Ceftazidime-Resistant *Klebsiella pneumoniae* and *Escherichia coli* Bloodstream Infection: A Case-Control and Molecular Epidemiologic Investigation

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In a molecular, microbiologic, and case-control study to describe the epidemiology of ceftazidime-resistant *Klebsiella pneumoniae* and *Escherichia coli* bloodstream infection, 32 unique isolates were recovered over 31 months from the blood of patients hospitalized in a 900-bed hospital in Chicago. Multivariate analysis revealed cases occurred more frequently in debilitated nursing home patients with central venous catheters than in younger, healthier patients. Mortality rates were similar for cases and controls. Case-patients were less likely to die if they received appropriate antibiotic treatment within 3 days of bacteremia onset ($P = 0.02$). Pulsed-field gel electrophoresis analysis indicated a polyclonal outbreak, with strain-specific temporal and geographic clustering. Isoelectric focusing results suggested that a predominant enzyme, TEM-10, was responsible for the ceftazidime resistance. The resistance gene was usually carried on a large conjugative plasmid. The polyclonality of the resistant strains suggests that ceftazidime resistance due to TEM-10 is now endemic in Chicago.

Nearly a decade after their initial description in 1987, extended-spectrum $\beta$-lactamase–producing strains of *Klebsiella pneumoniae* and *Escherichia coli* resistant to the oximino $\beta$-lactams continue to cause serious infections [1–21]. Outbreaks have been reported recently from pediatric and geriatric hospitals in France, from a cancer ward in California, from a large private hospital in Flushing, New York, and from hospitalized nursing home patients in Chicago and New York [22–29]. Isolates have been recovered from patients with urinary tract infections, pneumonia, meningitis, and bacteraemia. However, epidemiologic descriptions of extended-spectrum $\beta$-lactamase–producing *K. pneumoniae* and *E. coli* isolated from the bloodstream are limited [30]. In this report, we describe the molecular and clinical epidemiology of ceftazidime-resistant *K. pneumoniae* and *E. coli* bacteraemia at a single hospital between 1992 and 1994.

Materials and Methods

**Microbiologic Analysis**

_Bacterial strains._ Thirty-seven unique bloodstream isolates of *K. pneumoniae* and *E. coli* with increased resistance to ceftazidime were identified by the Clinical Microbiology Laboratory at Rush-Presbyterian-St. Luke’s Medical Center between April 1992 and November 1994 using Microscan Negative Combo-2 panels (Microscan, West Sacramento, CA) according to the manufacturer’s instructions. Thirty-two isolates, 11 *E. coli* and 21 *K. pneumoniae*, were recovered for further testing.

_Nalidixic acid–resistant E. coli C600* [31] and streptomycin-resistant *E. coli C600* [32] were used as plasmid-free recipients in mating experiments. The TEM-10–expressing *K. pneumoniae* strain KC2 with a 54-kb plasmid (pJPQ100) [33], an *E. coli* transconjugant carrying pJPQ100 [33], and 4 *E. coli* strains with known plasmids of 104, 66, 54, and 34 kb [34–36] were used as reference strains for $\beta$-lactamase and plasmid studies.

_Antibiotic susceptibility testing._ Susceptibilities to the following antibiotics were determined by Microscan Negative Combo-2 panels: ampicillin, piperacillin, ceftazidime, cefotaxime, aztreonam, trimethoprim-sulfamethoxazole, ciprofloxacin, tobramycin, amikacin, and imipenem. Results of selected antibiotics were confirmed and piperacillin-tazobactam MICs determined for all bloodstream isolates by a microdilution method according to National Committee for Clinical Laboratory Standards guidelines [37]. Antibiotics were supplied as follows: aztreonam, Bristol-Myers Squibb (Princeton, NJ); ceftazidime, Glaxo Group Research (Greenford, UK); cefotaxime, Hoechst-Roussel Pharmaceuticals (North Somerville, NJ); cefoxitin, Merek (Rahway, NJ); ciprofloxacin, Miles Pharmaceuticals (West Haven, CT); imipenem, Merck Sharpe & Dohme (West Point, PA); nalidixic acid, Sigma (St. Louis); piperacillin and tazobactam, Lederle Laboratories (Caroline, Puerto Rico); streptomycin, Pfizer (Grotton, CT); tobramycin, Eli Lilly (Indianapolis); and trimethoprim-sulfamethoxazole, Burroughs Wellcome (Research Triangle Park, NC). Piperacillin-tazobactam was tested at a constant concentration of 4 $\mu$g of tazobactam/mL. Standard dilutions of overnight broth cultures were inoculated into microtiter plates to achieve a final inoculum of $5 \times 10^5$ cfu/mL. The MIC was defined as the lowest concentration of antibiotic that inhibited visible growth after 18 h of incubation at 35°C.
Isolates were screened for extended-spectrum β-lactamase production by the double disk diffusion test [8]. Enhancement of the inhibitory zone between a clavulanate-impregnated disk (Augmentin: 20 µg of amoxicillin, 10 µg of clavulanate) and a disk impregnated with ceftazidime (30 µg), cefotaxime (30 µg), aztreonam (30 µg), or cefoxitin (30 µg) placed 20 or 30 mm apart (center to center) was interpreted as indicating the presence of an extended-spectrum β-lactamase. A previous study of 103 ceftazidime-susceptible and ceftazidime-resistant K. pneumoniae and E. coli bloodstream isolates from our institution showed complete concordance between ceftazidime susceptibility by Microscan and the results of the double disk diffusion test [38].

β-lactamase analysis. Crude cell-free bacterial extracts were prepared by sonication [39], and analytical isoelectric focusing (IEF) was done by the method of Matthew et al. [40] using a Hoefer Isobox and commercial LKB Ampholine PAG plates (pH range, 3.5–9.5). Gels were stained with the chromogenic cephalosporin nitrocefin (BBL, Hunt Valley, MD). Strains known to express a TEM-10 β-lactamase (pI = 5.6) were focused in parallel with the extracts.

Plasmid analysis. Plasmid DNA from K. pneumoniae and E. coli was extracted by the alkaline lysis method of Birnboim and Doly [41], analyzed by electrophoresis in 0.6% agarose gels, stained with ethidium bromide, and visualized with UV light. Plasmid markers of known molecular size were run in parallel with test extracts. Plasmid size was estimated by comparison with these markers.

Conjugation experiments. Tests for transfer of resistance were carried out in tryptic soy broth as described [31]. Transconjugants were selected on tryptic soy agar plates containing 10 µg/mL ceftazidime and 20 µg/mL nalidixic acid or 10 µg/mL streptomycin. Extended-spectrum β-lactamase production was confirmed in the transconjugants by the double disk diffusion test.

Pulsed-field gel electrophoresis (PFGE). Total genomic DNA was prepared as described [42]. DNA was digested with the restriction enzyme XbaI (Life Technologies GHBCO BRL, Gaithersburg, MD), and fragments were separated in a 1.2% agarose–0.5× TRIS-borate-EDTA–0.05% ethidium bromide gel using a CHEF-DRII apparatus (Bio-Rad, Richmond, CA). The pulse time was ramped from 5 to 35 s for 30 h at 200 V. Gels were illuminated with UV light and photographed. Strain types were considered unique if there was more than a three-band difference between their patterns [43].

Case-Control Study

Charts from 31 of 32 infected patients were available for review. Cases were matched with controls who had been bacteremic with ceftazidime-susceptible K. pneumoniae (n = 21) or E. coli (n = 10); matching was based on species and the closest date to isolation of a ceftazidime-resistant organism. Most controls had been bacteremic within 7–30 days of the corresponding case-patient. Demographic and clinical data collected from each chart included age, sex, ward, diagnosis, APACHE-II score, prior antibiotic administration, immune status (immunosuppressive medication or underlying immune dysfunction), and instrumentation. Antibiotic therapy during the 14 days preceding the bacteremic event was recorded, including outpatient therapy, except for 3 cases. Primary and secondary bloodstream infections were defined according to the 1988 Centers for Disease Control definitions [44]. Bacteremia was defined as secondary if a compatible primary site of infection was identified. Bacteremia was defined as community-acquired if positive blood cultures were obtained within the first 48 h of hospitalization and hospital-acquired if blood cultures obtained after 48 h of hospitalization were the first that yielded bacteria. Appropriate therapy was defined as administration for >1 day of an antibiotic to which the isolate was susceptible within 3 days of identification of bacteremia. Inappropriate therapy was defined as treatment with an antibiotic to which the isolate demonstrated in vitro resistance or treatment with an antibiotic to which the isolate was susceptible for <1 day. Patient follow-up continued for 28 days after the bacteremic event.

Statistical Analysis

Patient characteristics and outcome measures for cases and controls were compared by univariate analysis using the χ² or Fisher’s exact tests for categorical variables and Student’s t test for continuous variables. A two-tailed P < .05 was considered statistically significant. Multivariate analysis of the risk factors to determine the independence of the variables was done using SPSS for MS Windows software (release 6.0; SPSS, Chicago). Stepwise logistic regression models determined significant predictors and interactions. Final models included variables significant at a two-tailed P < .05 and their interactions [45].

Results

Prevalence of Extended-Spectrum β-Lactamase-Producing Strains of E. coli and K. pneumoniae

At Rush-Presbyterian-St. Luke’s Medical Center in Chicago, an increase in ceftazidime-resistant K. pneumoniae and E. coli bloodstream isolates was noted from 1986 to 1993 (figure 1). In 1986, no ceftazidime resistance was detected in bloodstream isolates of K. pneumoniae. By 1993, 27% of these isolates were resistant to ceftazidime. The percentage of ceftazidime-resistant E. coli bloodstream isolates remained at a stable level, between 5% and 8%, during this time.

Case-Control Study

Demographic and clinical characteristics for cases and controls are given in table 1. Bacteremia was community-acquired in 15 of 31 cases; 10 of them were nursing home residents, while 6 of the 16 with hospital-acquired bacteremia were nursing home residents. Factors associated with ceftazidime-resistant K. pneumoniae or E. coli bacteremia in univariate analysis included residence in a nursing home before admission; the presence of a device such as a Foley catheter, gastrostomy or jejunostomy tube, or central venous access catheter; a high APACHE-II score; and previous antibiotic use. Of the 20 case-patients who received antibiotics in the month preceding bacteremia, 11 received ceftazidime or aztreonam.
Figure 1. Percentage of ceftazidime-resistant *K. pneumoniae* and *E. coli* bloodstream isolates from 1986 to 1993. Hatched markings on abscissa indicate no data available for time period between 1986 and 1991. *n* = total number of ceftazidime-resistant *E. coli* or *K. pneumoniae* isolates recovered from bloodstream of patients hospitalized at Rush-Presbyterian-St. Luke's Medical Center for designated year.

Table 1. Univariate analysis of patient clinical characteristics and risk factors for bloodstream infection with ceftazidime-resistant versus ceftazidime-susceptible *K. pneumoniae* and *E. coli*.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ceftazidime sensitivity</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Resistant (<em>n</em> = 31)</td>
<td>Susceptible (<em>n</em> = 31)</td>
<td><em>P</em></td>
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<tr>
<td></td>
<td>66 ± 24.4</td>
<td>77 ± 58.4</td>
<td>.17</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (39)</td>
<td>16 (52)</td>
<td>.44</td>
</tr>
<tr>
<td><strong>Community-acquired bacteremia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (48)</td>
<td>23 (74)</td>
<td>.07</td>
</tr>
<tr>
<td><strong>Nursing home resident</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (52)</td>
<td>3 (10)</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Housed in an intensive care unit</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>16 (52)</td>
<td>10 (32)</td>
<td>.20</td>
</tr>
<tr>
<td><strong>APACHE-II score</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>21.8 ± 6.77</td>
<td>13.1 ± 5.18</td>
<td>&lt;.001</td>
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<tr>
<td><strong>Immunosuppressed</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>10 (32)</td>
<td>15 (48)</td>
<td>.30</td>
</tr>
<tr>
<td><strong>Instrumentation</strong></td>
<td></td>
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<tr>
<td>Foley catheter</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>25 (81)</td>
<td>5 (16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gastrostomy or jejunostomy tube</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>14 (45)</td>
<td>1 (3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (87)</td>
<td>11 (36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (64)</td>
<td>8 (26)</td>
<td>.001</td>
</tr>
<tr>
<td>Ceftazidime or aztreonam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (36)</td>
<td>0</td>
<td>.009</td>
</tr>
<tr>
<td>Bacteremic source urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 (45)</td>
<td>8 (26)</td>
<td>.19</td>
</tr>
</tbody>
</table>

NOTE. Age and APACHE-II scores are expressed as mean ± SD. Other values are expressed as no. (%).

* No. of *E. coli* (10) and *K. pneumoniae* (21) was the same for cases and controls.

* Not included were 3 case patients with unknown prior treatment status.
In multivariate analysis, the most significant risk factor for ceftazidime-resistant \textit{K. pneumoniae} or \textit{E. coli} bacteremia was the presence of a central venous access catheter. Logistic regression analysis to determine the interaction between the presence of a central venous access catheter and other variables was done. In the subset analysis of patients who had central venous catheters, residence in a nursing home was the most predictive of bloodstream infection with ceftazidime-resistant \textit{K. pneumoniae} or \textit{E. coli}. In fact, 7 of the 10 community-acquired cases occurred in patients from nursing homes who had Hickman catheters in place before hospital admission. In the subset analysis of patients without central venous access catheters, the presence of a Foley catheter and other variables suggested that these isolates also produced \(\beta\)-lactamases with pIs = 5.6 and 5.4, the latter suggestive of TEM-12 [46]. One \textit{K. pneumoniae} isolate produced \(\beta\)-lactamases with pIs = 5.6 and 5.2, and 1 \textit{E. coli} isolate produced \(\beta\)-lactamases with pIs = 5.6 and 5.4, the latter suggestive of TEM-1 [47, 48].

No commonality with regard to underlying disease, admitting diagnosis, or primary physician caring for the cases was noted. Five cases with community-acquired bacteremia (3 \textit{E. coli} and 2 \textit{K. pneumoniae}) were from a single nursing home, and 16 cases with hospital-acquired bacteremia (12 \textit{K. pneumoniae} and 4 \textit{E. coli}) were housed in a single intensive care unit. No clustering of controls was noted.

Initial therapy for bacteremia included ceftazidime or aztreonam in 17 of 31 cases. Of the 19 case-patients who received appropriate therapy within 3 days of bacteremia onset, 1 died of sepsis. Twelve case-patients received inappropriate therapy and 5 died of sepsis (\(P = .02\)). There was no significant difference between the mean APACHE-II scores for the appropriately versus inappropriately treated cases (21.4 vs. 22.6, \(P = .64\)). All 31 controls were treated appropriately and 6 died. Therefore, overall mortality was slightly lower for the appropriately treated cases than controls (1/19 vs. 6/31). The length of hospital stay after onset of the bacteremia was not significantly different between cases and controls; however, the total length of hospital stay (41.9 vs. 15.9 days, \(P = .001\)) and mean APACHE-II scores (21.8 vs. 13.1, \(P < .001\)) were significantly higher for patients with ceftazidime-resistant \textit{K. pneumoniae} or \textit{E. coli} bacteremia than for controls.

**Microbiologic Analysis**

**Antibiotic susceptibility testing.** All \textit{K. pneumoniae} and \textit{E. coli} bloodstream isolates demonstrated increased resistance to ceftazidime (MIC \(\geqslant 8 \mu g/mL\)) and were resistant to ampicillin and piperacillin. All isolates were positive by double disk diffusion testing, indicating the presence of an extended-spectrum \(\beta\)-lactamase. Two \textit{E. coli} isolates had ceftazidime MICs of 8 \(\mu g/mL\). Eight of 21 \textit{K. pneumoniae} and 3 of 11 \textit{E. coli} isolates were resistant to cefotaxime. Cefotaxime MICs ranged from \(\leqslant 0.125\) to 128 \(\mu g/mL\). Most isolates were resistant to aztreonam (21/21 \textit{K. pneumoniae}, 9/11 \textit{E. coli}), tobramycin (19/21 \textit{K. pneumoniae}, 8/11 \textit{E. coli}), and trimethoprim-sulfamethoxazole (19/21 \textit{K. pneumoniae}, 9/11 \textit{E. coli}). Fifteen of 32 isolates were resistant to ciprofloxacin (MICs \(\geqslant 4 \mu g/mL\)). All isolates were susceptible to imipenem, amikacin, and piperacillin-tazobactum.

**IEF.** Thirty of 32 isolates produced a \(\beta\)-lactamase with pI = 5.6 that comigrated with a previously characterized TEM-10 \(\beta\)-lactamase from \textit{K. pneumoniae} strain KC2 (pJPQ100), suggesting that these isolates also produced TEM-10. Two \textit{E. coli} isolates had a \(\beta\)-lactamase with a single pI = 5.2, suggestive of TEM-12 [46]. One \textit{K. pneumoniae} isolate produced \(\beta\)-lactamases with pIs = 5.6 and 5.2, and 1 \textit{E. coli} isolate produced \(\beta\)-lactamases with pIs = 5.6 and 5.4, the latter suggestive of TEM-1 [47, 48].

**PFGE.** There were 6 different strain types (U–Z) among the \textit{E. coli} and 8 different strain types (A–H) among the \textit{K. pneumoniae} isolates (figure 2). Of the 21 \textit{K. pneumoniae} isolates, 9 were strain type B (figure 2, lane 2), 2 of which were from patients hospitalized in the medical intensive care unit and 2 from patients hospitalized in the surgical intensive care unit. No temporal relationship was noted among these isolates. Six \textit{K. pneumoniae} isolates were strain type C (figure 2, lane 3), 4 of which were from patients hospitalized in the medical intensive care unit; 3 of the 4 latter patients had been there during the same 10-day time period. The 7 other strain types occurred in only 1 patient each. Of the 11 \textit{E. coli} isolates, 6 were strain type U (figure 2, lane 10), 3 of which were from patients from a single nursing home (2 of 3 patients were hospitalized during the same week). The other 5 \textit{E. coli} isolates had unique patterns.

**Plasmid analysis.** Plasmid profiles were determined for each of the PFGE strain types. Three of the 6 \textit{E. coli} strain types and 3 of the 8 \textit{K. pneumoniae} strain types carried a plasmid that comigrated with a 66-kb plasmid marker. Two \textit{E. coli} strain types and 5 of 8 \textit{K. pneumoniae} strain types carried a plasmid that comigrated with a 54-kb plasmid previously reported to carry TEM-10 [33].

Other lower-molecular-weight plasmids (<20 kb) were apparent in 3 \textit{E. coli} and 6 \textit{K. pneumoniae} strain types. One \textit{E. coli} and 3 \textit{K. pneumoniae} isolates had neither the 54- nor the 66-kb plasmid, although lower-molecular-weight plasmids were noted.

**Transfer of \(\beta\)-lactam resistance.** Two strains, \textit{E. coli} DAS-1 and \textit{K. pneumoniae} DAS-2, were used as donor strains in conjugation experiments. Each donor strain produced a single \(\beta\)-lactamase with a pI = 5.6 and carried a 54-kb plasmid. Transfer of ceftazidime resistance to the ceftazidime-susceptible recipients naldixic acid-resistant \textit{E. coli} C600 or streptomycin-resistant \textit{E. coli} C600 was found in association with the 54-kb plasmid at a frequency of \(1 \times 10^{-5}\) to \(2 \times 10^{-4}\) transconjugants per donor. Transconjugants derived from DAS-2 also acquired resistance to gentamicin, tobramycin, and trimethoprim-sulfamethoxazole. Conjugation studies using strains carrying the 66-kb plasmid were not done, as an appropriate counterselection recipient was not available.
Discussion

Our study represents the largest molecular epidemiologic analysis of K. pneumoniae and E. coli ceftazidime-resistant bloodstream isolates reported. Since these isolates were obtained from one tertiary care medical center in Chicago, conclusions drawn from our results may not be applicable to other settings, and the isolates recovered may not be representative of those prevalent at other institutions. Nonetheless, by the use of PFGE, IEF, plasmid evaluation, and case-control analysis, we were able to corroborate and expand the findings of other recent Chicago investigations [27, 28, 33, 49].

The IEF results suggest that the predominant enzyme responsible for ceftazidime resistance in this series of bloodstream isolates was the TEM-10 β-lactamase (pI = 5.6). Other extended-spectrum β-lactamases with a pI = 5.6 were not definitively ruled out by enzyme kinetic or genetic analysis. However, the β-lactamases from our strains comigrated with the previously reported TEM-10 enzyme from K. pneumoniae KC2 from Chicago. In addition, transferable ceftazidime resistance was demonstrated to be present in our strains on a 54-kb plasmid that comigrated on agarose gel electrophoresis with a 54-kb plasmid previously reported to carry the TEM-10 enzyme [33].

Two E. coli isolates had single enzymes with pI = 5.2, and 1 K. pneumoniae isolate coproduced enzymes with pI s = 5.6 and 5.2, suggesting that in those strains, extended-spectrum β-lactamase production may have been encoded by TEM-12 [18, 49]. TEM-10 differs from the parental enzyme, TEM-1, by two amino acid substitutions (serine for arginine at position 692 and lysine for glutamine at position 917) and differs from TEM-12 by a single amino acid substitution (lysine for glutamine at position 917) [49]. The coproduction of two different extended-spectrum β-lactamases may represent an intermediate step in the progression from TEM-12 to TEM-10, as proposed by Bradford et al. [49]. Additionally, ceftazidime MICs for the E. coli isolates with pI = 5.2 were 8.0 µg/mL, lower than the National Committee for Clinical Laboratory Standards breakpoint of >16 µg/mL for ceftazidime resistance [37]. The use of >16 µg/mL as the breakpoint for ceftazidime resistance may not be valid in isolates of K. pneumoniae and E. coli, when extended-spectrum β-lactamase production is present [50].

Plasmid analysis revealed that the resistance gene was usually carried on a 54-kb or 66-kb plasmid. Transfer of ceftazidime resistance occurred in association with transfer of the 54-kb plasmid from both an E. coli donor strain and a K. pneumoniae donor strain. The K. pneumoniae donor strain plasmid cotransferred resistance to tobramycin, gentamicin, and trimethoprim-sulfamethoxazole, further emphasizing the potential for spread of multiple drug resistance. One E. coli strain contained only a single <20-kb plasmid and produced a single β-lactamase with a pI = 5.2. This isolate may encode the chromosomally mediated TEM-12 resistance reported by Weber et al. [46]. That multiple plasmids of different molecular weights may all encode a TEM-10 enzyme suggests that the TEM-10 gene can arise independently, as has been proposed by Bradford et al. [49], or that the plasmids are undergoing transposition.

The PFGE results indicate a polyclonal outbreak. Eight unique patterns were seen among the K. pneumoniae isolates and 6 unique patterns were seen among the E. coli isolates. Interestingly, limited geographic and temporal clustering was noted. Three of the E. coli with identical PFGE patterns were from patients from a single nursing home (2 of whom were hospitalized the same week), and 3 K. pneumoniae isolates with identical patterns were from patients hospitalized in the medical intensive care unit within the same 10-day period (figure 2). These results suggest that cross-transmission or spread via an unidentified common source may have occurred. Therefore, the potential importance of barrier precautions should be emphasized [24–29]. No other epidemiologic links were found within this group of nursing home or medical intensive care unit patients.

Five variables were identified as risk factors for bacteremia with ceftazidime-resistant K. pneumoniae or E. coli by univariate analysis. Half of the bloodstream infections in the cases were community-acquired, and the majority occurred in patients from nursing homes. This corroborates earlier findings implicating nursing homes as a reservoir for extended-spectrum β-lactamase-producing E. coli and K. pneumoniae strains [27, 28]. Prior use of oxyimino β-lactams appears to be a selective
factor leading to bloodstream infections with these isolates, since more cases than controls received aztreonam or ceftazidime in the month preceding bacteremia (11/31 vs. 0/31, \( P = .001 \)). Other significant risk factors included longer total length of hospital stay, higher APACHE-II scores, and the presence of a device such as a Foley catheter, feeding tube, or central venous catheter, suggesting that extended-spectrum \( \beta \)-lactamase–producing \textit{K. pneumoniae} or \textit{E. coli} are pathogens in more debilitated patients with underlying illness. This agrees with results from other studies identifying similar markers for poor health status (the need for total care, invasive procedures, and longer duration of hospital stay) as predictors of acquisition of extended-spectrum \( \beta \)-lactamase–producing \textit{E. coli} or \textit{K. pneumoniae} [27, 28, 51, 52]. A case-control study of intensive care unit infections or colonization with TEM-3–producing \textit{K. pneumoniae} also identified longer duration of stay and instrumentation as risk factors [53]. However, after controlling for length of stay in the intensive care unit, prior gastric surgery was found to be the greatest risk factor for infection or colonization with a TEM-3–producing \textit{K. pneumoniae} [53]. We did not control for length of stay before the development of nosocomial bacteremia because only 16 of 31 case-patients acquired bacteremia in the hospital.

Multivariate analysis indicated that the most significant independent risk factor for bacteremia with a ceftazidime-resistant \textit{K. pneumoniae} or \textit{E. coli} was the presence of a central venous catheter. In a subset analysis of patients with ceftazidime-resistant bacteremia who had a central venous catheter, residence in a nursing home was the most predictive factor. In patients without a central venous catheter, the presence of a urinary catheter and an elevated APACHE-II score were significant predictors for ceftazidime-resistant bacteremia. This analysis suggests that many of the cases may have had catheter-related bacteremia.

Appropriate treatment of bacteremic patients infected with ceftazidime-resistant organisms is usually based on in vitro susceptibility studies. Most of the published reports on outbreaks of ceftazidime-resistant organisms contain limited information about therapy. Brun-Buisson et al. [3] described an outbreak of 62 patients infected or colonized with a ceftazidime-resistant strain of \textit{K. pneumoniae}. Ten patients (4 with bacteremia) required treatment; cefotaxime was effective in cases of uncomplicated urinary tract infection but failed in major infections at other sites. Rice et al. [54] described an outbreak that included 14 infected patients (1 with bacteremia) treated with agents active against ceftazidime-resistant isolates. All patients had a favorable response, including 4 who received cefotaxime. Naumovski et al. [26] described the clinical outcome of 13 patients (4 with bacteremia) with infections due to ceftazidime-resistant \textit{K. pneumoniae} or \textit{E. coli}. Two of the patients with bacteremia who received ceftazidime died and 2 survived after the antibiotic coverage was modified by the addition of tobramycin. Bingen et al. [23] described 19 patients infected with ceftazidime-resistant \textit{K. pneumoniae} (10 with bacteremia). All 19 had a favorable response to either imipenem or ciprofloxacin in combination with gentamicin or amikacin. Meyer et al. [25] described treatment and outcome in 43 patients, including 10 with bacteremia, infected with ceftazidime-resistant \textit{K. pneumoniae}. All 13 patients who received no therapy directed against ceftazidime-resistant \textit{K. pneumoniae} died. Treatment regimens that included imipenem yielded the most favorable results.

In our study, therapeutic results were available for 31 patients with bacteremia due to a ceftazidime-resistant \textit{K. pneumoniae} or \textit{E. coli}. Six (19%) of 31 patients died. The relatively low mortality of gram-negative bacteremia in this group appears to reflect the very low mortality in the group that received appropriate antibiotic therapy. Only 1 of 19 patients who received appropriate therapy died versus 5 of 12 who received inappropriate therapy, including a single pediatric patient with leukemia who developed bacteremia with a cefotaxime-susceptible, ceftazidime-resistant \textit{E. coli} and received cefotaxime for \(<\)1 day before death.

The preceding studies suggest that various antimicrobials (imipenem, ciprofloxacin, or amikacin) can be chosen to treat patients with serious infections due to ceftazidime-resistant gram-negative enteric bacilli but that third-generation cephalosporins should not be used. The lack of data in patients regarding therapy with the combination of a \( \beta \)-lactam plus a \( \beta \)-lactamase inhibitor limits their usage. Concomitant resistance to ciprofloxacin, as seen in 40% of our isolates, restricts empiric use of this agent in circumstances when an extended-spectrum \( \beta \)-lactamase–producing organism is suspected.

Results from our study indicating the polyclonal nature of the resistant strains suggest that ceftazidime resistance due to TEM-10 is now endemic in Chicago. Its higher prevalence in bacterial strains from debilitated nursing home patients with central venous catheters has therapeutic and infection control implications. Strain-specific clustering underscores the importance of barrier precautions and isolation in an attempt to prevent intrahospital dissemination of ceftazidime resistance.

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References


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