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Cefotaxime-Resistant Bacteria Colonizing Older People Admitted to an Acute Care Hospital

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Abstract

OBJECTIVES—To determine the frequency of fecal colonization by cefotaxime-resistant gram-negative bacilli in older patients living in the community and in long-term care facilities (LTCFs) admitted to an acute care hospital.

DESIGN—Case-control, point prevalence study.

SETTING—Hospital.

PARTICIPANTS—One hundred forty-three patients aged 65 and older.

MEASUREMENTS—Rectal swab cultures, antibiotic drug sensitivity, beta lactamase isolation, and clonal identity.

RESULTS—Of the 190 surveillance cultures obtained from 143 patients, 26 cefotaxime-resistant gram-negative isolates from 22 patients were recovered. The prevalence rate of cefotaxime-resistant isolates on admission was 13.3% (19/143). A logistic regression model using cefotaxime colonization as the dependent variable found that multiple comorbidities, admission to a surgical service, and having a diagnosis of infection on presentation and a transfusion history were factors associated with the presence of colonization. These four clinical items accurately classified 74% of patients colonized. Antibiotic use and nursing home residence were not associated with the presence of colonization by cefotaxime-resistant organisms. Twelve of the cefotaxime-resistant isolates (46%) were identified as *Pseudomonas aeruginosa*, and 14 (54%) were other gram-negative bacilli. In six of the 14 isolates that were not *P. aeruginosa* (36%), it was possible to demonstrate the presence of an AmpC β-lactamase related to the CMY-2 β-lactamase, a plasmid-borne cephalosporinase.

CONCLUSION—These data raise awareness that there are community- and LTCF-dwelling older patients colonized with gram-negative enteric bacilli resistant to third-generation

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cephalosporins on admission to the hospital. The “reservoir of resistant bacteria” in older people is no longer confined to LTCFs.

Keywords

cefotaxime; cephalosporinase; long-term care facilities; antibiotic resistance

Infectious diseases are a major cause of morbidity and mortality in older people.[1] Excessive antibiotic use in long-term care facilities (LTCFs) has been associated with the emergence of β-lactam-resistant enteric bacilli possessing β-lactamases that confer resistance to third-generation cephalosporins and β-lactam β-lactamase inhibitor combinations.[2–7] The increasing occurrence of β-lactam-resistant gram-negative bacilli colonizing older people and causing significant infections in LTCFs threatens the quality of life of the institutionalized older people and compromises the utility of the most-trusted and highly effective antibiotics.[8–14] The fecal flora represent a large potential repository for the evolution of antibiotic-resistant organisms and a site where resistance genes transfer from commensal flora to virulent microorganisms.[15–18] To assess the frequency with which community- and LTCF-dwelling older people are colonized by third-generation cephalosporin-resistant organisms, the enteric flora of patients aged 65 and older admitted to a dedicated geriatrics unit at the University Hospital of Cleveland were screened.

MATERIALS AND METHODS

Patient Population

Older patients (≥65) admitted to the geriatrics unit were enrolled in the study. The characteristics and features of the unit were patterned after a previously described Acute Care for Elders unit at this hospital.[19] Criteria for admission and enrollment into this study were modified to include medical and surgical patients on a single unit. Unlike the previous study performed by Landefeld et al., random assignment to this unit was not performed.[19] Attending and resident physicians provided care to the study group and the control group. During the period of the survey, an average of 65 patients was admitted to this unit per month. A convenience sample of patients (n = 143) was studied during a 6-month period. Verbal consent was obtained from each patient or responsible caregiver (proxy) according to procedures approved by the hospital institutional review board and documented in the medical record.

Microbiology

Rectal swabs were obtained from 143 admitted patients and were initially streaked on MacConkey agar (Fisher Scientific, Pittsburgh, PA). Three single colonies were randomly picked, suspended in Luria Bertani (Fisher Scientific) broth (approximate 0.5 MacFarland density), and plated as a lawn on Mueller-Hinton agar. Commercially available cefotaxime discs were placed on each plate, and plates were incubated for 18 to 24 hours at 37°C. Isolates demonstrating a cefotaxime zone size of 27 mm or less were identified, and minimum inhibitory concentrations were performed using microdilution trays. All isolates were tested using a standard panel of β-lactams (imipenem, piperacillin, piperacillin/tazobactam, ceftriaxone, ceftazidime) and ciprofloxacin. The criteria established by the National Committee on Clinical Laboratory Standards were followed.[20,21]

Definitions and Analysis

In this case-control study, the patients who were colonized with cefotaxime-resistant organisms on admission or upon discharge were identified as the cefotaxime (+) group. Medical records of 22 of the 24 individual patients in the cefotaxime (+) group were

reviewed (two charts were not found). Twenty-four age-matched patients admitted to the geriatrics unit during the period of the study who were not colonized by cefotaxime-resistant organisms on admission or discharge were designated as the control group, cefotaxime (−). Univariate and multivariate analyses (logistic regression analysis) were used to compare cases and controls.[22] Factors chosen for analysis were based upon previous studies.[8,10,11,18,19] Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) scores were determined.[23]

Pulsed Field Gel Electrophoresis

Pulsed field gel electrophoresis (PFGE) methods previously described were used to type cefotaxime-resistant isolates.[24] The banding patterns of different isolates were compared according to published standards.[25]

Immunoblotting

Immunoblots were performed according to a recently developed method.[26] A polyclonal anti-TEM antibody was obtained from Dr. Timothy Palzkill.

RESULTS

Screening for Cefotaxime-Resistant Isolates

One hundred ninety surveillance cultures were obtained from 143 patients. Paired admission and discharge samples were collected for 47 patients; for the remaining 96 patients, samples were obtained only on admission.

Twenty-six isolates from 22 patients were identified as resistant to cefotaxime (zone size <27 mm). Nineteen patients with cefotaxime-resistant isolates (cefotaxime (+) group), had the organism cultured from stool at the time of admission (19/143 = 13.3% prevalence rate). Of the 47 patients who had paired samples (admission and discharge) and who possessed organisms that were not cefotaxime-resistant (cefotaxime (−) group) on admission, seven acquired cefotaxime-resistant pathogens during hospitalization.

Univariate Analysis

Factors significantly associated with colonization by cefotaxime-resistant gram-negative bacilli at $P < .05$ were multiple comorbidities, higher APACHE II score on admission, and diagnosis of infection upon presentation (Table 1). Patients treated with antibiotics or hospitalized in the preceding 4 weeks were not found to have been statistically more likely to be colonized with cefotaxime-resistant bacteria.

Multivariate Analysis

The chi-square test for the significance of this model (over a model with a constant alone) was $P = .0007$, indicating that this model demonstrated good fit with the data in the present study. Within the sample of subjects included in this case-control study, four factors properly classified individuals as colonized/not colonized 74% of the time. These included number of coexisting medical conditions, diagnosis of infection on admission, a history of transfusion, and admission to a surgical service (Table 2).

Microbiology

The predominant cefotaxime-resistant organism was *Pseudomonas aeruginosa*. *Escherichia coli* and *Enterobacter* spp. were the next most-common isolates resistant to cefotaxime. Cefotaxime-resistant isolates were tested against a standard set of antibiotics. The susceptibility data show that seven of the 26 cefotaxime-resistant isolates (26.1%) were

ceftazidime resistant. A smaller percentage of isolates was resistant to ceftriaxone (15.4%), piperacillin (15.4%), and piperacillin/tazobactam (11.5%). Only one isolate (*P. aeruginosa*) was resistant to imipenem and ertapenem. Three *E. coli* isolates that were cefotaxime-resistant were susceptible to piperacillin/tazobactam (suggesting the presence of an extended spectrum β-lactamase (ESBL). Four of 26 isolates (15.4%) were resistant to ciprofloxacin.

Pulsed Field Gel Electrophoresis

The only strains that were clonally identical were the three cefotaxime-resistant *E. coli* isolates obtained from a single patient. The remaining isolates demonstrated different PFGE patterns.

Immunoblotting

Three of the four *E. coli* isolates, the *Citrobacter freundii, E. cloacae*, and *Morganella morganii* isolates possessed a Class C β-lactamase related to CMY-2 β-lactamase (data not shown). Using the anti-TEM antibody that detects both TEM and SHV β-lactamases, a β-lactamase of the TEM or SHV type was detected in *C. freundii*.

DISCUSSION

Using this study's enrollment method, 13.3% of patients admitted to the geriatrics unit were colonized by cefotaxime-resistant pathogens. The screening method (swabs obtained from nearly half of the patients admitted to this unit during the 6-month study period) and cefotaxime-resistance detection method (three colonies randomly picked from a nonselective MacConkey plate) may not have identified all the resistant isolates. Multivariate analysis identified four factors that correctly predicted 74% of patients colonized with cefotaxime-resistant organisms (Table 2). It was also determined that having cefotaxime-resistant flora colonizing the stool was unrelated to previous residence in an LTCF. Equally surprising, these data did not show that receiving antibiotics within the 4 weeks before admission was associated with colonization. It is important to acknowledge specific limitations of these findings; medical admission histories documented in the charts and reviews of information on transfer to the hospital may not have included accurate information regarding antibiotic use in the preceding 4 weeks. Despite this careful review of the available data, the use of antibiotics may have been more common than was determined

To explain these findings, it is proposed that older patients with multiple comorbidities have their flora altered numerous times by the remote use of prescribed antibiotics or have acquired the resistant flora from an “antibiotic rich” environment. The net effect observed (cefotaxime-resistant isolates in the fecal flora) might be a cumulative one: an adaptation of intestinal microflora to many antibiotic “challenges.” In the gastrointestinal tract with multiple bacterial populations, the half-life of enteric carriage of resistant β-lactam genes is unknown. If establishment and stable maintenance of resistance genes and resistance transfer elements occurs even in the absence of antibiotic selection, efforts to control the emergence of resistant bacteria infecting and colonizing older people need to include more than antibiotic restriction and antibiotic cycling policies.

The molecular analysis of a subset of pathogens from patients admitted to this hospital revealed that the major β-lactamase present was related to CMY-2 β-lactamase, the most-prevalent plasmid-mediated AmpC cephalosporinase.[26,27] The antibody test detected AmpC β-lactamase in the *Enterobacter cloacae, Morganella* spp., *C. freundii*, and *E. coli* isolates. Although this specific β-lactamase was not identified using polymerase chain reaction amplification and deoxyribonucleic acid sequencing, the β-lactamase might represent plasmid-encoded AmpC cephalosporinase. If so, this finding would have significant

implications for this hospital's infection control policy because the plasmid-mediated β-lactamases can be transmitted to other genera of bacteria more readily.

Older patients are frequently mobile between acute care settings, LTCFs, and the community. Current studies have exclusively focused on epidemiological factors associated with colonization by third-generation cephalosporin-resistant bacteria of older people in LTCFs.[3,4,8,10,11] This study, despite its limitations, is a recent study of community and LTCF populations admitted to an acute care hospital. This study urges the investigation of the emergence of antibiotic resistant pathogens in older people in the community and LTCFs in the area.

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Table 1

Comparison of Cefotaxime (+) and Cefotaxime (−) Groups: Selected Demographic, Background, Pre-Admission, and Admission Factors

Factor	Cefotaxime (+) (n = 22)	Cefotaxime (−) (n = 24)	*P*-value	Odds Ratio	95% Confidence Interval
Demographics					
Age, mean ± standard deviation (SD)	80.64 ± 8.05	79.83 ± 8.11	.738	1.01	0.94–1.09
Gender (female), %	54.5	62.5	.804	0.72	0.22–2.34
Race (white), %	40.9	58.3	.376	0.50	0.15–1.60
Medical history					
Diabetes mellitus, %	45.5	20.8	.143	3.17	0.87–11.55
Malignancy (solid organ), %	45.5	25.0	.252	2.50	0.72–8.71
Prior surgery, %	72.7	70.8	.999	1.10	0.30–3.98
Infectious disease history, %*	27.3	16.7	.484	1.88	0.45–7.80
Transfusion history before admission, %	31.8	8.3	.066+	5.13	0.94–28.18
Number of hospitalizations in past year ± SD	2.27 ± 1.35	2.46 ± 2.09	.725	0.94	0.67–1.32
Hospital admission/discharge within 4 weeks, %	31.8	20.8	.609	1.77	0.47–6.72
Pre-admission					
Residence (nursing home), %	31.8	20.8	.609	1.77	0.47–6.72
Corticosteroid use, %	22.7	4.2	.090+	6.76	0.72–63.33
Antibiotic use (within 4 weeks), %	50.0	25.0	.147	3.00	0.86–10.43
Number of antibiotics used in hospital ± SD	0.73 ± 1.24	0.33 ± .76	.208	1.51	1.26–2.87
Admission					
Admitting service (surgical), %	31.8	20.8	.066+	5.13	0.94–28.18
Acute Physiology, Age, and Chronic Health Evaluation II score ± SD	18.59 ± 6.90	14.79 ± 5.00	.037§	1.12	1.00–1.25
Comorbidities‡ ± SD	0.91 ± 1.15	0.33 ± .57	.042§	2.24	1.00–5.03
PEG tube, %	22.7	4.2	.090+	6.77	0.72–63.33
Anemia, %	4.5	25.0	.098+	0.14	0.02–1.30
Infection•, %	59.1	25.0	.041§	4.33	1.24–15.21

Cefotaxime (+) = patients who were colonized with cefotaxime-resistant organisms on admission or discharge; Cefotaxime (−) = patients admitted to the geriatrics unit during the period of the study who were not colonized by cefotaxime-resistant organisms on admission or discharge.

PEG = percutaneous endoscopic gastrostomy.

[*] Infectious disease history is defined as a history of human immunodeficiency virus infection, acquired immunodeficiency syndrome, chronic osteomyelitis, endocarditis, treated diabetic foot ulcer or pressure ulcer in the past 6 months, or syphilis.

[+] Approaches significance (<0.10 but >0.05).

[‡] Comorbidities include wheelchair use, chronic indwelling bladder catheter, and malnutrition present at time of admission.

[•] Infection on admission is defined as the diagnosis of pneumonia, urinary tract infection, cellulitis, acute infected pressure ulcer, acute osteomyelitis, or sepsis.

[§] $P < .05$.

Table 2

Logistic Regression Model with Cefotaxime (+)/Cefotaxime (−) as the Dependent Variable

Independent Variable	*P*-value	Odds Ratio	95% Confidence Interval
Diagnosis of infection on admission	.067	4.23	0.90–19.85
History of transfusion	.053	8.09	0.98–67.22
Admitting service (surgical)	.015	12.80	1.65–99.20
Number of coexisting medical conditions	.058	2.79	0.97–8.07