroquinolone-resistant *E. coli* bacteremia reported by Cheong et al. (30% in patients with fluoroquinolone-resistant *E. coli* bacteremia vs. 16% in patients with fluoroquinolone-susceptible *E. coli*;  $p=0.08$ )<sup>12</sup>. In Cheong's article only a high APACHE II score remained an independent risk factor for mortality. And although both Laupland et al. and Ortega et al. used regression analyses to describe factors associated with mortality, the respective crude mortality rates stratified by fluoroquinolone susceptibility were not reported<sup>9, 11</sup>. In our study, the univariate analysis yielded both APACHE II score and Charlson comorbidity score as predictors for in-hospital mortality but not in the multivariate analysis.

Our findings have important implications in the treatment of Gram-negative infections. *E. coli* is one of most common Gram-negative bacilli causing hospital-acquired infections and is the most common pathogen associated with community-acquired urinary tract infections. The latest Infectious Diseases Society of America (IDSA) guideline for treatment of acute pyelonephritis recommends the use of fluoroquinolones for empiric therapy of acute pyelonephritis<sup>21</sup>. Unfortunately, these guidelines were published in 1999, before reports of



the rise in fluoroquinolone resistance among *E. coli* isolates were available. The majority of the patients in our cohort (60%) developed a bacteremia following a complicated urinary tract infection and they would have received a fluoroquinolone for empiric therapy. The risk of providing inappropriate empiric therapy to patients with *E. coli* bacteremia is evident, especially since inappropriate treatment was delivered in approximately half of our patients.

Another group of patients who are at high risk for mortality and are also at risk for development of fluoroquinolone-resistant *E. coli* bacteremia are patients with liver cirrhosis. Gram-negative bacilli like *E. coli* are common pathogens implicated in spontaneous bacterial peritonitis (SBP) in these patients<sup>22</sup>. Since some patients with cirrhosis are exposed to fluoroquinolones for primary or secondary prophylaxis against SBP<sup>23</sup>, they are likely to be colonized, and eventually can develop infections with fluoroquinolone-resistant *E. coli* isolates<sup>8</sup>. It may be prudent to select an antimicrobial class that is different from fluoroquinolones in treating sepsis syndrome in this patient population.

Our study has a few limitations. One is that this is a retrospective case-control study and the accuracy of the data is dependent on the availability of complete medical records. All the admitted patients' charts or medical records were available for review in this study and so we were able to minimize any potential bias that may arise from missing data. This study was conducted at an academic medical center and results may not be generalizable to other healthcare institutions. The rate of inappropriate therapy was particularly high in this study but it is unlikely to have influenced the final results since this was observed in both cases and controls.

Based on our finding that fluoroquinolone resistance is an independent predictor for mortality we recommend that an alternative antimicrobial class rather than fluoroquinolones be initiated as empiric therapy in patients who are suspected to have an invasive *E. coli* infection. The reason for this increased mortality in fluoroquinolone-resistant *E. coli* is, at least in our study, not related to inappropriate therapy or a higher severity of illness and may be related to more virulent organisms.

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## References

1. Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis*. Sep 15; 2005 41(6):848–854. [PubMed: 16107985]
2. Diekema DJ, Pfaller MA, Jones RN, et al. Survey of bloodstream infections due to gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. *Clin Infect Dis*. Sep; 1999 29(3):595–607. [PubMed: 10530454]
3. Kern WV, Andriof E, Oethinger M, Kern P, Hacker J, Marre R. Emergence of fluoroquinolone-resistant *Escherichia coli* at a cancer center. *Antimicrob Agents Chemother*. Apr; 1994 38(4):681–687. [PubMed: 8031031]
4. Carratala J, Fernandez-Sevilla A, Tubau F, Callis M, Gudiol F. Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis*. Mar; 1995 20(3):557–560. discussion 561–553. [PubMed: 7756475]
5. Oteo J, Lazaro E, de Abajo FJ, Baquero F, Campos J. Antimicrobial-resistant invasive *Escherichia coli*, Spain. *Emerg Infect Dis*. Apr; 2005 11(4):546–553. [PubMed: 15829192]

6. Garau J, Xercavins M, Rodriguez-Carballeira M, et al. Emergence and dissemination of quinolone-resistant *Escherichia coli* in the community. *Antimicrob Agents Chemother*. Nov; 1999 43(11): 2736–2741. [PubMed: 10543756]
7. Huotari K, Tarkka E, Valtonen V, Kolho E. Incidence and risk factors for nosocomial infections caused by fluoroquinolone-resistant *Escherichia coli*. *Eur J Clin Microbiol Infect Dis*. Aug; 2003 22(8):492–495. [PubMed: 12884069]
8. Lautenbach E, Fishman NO, Bilker WB, et al. Risk factors for fluoroquinolone resistance in nosocomial *Escherichia coli* and *Klebsiella pneumoniae* infections. *Arch Intern Med*. Nov 25; 2002 162(21):2469–2477. [PubMed: 12437407]
9. Ortega M, Marco F, Soriano A, et al. Analysis of 4758 *Escherichia coli* bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. *J Antimicrob Chemother*. Mar; 2009 63(3):568–574. [PubMed: 19126669]
10. 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*. Feb; 1995 39(2):520–524. [PubMed: 7726525]
11. Laupland KB, Gregson DB, Church DL, Ross T, Pitout JD. Incidence, risk factors and outcomes of *Escherichia coli* bloodstream infections in a large Canadian region. *Clin Microbiol Infect*. Nov; 2008 14(11):1041–1047. [PubMed: 19040476]
12. Cheong HJ, Yoo CW, Sohn JW, Kim WJ, Kim MJ, Park SC. Bacteremia due to quinolone-resistant *Escherichia coli* in a teaching hospital in South Korea. *Clin Infect Dis*. Jul 1; 2001 33(1): 48–53. [PubMed: 11389494]
13. Lautenbach E, Metlay JP, Bilker WB, Edelstein PH, Fishman NO. Association between fluoroquinolone resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections: the role of inadequate empirical antimicrobial therapy. *Clin Infect Dis*. Oct 1; 2005 41(7):923–929. [PubMed: 16142655]
14. Killgore KM, March KL, Guglielmo BJ. Risk factors for community-acquired ciprofloxacin-resistant *Escherichia coli* urinary tract infection. *Ann Pharmacother*. Jul-Aug; 2004 38(7–8):1148–1152. [PubMed: 15150380]
15. Peralta G, Sanchez MB, Garrido JC, et al. Impact of antibiotic resistance and of adequate empirical antibiotic treatment in the prognosis of patients with *Escherichia coli* bacteraemia. *J Antimicrob Chemother*. Oct; 2007 60(4):855–863. [PubMed: 17644532]
16. Drews SJ, Poutanen SM, Mazzulli T, et al. Decreased prevalence of virulence factors among ciprofloxacin-resistant uropathogenic *Escherichia coli* isolates. *J Clin Microbiol*. Aug; 2005 43(8): 4218–4220. [PubMed: 16081983]
17. Vila J, Simon K, Ruiz J, et al. Are quinolone-resistant uropathogenic *Escherichia coli* less virulent? *J Infect Dis*. Oct 1; 2002 186(7):1039–1042. [PubMed: 12232848]
18. Takahashi A, Muratani T, Yasuda M, et al. Genetic profiles of fluoroquinolone-resistant *Escherichia coli* isolates obtained from patients with cystitis: phylogeny, virulence factors, PAI<sub>usp</sub> subtypes, and mutation patterns. *J Clin Microbiol*. Mar; 2009 47(3):791–795. [PubMed: 19158256]
19. Moreno E, Planells I, Prats G, Planes AM, Moreno G, Andreu A. Comparative study of *Escherichia coli* virulence determinants in strains causing urinary tract bacteremia versus strains causing pyelonephritis and other sources of bacteremia. *Diagn Microbiol Infect Dis*. Oct; 2005 53(2):93–99. [PubMed: 16168618]
20. Bonacorsi S, Houdouin V, Mariani-Kurkdjian P, Mahjoub-Messai F, Bingen E. Comparative prevalence of virulence factors in *Escherichia coli* causing urinary tract infection in male infants with and without bacteremia. *J Clin Microbiol*. Mar; 2006 44(3):1156–1158. [PubMed: 16517919]
21. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. *Infectious Diseases Society of America (IDSA)*. *Clin Infect Dis*. Oct; 1999 29(4):745–758. [PubMed: 10589881]
22. Parsi MA, Atreja A, Zein NN. Spontaneous bacterial peritonitis: recent data on incidence and treatment. *Cleve Clin J Med*. Jul; 2004 71(7):569–576. [PubMed: 15320366]

23. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol.* Jan; 2000 32(1): 142–153. [PubMed: 10673079]



**Table 1**

Comparison of demographic and clinical characteristics and outcome measures in fluoroquinolone-resistant versus fluoroquinolone-susceptible *E. coli* bacteremias

Variable	Cases n (%) n=93	Controls n (%) n=93	p value
<b>Demographic characteristics</b>			
Mean age ( $\pm$ SD)	60.1 $\pm$ 17.0 years	63.2 $\pm$ 19.4 years	0.2
Female gender	61 (66)	49 (53)	0.1
Race: African-American	26 (28)	42 (45)	0.1
Caucasian	60 (65)	50 (54)	
Other	7 (7)	1 (1)	
Residence: Home	55 (59)	79 (85)	<0.001
LTCF/SNF	32 (35)	8 (9)	
Other	6 (6)	6 (6)	
Hospital-acquired bacteremia	50 (54)	31 (33)	<b>0.008</b>
<b>Comorbidities</b>			
Alcohol abuse	6 (6)	5 (5)	1.0
APACHE II score $\geq$ 10	50 (54)	49 (53)	0.9
Mean APACHE II score	13.4 $\pm$ 8.3	11.9 $\pm$ 6.1	0.6
Cardiac dysfunction	28 (30)	22 (24)	0.3
Charlson Index $\geq$ 4	36 (39)	29 (31)	0.3
Mean Charlson Index	3.6 $\pm$ 2.8	3.4 $\pm$ 2.8	0.7
Chemotherapy	18 (19)	11 (12)	0.2
Cirrhosis	7 (8)	4 (4)	0.5
Diabetes mellitus	30 (32)	28 (30)	0.9
Hypertension	48 (52)	47 (51)	0.9
Malignancy	35 (38)	29 (31)	0.4
MRSA colonization	11 (12)	4 (4)	0.07
Obesity	17 (18)	20 (22)	0.7
Neutropenia	19 (20)	9 (10)	0.07
Previous hospital admission	43 (46)	19 (20)	<0.001
Renal dysfunction	41 (44)	39 (42)	0.9

Variable	Cases n (%) n=93	Controls n (%) n=93	p value
Tobacco use	20 (22)	13 (14)	0.3
Trauma	3 (3)	12 (13)	<b>0.03</b>
VRE colonization	23 (25)	8 (9)	<b>0.006</b>
Previous antibiotic use	35 (38)	12 (13)	<b>&lt;0.001</b>
Fluoroquinolone use	37 (40)	9 (10)	<b>&lt;0.001</b>
History of UTI	32 (34)	23 (25)	0.2
Corticosteroids	30 (32)	9 (10)	<b>&lt;0.001</b>
CVC	55 (59)	40 (43)	<b>0.04</b>
<b>Source of bacteremia</b>			
Urinary tract	57 (61)	55 (59)	0.8
Intraabdominal infection	5 (5)	11 (12)	0.1
Primary/catheter-related	17 (18)	4 (4)	<b>0.005</b>
Chemotherapy-related/mucositis	6 (6)	1 (1)	0.09
Pneumonia	0 (0)	7 (8)	--
Other	8 (9)	15 (16)	
<b>Management and outcome</b>			
Appropriate empiric therapy	48 (52)	51 (55)	0.8
Clinical cure	67 (72)	85 (91)	<b>0.001</b>
Mean length of stay	18.2 ± 21.9 days	10.4 ± 10 days	<b>0.002</b>
Median length of stay	9 days	6 days	<b>0.002</b>
In-hospital mortality	24 (26)	7 (8)	<b>0.002</b>

NOTE. SD = standard deviation. LTCF/SNF = long-term care facility/skilled nursing facility. MRSA = methicillin-resistant *Staphylococcus aureus*. VRE = vancomycin-resistant enterococcus. UTI = urinary tract infection. CVC = central venous catheter.

**Table 2**Results of univariate analysis determining risk factors for in-hospital mortality of *E. coli* bacteremia

Variable	Died, n (%)n=31	Survived, n (%)n=155	p value	Unadjusted Odds Ratio (uOR)
<b>Demographic characteristics</b>				
Mean age (±SD)	61.2 ± 18.9 years	63.8 ± 14.4 years	1.0	
Age ≥65 years	11 (36)	66 (43)	0.4	0.73 (0.33, 1.62)
Female gender	19 (61)	57 (37)	<b>0.01</b>	<b>2.29 (1.18, 4.44)</b>
Race: African-American	9 (29)	59 (38)	0.1	1.86 (0.81, 4.30)
Caucasian	22 (71)	88 (57)		
Other	0 (0)	8 (5)		
Residence: Home	13 (42)	121 (78)	<b>0.02</b>	<b>3.13 (1.24, 7.76)</b>
LTCF/SNF	10 (32)	30 (19)		
Other	8 (26)	4 (3)		
Hospital-acquired bacteremia	18 (58)	63 (41)	0.08	2.02 (0.93, 4.42)
<b>Comorbidities</b>				
Alcohol abuse	4 (13)	7 (5)	0.2	3.13 (0.86, 11.44)
APACHE II score ≥10	22 (71)	77 (50)	<b>0.03</b>	<b>2.48 (1.07, 5.72)</b>
Mean APACHE II score	17.8 ± 9.9	11.6 ± 6.2	<b>0.002</b>	
Cardiac dysfunction	15 (48)	35 (23)	<b>0.004</b>	<b>3.43 (1.53, 7.70)</b>
<i>C. difficile</i> colitis	4 (13)	7 (5)	0.08	3.13 (0.86, 11.43)
Charlson Index ≥4	16 (52)	49 (32)	<b>0.04</b>	<b>2.31 (1.06, 5.04)</b>
Mean Charlson Index	4.8 ± 3.0	3.2 ± 2.7	<b>0.006</b>	
Chemotherapy	6 (19)	23 (15)	0.5	1.38 (0.51, 3.73)
Cirrhosis	6 (19)	5 (3)	<b>0.002</b>	<b>7.2 (2.04, 25.4)</b>
Diabetes mellitus	11 (36)	47 (30)	0.6	1.26 (0.56, 2.85)
Hypertension	17 (55)	78 (50)	0.7	1.20 (0.55, 2.60)
Malignancy	14 (45)	50 (32)	0.2	1.73 (0.79, 3.79)
MRSA colonization	3 (10)	12 (8)	0.7	1.28 (0.34, 4.82)
Obesity	5 (16)	32 (21)	0.6	0.74 (0.63, 2.08)
Neutropenia	5 (16)	23 (15)	0.9	1.10 (0.38, 3.17)

Variable	Died, n (%)n=31	Survived, n (%)n=155	p value	Unadjusted Odds Ratio (uOR)
Previous hospital admission	15 (48)	47 (30)	0.06	2.15 (0.98, 4.72)
Renal dysfunction	20 (65)	60 (39)	<b>0.01</b>	<b>2.88 (1.29, 6.43)</b>
Tobacco use	7 (23)	26 (17)	0.4	1.45 (0.56, 3.71)
Trauma	1(3)	14 (9)	0.3	0.34 (0.04, 2.65)
VRE colonization	7 (23)	24 (16)	0.3	1.59 (0.62, 4.11)
Previous antibiotic use	9 (29)	38 (25)	0.6	1.26 (0.53, 2.97)
Fluoroquinolone use	8 (26)	38 (25)	0.9	1.07 (0.44, 2.59)
History of UTI	8 (26)	47 (30)	0.6	0.80 (0.33, 1.92)
Corticosteroids	12 (39)	27 (17)	<b>0.01</b>	<b>2.99 (1.30, 6.89)</b>
CVC	17 (55)	78 (50)	0.7	1.20 (0.55, 2.6)
<b>Source of bacteremia</b>				
Urinary tract	15 (48)	97 (63)	0.1	0.56 (0.26, 1.22)
Intraabdominal infection	5 (16)	11 (7)	0.1	2.52 (0.81, 7.85)
Primary/catheter-related	3 (10)	18 (12)	0.8	0.82 (0.23, 2.96)
Chemotherapy-related/mucositis	3 (10)	4 (3)	0.08	0.05 (0.86, 19.06)
<b>Management and outcome</b>				
Appropriate empiric therapy	15 (48)	69 (45)	0.38	0.70 (0.31, 1.56)
Mean length of stay	19.9 ± 24.8 days	13.2 ± 15.4 days	0.2	
In-hospital mortality	24 (26)	7 (8)	<b>0.002</b>	
Fluoroquinolone resistance	24 (77)	69 (45)	<b>0.002</b>	<b>4.27 (1.74, 10.5)</b>

NOTE. SD = standard deviation. LTCF/SNF = long-term care facility/skilled nursing facility. MRSA = methicillin-resistant *Staphylococcus aureus*. VRE = vancomycin-resistant Enterococcus. UTI = urinary tract infection. CVC = central venous catheter.

**Table 3**Multivariate analysis determining independent predictors of in-hospital mortality from *E. coli* bacteremia

	<b>Adjusted Odds Ratio</b>	<b>95% Confidence Interval</b>	<b>P-value</b>
Cirrhosis	7.2	(1.7, 29.8)	0.007
Fluoroquinolone resistance	3.9	(1.5, 10.2)	0.005
Cardiac dysfunction	3.9	(1.6, 9.4)	0.003
Female gender	0.5	(0.2, 1.2)	0.11