Class Restriction of Cephalosporin Use to Control Total Cephalosporin Resistance in Nosocomial Klebsiella

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Context.—Resistance to most or all cephalosporin antibiotics in Klebsiella species has developed in many European and North American hospitals during the past 2 decades.

Objective.—To determine if restriction of use of the cephalosporin class of antibiotics would reduce the incidence of patient infection or colonization by cephalosporin-resistant Klebsiella.

Design.—A before-after comparative 2-year trial.

Setting.—A 500-bed, university-affiliated community hospital in Queens, NY.

Patients.—All adult medical and surgical hospital inpatients.

Intervention.—A new antibiotic guideline excluded the use of cephalosporins except for pediatric infection, single-dose surgical prophylaxis, acute bacterial meningitis, spontaneous bacterial peritonitis, and outpatient gonococcal infection. All other cephalosporin use required prior approval by the infectious disease section.

Main Outcome Measure.—Incidence of patient infection or colonization by ceftazidime-resistant Klebsiella during 1995 (control period) compared with 1996 (intervention period).

Results.—An 80.1% reduction in hospital-wide cephalosporin use occurred in 1996 compared with 1995. This was accompanied by a 44.0% reduction in the incidence of ceftazidime-resistant Klebsiella infection and colonization throughout the medical center (P<.01), a 70.9% reduction within all intensive care units (P<.001), and an 87.5% reduction within the surgical intensive care unit (P<.001). A concomitant 68.7% increase in the incidence of imipenem-resistant Pseudomonas aeruginosa occurred throughout the medical center (P<.01). All such isolates except one were susceptible to other antibiotics.

Conclusion.—Extensive cephalosporin class restriction significantly reduced nosocomial, plasmid-mediated, cephalosporin-resistant Klebsiella infection and colonization. This occurred at the price of increased imipenem resistance in P aeruginosa, which remained susceptible to other agents. Thus, an overall reduction in multiply-resistant pathogens was achieved within 1 year.

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ANTIBIOTIC RESISTANCE among nosocomial pathogens has been an evolving process since the development of penicillin-resistant Staphylococcus aureus more than 40 years ago.1 During the past decade, resistance in gram-negative bacilli to cephalosporin antibiotics has accelerated because of the appearance of plasmid-mediated extended spectrum β-lactamases (ESBLs) in Klebsiella, Escherichia coli, and Proteus mirabilis.2-4 More recently, cefepime resistance in ESBL-producing Klebsiella has occurred because of decreased antibiotic uptake and/or acquisition of a novel ESBL.5-7 Thus, most clinicians have relied on imipenem, piperacillin-tazobactam, ciprofloxacin, or amikacin for effective treatment of serious infection due to multiply-resistant Klebsiella.5,7

At our institution an outbreak of ESBL-producing Klebsiella infection occurred in 1990 despite an antibiotic restriction program that required prior approval of all third-generation cephalosporins and imipenem.8 From 1991 to 1995 the hospital prevalence of ESBL-producing Klebsiella gradually increased from 5 to 10 isolates to 10 to 20 isolates per month. Also, in 1995, cephamycin resistance emerged in approximately 30% to 40% of ESBL-producing Klebsiella.9 This ominous development created a unique situation in which all cephalosporins/cephemycins became ineffective against an increasing proportion of Klebsiella isolates.

There is almost universal agreement that increasing antimicrobial resistance is related to selective pressure exerted by the use of these agents.8,10 Withdrawal of such pressure has been suggested frequently as a method by which specific resistance may be reversed.8,11 In addition, in vitro propagation of ESBL-producing Klebsiella in the absence of antibiotics has resulted in reversion to cephalosporin susceptibility.12

The purpose of this study was to test the clinical corollary of this phenomenon, specifically, that hospital-wide restriction of use of a specific class of antimicrobial agents (cephalosporins/cephemycins) would result in significant reduction of resistance to the restricted class. Following our prior restriction of only late-generation cephalosporins, increased imipenem use was accompanied by the emergence of imipenem-resistant Acinetobacter.13 After control of this outbreak, imipenem resistance was limited to Pseudomonas aeruginosa. Thus, a...
secondary purpose of this study was to determine whether class restriction of cephalosporins would further increase both the use of imipenem and resistance to this agent in *P aeruginosa*.

**METHODS**

**Study Plan**

The study plan included the following objectives: (1) to restrict the hospital use of parenteral and oral cephalosporins, with 5 specific exceptions, between January 1, 1996, and December 31, 1996, and to compare the incidence of colonizing and infecting isolates of ceftazidime-resistant *Klebsiella* with that recorded by identical surveillance methods from January 1, 1995, to December 31, 1995; (2) to compare the incidence of colonizing and infecting isolates of imipenem-resistant *P aeruginosa* during the same periods; (3) to compare parenteral cephalosporin and imipenem-cilastatin sodium use during 1995 and 1996 by examination of pharmacy case records; (4) to make the above comparisons using surveillance and antibiotic use data from the entire hospital, individual intensive care units, and combined intensive care units.

**Surveillance**

Surveillance of multiresistant pathogens in our 500-bed medical center has been conducted for purposes of infection control since 1989. Following our initial identification of ceftazidime-resistant *Klebsiella* and imipenem-resistant *Acinetobacter* in the years 1989 and 1990, we conducted surveillance of all ceftazidime- or imipenem-resistant isolates of *E coli, Klebsiella, Enterobacter, Acinetobacter, and P aeruginosa.* For purposes of this study, identical surveillance methods were conducted in 1995 prior to hospital-wide cephalosporin restriction and in 1996 after such restriction had been implemented. Infection control practitioners reviewed daily susceptibility data from the clinical microbiology laboratory on all of the above species. Cultures were obtained according to clinical indications. All ceftazidime- or imipenem-resistant isolates were recorded according to body site and hospital location. One isolate was recorded per body site per patient. The number of patients harboring ceftazidime- or imipenem-resistant isolates of each species was recorded, as well as the number of patients harboring each species, regardless of antibiotic susceptibility. From these data, the proportion of ceftazidime and imipenem resistance within each species was calculated monthly. Also, the incidence of ceftazidime or imipenem resistance for each species was defined by a ratio equal to the total number of colonized and infected patients (patient-related isolates) divided by the average daily census (patient-days/days per month). Incidence ratios were determined for the total hospital, individual intensive care units, and combined intensive care units. Colonization or infection by each isolate was determined by criteria of the Centers for Disease Control and Prevention, Atlanta, Ga.14 Ceftazidime- or imipenem-resistant isolates from patients admitted from nursing homes or other community sources were recorded but were not included in the calculation of nosocomial incidence unless recovery of the isolate occurred 72 hours or more after admission. Isolates recovered within 72 hours of admission from a nursing home were defined as nursing home associated.

**Infection Control**

All patients from whom ceftazidime-resistant *Klebsiella* (or other gram-negative bacilli) were recovered were cared for with standard contact precautions. Those in intensive care units were placed in a cohort. This policy remained constant during both study years.

**Antibiotic Restriction**

Antibiotic therapy was prescribed by the house staff and attending physicians with consultative advice by the hospital’s infectious disease section. During 1995, approval by the infectious disease fellows or attending physicians was required for the use of parenteral cephalosporins (ceftazidime, ceftriaxone, cefotaxime) and imipenem-cilastatin beyond a single dose for immediate therapy. Approval was obtained by telephone or formal consultation with suggestions for alternative therapy, as indicated. In 1996, the hospital’s pharmacy and therapeutics committee adopted an antibiotic utilization guideline, which required such approval for all-hospital cephalosporin use (parenteral and oral) with the exceptions of pediatric infection and use of ceftriaxone for treatment of meningitis or presumed gonococcal infection, cefotaxime for presumed spontaneous bacterial peritonitis, and cefazolin for surgical prophylaxis. Treatment with imipenem required the same approval with the exception of use in the medical, surgical, and cardiac intensive care units. In these units, imipenem use was allowed for 72 hours. Continued administration then required approval. The following parenteral antibacterial agents were available without prior approval: ampicillin-sulbactam, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, doxycycline, ofloxacin, gentamicin, tobramycin, amikacin, oxacillin sodium, erythromycin, clindamycin, and vancomycin hydrochloride. Ciprofloxacin was available without prior approval in intensive care units only. Available oral antibacterials were penicillin, ampicillin, amoxicillin, chloramphenicol, clavulanic acid-potassium, erythromycin, clarithromycin, clindamycin, diacoxacin sodium, doxycycline, ofloxacin, ciprofloxacin, and trimethoprim-sulfamethoxazole.

All physicians annually received a summary of the hospital’s antibiotic susceptibility patterns. For this study, the rationale for new guidelines was reinforced with presentations by members of the infectious disease section at conferences and grand rounds.

**Antibiotic Use**

The use of cephalosporins and imipenem throughout the hospital and in individual intensive care units in 1995 and 1996 was recorded after examining all noncomputerized pharmacy patient records and by retrieving computerized data from the remaining portion of patient records.

**Statistical Analyses**

The incidence ratios for ceftazidime-resistant *Klebsiella* and imipenem-resistant *P aeruginosa* were computed monthly during 1995 and 1996. Differences between the 2 years with regard to the ratios were tested in 2 ways. The first was to consider the 2 years as independent samples (unpaired) and to perform a distribution-free analysis (Wilcoxon rank sum test) since sample sizes were small and ratios were typically not normally distributed. The second method, which accounted for possible seasonal variations, involved pairing the ratios by corresponding months and testing their differences for significance using a Wilcoxon signed rank test.

Monthly data describing use of all cephalosporins, individual cephalosporins, and imipenem-cilastatin were analyzed in the same manner.

**RESULTS**

**Changes in Antibiotic Use**

Table 1 demonstrates statistically significant reductions in hospital cephalosporin use, accompanied by a similarly significant increase in imipenem use in 1996 as compared with 1995. The average daily census for the hospital in 1995 and 1996 remained essentially constant (576 and 368, respectively). The use of all cephalosporins decreased by 80.1%, while the use of ceftazidime and cefotetan decreased by 72.5% and 95.7%, respectively. A 140.6% increase in imipenem-cilastatin use occurred in 1996. The majority of this increase was in the intensive care units.
Table 1.—Change in Parenteral Cephalosporin and Imipenem/Cilastatin Use From 1995 to 1996 Following Cephalosporin Restriction in 1996

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Year</th>
<th>Unpaired Median Monthly Gram Use (Range)</th>
<th>Change, %</th>
<th>Paired Median Monthly Gram Use (Range)</th>
<th>Change, %</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cephalosporins</td>
<td>1995</td>
<td>5558 (4452 to 8858)</td>
<td>-80.1</td>
<td>.001</td>
<td>-4709 (-7168 to -3208)</td>
<td>&lt;.001</td>
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</tr>
<tr>
<td></td>
<td>1996</td>
<td>1106 (259 to 1690)</td>
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<tr>
<td>Cefazidime</td>
<td>1995</td>
<td>383 (60 to 523)</td>
<td>-72.5</td>
<td>&lt;.001</td>
<td>-248 (-494 to 80)</td>
<td>&lt;.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>66 (0 to 19)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cefotaxime</td>
<td>1995</td>
<td>253 (129 to 910)</td>
<td>-10.3</td>
<td>&gt;.05</td>
<td>-96 (-750 to 208)</td>
<td>&gt;.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>227 (6 to 350)</td>
<td></td>
<td></td>
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<tr>
<td>Ceftriaxone sodium</td>
<td>1995</td>
<td>155 (61 to 296)</td>
<td>-39.4</td>
<td>&lt;.005</td>
<td>-78 (-151 to 81)</td>
<td>&lt;.05</td>
<td></td>
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<tr>
<td></td>
<td>1996</td>
<td>94 (8 to 249)</td>
<td></td>
<td></td>
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<tr>
<td>Cefotetan</td>
<td>1995</td>
<td>1450 (1068 to 2443)</td>
<td>-95.7</td>
<td>&lt;.001</td>
<td>-1390 (-2386 to 899)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>63 (5 to 187)</td>
<td></td>
<td></td>
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<tr>
<td>Cefuroxime</td>
<td>1995</td>
<td>2210 (995 to 4949)</td>
<td>-91.3</td>
<td>&lt;.001</td>
<td>-1928 (-4117 to -821)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>192 (34 to 377)</td>
<td></td>
<td></td>
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<tr>
<td>Cefazolin</td>
<td>1995</td>
<td>1428 (1177 to 2145)</td>
<td>-69.2</td>
<td>&lt;.001</td>
<td>-1050 (-1898 to 568)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>440 (106 to 676)</td>
<td></td>
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<tr>
<td>Imipenem</td>
<td>1995</td>
<td>197 (76 to 463)</td>
<td>140.6</td>
<td>&lt;.05</td>
<td>258 (-140 to 551)</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>474 (119 to 627)</td>
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</table>

Table 2.—Geographic Source of All Cefazidime-Resistant Klebsiella and Imipenem-Resistant Pseudomonas aeruginosa Patient Isolates in 1995 and 1996

<table>
<thead>
<tr>
<th>Source of Patient Isolates</th>
<th>Cefazidime-Resistant Klebsiella</th>
<th>Imipenem-Resistant P aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial</td>
<td>150</td>
<td>84</td>
</tr>
<tr>
<td>Nursing home acquired*</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Outpatient</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Emergency</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nursing home†</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>192</td>
<td>136</td>
</tr>
</tbody>
</table>

* Nursing home—acquired source was defined by isolation of a resistant isolate from a hospitalized patient within 72 hours after transfer from a nursing home.
† Nursing home residence indicates isolates from patients in an affiliated nursing home, not admitted to the hospital.

Changes in All Cefazidime-Resistant Klebsiella and Imipenem-Resistant P aeruginosa Patient Isolates From 1995 to 1996

Table 2 provides the geographic source of all patient-related resistant isolates of both species in 1995 and 1996, including (1) those isolated from nosocomial sources, (2) those isolated within 72 hours of admission from a nursing home, (3) those isolated from outpatients, (4) those isolated from patients seen in the emergency department, and (5) those isolated from patients in an affiliated nursing home but not admitted to the hospital.

Among hospitalized patients, the proportion of cefazidime-resistant Klebsiella that was nursing home associated, rather than nosocomial, rose from 15.3% in 1995 to 27.0% in 1996, despite fewer total isolates in 1996. This was not true for the nursing home—associated proportion of imipenem-resistant P aeruginosa, which declined from 14.1% in 1995 to 11.6% in 1996.

The proportion of all Klebsiella patient isolates that were cefazidime resistant declined from 19.6% in 1995 to 14.2% in 1996. The proportion of all P aeruginosa patient isolates that were imipenem resistant rose from 8.9% in 1995 to 16.7% in 1996.

Changes in Nosocomial Antibiotic Resistance

Cefazidime-Resistant Klebsiella.—The absolute number of patient-related cefazidime-resistant Klebsiella isolates increased hospital-wide from 67 in 1995 to 113 in 1996, a 68.7% increase (Table 4). The greatest increase occurred in all intensive care units combined, from 20 to 35 isolates (75.0% increase). The changes in incidence when related to average daily census were statistically significant hospital-wide (P<.01) and in all intensive care units (P<.01). Among individual intensive care units, only the cardiac care unit demonstrated a significant increase in incidence by unpaired analysis (P<.05). The hospital-wide incidence of infection due to cefazidime-resistant P aeruginosa rose from 0.35 to 0.55 per 1000 patient-days, an increase of 57%. All isolates except 1 remained susceptible to an alternative agent.

Anatomic Source and Nosocomial Distribution of Cefazidime-Resistant Klebsiella and Imipenem-Resistant P aeruginosa.—The decrease in nosocomial cefazidime-resistant Klebsiella during 1996 occurred primarily in the number of patient-related sputum isolates, which were reduced by more than two thirds (Table 5). The number of pulmonary infections were reduced proportionately. A two-thirds increase in imipenem-resistant P aeruginosa occurred predominantly among sputum isolates with a proportionate increase in pulmonary infections. Blood isolates of cefazidime-resistant Klebsiella were reduced by half in 1996, while those of imipenem-resistant P aeruginosa remained at a low level.

COMMENT

Previous attempts to reduce ESBL-mediated resistance to cephapolorins in Klebsiella by antibiotic control have focused on restriction of cefazidime or all third-generation cephalosporins. Reduction of resistance by such restriction plus infection control measures, or infection control alone, has been described.15-16 Other studies have failed to demonstrate any such reduction or have yielded mild-to-moderate declines in resistance by restriction of third-generation cephalosporins, with or without concomitant changes in infection control policies.17-20 At our institution, approval by an infectious disease pharmacist was required for use of all late-generation cephalosporins (cefazidime, cefotaxime, ceftiraxone) and imipenem from 1988 through 1995. Nevertheless, the prevalence of cefazidime-resistant Klebsiella increased steadily in...
association with newly superimposed cephamycin (ceftetan) and imipenem resistance. Thus, we chose to test the concept of total antibiotic class restriction, which resulted in an 80.1% reduction of all cephalosporin use in 1996 and a 44% decline in the incidence of ceftazidime-resistant \textit{Klebsiella} compared with 1995. The greatest reduction, by 87.5\%, occurred in the surgical intensive care unit. This was associated with a shift in the predominant site of ceftazidime-resistant \textit{Klebsiella} from sputum of patients in intensive care units to the urine of those in general medical and surgical units. Thus, omission of a lag period may have diminished the true effect of cephalosporin restriction in 1996. In a similar study by Ma et al,\textsuperscript{20} conducted in the late 1970s, intensive cephalosporin restriction resulted in a 46% reduction of cephalothin-resistance among \textit{Klebsiella} isolates but only after a 1-year lag. In our study the reduction in ceftazidime resistance after 1 month of cephalosporin restriction may have been because of the simultaneously increased use of imipenem, particularly in intensive care units. Similarly, a reduction in the prevalence of ceftazidime-resistant \textit{Klebsiella} was noted by Rice et al\textsuperscript{7} within 1 year after restriction of ceftazidime and introduction of piperacillin-tazobactam.\textsuperscript{7} In our institution, prior failure of third-generation cephalosporins alone may have been due to the continued use of ceftetan, a cephamycin that selected for a novel ESBL among ceftazidime-resistant strains of \textit{Klebsiella}.\textsuperscript{4} Whether restriction of only third-generation cephalosporins and cephemycins would have yielded the same results as total class withdrawal remains to be determined.

Despite the complexity of factors that influence the incidence of antibiotic resistance, the results of this study suggest that class restriction of use of cephalosporins was the major determinant in the hospital-wide reduction of ceftazidime-resistant
Ceftazidime-resistant Klebsiella in 1996. Methods of infection control, detection of ceftazidime-resistant isolates, and exclusion of multiple isolates from the same patient have remained constant during 1995 and 1996. However, new antibiotic guidelines may have increased awareness of cephalosporin-resistance sufficiently to alter personnel behavior and affect outcome. Further, the efficacy of antibiotic restriction is influenced by the activity of substituted agents and by the prevalent mechanisms of resistance. Dissemination of resistance genes by bacterial conjugation and plasmid or transposon transfer, as in ceftazidime-resistant Klebsiella, leads rapidly to large polyclonal populations of resistant organisms, which may escape the most stringent infection control efforts. Since many resistant genes may be transferred on the plasmid, clinical use of any of several antibiotics may place selective pressure which favors survival of that plasmid. Thus, antibiotic class restriction alone is unlikely to eliminate plasmid-mediated antimicrobial resistance. Antibiotic restriction and infection control play complementary roles in preventing both the selection and spread of resistant bacterial pathogens. Our ongoing molecular epidemiologic studies by pulsed-field gel electrophoresis have demonstrated multiple clusters (defined by 75%-90% genetic similarity) among ceftazidime-resistant Klebsiella. This finding suggests that nosocomial transmission may be responsible for a persistent, but lower, incidence of ceftazidime resistance following cephalosporin class restriction.

The reduction in cephalosporin resistance among our nosocomial Klebsiella isolates was accompanied by an increased incidence of imipenem-resistant P aeruginosa. Unlike our earlier experience with increased use of imipenem, imipenem-resistant Acinetobacter did not appear during 1996.15 Imipenem resistance in P aeruginosa among North American isolates is due primarily to an alteration in outer membrane permeability, possibly combined with slow hydrolysis by class 1 β-lactamases.22 Both mechanisms are chromosomal rather than plasmid mediated. Permeability alterations may result in selective resistance to carbapenems or multidrug resistance. However, all of our imipenem-resistant P aeruginosa isolates, with 1 exception, remained susceptible to other β-lactam agents, quinolones, or aminoglycosides. In contrast, our ceftazidime-resistant Klebsiella strains were frequently resistant to all antibiotics except imipenem and those strains that developed imipenem resistance were not susceptible to any commonly used agent.23 Thus, the decrease in ceftazidime-resistant Klebsiella that occurred in 1996 represented an overall reduction in nosocomial multiresistant gram-negative pathogens.

Potential antiinfectious resistance patterns vary widely among institutions, antibiotic use policies must be adjusted in response to specific situations. Class restriction of cephalosporins, if adopted, need not be permanent but may lead to rotation of antibiotic classes in response to evolving resistance patterns. A recent position paper by the Society for Healthcare Epidemiology of America, Mount Royal, NJ, and Infectious Diseases Society of America, Alexandria, Va, has proposed methods to “interdict the dissemination of resistant strains.”24 Implementation of these methods requires multidisciplinary collaboration to define and monitor resistance; identify mechanisms; characterize resistant organisms phenotypically and genotypically; maintain control of selected antibiotics; educate medical personnel to achieve cooperation; establish stable infection control methods; and measure outcomes. Strong administrative and medical staff support are essential to such a collaboration. Our study demonstrates that application of these elements to a program of extensive antimicrobial class restriction can yield positive results but not without the potential development of new and possibly unexpected resistance patterns. Further refinement of such methods and the addition of novel microbiologic, epidemiologic, pharmacologic, and clinical techniques will be necessary to address the continuing challenge of antimicrobial resistance.

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