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Major article

Risk factors for acquisition of extended-spectrum β-lactamase–producing *Escherichia coli* in an urban county hospital

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Background: Better characterization of risk factors for extended-spectrum β-lactamase (ESBL)-producing bacteria is important for prevention, control, and treatment. This study aimed to identify risk factors for ESBL-producing *Escherichia coli* in a population of patients at an acute care urban teaching hospital.
Methods: A matched case-control study was performed. Cases comprised adults with ESBL *E coli* isolated from any source and matched with controls on year of hospitalization. One control group included patients with non-ESBL *E coli*, and a second control group consisted of patients with another resistant bacterium with well-characterized risk factors, *Pseudomonas aeruginosa*.
Results: There were 93 subjects in each group. Risk factors associated with ESBL cases compared with both control groups in a univariate model included sex, age, comorbidity, health care facility residence, recent hospitalization, and hemodialysis. In multivariate analysis, only Charlson comorbidity score remained significant between the cases and both control groups. Recent receipt of antibiotics was a risk factor for ESBL *E coli* versus non-ESBL *E coli* but not versus *P aeruginosa*.
Conclusions: Underlying comorbid illness appears to be a robust risk factor for acquisition of ESBL-producing *E coli*. Antibiotic use is a less clear risk factor and may be a surrogate for health care exposure in general.

Antibiotic resistance is a growing problem in acute care hospitals. Extended-spectrum β- lactamases (ESBLs) are heterogeneous bacterial enzymes that result in cleavage and inactivation of extended-spectrum cephalosporins, monobactams, and penicillins.[1-3] These enzymes are found most commonly in the Enterobacteriaceae family, and organisms that produce ESBLs are often resistant to non–β-lactam antibiotics, such as fluoroquinolones and aminoglycosides, by additional mechanisms.[1] Given that many of these antibiotics are used as first-line agents for empirical therapy of serious infections in hospitalized patients, the increase in bacteria carrying ESBLs is alarming and likely to lead to delays in instituting appropriate therapy, which in turn has been shown to increase mortality.[4,5]

According to data from the National Nosocomial Surveillance System for 1998-2004, 1.3% of *E coli* strains in intensive care units (ICUs), 1.5% of strains in non-ICU inpatient areas, and 0.6% of strains in outpatient areas in the United States showed resistance to third-generation cephalosporins.[3] Worldwide, ESBLs and other resistance enzymes are even more of a problem. During 2003-2008, the International Nosocomial Infection Control Consortium found that 53.9% of *E coli* causing catheter-associated bloodstream infections were resistant to either ceftriaxone or ceftazadime.[6] Several groups have described risk factors for infection with ESBL-producing bacteria, including presence of indwelling catheters, ICU stay, extended hospital stay, previous antibiotic therapy, and residence in a nursing home.[7,8] Many of these studies are small and combine groups of bacteria when looking at risk factors. As ESBLs become more common, better characterization of risk factors is an important aspect of prevention, infection control, and treatment.

At San Francisco General Hospital, the majority of infections with ESBL-producing bacteria are from *E coli*. The rate has increased from <1% in 2003 up to the current rate of approximately 5% (unpublished data, San Francisco General Hospital Microbiology Laboratory). This case-control study was designed to examine risk factors for colonization or infection with ESBL-producing *E coli* in a

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large sample of hospitalized patients. Because using the antibiotic-sensitive organism as a control might overestimate the risk attributed to antibiotic exposure, 2 control groups were used: patients infected or colonized with nonresistant *E coli* and those infected or colonized with *Pseudomonas aeruginosa*, another resistant bacterium with well-characterized risk factors.[9] Because increasing medical comorbidity and immunosuppression are risk factors for *Pseudomonas* colonization and infection, this population is presumed to be at greater risk for other antibiotic-resistant organisms, such as ESBL *E coli*.[10,11] The *Pseudomonas* control group was chosen to allow us to better characterize risk factors for ESBL *E coli* specifically in a high-risk population rather than risk factors for resistant organisms in general. In other words, choosing this control group allowed us to examine the particular risk factors for ESBL-producing *E coli* in patients at high risk for resistant infections (eg, those with *P aeruginosa*).

METHODS

Study design and population

We conducted a matched case-control study to assess risk factors for acquisition of ESBL-producing *E coli*. The study population comprised inpatients treated at San Francisco General Hospital, a 300-bed county hospital serving San Francisco. The University of California San Francisco's Committee on Human Research approved this study.

Identification of cases and controls

Cases were identified from the San Francisco General Hospital's microbiology database and comprised adult inpatients over age 18 years with ESBL *E coli* isolated from any source between January 1, 2004, and December 31, 2007. From the microbiological database, we identified 2 control groups of adult inpatients with positive microbiologic cultures from any site during the same time period, one group with non–ESBL-producing *E coli* and one with *P aeruginosa*. Non-ESBL *E coli* controls could have any susceptibility pattern but were not allowed to be ESBL-producers. *P aeruginosa* controls could have any susceptibility pattern. Cases and controls were matched by year of hospitalization using frequency matching. Year of hospitalization was chosen for matching to help control for temporal trends, as ESBLs became more frequent throughout the study period. Controls were eligible only for the year of the first positive culture. When there were more controls available than required for 1:1 matching, subjects were chosen randomly. Potential controls with more than one positive culture had an equal chance of being selected as potential controls with only one positive culture. Subjects with *E coli* or *P aeruginosa* isolated from multiple sites or on multiple dates were counted only once as either a case or a control. Those who had the bacteria isolated as outpatients or as patients in the extended-care facility were excluded from the analysis.

Laboratory identification of ESBL

ESBLs were identified in a 2-step process in accordance with Clinical and Laboratory Standards Institute guidelines.[12] When indicated, phenotypic testing was done by the hospital's microbiology laboratory using semiautomated dehydrated broth microdilution (Microscan ESBL Plus; Siemens Healthcare Diagnostics, West Sacramento, CA). An organism was defined as an ESBL-producer if the minimum inhibitory concentration decreased 3-fold to ceftazidime or cefotaxime plus clavulanic acid compared with ceftazidime or cefotaxime alone.

Assessment of risk factors

Clinical data were collected from the electronic medical records. Variables collected included sex, race/ethnicity, age, residence before admission (eg, private home, shelter, skilled nursing facility), country of origin, comorbidities, medications, drug and alcohol use, hospitalization in the 6 months before admission, invasive procedures, use of renal replacement therapy, mechanical ventilation, ICU stay, treating service, site of infection/colonization, death, and length of hospital stay. Antimicrobial resistance patterns were obtained from the clinical laboratory database based on routine clinical testing, and antibiotic history was provided by the hospital pharmacy database. A Charlson comorbidity index score was calculated for each subject using the data collected.[13] A single researcher collected the clinical data for the entire study population.

Statistics

Univariate analysis was performed initially to search for possible risk factors. The χ^2 test was used to compare dichotomous data unless the cell size was <5, in which case Fisher's exact test was used. The t test was used for continuous variables. Multivariate analysis was performed with the use of conditional logistic regression. Variables chosen for inclusion in the multivariate model had a univariate P value of $<.10$ and were considered to fit a clinically feasible model. Significance was set at $P < .05$, and all relevant tests were 2-tailed. All statistical analyses were done using Stata software (StataCorp, College Station, TX).

RESULTS

Demographic data

Ninety-three cases of ESBL *E coli* infection or colonization (ie, the ESBL group) were identified between June 1, 2004, and December 31, 2007, and were matched with 93 controls with non-ESBL *E coli* infection or colonization (the non-ESBL group) and 93 controls with *P aeruginosa* infection or colonization (the *Pseudomonas* group). The distributions of age, sex, race, and comorbidities are shown in Table 1. The non-ESBL and *Pseudomonas* groups were significantly younger than the ESBL group (mean age, 58 years, 53 years, and 59 years, respectively). The ESBL group had a higher percentage of males compared with the non-ESBL group (53% vs 34%; $P = .01$) but a lower percentage of males compared with the *Pseudomonas* group (53% vs 71%; $P = .01$). There were no differences in race among the 3 groups.

Overall, the ESBL group had more medical comorbidities than either of the control groups. In particular, the ESBL group had significantly higher rates of HIV, liver disease, diabetes mellitus, and cerebrovascular disease compared with the non-ESBL group, and significantly higher rates of HIV, liver disease, diabetes mellitus, cardiovascular disease, cerebrovascular disease, and peptic ulcer disease compared with the *Pseudomonas* group.

Site of positive culture

The sites of isolation of bacteria from the ESBL, non-ESBL, and *Pseudomonas* groups are listed in Table 1. Compared with the non-ESBL group, the ESBL group was more likely to have a catheter-associated bloodstream infection ($P < .01$). Compared with the *Pseudomonas* group, the ESBL bacteria more often came from a urinary source ($P < .01$) and were less frequently isolated from wound ($P = .02$) or respiratory cultures ($P < .01$).