Epidemiology of Ciprofloxacin Resistance and Its Relationship to Extended-Spectrum β-Lactamase Production in *Klebsiella pneumoniae* Isolates Causing Bacteremia

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A prospective study of *Klebsiella pneumoniae* bacteremia was performed in 12 hospitals in 7 countries. Of 452 episodes of bacteremia, 25 (5.5%) were caused by *K. pneumoniae* that was resistant in vitro to ciprofloxacin. Extended-spectrum β-lactamase (ESBL) production was detected in 15 (60%) of 25 ciprofloxacin-resistant isolates, compared with 68 (16%) of 427 ciprofloxacin-susceptible strains ($P = .0001$). Multivariate analysis revealed that risk factors for ciprofloxacin resistance in *K. pneumoniae* included prior receipt of a quinolone ($P = .0065$) and an ESBL-producing strain ($P = .012$). In all, 18% of ESBL-producing isolates were also ciprofloxacin-resistant. Pulsed-field gel electrophoresis showed that 11 of the 15 ciprofloxacin-resistant ESBL-producing strains belonged to just 4 genotypes, suggesting that patient-to-patient transmission of such strains occurred. The close relationship between ESBL production and ciprofloxacin resistance is particularly worrisome because the first reported instance of plasmid-mediated ciprofloxacin resistance has been in an isolate of *K. pneumoniae* also possessing an ESBL.

Before the introduction of quinolones, ciprofloxacin resistance in *Klebsiella pneumoniae* and other Enterobacteriaceae, such as *Escherichia coli,* was virtually unknown. However, in the last 10 years, cases of bacteremia with ciprofloxacin-resistant *E. coli* have increased in number, together with upward trends in the use of quinolones in the community and in hospitals [1]. Although the occurrence of ciprofloxacin resistance in *K. pneumoniae* is now well known and, indeed, exceeds 5% in many centers in North America, Europe, and Asia [2–5], to our knowledge, the epidemiology of infections with ciprofloxacin-resistant *K. pneumoniae* has never been previously described.

At the same time as ciprofloxacin resistance has appeared, resistance to β-lactam antibiotics in *K. pneumoniae* has also become prominent. Extended-spectrum β-lactamases (ESBLs) were first described soon after the introduction of third-generation cephalosporins in the early 1980s [6]. ESBLs mediate resistance to newer β-lactam agents possessing an oxyimino group, such as ceftazidime, ceftriaxone, cefotaxime, and aztreonam. In addition, the plasmids that contain genes encoding the ESBLs also harbor the genes that encode mechanisms of resistance to many of the aminoglycosides and trimethoprim-sulfamethoxazole (TMP-SMZ). In many regions of the world, ESBLs are present in ~25% of all *K. pneumoniae* isolates from intensive care units [7], where antibiotic use is high and patient-to-patient transfer of resistant organisms frequently occurs.

Patients and Methods

A prospective study of consecutive patients with community-acquired and nosocomially acquired *K. pneumoniae* bacteremia was performed in 12 hospitals: in Australia, 3; in the United States, 2; in South Africa, 2; in Argentina, 2; in Taiwan, 1; in Turkey, 1; and in Belgium, 1. The study period was from 1 January 1996 to 31 December 1997. Patients aged >16 years, for whom blood cultures were positive for *K. pneumoniae,* were monitored by the investigators. The study was observational because the administration of antimicrobial agents and other therapeutic management was controlled by the patients' physicians and not by the investigators.

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Patients were followed up for 30 days after the onset of bacteremia to assess clinical outcome, including mortality and infectious complications.

Definitions. An episode of bacteremia was defined as the period of 14 days from the time of collection of the first blood culture specimen positive for *K. pneumoniae*. Severity of illness at the time of onset of bacteremia was assessed by use of the Pitt bacteremia score, a previously validated scoring system that is based on mental status, body temperature, blood pressure, requirement of mechanical ventilation, and recent cardiac arrest [8]. Site of infection leading to bacteremia was determined as pneumonia, urinary tract infection, incisional wound infection, intra-abdominal infection, and primary bloodstream infection by use of definitions of the Centers for Disease Control and Prevention [9]. Nosocomial bacteremia was defined as occurring >2 days after admission to the hospital. Mortality was defined as all-cause death within 14 days from the date of the first blood culture positive for *K. pneumoniae*. Prior antibiotic use was defined as receipt of an antibiotic for at least 24 h in the 14 days before the first positive blood culture. Therapeutic antibiotics were defined as antibiotics given for at least 48 h in the first 5 days after the first positive blood culture.

Microbiology. Susceptibility of *K. pneumoniae* isolates from blood cultures to ciprofloxacin was determined at each study site by disk diffusion, according to guidelines of the National Committee for Clinical Laboratory Standards [10], or by semiautomated broth microdilution methods (VITEK; bioMérieux Vitek, Hazelwood, MO; and MicroScan; Dade Microscan, West Sacramento, CA). Isolates were then sent to a central study laboratory in Pittsburgh. There, the identity of each isolate as *K. pneumoniae* was confirmed. The MIC of ciprofloxacin was determined by the Etest (AB BIODISK, Solna, Sweden) for each isolate that was found to be intermediately resistant or resistant to ciprofloxacin at the referring laboratory. Ciprofloxacin resistance was defined as an MIC $\geq$4 μg/mL, and ciprofloxacin susceptibility was defined as an MIC $\leq$1 μg/mL [11].

In the central laboratory, ESBL production was phenotypically determined by broth dilution testing according to new guidelines of the National Committee for Clinical Laboratory Standards [11]. In brief, *K. pneumoniae* isolates for which ceftazidime or cefotaxime MICs were $\geq$2 μg/mL were considered suspicious for harboring ESBLs. The MICs for these suspicious isolates were then retested with cefotaxime alone, ceftazidime alone, cefotaxime in combination with 4 μg of clavulanic acid/mL, and ceftazidime in combination with 4 μg of clavulanic acid/mL. A decrease of >8-fold in the MIC of either antimicrobial agent tested in combination with clavulanic acid versus the MIC of either agent when tested alone was considered as phenotypic confirmation of ESBL production.

Other laboratory studies. Ciprofloxacin-resistant ESBL-producing strains of *K. pneumoniae* were subject to pulsed-field gel electrophoresis (PFGE). PFGE was performed by means of the CHEF-DR II system (Bio-Rad, Richmond, CA) with use of the restriction endonuclease *Xba 1* (New England Biolabs, Beverly, MA). DNA was electrophoresed for 22 h at 14°C in a 1% agarose gel at 6 V/cm with a linear gradient pulse time of 5–35 s. Interpretation of PFGE patterns was based on the criteria of Tenover et al. [12].

Initial characterization of the β-lactamases was performed by isoelectric focusing with use of precast gels (Ampholine PAGplate; Pharmacia, Uppsala, Sweden). Gels in which the pH range was 3.5–9.5 were used during initial screening. Isolates with previously characterized β-lactamases (kindly provided by P. Bradford, Wyeth-Ayerst Research, Pearl River, NY) were used as controls. The of β-lactamases of test isolates were further characterized by use of precast gels in which the pH ranges were 4–6.5 and 5.5–8.5, respectively. Running conditions were 2000 V, 30 mA, and a constant power of 8 W. β-lactamase detection was performed by overlaying the gel with a 100-μM solution of nitrocefin (Becton Dickinson, Cockeysville, MD). The isoelectric points of the β-lactamases were determined by comparing the positions of their bands with those of bands for previously characterized controls. Sequencing of selected genes was performed according to previously reported methods [13].

Statistics. Data were entered into a central database (PROPHET Version 5.1; BBN Systems and Technologies, Cambridge, MA). Contingency data were analyzed by the two-tailed χ^2 test or Fisher's exact test, and continuous data were analyzed by use of the Student *t* test or Mann-Whitney *U* test. Multivariate analysis was utilized to determine which risk factors demonstrated by univariate analysis were independently significant.

Results

There were 455 episodes of *K. pneumoniae* bacteremia in 440 patients. Three episodes were excluded (2 because of intermediate resistance to ciprofloxacin and 1 because the organism was nonviable at the time of arrival at the central laboratory); thus, 452 episodes of *K. pneumoniae* bacteremia were included in this analysis. The isolates with intermediate resistance to ciprofloxacin were excluded to clearly delineate epidemiological differences between patients with infections caused by ciprofloxacin-susceptible and ciprofloxacin-resistant organisms. Of the 452 episodes of bacteremia, 25 (5.5%) were due to ciprofloxacin-resistant *K. pneumoniae,* and 427 (94.5%) were due to ciprofloxacin-susceptible *K. pneumoniae.* Of 25 cases of bacteremia due to ciprofloxacin-resistant *K. pneumoniae,* 18 (72%) were nosocomially acquired versus 232 (54%) of 427 cases of bacteremia due to ciprofloxacin-susceptible *K. pneumoniae* (P = .08).

The MICs of ciprofloxacin for ciprofloxacin-resistant isolates were as follows: 4 μg/mL, 7 cases (28%); 8 μg/mL, 3 (12%); 16 μg/mL, 2 (8%); 32 μg/mL, 1 (4%); and >32 μg/mL, 12 (48%).

Ciprofloxacin resistance was statistically significantly most common in *K. pneumoniae* from Turkey (5 [42%] of 12 cases were due to ciprofloxacin-resistant isolates; P = .0002) or Argentina (6 [15%] of 41 cases were due to ciprofloxacin-resistant isolates; P = .018). Five (9%) of 56 blood culture isolates from the United States and 9 (6%) of 142 isolates from Taiwan were ciprofloxacin-resistant. In contrast, no cases of bacteremia due to ciprofloxacin-resistant *K. pneumoniae* were detected in the centers in South Africa (115 episodes of *K. pneumoniae* bacteremia), Australia (71), or Belgium (15).

Sites of infection associated with the 25 cases of bacteremia with ciprofloxacin-resistant *K. pneumoniae* included urinary

Table 1. Risk factors for bacteremia due to *Klebsiella pneumoniae* with reduced susceptibility to ciprofloxacin.

Factor	Patients with bacteremia due to: Cpfx-Res *K. pneumoniae* (n = 25)	Cpfx-Sus *K. pneumoniae* (n = 427)	P
Median age, y	63	57	NS (.17)
Female	7 (28)	166 (39)	NS
Nosocomial bacteremia	18 (72)	232 (54)	NS (.08)
Median time to bacteremia, d[a]	23	24	NS
Transfer from nursing home	2 (8)	11 (3)	NS (.16)
In intensive care unit	4 (16)	66 (15)	NS
Diabetes mellitus	6 (24)	96 (22)	NS
Chronic liver disease	8 (32)	80 (29)	NS (.10)
Chronic renal failure	2 (8)	28 (7)	NS
Malignancy	9 (36)	130 (30)	NS
Transplantation	3 (12)	17 (4)	NS (.06)
Neutropenic[b]	2 (8)	50 (12)	NS
Indwelling urinary catheter	16 (64)	162 (38)	.0095
Mechanical ventilation	4 (16)	87 (20)	NS

NOTE. Data are no. (%) of case patients, except as indicated. Cpfx-Res, ciprofloxacin-resistant; Cpfx-Sus, ciprofloxacin-susceptible; NS, not significant.

[a] From admission; nosocomial cases only.

[b] At time blood culture specimen obtained.

tract infection (8 cases [32%]), pneumonia (7 [28%]), vascular catheter infections (3 [12%]), intra-abdominal infections (3 [12%]), and others (4 [16%]). The sites of infection associated with bacteremia due to ciprofloxacin-resistant or ciprofloxacin-susceptible *K. pneumoniae* were not statistically significantly different, although urinary tract infections were less likely to be associated with bacteremia due to ciprofloxacin-susceptible *K. pneumoniae* (74 [17%] of 427 cases; P = .10).

The sites of infection associated with community-acquired bacteremia due to ciprofloxacin-resistant *K. pneumoniae* were urinary tract infections (3 cases), pneumonia (3), and cholangitis (1). Five of the 7 cases of community-acquired bacteremia due to ciprofloxacin-resistant *K. pneumoniae* occurred in Taiwan. None of the 7 patients with community-acquired bacteremia due to ciprofloxacin-resistant *K. pneumoniae* had received a quinolone in the 14 days preceding their infections. Two patients resided in nursing homes (both of whom developed pneumonia). Every patient with community-acquired infection had a significant underlying disease, including renal transplantation (2 patients), advanced cervical cancer (1), cirrhosis and diabetes mellitus (1), diabetes mellitus alone (2), and cerebrovascular accident (1).

Risk factors for bacteremia with ciprofloxacin-resistant *K. pneumoniae* are described in tables 1 and 2. Univariate analysis revealed a statistically significant relationship between bacteremia with ciprofloxacin-resistant *K. pneumoniae* and an indwelling urinary catheter (P = .0095), receipt of a quinolone in the 2 weeks before the onset of *K. pneumoniae* bacteremia (P = .0008), and receipt of a third-generation cephalosporin in the 2 weeks before *K. pneumoniae* bacteremia (P = .006). There were nonsignificant trends between bacteremia due to ciprofloxacin-resistant *K. pneumoniae* and transplantation (P = .06) and chronic liver disease (P = .10). Neutropenia was not a risk factor for bacteremia due to ciprofloxacin-resistant *K. pneumoniae* (P = .57). No patient with chronic liver disease or neutropenia who developed bacteremia with ciprofloxacin-resistant *K. pneumoniae* had been receiving quinolone prophylaxis for infection at the time of bacteremia.

ESBL production was detected in 15 (60%) of the 25 ciprofloxacin-resistant *K. pneumoniae* isolates. In comparison, only 68 (16%) of the 427 ciprofloxacin-susceptible *K. pneumoniae* isolates were ESBL producers (P = .0001). Fourteen (78%) of the 18 ciprofloxacin-resistant *K. pneumoniae* isolates that caused nosocomial bacteremia were ESBL producers, compared with 1 (14%) of 7 of these isolates that caused community-acquired bacteremia (P = .003).

Multivariate analysis of predictors of ciprofloxacin resistance in *K. pneumoniae* was performed. Prior receipt of a quinolone (P = .0065), an ESBL-producing strain (P = .012), and hospitalization in a Turkish center (P = .011) were predictors of ciprofloxacin resistance, but receipt of a third-generation cephalosporin (P = .17) and an indwelling urinary catheter (P = .24) were not.

Globally, 15 (18%) of 83 ESBL-producing organisms were also ciprofloxacin-resistant. The proportions of ESBL producers that were also ciprofloxacin-resistant were as follows: 56% (5/9) in Turkey, 33% (4/12) in the United States, 33% (1/3) in Taiwan, and 25% (5/20) in Argentina. No cases of ciprofloxacin resistance in ESBL producers were found in Africa (30 total ESBL producers), Australia (6), or Belgium (3).

All ESBL-producing *K. pneumoniae* isolates that were ciprofloxacin-resistant possessed multiple β-lactamases. Eight isolates possessed 1 SHV enzyme and 1 TEM enzyme; 1 had 2 SHV enzymes; 3 had 2 SHV enzymes and 1 TEM enzyme; and 3 had 1 TEM enzyme and the CTX-M2 β-lactamase.

PFGE revealed that there were 4 clusters of bacteremia due to genetically related ciprofloxacin-resistant ESBL-producing

Table 2. Relationship between ciprofloxacin resistance and antibiotic use in the 2 weeks before *Klebsiella pneumoniae* bacteremia.

Antibiotic	No. (%) of patients with bacteremia due to: Cpfx-Res *K. pneumoniae* (n = 25)	Cpfx-Sus *K. pneumoniae* (n = 427)	P
Any antibiotic	14 (56)	173 (41)	NS (.13)
Quinolone	6 (24)	17 (4)	.0008
Third-generation Csp	6 (24)	27 (6)	.006
Any Csp	6 (24)	55 (13)	NS (.11)
Penicillin	3 (12)	48 (11)	NS
β-lactamase inhibitor	1 (4)	35 (8)	NS
Carbapenem	1 (4)	20 (5)	NS
Aminoglycoside	1 (4)	55 (13)	NS
Macrolide	0	3 (1)	NS
TMP-SMZ	1 (4)	12 (3)	NS
Clindamycin	0	10 (2)	NS
Metronidazole	1 (4)	32 (7)	NS

NOTE. Cpfx-Res, ciprofloxacin-resistant; Cpfx-Sus, ciprofloxacin-susceptible; Csp, cephalosporin; TMP-SMZ, trimethoprim-sulfamethoxazole.

Table 3. Genetically related clusters of bacteremia due to quinolone-resistant, extended-spectrum β-lactamase–producing *Klebsiella pneumoniae.*

Cluster	Hospital	Dates of bacteremia
A	Argentina 1	10/21/97,[a] 11/24/97
B	Turkey	6/12/96, 8/16/96, 4/24/97[a]
C	Turkey	12/12/97,[a] 12/24/97
D	United States 1	7/7/96, 7/31/96, 8/16/96, 10/12/96

[a] Patient had received a fluoroquinolone antibiotic in the 2 weeks before onset of *K. pneumoniae* bacteremia.

organisms in 3 hospitals. The dates of bacteremia and prior receipt of quinolones are detailed in table 3. There were an additional 3 isolates, which were genotypically unrelated, in 2 hospitals in Argentina. None of the patients from whom these isolates were recovered had received quinolones in the 2 weeks before bacteremia. A single patient from Taiwan, who had not received quinolones, was infected with a ciprofloxacin-resistant ESBL-producing organism.

Patients with bacteremia due to ciprofloxacin-resistant ESBL-producing *K. pneumoniae* were more likely to reside in Turkey ($P = .0082$) and to have underlying chronic liver disease ($P = .0015$), lower median platelet counts ($P = .002$), and higher blood urea nitrogen levels ($P = .046$) than were patients infected with ciprofloxacin-susceptible ESBL-producing *K. pneumoniae*. There was no increased receipt of quinolones, third-generation cephalosporins, or other antibiotic classes in patients infected with ciprofloxacin-resistant ESBL producers versus patients infected with ciprofloxacin-susceptible ESBL producers ($P > .20$ for all comparisons). Multivariate analysis revealed that ciprofloxacin resistance, together with ESBL production in *K. pneumoniae,* was statistically significantly associated with residing in Turkey ($P = .002$) and having underlying liver disease ($P = .009$) but not with a low platelet count ($P = .12$) or a higher blood urea nitrogen level ($P = .10$).

Two patients with bacteremia due to ciprofloxacin-resistant *K. pneumoniae* were treated empirically with ciprofloxacin, and 1 patient was treated empirically with ofloxacin. The first patient, a 71-year-old man from Taiwan who had cholangiocarcinoma, had been receiving pefloxacin as prophylaxis for cholangitis. He received ciprofloxacin empirically when bacteremic cholangitis (due to *K. pneumoniae* for which the ciprofloxacin MIC was >32 μg/mL) developed, and he died of the infection. A 37-year-old recipient of a kidney-pancreas transplant developed bacteremic urinary tract infection with *K. pneumoniae* (ciprofloxacin MIC, 8 μg/mL) and was empirically treated with ciprofloxacin for 3 days. Clinical manifestations of infection continued; he was cured after his treatment was switched to TMP-SMZ. A 70-year-old patient with vascular catheter–related *K. pneumoniae* bacteremia was treated with ofloxacin (ciprofloxacin MIC, >32 μg/mL; ofloxacin MIC, >32 μg/mL) for 4 days. The vascular catheter was removed on the day of bacteremia, and he was cured without changing antibiotic therapy. Overall, the 14-day mortality rate among patients with bacteremia due to ciprofloxacin-resistant *K. pneumoniae* was 16% (4/25) versus 28% (120/427) among patients with bacteremia due to ciprofloxacin-susceptible *K. pneumoniae* ($P = .19$).

Discussion

We found ciprofloxacin resistance in 25 (5.5%) of 452 cases of *K. pneumoniae* bacteremia. There were marked geographic differences in the occurrence of ciprofloxacin resistance: resistance rates were at least 6% in Turkey, Argentina, the United States, and Taiwan, whereas no resistance was found in isolates from Belgium, Australia, or South Africa. When previously reported rates of ciprofloxacin resistance in disparate geographic sites are reviewed (table 4), it can be noted that rates of ciprofloxacin resistance in *K. pneumoniae* strains from parts of Europe, North America, and Asia have been ~6% over the last 6 years. The extent of ciprofloxacin resistance in Turkey and South America has not previously been reported. Our study included 1 hospital in Turkey and 2 hospitals in Argentina; therefore, our findings of high rates of ciprofloxacin resistance in these areas need to be confirmed in larger samples from other centers in these countries.

Not surprisingly, prior receipt of a quinolone was a significant risk factor for development of bacteremia due to ciprofloxacin-resistant *K. pneumoniae.* In antibiotic susceptibility studies for *K. pneumoniae* isolates obtained before the release of ciprofloxacin, no ciprofloxacin-resistant strains of *K. pneumoniae* were detected [14]. In studies of the epidemiology of ciprofloxacin-resistant *E. coli,* it was noted that as quinolone use increased both in the community and in the hospital, the number of cases of bacteremia with ciprofloxacin-resistant *E. coli* also increased [1]. A similar finding was made for ciprofloxacin-resistant *E. coli* from urinary tract samples [17]. We hypothesize that as use of the newer quinolones (levofloxacin, trovafloxacin, gatifloxacin, moxifloxacin, etc.) increases for in-

Table 4. Data from previous reports on the geographic spread of ciprofloxacin resistance in *Klebsiella pneumoniae.*

Reference	Year(s) of survey	Country	% Cpfx-Res *K. pneumoniae* isolates
[4]	1993	Germany	0.8
[5]	1993	New Zealand	1.2
[14]	1990–1995	Canada	2
[5]	1993	Japan	2
[5]	1993	Australia	3.5
[4]	1995	United Kingdom	4
[5]	1993	Korea	5
[2]	1993–1994	Canada	5
[15]	1992	Spain	
[16]	1995–1998	United States	5.7
[4]	1993	France and Italy	6
[3]	1993–1994	United States	6.3
[5]	1993	Singapore	7
[5]	1993	China	7.4
[5]	1993	Thailand	8
[5]	1993	Philippines	12.6

NOTE. Cpfx-Res, ciprofloxacin-resistant.

dications such as respiratory tract infections, the rate of ciprofloxacin resistance in *K. pneumoniae* and *E. coli* will also increase. It should be noted that the newer quinolones are generally less active in vitro than is ciprofloxacin against wild type *K. pneumoniae* and that cross-resistance between the quinolones occurs in most cases [18].

Quinolones find widespread use as prophylaxis for spontaneous bacterial peritonitis (in patients with cirrhosis) and for bacteremia due to gram-negative organisms (in patients with neutropenia). Despite this use, we did not find any patient with bacteremia due to ciprofloxacin-resistant *K. pneumoniae* who had been receiving quinolone prophylaxis for these indications. In contrast, there have been several reports of ciprofloxacin-resistant *E. coli* bacteremia in patients receiving quinolone prophylaxis [19–22]. In one of these studies, >90% of *E. coli* isolates from patients with leukemia were ciprofloxacin-resistant [22]. The investigators did not comment on rates of resistance in *K. pneumoniae* isolates from this same patient population.

Ciprofloxacin resistance in *K. pneumoniae* is closely associated with ESBLs. This association is of grave concern since ESBL-producing isolates are usually resistant to penicillins, cephalosporins, aminoglycosides, and TMP-SMZ. Therefore, ciprofloxacin resistance severely limits already restricted treatment options. We found evidence of ESBL production by 60% of the *K. pneumoniae* isolates that were ciprofloxacin-resistant. Indeed, 78% of ciprofloxacin-resistant *K. pneumoniae* isolates that caused nosocomial bacteremia were ESBL producers. In total, 18% of ESBL-producing *K. pneumoniae* isolates were ciprofloxacin-resistant. However, there was significant global diversity in this association. It was most likely in Turkey and the United States, where at least 33% of ESBL producers were ciprofloxacin-resistant.

Our molecular epidemiological study of ciprofloxacin-resistant ESBL-producing *K. pneumoniae* showed that clusters of infections with genotypically similar organisms occurred. In 2 clusters, the first patient in the cluster to develop bacteremia had received a quinolone before development of bacteremia. The implication of this finding is that the relationship between ciprofloxacin resistance and ESBL production in some cases may be due to the interplay between prior heavy antibiotic use and conditions favoring patient-to-patient transfer of multidrug-resistant organisms.

A further possible explanation for the coexistence of the 2 resistance mechanisms is transfer on the same plasmid. Ciprofloxacin resistance in *K. pneumoniae* and *E. coli* is predominantly due to chromosomal mutations in the genes gyrA and parC, which code for the targets of quinolone activity [23–25]. However, the first study of plasmid-mediated ciprofloxacin resistance has recently been reported [26]. Of particular concern is that the plasmid also contained an ESBL and came from an isolate of *K. pneumoniae!* The plasmid provided only low-level ciprofloxacin resistance. However, it facilitated high-level resistance when the organism possessed other properties such as porin deficiencies. The basis for ciprofloxacin resistance provided by this plasmid has not yet been fully explained. There are other potential explanations for the association between resistance to third-generation cephalosporins and quinolones, including active efflux and outer membrane protein alterations. We are currently attempting to elucidate the mechanism of resistance to ciprofloxacin in our strains of ESBL-producing *K. pneumoniae*.

In summary, both ciprofloxacin resistance and ESBL production in *K. pneumoniae* isolates causing bacteremia are geographically widespread. Continued worldwide surveillance of *K. pneumoniae* isolates is necessary to provide information on the dissemination of these important limitations to the use of commonly used antibiotics.

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