Are Fluoroquinolones Appropriate for the Treatment of Extended-Spectrum β -Lactamase-Producing Gram-Negative Bacilli?

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Abstract

Objective: To review the data analyzing the role of fluoroquinolones in the treatment of extended-spectrum β -lactamase (ESBL)-producing infections and rates and methods of co-transmission of resistance. **Data Sources:** A MEDLINE literature search was performed using the search terms *extended-spectrum beta-lactamase*, *fluoroquinolone*, *ciprofloxacin*, *levofloxacin*, *plasmid transmission*, and *resistance* from 1996 to June 2015. Additional references were identified from a review of literature citations. **Study Selection and Data Extraction:** All English-language retrospective studies, prospective studies, and meta-analyses assessing efficacy of fluoroquinolone use in ESBL infections, assessing methods of resistance transmission, or analyzing patient risk factors were reviewed. **Data Synthesis:** A total of 18 studies that analyzed fluoroquinolone resistance and association to ESBL producing bacteria from either molecular or clinical perspectives were identified. Four studies evaluated the genetic association between ESBL transmission and fluoroquinolone resistance. Plasmid mediated quinolone resistance was found in higher rates in ESBL-producing bacteria. Numerous studies analyzed the risk factors of co-occurring resistance identifying nosocomial acquired infections, recent hospitalization, long-term care facility residence, and intensive care unit stay as the most common. Conclusive clinical data are lacking; however, a meta-analysis showed fluoroquinolones had higher odds of all-cause mortality when used empirically to treat ESBL bacteremia compared with carbapenems. **Conclusions:** Fluoroquinolone resistance may be co-transmitted in ESBL-producing Enterobacteriaceae. There are limited data on the efficacy for fluoroquinolones in the treatment of ESBL-producing infections. Additional prospective trials are needed to definitively determine the role of fluoroquinolones in ESBL infections.

Keywords

infectious disease, fluoroquinolones, antibiotic resistance, extended-spectrum β -lactamase

Background

Extended-spectrum β -lactamase (ESBL) enzymes were first identified in the 1980s and have become increasingly prevalent in both health care-associated and community-acquired infections.¹ ESBLs are enzymes that hydrolyze not only penicillins but also oxymino (third generation) cephalosporins and monobactams. They confer resistance in Gram-negative bacilli including Enterobacteriaceae, specifically *Escherichia coli* and *Klebsiella pneumoniae*, and less commonly in *Proteus mirabilis*.² More than 200 different alleles have been discovered that vary in epidemiology and resistance patterns.³

Historically, the detection of ESBLs was performed using the double disk diffusion method or the broth microdilution method. These methods take advantage of the enzymatic property that ESBL enzymes are inhibited by β -lactamase

inhibitors. Ceftazidime and cefotaxime were placed on an agar plate or in broth alone and in combination with clavulanic acid, a β -lactamase inhibitor. An increase of >5 mm difference in the zones of inhibition between antibiotic alone and antibiotic in combination with clavulanic acid or a 3-fold decrease in minimum inhibitory concentration (MIC) for any 2-fold dilution for clavulanic acid combination compared

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Table 1. Typical Susceptibility Pattern of ESBL-Producing Enterobacteriaceae.

Antibiotic	Susceptibility
Amikacin	S
Ampicillin-sulbactam	S/I/R
Aztreonam	R
Cefazolin	R
Cefepime	S/I/R
Cefoxitin	S
Ceftriaxone	R
Ertapenem	S
Gentamicin	S
Levofloxacin	S/R
Meropenem	S
Piperacillin-tazobactam	S/I/R
Tigecycline	S
Trimethoprim/sulfamethoxazole	R
Polymixin	S

Abbreviations: ESBL, extended-spectrum β -lactamase; S, susceptible; I, intermediate; R, resistant; S/I/R, variability in susceptibility depending on the specific ESBL present.

Adapted from Chaubey et al.²⁵

with the β -lactamase alone indicates presence of an ESBL.^{4,5} Testing for ESBL using this method became standard for many hospitals because many ESBL-producing organisms fell within the susceptible MIC breakpoints, the predefined levels of susceptibility or resistance, for third-generation cephalosporins. Until ESBL screening tests became routine, these resistant bacteria were being reported as susceptible to third-generation cephalosporins and aztreonam leading to possible inappropriate treatment selection.⁶ However, in the 2010 Clinical and Laboratory Standards Institute (CLSI) guidelines, cephalosporin breakpoints were lowered. Thus, the recommendation to qualitatively test for the presence of ESBL as part of routine susceptibility testing was removed.⁵ Therefore, many laboratories that have implemented these guidelines do not explicitly report the presence of ESBL production, and treatment decisions rely on MIC alone. The typical susceptibility of an ESBL-producing Enterobacteriaceae is presented in Table 1. Carbapenems remain the mainstay of treatment for ESBL-producing infections,⁷ and it is unclear whether alternatives to carbapenems, such as fluoroquinolones, are possible treatment options for these infections.

Fluoroquinolone resistance has increased in Enterobacteriaceae since the introduction of the class of antibiotics nearly 30 years ago.⁸ Resistance has generally been attributable to chromosomal genetic mutations in the quinolone-resistance determining regions (QRDR). Since quinolones act by binding to enzyme–DNA complexes, which form between cleaved bacterial DNA and DNA gyrase or topoisomerase IV, QRDR mutations in regions coding these enzymes confer resistance.⁸ In the 1990s,

decreased quinolone susceptibility was linked to plasmid-mediated quinolone resistance (PMQRs). Since that time, the discovery of multiple PMQRs have been discovered. The most common PMQR is the family of qnr proteins (A, B, and S). Qnr proteins are protective of DNA gyrase and thus raise the MIC of quinolones resulting in low-level resistance.⁹ Originally found to confer resistance to tobramycin, amikacin, and kanamycin, a new variety found in 2004 also conferred resistance to ciprofloxacin.⁸ The other PMQRs that leads to quinolone resistance, *aac(6')-Ib-cr*, is found mostly in *E coli*. Given that ESBL production and quinolone resistance mechanisms both occur in Gram-negative bacilli, it is important to consider if there are similar transmission mechanisms leading to higher rates of resistance to both antibiotic classes.

Increased use of carbapenems in response to ESBL and other resistant infections has led to the emergence of carbapenem resistance.⁷ In order to preserve carbapenems, all antibiotic options that may be available to treat ESBL-producing infections should be considered. This review explores the methods of resistance transmission, risk factors for resistant infections, and whether fluoroquinolones are a viable treatment option for infections due to ESBL-producing organisms.

Methods

A review of the literature published between 1996 and June 2015 was conducted using a MEDLINE search using search terms such as *extended-spectrum beta-lactamase*, *fluoroquinolone*, *levofloxacin*, *ciprofloxacin*, *plasmid transmission*, and *resistance*. Further identification of articles was done by hand review of literature citations. All English-language prospective, retrospective, and meta-analyses were reviewed. Articles selected for inclusion discussed either methods of transmission of ESBL and fluoroquinolone resistance, risk factors for fluoroquinolone-resistant ESBL infections, or efficacy of fluoroquinolone antibiotics as empirical and/or definitive treatment in ESBL bacterial infections. Specific inclusion criteria for resistance transmission articles included polymerase chain reaction analysis of quinolone-specific mutations in ESBL-producing isolates. Epidemiological assessment of fluoroquinolone-resistant ESBL-producing infections was the major inclusion criterion for articles included in the risk factor review. Criteria for clinical outcome articles were limited to articles analyzing disease specific outcomes.

Literature Review

Plasmid Co-transmission

Multiple studies have analyzed occurrence of co-resistance between fluoroquinolones and ESBL production mainly in

Enterobacteriaceae.¹⁰⁻¹² In a study of resistant *E coli* strains (resistant at least to ampicillin and cotrimoxazole) isolated from urine, 12 out of 64 isolates (18%) were both fluoroquinolone resistant and ESBL positive.¹⁰ All ESBL-producing strains were found to carry a 42 kb plasmid, which was responsible for resistance to penicillins and third-generation cephalosporins including ceftazidime and cefepime as well as cotrimoxazole and tetracycline. All fluoroquinolone-resistant strains carried the PMQR, *aac(6')-lb-cr*, gene, and 6 additionally carried *qnrA* and *qnrB*. These genes were not transmitted on the 42 kb plasmid. However, the fluoroquinolone resistance could also be attributable to point mutations in the QRDR, which were detected in the same strains of bacteria with *aac(6')-lb-cr*, *qnrA*, and *qnrB*.

One study analyzed chromosomal and plasmid-mediated mechanisms of ciprofloxacin resistance in ESBL-producing bacteria.¹² Eighty-five percent of strains with reduced ciprofloxacin susceptibility carried both *qnrB* and *aac(6')-lb-cr* plasmid-mediated genes. This evidence further strengthens the theory of plasmid transmission of ESBLs and fluoroquinolone resistance.

A French study analyzed the genetic morphologies in ESBL-producing Enterobacteriaceae isolates, which also exhibited reduced susceptibility to fluoroquinolones. Isolates included *E coli* (76%), *P mirabilis* (11%), *K pneumoniae* (6%), *P stuartii* (4%), and *E aerogenes* (2%). Of resistant Enterobacteriaceae, 45% carried at least one PMQR, namely, *qnrS* or *aac(6')-lb-cr*. Following characterization, multiple conjugation studies were conducted to determine transferability of different resistances.¹³ One of the *K pneumoniae* strains successfully transmitted both ESBL production and fluoroquinolone resistance via plasmid conjugation to an *E coli* recipient on a large 170 kb plasmid.

Collective consideration of these studies reinforces the hypothesis of ESBL and fluoroquinolone resistance co-transmission. Although the presence of ESBL is not a definitive marker of this resistance, there is a higher risk of fluoroquinolone resistance among ESBL-producing bacteria.

Overall presence of *qnr* in Enterobacteriaceae isolates is rather low. However, in ESBL-producing bacteria, the prevalence exceeds 20%.⁸ Thus, one cannot discount the possibility of *qnr* presence in ESBL-producing bacteria. However, now that CLSI guidelines no longer recommend definitive ESBL testing, it may be difficult to discern at what point the increased *qnr* prevalence should be taken into account. In cultures reported as resistant to third-generation cephalosporins and aztreonam, it may be prudent to consider increased *qnr* gene presence and thus to strongly consider other options before initiation of fluoroquinolones.

Risk Factors

It is known that resistance patterns of any bacterial infection are highly variable based on different factors such as setting

of transmission (hospital, community, or skilled nursing facilities), recent antibiotic treatment, location of infection, and comorbid conditions. There have been many epidemiological studies that have identified characteristics that increase the risk for infection with fluoroquinolone-resistant, ESBL-producing bacteria.^{1,9,14-19}

Factors that were positively correlated with ESBL-producing fluoroquinolone-resistant bacteria included nosocomial acquired infections,^{1,9,14} recent hospitalization,^{15,16} long-term care facility residence,^{15,17} and intensive care unit stay.^{15,17} Study results differed on previous antibiotic exposure and the associated risk in ESBL and fluoroquinolone resistance. One study found no association between previous third-generation cephalosporin or fluoroquinolone use on drug resistance in ESBL-ciprofloxacin co-resistant strains.¹ However, other studies found correlation between fluoroquinolone or aminoglycoside use within 30 days,^{17,20} aminoglycosides or sulfamethoxazole-trimethoprim in the past 30 days,¹⁴ previous use of β -lactam/lactamase inhibitors, penicillins, aminoglycosides, fluoroquinolones, and metronidazole,¹⁸ or third-generation cephalosporins and fluoroquinolones.¹⁹

Overall, the factors that put a person at risk of ESBL-producing fluoroquinolone-resistant infections include recent hospitalizations and recent antibiotic use although there are discrepancies as to which antibiotics pose significant risks.

Clinical Outcomes

Several studies have analyzed the use of fluoroquinolones in the treatment of ESBL infections with a variety of outcomes. A meta-analysis and systematic review analyzed mortality rates in patients with ESBL-producing Enterobacteriaceae bacteremia treated with carbapenems compared with other antibiotics.²¹ Twenty-one studies were included in the analysis with a total of 1584 patients. The meta-analysis included patients with community-acquired and health care-acquired bacteremias. Studies were not differentiated based on severity of infection. Eight of the studies included in the meta-analysis used fluoroquinolones as a comparator. Across these trials a total of 80 (21%) patients received fluoroquinolones empirically and an additional 65 (28%) patients received definitive fluoroquinolone treatment. Empiric treatment was considered appropriate if in vitro sensitivities for prescribed antibiotics were below the CLSI susceptibility breakpoints. If empiric treatment was correct and therapy was correctly modified in response to culture data, the authors defined this as definitive treatment. For example, if a patient initially received a carbapenem and then was narrowed to a fluoroquinolone for an infection susceptible to both carbapenems and fluoroquinolones, the patient was considered to receive appropriate empiric and definitive treatment. However, if a patient initially received a β -lactam/ β -lactamase

inhibitor and then changed to a carbapenem when the culture data came back resistant to the initial agent, it was considered inappropriate empiric therapy but appropriate definitive therapy. The analysis showed that carbapenems were associated with a lower mortality rate than fluoroquinolones when used empirically (relative risk = 0.34, 95% confidence interval = 0.19-0.62), but when used as definitive treatment, no difference in mortality was seen (relative risk = 0.63, 95% confidence interval = 0.34-1.15). Although the analysis did not include illness severity ratings or comorbidities, individual studies did. Common comorbidities in many of the studies included malignancy, chronic renal failure, and diabetes mellitus. Nosocomial infections were most common for a majority of patients in the studies that included fluoroquinolones. It is important to consider that this analysis only included bacteremia and the source of infection varied significantly between studies giving rise to heterogeneity within the study population. Analysis was also limited to all-cause mortality. Given the high percentage of malignancy (40% to 60%) in half the studies, it is important to consider infectious processes may not be the primary cause of death in all patients. Clearance of infection or cause-stratified mortality rates would be of greater utility in discerning efficacy of different treatments.

Endimiani and colleagues conducted a retrospective review of blood stream infections attributed to ESBL-producing *K pneumoniae*. The study compared response to treatment of patients receiving imipenem or ciprofloxacin over a 2-year period. The primary outcome was complete or partial response defined as resolution of SIRS criteria. Treatment failure was defined as lack of improvement or worsening of symptoms. Relapse was defined as infection with the same organism within 1 month of antibiotic discontinuation. Patients who died or were transferred within 72 hours of blood stream infection identification were deemed not assessable. Of 28 isolates, 21 were ciprofloxacin susceptible in vitro with an MIC of 0.38 µg/mL. Subgroup analysis was performed on 17 of these isolates. Excluded patients either received diverse antimicrobials (n = 3) or were not assessable (n = 1). Complete response was seen in 80% of imipenem cases compared with 28.5% of ciprofloxacin cases with the remaining of each being nonresponders ($P = .03$).²² This analysis supports the use of carbapenems over fluoroquinolones even when fluoroquinolones are reported as susceptible. It is important to take the limitations of this study into consideration. Despite collecting data on primary site of infection, Charlson comorbidity scores, appropriateness of empiric therapy, or time to antibiotic administration, lack of analysis of these variables make it difficult to determine whether or not other factors contributed to poor outcomes.

A retrospective chart review conducted in an Italian hospital analyzed mortality in patients with bacteremia caused by ESBL-producing *E coli*, *Klebsiella* spp, or *P mirabilis*.

The study included all patients over a 5-year period who had a blood stream infection with one of these bacteria identified. The authors analyzed the association of several factors with mortality including age, gender, Charlson comorbidity index, underlying disease, immunosuppressive therapy, duration of hospitalization, intensive care unit stay at time of infection, and history of previous hospitalization, surgery, invasive procedures, or antibiotic exposure prior to onset of blood stream infection. Further considerations included acquisition setting, presentation, inadequacy of initial treatment, as well as species, drug resistance patterns, and multiplicity of β -lactamase production. Treatment adequacy was determined by time to administration of a susceptible agent after identification of first positive blood culture. If this time exceeded 72 hours, treatment was considered inadequate. Of the 186 patients included in the study, over half had comorbid neoplastic disease. Ninety percent of infections were health care acquired and 60.7% had a history of recent antimicrobial therapy. The most common primary site of infection was the urinary tract. The mortality rate at 21 days was 50% in patients receiving fluoroquinolones as adequate initial treatment.²³ In all nonsurviving fluoroquinolone-treated patients, MICs of isolates ranged from 0.5 to 1 µg/mL, the high end of the susceptibility breakpoint. Half of the organisms isolated from patients who died had a DNA gyrase mutation while the other half contained the *qnrB* gene. Both of these genetic factors have previously been linked with increased MICs.⁸ The authors theorize that higher mortality rates in the fluoroquinolone-treated patients could have been due to inadequate dosing rather than inappropriate drug selection. All patients were on a regimen of intravenous ciprofloxacin 400 mg twice daily. There are data to suggest that higher doses of ciprofloxacin (400 mg 3 times daily) may be a more optimal option for isolates with MICs closer to the intermediate breakpoints, especially in critically ill patients.²⁴ Furthermore, patients with infections originating in the urinary tract were more likely to survive than patients with bacteremias originating from other sites. The authors concluded this could be due to concentration of fluoroquinolones in the urine. Univariate analysis showed that certain infection-related characteristics were risk factors for 21-day odds of mortality including septic shock (odds ratio [OR] = 7.17, $P = .005$), inadequate initial treatment (OR = 6.46, $P < .001$), infection with *K pneumoniae* (OR = 1.84, $P = .05$), multidrug resistance (OR = 4.17, $P < .001$), or multiple β -lactamase-producing bacteria (OR = 1.91, $P = .05$). Infection with *E coli* had lower odds of mortality (OR = 0.53, $P = .04$). Liver disease and previous hospitalization were associated with increased mortality (OR = 2.53, $P = .02$, and OR = 2.33, $P = .005$, respectively). Baseline and infection characteristics were not broken down by treatment option, and it is possible that those treated with fluoroquinolones had more severe disease or were infected with multidrug-resistant or multiple β -lactamase-producing

bacteria. Although mortality rates were reported for inadequate treatment, it was not stratified by drug selected. This greatly limits the conclusions that can be drawn regarding adequacy of fluoroquinolones as empiric therapy. Another limitation of this study is the high percentage of health care-acquired infections, which limits the generalizability to infections contracted in settings outside of health care facilities. Despite noting that a majority of the patient population had neoplastic disease, the data presented did not adequately address whether cause of death was attributable to neoplasm or bacteremia. Data from this study suggest that despite fluoroquinolones being reported as susceptible, their use in ESBL-producing bacteremias was associated with increased mortality.²⁵

Conclusion

There is a high risk of fluoroquinolone resistance in ESBL-producing Gram-negative bacilli. The *qnr* genes, commonly found on ESBL-producing Enterobacteriaceae, have not been linked to outright resistance, but rather confer reduced susceptibility to fluoroquinolones. In such situations, the MIC should be taken into consideration and it may be prudent to use increased doses of fluoroquinolones. For infections at sites such as the urinary tract where ciprofloxacin and levofloxacin concentrate, selection of these agents may be more appropriate. It is important, nevertheless, to consider historical patterns of quinolone use leading to QRDR and the potential for increased resistance with continued use. Data regarding the use of fluoroquinolones, when reported as susceptible, in the treatment of ESBL-producing organisms have conflicting results. Prospective studies of fluoroquinolone use in ESBL-producing bacteria are necessary to establish a role for these agents as an alternative to carbapenem antibiotics.

Declaration of Conflicting Interests

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References

1. 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.
2. Wang P, Hu F, Xiong Z, et al. Susceptibility of extended-spectrum-beta-lactamase-producing Enterobacteriaceae according to the new CLSI breakpoints. *J Clin Microbiol*. 2011;49:3127-3131. doi:10.1128/JCM.00222-11.
3. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. *Antimicrob Agents Chemother*. 2010;54:969-976. doi:10.1128/AAC.01009-09.
4. Kuper KM, Boles DM, Mohr JF, Wanger A. Antimicrobial susceptibility testing: a primer for clinicians. *Pharmacotherapy*. 2009;29:1326-1343. doi:10.1592/phco.29.11.1326.
5. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing* (Twentieth Informational Supplement; M100-S20). Wayne, PA: Clinical and Laboratory Standards; 2010.
6. Dudley MN, Ambrose PG, Bhavnani SM, Craig WA, Ferraro MJ, Jones RN. Background and rationale for revised clinical and laboratory standards institute interpretive criteria (breakpoints) for Enterobacteriaceae and *Pseudomonas aeruginosa*: I. Cephalosporins and aztreonam. *Clin Infect Dis*. 2013;56:1301-1309. doi:10.1093/cid/cit017.
7. Kanj SS, Kanafani ZA. Current concepts in antimicrobial therapy against resistant gram-negative organisms: extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. *Mayo Clin Proc*. 2011;86:250-259. doi:10.4065/mcp.2010.0674.
8. Robicsek A, Jacoby GA, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect Dis*. 2006;6:629-640. doi:10.1016/S1473-3099(06)70599-0.
9. Longhi C, Conte MP, Marazzato M, et al. Plasmid-mediated fluoroquinolone resistance determinants in *Escherichia coli* from community uncomplicated urinary tract infection in an area of high prevalence of quinolone resistance. *Eur J Clin Microbiol Infect Dis*. 2012;31:1917-1921. doi:10.1007/s10096-011-1521-6.
10. Kariuki S, Revathi G, Corkill J, et al. *Escherichia coli* from community-acquired urinary tract infections resistant to fluoroquinolones and extended-spectrum beta-lactams. *J Infect Dev Ctries*. 2007;1:257-262. doi:10.3855/jidc.361.
11. Tolun V, Kucukbasmaci O, Torumkuney-Akbulut D, Catal C, Ang-Kucuker M, Ang O. Relationship between ciprofloxacin resistance and extended-spectrum beta-lactamase production in *Escherichia coli* and *Klebsiella pneumoniae* strains. *Clin Microbiol Infect*. 2004;10:72-75. doi:10.1111/j.1469-0691.2004.00723.x.
12. Al-Marzooq F, Mohd Yusof MY, Tay ST. Molecular analysis of ciprofloxacin resistance mechanisms in Malaysian ESBL-producing *Klebsiella pneumoniae* isolates and development of mismatch amplification mutation assays (MAMA) for rapid detection of *gyrA* and *parC* mutations. *Biomed Res Int*. 2014;2014:601630. doi:10.1155/2014/601630.
13. Crémet L, Caroff N, Dauvergne S, Reynaud A, Lepelletier D, Corvec S. Prevalence of plasmid-mediated quinolone resistance determinants in ESBL Enterobacteriaceae clinical isolates over a 1-year period in a French hospital. *Pathol Biol (Paris)*. 2011;59:151-156. doi:10.1016/j.patbio.2009.04.003.
14. Chong YP, Choi SH, Kim ES, et al. Bloodstream infections caused by *qnr*-positive Enterobacteriaceae: clinical and microbiologic characteristics and outcomes. *Diagn Microbiol Infect Dis*. 2010;67:70-77. doi:10.1016/j.diagmicrobio.2009.12.003.
15. Saely S, Kaye KS, Fairfax MR, Chopra T, Pogue JM. Investigating the impact of the definition of previous antibiotic

- exposure related to isolation of extended spectrum β -lactamase-producing *Klebsiella pneumoniae*. *Am J Infect Control*. 2011;39:390-395. doi:10.1016/j.ajic.2010.08.010.
16. Rossotti R, Orani A. Clinical management of ESBL-producing Enterobacteriaceae: the insidious role of fluoroquinolones. *Eur J Clin Microbiol Infect Dis*. 2012;31:1517-1522. doi:10.1007/s10096-011-1472-y.
 17. 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. doi:10.1086/322667.
 18. Wener KM, Schechner V, Gold HS, Wright SB, Carmeli Y. Treatment with fluoroquinolones or with beta-lactam-beta-lactamase inhibitor combinations is a risk factor for isolation of extended-spectrum-beta-lactamase-producing *Klebsiella* species in hospitalized patients. *Antimicrob Agents Chemother*. 2010;54:2010-2016. doi:10.1128/AAC.01131-09.
 19. Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Clinical and molecular epidemiology of community-onset, extended-spectrum beta-lactamase-producing *Escherichia coli* infections in Thailand: a case-case-control study. *Am J Infect Control*. 2007;35:606-612. doi:10.1016/j.ajic.2007.05.008.
 20. Lee CC, Lee NY, Yan JJ, et al. Bacteremia due to extended-spectrum-beta-lactamase-producing *Enterobacter cloacae*: role of carbapenem therapy. *Antimicrob Agents Chemother*. 2010;54:3551-2556. doi:10.1128/AAC.00055-10.
 21. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to enterobacteriaceae producing extended-spectrum β -lactamases: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2012;67:2793-2803. doi:10.1093/jac/dks301.
 22. Endimiani A, Luzzaro F, Perilli M, 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;38:243-251. doi:10.1086/380645.
 23. Tumbarello M, Sanguinetti M, Montuori E, 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;51:1987-1994. doi:10.1128/AAC.01509-06.
 24. Pea F, Poz D, Viale P, Pavan F, Furlanut M. Which reliable pharmacodynamic breakpoint should be advised for ciprofloxacin monotherapy in the hospital setting? A TDM-based retrospective perspective. *J Antimicrob Chemother*. 2006;58:380-386. doi:10.1093/jac/dkl226.
 25. Chaubey VP, Pitout JD, Dalton B, et al. Clinical outcome of empiric antimicrobial therapy of bacteremia due to extended-spectrum beta-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*. *BMC Res Notes*. 2010;3:116. doi:10.1186/1756-0500-3-116.