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ARTICLE

International Prospective Study of *Klebsiella pneumoniae* Bacteremia: Implications of Extended-Spectrum β-Lactamase Production in Nosocomial Infections

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Background: Commonly encountered nosocomially acquired gram-negative bacteria, especially *Klebsiella pneumoniae*, produce extended-spectrum β-lactamases (ESBLs) as an antibiotic resistance mechanism.

Objective: To determine whether microbiology laboratories should report the presence of ESBLs and to establish the infection-control implications of ESBL-producing organisms.

Design: Prospective observational study.

Setting: 12 hospitals in South Africa, Taiwan, Australia, Argentina, the United States, Belgium, and Turkey.

Patients: 440 patients with 455 consecutive episodes of *K. pneumoniae* bacteremia between 1 January 1996 and 31 December 1997; of these, 253 episodes were nosocomially acquired.

Measurements: The *K. pneumoniae* isolates were examined for the presence of ESBLs. Pulsed-field gel electrophoresis was used to analyze the molecular epidemiology of nosocomial bacteremia with ESBL-producing *K. pneumoniae*.

Results: Overall, 30.8% (78 of 253) episodes of nosocomial bacteremia and 43.5% (30 of 69) episodes acquired in intensive care units were due to ESBL-producing organisms. After adjustment for potentially confounding variables, previous administration of β-lactam antibiotics containing an oxyimino group (cefuroxime, cefotaxime, ceftriaxone, ceftazidime, or aztreonam) was associated with bacteremia due to ESBL-producing strains (risk ratio, 3.9 [95% CI, 1.1 to 13.8]). In 7 of 10 hospitals with more than 1 ESBL-producing isolate, multiple strains with the same genotypic pattern were observed, indicating patient-to-patient spread of the organism.

Conclusions: Production of ESBLs by *Klebsiella pneumoniae* is a widespread nosocomial problem. Appropriate infection control and antibiotic management strategies are needed to stem the spread of this emerging form of resistance.

Since the discovery that resistance of *Staphylococcus aureus* to penicillin is mediated by a β-lactamase, much effort has been made to create β-lactam antibiotics that are stable to common β-lactamases. Cephalosporin antibiotics containing an oxyimino side-chain represent a major advance in antibiotic development. The merger of the oxyimino chain and a 2-amino-5-thiazolyl nucleus (in such antibiotics as ceftriaxone, cefotaxime, and ceftazidime) resulted in stability to the effects of the common TEM-1 and SHV-1 β-lactamases produced by gram-negative bacilli, such as *Escherichia coli* and *Klebsiella pneumoniae*. However, within a few years of the commercial release of these antibiotics, gram-negative bacilli (especially *K. pneumoniae*) that harbored mutated versions of the parent TEM and SHV enzymes were detected. These and other newly detected β-lactamases (for example, the functionally similar CTX-M types) hydrolyze β-lactam antibiotics containing the oxyimino side-chain. Genes encoding these extended-spectrum β-lactamases (ESBLs) were carried on transferable plasmids. These plasmids frequently carried determinants of resistance to other classes of antibiotics, particularly the aminoglycosides (1, 2).

Thus, ESBL-producing gram-negative bacilli were found to truly be multiresistant pathogens: The majority of these strains were resistant to all β-lactam antibiotics (with the exception of cephamycins and carbapenems), most aminoglycosides, trimethoprim–sulfamethoxazole, and sometimes the fluoroquinolones. Although the prevalence of ESBL production among gram-negative bacilli varies geographically (and may even vary from hospital to hospital within a city), widespread recognition of the advent of these β-lactamases has been lacking (3).

Previous studies of the epidemiology of ESBL-producing organisms have been largely limited to single institutions (4, 5). Because substantial information on the epidemiology of ESBL-producing *K. pneumoniae* or other gram-negative bacilli is lacking, we established a collaboration of researchers from 7 countries on 6 continents to prospectively enroll consecutive patients with *K. pneumoniae* bacteremia.

METHODS
Study Design

We performed a prospective observational study of 440 consecutive, sequentially encountered patients with *K. pneumoniae* bacteremia at 12 hospitals in South Africa, Taiwan, Australia, Argentina, the United States, Belgium, and Turkey. No patient was excluded from analysis. Patients were enrolled from 1 January 1996 to 31 December 1997. Patients were older than 16 years of age and had positive blood cultures for *K. pneumoniae*. The investiga-

Context

Worldwide prevalence of extended-spectrum β-lactamase (ESBL)–producing organisms is of great concern because of their broad antibiotic resistance.

Contribution

Analysis of consecutive cases of *Klebsiella pneumoniae* bacteremia at 12 hospitals on 6 continents shows that although incidence varies widely among institutions, almost one third of cases of nosocomial bacteremia and almost one half of intensive care unit–based infections were caused by ESBL-producing organisms. Patient-to-patient spread is common, and prevention requires careful attention to routine infection control measures.

Cautions

Specific antibiotic exposures before *K. pneumoniae* infection cannot be confirmed as risk factors for ESBL-related infections on the basis of this study.

–The Editors

tors completed a 188-item study form on each episode of *K. pneumoniae* bacteremia. Patients were followed for 1 month after the onset of bacteremia to assess clinical outcome, including death and infectious complications. The study was observational in that administration of antimicrobial agents and other therapeutic management was controlled by the patient's physician rather than the investigators (6). The study was approved by institutional review boards as required by local hospital policy at the time of the study.

Definitions

All study definitions were established before data analysis. Nosocomial bacteremia was defined as *K. pneumoniae* bacteremia occurring more than 48 hours after admission to hospital. An episode of bacteremia was defined as the period of 14 days from the time of collection of the first blood culture positive for *K. pneumoniae*. Severity of acute illness was assessed at the time of the positive blood cultures by using the Pitt bacteremia score, a previously validated scoring system that is based on mental status, vital signs, requirement for mechanical ventilation, and recent cardiac arrest (**Table 1**) (7, 8). Severity of illness in patients in an intensive care unit at the time of onset of bacteremia was assessed by using the Acute Physiology and Chronic Health Evaluation-3 score (9). Site of infection was determined to be pneumonia, urinary tract infection, meningitis, incisional wound infection, other soft-tissue infection, intra-abdominal infection, or primary bloodstream infection according to Centers for Disease Control and Prevention definitions (10). Previous antibiotic therapy was defined as antibiotics given for at least 2 days within the 14 days before an episode of *K. pneumoniae* bacteremia (11). Antibiotic therapy for the episode of *K. pneumoniae* bacteremia was the receipt of antibiotics that are active in vitro against the blood culture isolate (that is, susceptible according to 1999 NCCLS breakpoints (12), given for at least 2 days within the first 5 days of collection of the first positive blood culture. Mortality was death from any cause within 14 days from the date of the first positive blood culture for *K. pneumoniae*.

Microbiological Analysis

Production of ESBL was phenotypically determined by broth dilution using the NCCLS performance standards current as of January 1999 (12). A ≥3 twofold decrease in the minimal inhibitory concentration (MIC) for cefotaxime or ceftazidime tested in combination with clavulanic acid compared with its MIC when tested alone was considered phenotypic confirmation of ESBL production. For example, an isolate with a ceftazidime MIC of 8 μg/mL and a ceftazidime–clavulanic acid MIC of 1 μg/mL fulfills this definition of an ESBL-producing organism (12). The MICs of antibiotics commonly used in the treatment of gram-negative sepsis were determined for the ESBL-producing isolates by using the gradient diffusion method (Etest, AB Biodisk, Solna, Sweden).

Pulsed-field gel electrophoresis was used to establish the genotypic relationships of ESBL-producing isolates from each hospital (11).

Statistical Analysis

All statistical comparisons were made by using PROPHET Statistics software, version 6.0 (ABTech-BBN Corp., Charlottesville, Virginia) or Stata software, version 7.0 (Stata Corp., College Station, Texas). For bivariate comparisons, the chi-square or Fisher exact test was used to compare categorical variables. Continuous variables were compared by using the *t*-test or the Mann–Whitney test. Length of stay before positive blood culture was missing for

Table 1. **The Pitt Bacteremia Score***

Criterion	Points
Fever (oral temperature)	
≤35°C or ≥40°C	2
35.1–36.0°C or 39.0–39.9°C	1
36.1–38.9°C	0
Hypotension	2
Acute hypotensive event with drop in systolic blood pressure > 30 mm Hg and diastolic blood pressure > 20 mm Hg or Requirement for intravenous vasopressor agents or Systolic blood pressure < 90 mm Hg	
Mechanical ventilation	2
Cardiac arrest	4
Mental status	
Alert	0
Disoriented	1
Stuporous	2
Comatose	4

* All criteria are graded within 48 hours before or on the day of first positive blood culture. The highest point score during that time is recorded.

Table 2. **Characteristics of 244 Patients with Nosocomial *Klebsiella pneumoniae* Bacteremia**

Characteristic	Data
Country of residence, *% (n)*	
South Africa	31.1 (76)
Taiwan	18.9 (46)
Australia	17.2 (42)
Argentina	13.9 (34)
United States	10.2 (25)
Belgium	4.9 (12)
Turkey	3.7 (9)
Demographic	
Men, *% (n)*	60.7 (148)
Women, *% (n)*	39.3 (96)
Median age (range), y	58 (17–90)
Nursing home resident	2.9 (7)
Underlying disease	
Cancer	38.5 (94)
Diabetes mellitus	15.2 (37)
Chronic liver disease	13.1 (32)
Chronic renal failure	6.6 (16)
Transplant recipient	4.5 (11)
Burns	3.7 (10)
No underlying chronic condition	21.3 (52)

10 (4%) patients, all of whom had been readmitted within 1 week of discharge. Length of stay for these 10 patients was therefore estimated by using a predictive model that assumed "missing at random."

Because previous receipt of antibiotics was not random, a propensity score model was used to further evaluate the effect of receipt of antibiotics containing an oxyimino group as a risk for ESBL production. The score was calculated by using a logistic model in which receipt of β-lactam antibiotics containing an oxyimino group (cefuroxime, ceftriaxone, cefotaxime, ceftazidime, or aztreonam) was the dependent variable (scored as yes or no) and predictors were all available factors hypothesized to influence the receipt of antibiotic therapy (underlying patient conditions), with adjustment for center by using the indicator variables for site. Factors included in the calculation of this score were age, sex, admission from nursing home, underlying diseases (cancer, HIV infection, diabetes, or renal and liver disease), previous surgery, use of corticosteroids, presence of a central line, mechanical ventilatory support, presence of a nasogastric tube, and the indicator variables for site. A logistic model clustered on the patient that used receipt of antibiotics containing an oxyimino group and the quintile stratified score was then used to evaluate the risk for ESBL production.

Role of the Funding Source

Merck and Company provided support for laboratory studies but played no role in study design, conduct of the study, interpretation of the results, or approval of the study before publication.

RESULTS

During the study period, 455 episodes of *K. pneumoniae* bacteremia occurred in 440 patients; of these, 202

(44.4%) episodes in 196 patients were community acquired and 253 (55.6%) episodes in 244 patients were nosocomially acquired. **Table 2** shows the characteristics of the participants.

Of the episodes of *K. pneumoniae* bacteremia, 18.7% (85 of 455) were due to ESBL-producing organisms and 81.1% (369 of 455) were due to non–ESBL-producing organisms. One additional episode involved an isolate that showed a markedly elevated MIC for the oxyimino β-lactam antibiotics but no decrease in MIC with the addition of clavulanic acid. This isolate had an MIC for cephamycin antibiotics in the resistant range and may have possessed an AmpC-like enzyme. This episode was excluded from further analysis.

Seventy-eight of 253 (30.8%) episodes of nosocomial bacteremia were due to ESBL-producing organisms. **Table 3** shows the sites of infection associated with nosocomial ESBL-producing *K. pneumoniae* bacteremia. Fewer episodes of community-acquired *K. pneumoniae* bacteremia (3.5% [7 of 202]) were due to ESBL-producing organisms (*P* <0.001) (risk ratio, 8.9 [95% CI, 4.2 to 18.8]). Of the 253 episodes of nosocomial bacteremia, 69 were acquired in the intensive care unit. Of these 69 episodes, 30 (43.5%) episodes of *K. pneumoniae* bacteremia acquired in the intensive care unit were due to ESBL-producing organisms. Polymicrobial bacteremia was noted in 15.4% (12 of 78) episodes of nosocomial *K. pneumoniae* bacteremia due to ESBL-producing organisms, 21.7% (38 of 175) episodes of nosocomial bacteremia due to non–ESBL-producing organisms, and 16.3% (33 of 202) episodes of community-acquired bacteremia.

Risk Factors for Nosocomial Bacteremia Due to ESBL-Producing *K. pneumoniae*

The proportion of episodes of nosocomial bacteremia due to ESBL-producing *K. pneumoniae* by country was 78% (7 of 9) in Turkey, 59% (20 of 34) in Argentina, 37% (28 of 76) in South Africa, 36% (12 of 33) in the United States, 25% (3 of 12) in Belgium, 12% (5 of 43) in Australia, and 7% (3 of 46) in Taiwan. On bivariate analysis, compared with patients from the 2 U.S. hospitals, patients in the Turkish hospital were more likely to be infected with ESBL-producing organisms (risk ratio, 6.1 [CI, 1.1 to 34.3]) and those in the Taiwanese hospital were less likely to be infected with ESBL-producing organisms (risk ratio, 0.12 [CI, 0.03 to 0.48]).

The following variables were not significantly associated with nosocomial bacteremia due to an ESBL-producing organism on bivariate analysis: sex, age, admission from a nursing home, severity of illness, underlying diabetes mellitus, liver disease or HIV infection, previous transplantation surgery, any surgery in the 30 days before the onset of bacteremia, use of corticosteroids, presence of a central venous line, mechanical ventilatory support, or presence of a nasogastric tube.

Table 4 shows the relationships between antibiotic ex-

Table 3. Characteristics of Episodes of Nosocomial Bacteremia with and without Organisms That Produce Extended-Spectrum β-Lactamase*

Variable	ESBL-Producing Organisms (n = 78)	Non-ESBL Producing Organisms (n = 175)	All Episodes (n = 253)†	Bivariate Risk Ratio (95% CI)
In intensive care unit at first positive blood culture, % (n/n)				
Yes	43.5 (30/69)	56.5 (39/69)	27.3 (69/253)	1.67 (1.16–2.40)
No	26.1 (48/184)	73.9 (136/184)	72.7 (184/253)	
Mean length ± SE of hospitalization before positive blood culture, d	36.3 ± 5.4	19.9 ± 1.9	25.1 ± 2.2	1.01 (1.00–1.02)
Renal failure, % (n/n)				
Yes	55.6 (10/18)	44.4 (8/18)	7.1 (18/253)	1.92 (1.21–3.04)
No	28.9 (68/235)	71.1 (167/235)	92.9 (235/253)	
Burns, % (n/n)				
Yes	80.0 (8/10)	20.0 (2/10)	4.0 (10/253)	2.78 (1.92–4.01)
No	28.8 (70/243)	71.2 (173/243)	96.0 (243/253)	
Total parenteral nutrition, % (n/n)				
Yes	46.1 (24/52)	53.9 (28/52)	20.6 (52/253)	1.72 (1.18–2.49)
No	26.9 (54/201)	73.1 (147/201)	79.4 (201/253)	
Indwelling urinary catheter, % (n/n)				
Yes	39.6 (53/134)	60.4 (81/134)	53.0 (134/253)	1.88 (1.25–2.83)
No	21.0 (25/119)	79.0 (94/119)	47.0 (119/253)	
Neutropenia, % (n/n)				
Yes	8.3 (3/36)	91.7 (33/36)	14.2 (36/253)	0.24 (0.08–0.72)
No	34.6 (75/217)	65.4 (142/217)	85.85 (217/253)	
Positive test for *Klebsiella* within 2 weeks, % (n/n)				
Yes	59.3 (32/54)	40.7 (22/54)	21.3 (54/253)	2.56 (1.83–3.59)
No	23.1 (46/199)	76.9 (153/199)	78.7 (199/253)	
Previous use of an oxymino group antibiotic, % (n/n)				
Yes	75.05 (30/40)	25.0 (10/40)	15.8 (40/253)	3.33 (2.45–4.52)
No	22.5 (48/213)	77.5 (165/213)	84.2 (213/253)	
Source of infection, % (n/n)				
Undetermined	11.9 (5/42)	88.1 (37/42)	16.6 (42/253)	
Pneumonia	33.3 (20/60)	66.7 (40/60)	27.7 (60/253)	
Urinary tract infection	33.3 (14/42)	66.7 (28/42)	16.6 (42/253)	
Vascular catheter	47.2 (17/36)	52.8 (19/36)	14.2 (36/253)	
Intra-abdominal collection	32.4 (12/37)	67.6 (25/37)	14.6 (37/253)	
Wound infection	28.6 (4/14)	71.4 (10/14)	5.5 (14/253)	
Other	27.3 (6/22)	72.7 (16/22)	6.3 (16/253)	

* ESBL = extended-spectrum β-lactamase.
† Six patients had multiple episodes of *Klebsiella* bacteremia.

posure and subsequent bacteremia with an ESBL-producing *K. pneumoniae* strain. Because exposure to a β-lactam antibiotic containing an oxymino group is a key clinical question, we used a propensity score–adjusted logistic model to control for all confounders related to use of such agents. After this adjustment, the risk ratio for ESBL production associated with use of β-lactam antibiotics containing an oxymino group was 3.8 (CI, 1.1 to 13.8).

Death from Nosocomial *K. pneumoniae* Bacteremia

The mortality rate by 14 days after onset of nosocomial *K. pneumoniae* bacteremia was 24% (61 of 253 patients). Bacteremic nosocomial pneumonia was associated with a 37% mortality rate, bacteremia related to vascular line placement was associated with a 22% mortality rate, bacteremia related to wound infection was associated with a 20% mortality rate, bacteremia related to intra-abdominal collections was associated with a 16% mortality rate, and bacteremia related to urinary tract infection was associated with a 12% mortality rate. Mortality rates from nosocomial bacteremia were 27% (21 of 78) among patients infected with ESBL-producing *K. pneumoniae* and 23%

(40 of 175) among patients infected with non–ESBL-producing *K. pneumoniae.*

Molecular Epidemiology of ESBL-Producing *K. pneumoniae* Strains That Caused Bacteremia

In 7 of 10 (70%) hospitals in which multiple bloodstream isolates of ESBL-producing *K. pneumoniae* were found, at least two isolates shared the same genotypic pattern on pulsed-field gel electrophoresis, implying patient-to-patient transfer of identical organisms. In 6 of these 7 hospitals, patients were not routinely placed in contact isolation (single rooms and receipt of nursing with gown and gloves) as part of infection control policy after isolation of an ESBL-producing organism. In contrast, in 3 of the 5 (60%) hospitals in which no transmission of ESBL-producing organisms was documented, all patients were placed in contact isolation after the detection of such organisms.

DISCUSSION

For the past 30 years, *Klebsiella* species that are resistant to aminoglycosides have been known to cause out-

breaks of hospital-acquired infection (13). However, the advent of plasmid-mediated ESBL production by *Klebsiella* species, together with plasmid-mediated aminoglycoside resistance, in the early 1980s (14–16) signaled a major new problem with antibiotic resistance. In the 12 hospitals studied, we found that 30.8% of episodes of nosocomial *K. pneumoniae* bacteremia were with ESBL-producing strains. In intensive care units, in which antibiotic use is heaviest and the potential for patient-to-patient transmission of organisms is greatest, 43.5% of episodes of bacteremia due to *K. pneumoniae* involved ESBL-producing strains.

Many clinicians are probably unaware of the problem of ESBL production by gram-negative bacilli. Presence of genes encoding vancomycin resistance in *E. faecium* is readily apparent to clinicians by routine laboratory reports indicating resistance of the organism to vancomycin. However, there is no universally applicable marker of the presence of ESBLs. Although resistance of *K. pneumoniae* to ceftazidime is a useful marker of presence of ESBLs, fewer than 50% of *Klebsiella* isolates in the United States undergo testing for susceptibility to ceftazidime (17). Moreover, some types of ESBL-producing organisms appear susceptible to ceftazidime according to standard methods, and ceftazidime resistance may be due to mechanisms other than ESBL production. Unfortunately, many laboratories do not test for ESBL production (18).

Our results show that awareness of ESBL production by *K. pneumoniae* is clinically important. In the absence of infection control measures, ESBL-producing organisms readily pass horizontally from patient to patient. Reliable laboratory methods are now available by which ESBL production can be detected by clinical microbiology laboratories. These methods, which have been promoted by the NCCLS (12), rely on initial screening tests and follow-up confirmatory tests. We believe that clinicians should not have to specifically request these tests; rather, all significant *K. pneumoniae* isolates should undergo routine screening by clinical microbiology laboratories. Isolates suspected of producing ESBLs should not be reported as susceptible to third-generation cephalosporins or cefepime until follow-up confirmatory tests are performed.

We found that recent use of a β-lactam antibiotic containing an oxyimino group appeared to be a risk factor for ESBL production by *K. pneumoniae*. However, the relatively few patients who received these antibiotics and the relatively few ESBL producers preclude definitive conclusions about this link. In addition, clustering of episodes within patients was not considered in the statistical analy-

Table 4. **Relationship of Antibiotics Received within 14 Days of a Positive Blood Culture for *Klebsiella* and Development of Bacteremia with an ESBL-Producing Strain***

Antibiotic	ESBL-Producing Organisms (*n* = 78)	Non-ESBL Producing Organisms (*n* = 175)	Episodes in Which Antibiotic Was Given (*n* = 253)	Bivariate Risk Ratio (95% CI)
	←————————— % (*n/n*) —————————→			
Penicillins	26.1 (12/46)	73.9 (34/46)	18.2 (46/253)	0.82 (0.48–1.38)
β-Lactam–β-lactamase inhibitor combinations				
Ticarcillin–clavulanate	0 (0/7)	100.0 (7/7)	2.8 (7/253)	–
Ampicillin–sulbactam	28.6 (2/7)	71.4 (5/7)	2.8 (7/253)	0.92 (0.3–3.0)
Amoxicillin–clavulanate	14.3 (1/7)	85.7 (6/7)	2.8 (7/253)	0.46 (0.1–2.8)
Piperacillin–tazobactam	46.7 (7/15)	53.3 (8/15)	5.9 (15/253)	1.56 (0.9–2.8)
Any combination	29.4 (10/34)	70.6 (24/34)	13.4 (34/253)	0.95 (0.5–1.7)
First-generation cephalosporins	28.6 (4/14)	71.4 (10/14)	5.5 (14/253)	0.92 (0.4–2.2)
Second-generation cephalosporins				
Cefoxitin or cefotetan	0 (0/4)	100 (4/4)	1.6 (4/253)	–
Cefuroxime	75 (6/8)	25 (2/8)	3.2 (8/253)	2.55 (1.6–4.0)
Third-generation cephalosporins				
Cefotaxime	33.3 (1/3)	66.7 (2/3)	1.2 (3/253)	1.1 (0.2–5.4)
Ceftriaxone	85.7 (18/21)	14.3 (3/21)	8.3 (21/253)	3.31 (2.5–4.4)
Ceftazidime	66.7 (6/9)	33.3 (3/9)	3.6 (9/253)	2.26 (1.4–3.7)
Any third-generation cephalosporin	75.2 (23/31)	25.8 (8/31)	12.3 (31/253)	2.99 (2.2–4.1)
Any β-lactam antibiotic containing an oxyimino group	75.0 (30/40)	25.0 (10/40)	15.8 (40/253)	3.33 (2.45–4.52)
Fourth-generation cephalosporin (cefepime)	50 (1/2)	50 (1/2)	<1.0 (2/253)	1.63 (0.4–6.6)
Other antibiotics				
Aztreonam	100 (1/1)	0 (0/1)	<1.0 (1/253)	3.27 (2.7–3.9)
Carbapenems	35 (7/20)	65 (13/20)	7.9 (20/253)	1.15 (0.6–2.2)
Aminoglycosides	34.5 (20/58)	65.5 (38/58)	22.9 (58/253)	1.16 (0.8–1.8)
Macrolides	100 (3/3)	0 (0/3)	1.1 (3/253)	3.33 (2.8–4.0)
Glycopeptides	40.5 (17/42)	59.5 (25/42)	16.6 (42/253)	1.40 (0.9–2.1)
Quinolones	40.0 (8/20)	60.0 (12/20)	7.9 (20/253)	1.33 (0.8–2.4)
Trimethoprim–sulfamethoxazole	40.0 (4/10)	60.0 (6/10)	3.9 (10/253)	1.31 (0.6–2.9)
Clindamycin	60.0 (6/10)	40.0 (4/10)	3.9 (10/253)	2.0 (1.2–3.5)
Metronidazole	34.4 (11/32)	65.6 (21/32)	12.6 (32/253)	1.15 (0.7–1.9)

* ESBL = extended-spectrum β-lactamase.

ses; therefore, the true 95% CIs may be wider than those presented. Finally, the effect of previous administration of β-lactam antibiotics containing an oxyimino group may differ by hospital. However, the data are too few to test for such an interaction. Our analyses therefore can only provide hypotheses for further investigation. Several studies have shown that reducing use of ceftazidime (19, 20), all oxyimino β-lactam antibiotics (21, 22), or all cephalosporins (5) decreases the occurrence of ESBL-producing organisms. It has also been speculated that replacing cephalosporins with antibiotics containing β-lactamase inhibitors (such as piperacillin–tazobactam) may help to reduce the occurrence of ESBL-producing organisms (23–25).

The infection control implications of ESBL-producing *K. pneumoniae* are underrecognized. In 70% of the study hospitals, molecular genetic evidence indicated patient-to-patient transmission of ESBL-producing strains of *K. pneumoniae*. More than 50 hospital outbreaks of infection with ESBL-producing organisms have now been reported (26). In all hospitals that used molecular typing methods (such as pulsed-field gel electrophoresis), strains with the same genotypic pattern have been isolated from different patients (26). Removable environmental foci are rarely found (26, 27). Rather, as has been explicitly documented by several investigators (21, 28, 29), ESBL-producing *K. pneumoniae* transiently colonizes the hands of hospital staff members, thereby facilitating patient-to-patient transmission of the organism. In 6 of 7 hospitals in which genotypically related strains of ESBL-producing *K. pneumoniae* were found, the infection control policy did not mandate placing patients infected with these strains in contact isolation. Neutropenic patients were significantly less likely to have bacteremia with an ESBL-producing strain than with a non–ESBL-producing strain. This may be noteworthy because neutropenic patients are usually subjected to enhanced infection control measures.

We have documented the global distribution of ESBL-producing *K. pneumoniae*. However, the hospitals studied showed marked diversity in occurrence of ESBL-producing strains. Whether this is due to the differences in infection control practices among hospitals or to differences in use of antibiotics containing an oxyimino chain is uncertain. Despite the frequent occurrence of ESBL-producing organisms, laboratory detection of ESBLs has long been suboptimal. We have shown that detection of ESBLs is clinically relevant, given that patient-to-patient transmission of organisms harboring ESBLs clearly occurs. Reduction in use of β-lactam antibiotics containing an oxyimino group and infection control interventions may reduce the spread of ESBL-producing organisms within a hospital. In many hospitals, vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* are endemic. We may still be able to prevent ESBL-producing gram-negative bacilli from becoming endemic as well.

References

1. **Jacoby GA.** Genetics of extended-spectrum beta-lactamases. Eur J Clin Microbiol Infect Dis. 1994;13 Suppl 1:S2-11. [PMID: 7821301]

2. **Jacoby GA.** Extended-spectrum beta-lactamases and other enzymes providing resistance to oxyimino-beta-lactams. Infect Dis Clin North Am. 1997;11:875-87. [PMID: 9421705]

3. **Tenover FC, Mohammad JM, Gorton T, Dembek ZF.** Detection and reporting of extended-spectrum beta-lactamase (ESBL) producing organisms in Connecticut. Clin Infect Dis. 1998;27:1064.

4. **Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ.** Nosocomial outbreak of *Klebsiella* infection resistant to late-generation cephalosporins. Ann Intern Med. 1993;119:353-8. [PMID: 8135915]

5. **Rahal JJ, Urban C, Horn D, Freeman K, Segal-Maurer S, Maurer J, et al.** Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial Klebsiella. JAMA. 1998;280:1233-7. [PMID: 9786372]

6. **Korvick JA, Bryan CS, Farber B, Beam TR Jr, Schenfeld L, Muder RR, et al.** Prospective observational study of *Klebsiella* bacteremia in 230 patients: outcome

for antibiotic combinations versus monotherapy. Antimicrob Agents Chemother. 1992;36:2639-44. [PMID: 1482131]

7. **Chow JW, Fine MJ, Shlaes DM, Quinn JP, Hooper DC, Johnson MP, et al.** *Enterobacter* bacteremia: clinical features and emergence of antibiotic resistance during therapy. Ann Intern Med. 1991;115:585-90. [PMID: 1892329]

8. **Chow JW, Yu VL.** Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. Int J Antimicrob Agents. 1999;11:7-12. [PMID: 10075272]

9. **Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al.** The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100:1619-36. [PMID: 1959406]

10. **Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM.** CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16:128-40. [PMID: 2841893]

11. **Paterson DL, Mulazimoglu L, Casellas JM, Ko WC, Goossens H, Von Gottberg A, 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;30:473-8. [PMID: 10722430]

12. **National Committee for Clinical Laboratory Standards.** Performance standards for antimicrobial susceptibility testing. Ninth Informational Supplement. Wayne, PA: National Committee for Clinical Laboratory Standards; 1999.

13. **Casewell MW, Phillips I.** Aspects of the plasmid-mediated antibiotic resistance and epidemiology of *Klebsiella* species. Am J Med. 1981;70:459-62. [PMID: 7468627]

14. **Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S.** Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of *Klebsiella pneumoniae* and Serratia marcescens. Infection. 1983;11:315-7. [PMID: 6321357]

15. **Payne DJ, Marriott MS, Amyes SG.** Characterisation of a unique ceftazidime-hydrolysing beta-lactamase, TEM-E2. J Med Microbiol. 1990;32:131-4. [PMID: 2192063]

16. **Casellas JM, Goldberg M.** Incidence of strains producing extended spectrum beta-lactamases in Argentina. Infection. 1989;17:434-6. [PMID: 2613338]

17. **Monnet DL, Biddle JW, Edwards JR, Culver DH, Tolson JS, Martone WJ, et al.** Evidence of interhospital transmission of extended-spectrum beta-lactam-resistant *Klebsiella pneumoniae* in the United States, 1986 to 1993. The National Nosocomial Infections Surveillance System. Infect Control Hosp Epidemiol. 1997;18:492-8. [PMID: 9247832]

18. Laboratory capacity to detect antimicrobial resistance, 1998. MMWR Morb Mortal Wkly Rep. 2000;48:1167-71.

19. **Rice LB, Willey SH, Papanicolaou GA, Medeiros AA, Eliopoulos GM, Moellering RC Jr, et al.** Outbreak of ceftazidime resistance caused by extended-spectrum beta-lactamases at a Massachusetts chronic-care facility. Antimicrob Agents Chemother. 1990;34:2193-9. [PMID: 2073110]

20. **Naumovski L, Quinn JP, Miyashiro D, Patel M, Bush K, Singer SB, et al.** Outbreak of ceftazidime resistance due to a novel extended-spectrum beta-lactamase in isolates from cancer patients. Antimicrob Agents Chemother. 1992;36:1991-6. [PMID: 1416892]

21. **Coulter C, Faoagali JC, Doige S, Bodman J, George N.** Hand culture surveillance to investigate transmission of epidemic extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* in a major intensive care unit [Abstract]. Austr N Z J Med. 1995;25:572.

22. **Pena C, Pujol M, Ricart A, Ardanuy C, Ayats J, et al.** Risk factors for faecal carriage of *Klebsiella pneumoniae* producing extended spectrum beta-lactamase (ESBL-KP) in the intensive care unit. J Hosp Infect. 1997;35:9-16. [PMID: 9032631]

23. **Rice LB, Eckstein EC, DeVente J, Shlaes DM.** Ceftazidime-resistant *Klebsiella pneumoniae* isolates recovered at the Cleveland Department of Veterans Affairs Medical Center. Clin Infect Dis. 1996;23:118-24. [PMID: 8816140]

24. **Piroth L, Aube H, Doise JM, Vincent-Martin M.** Spread of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*: are beta-lactamase inhibitors of therapeutic value? Clin Infect Dis. 1998;27:76-80. [PMID: 9675456]

25. **Amyes SG, Miles RS.** Extended-spectrum beta-lactamases: the role of inhibitors in therapy. J Antimicrob Chemother. 1998;42:415-7. [PMID: 9818738]

26. **Paterson DL, Yu VL.** Extended-spectrum beta-lactamases: a call for improved detection and control [Editorial]. Clin Infect Dis. 1999;29:1419-22. [PMID: 10585789]

27. **Gaillot O, Maujouls C, Abachin E, Lecuru F, Arlet G, Simonet M, et al.** Nosocomial outbreak of *Klebsiella pneumoniae* producing SHV-5 extended-spectrum beta-lactamase, originating from a contaminated ultrasonography coupling gel. J Clin Microbiol. 1998;36:1357-60. [PMID: 9574705]

28. **Eisen D, Russell EG, Tymms M, Roper EJ, Grayson ML, Turnidge J.** Random amplified polymorphic DNA and plasmid analyses used in investigation of an outbreak of multiresistant *Klebsiella pneumoniae*. J Clin Microbiol. 1995;33:713-7. [PMID: 7751382]

29. **Hobson RP, MacKenzie FM, Gould IM.** An outbreak of multiply-resistant *Klebsiella pneumoniae* in the Grampian region of Scotland. J Hosp Infect. 1996;33:249-62. [PMID: 8864938]

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