Risk of Acquiring Extended-Spectrum β-Lactamase–Producing *Klebsiella* Species and *Escherichia coli* from Prior Room Occupants in the Intensive Care Unit

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Abstract

OBJECTIVE—To quantify the association between admission to an intensive care unit (ICU) room most recently occupied by a patient positive for extended-spectrum β-lactamase (EBSL)–producing gram-negative bacteria and acquisition of infection or colonization with that pathogen.

DESIGN—Retrospective cohort study.

SETTING AND PATIENTS—The study included patients admitted to medical and surgical ICUs of an academic medical center between September 1, 2001, and June 30, 2009.

METHODS—Perianal surveillance cultures were obtained at admission to the ICU, weekly, and at discharge from the ICU. Patients were included if they had culture results that were negative for ESBL-producing gram-negative bacteria at ICU admission and had an ICU length of stay longer than 48 hours. Pulsed-field gel electrophoresis (PFGE) was performed on ESBL-positive isolates from patients who acquired the same bacterial species (eg, *Klebsiella* species or *Escherichia coli*) as the previous room occupant.

RESULTS—Among 9,371 eligible admissions (7,651 unique patients), 267 (3%) involved patients who acquired an ESBL-producing pathogen in the ICU; of these patients, 32 (12%) were hospitalized in a room in which the prior occupant had been positive for ESBL. Logistic regression results suggested that the prior occupant's ESBL status was not significantly associated with acquisition of an ESBL-producing pathogen (adjusted odds ratio, 1.39 [95% confidence interval, 0.94–2.08]) after adjusting for colonization pressure and antibiotic exposure in the ICU. PFGE results suggested that 6 (18%) of 32 patients acquired a bacterial strain that was the same as or closely related to the strain obtained from the prior occupant.

CONCLUSIONS—These data suggest that environmental contamination may not play a substantial role in the transmission of ESBL-producing pathogens among ICU patients.

Intensifying environmental decontamination may be less effective than other interventions in preventing transmission of ESBL-producing pathogens.

Infections due to extended-spectrum β-lactamase (ESBL)–producing gram-negative bacteria are associated with considerable morbidity, mortality, and costs among hospitalized patients.[1,2] Intensive care unit (ICU) patients are at increased risk of colonization and infection with ESBL-producing bacteria due to frequent contact with healthcare workers and increased exposure to broad spectrum antibiotic therapy.[3,4]

Previous studies have observed an association between persistent environmental contamination and acquisition of several antibiotic-resistant bacterial species, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Clostridium difficile*, multidrug-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumanii*.[5–8] However, this relationship has not been observed for ESBL-producing bacteria.[6,9,10] In addition, earlier studies that have examined the role of the environment in the acquisition of ESBL-producing bacteria have been conducted in outbreak settings and have not demonstrated an epidemiological link between environmental and clinical strains.[9,10] Furthermore, a recent study that did assess acquisition of ESBL-producing bacteria from ESBL-positive previous occupants in a nonoutbreak setting was limited by a small sample size and did not include molecular typing for bacterial strain comparison.[6] To address these limitations, we aimed to quantify the role of the environment in the transmission of ESBL-producing bacteria in a large sample of ICU patients in a nonoutbreak setting. In addition, we used molecular typing to compare bacterial strains to improve on earlier studies.

METHODS

Study Design

This was a retrospective cohort study that used data from patients admitted to the University of Maryland Medical Center (UMMC) medical ICU (MICU) and surgical ICU (SICU) from September 1, 2001, to June 30, 2009. This study was approved by the University of Maryland, Baltimore, institutional review board. During the study period, UMMC was a 650–730-bed tertiary care hospital in Baltimore, Maryland. The MICU was a 10-bed private room unit that became a 29-bed private room unit in April 2006, and the SICU was a 19-bed private room unit. The nurse-to-patient ratio in both the MICU and SICU was 1 : 1. Patients admitted to both units had perianal cultures obtained as part of an ongoing VRE active surveillance hospital epidemiology program. Perianal cultures were obtained using Staplex II swabs (Staplex) within 48 hours after ICU admission, weekly, and at ICU discharge. Compliance with obtaining perianal cultures was approximately 90%.[11,12] The sensitivity of perianal cultures for detecting colonization with ESBLs has not been reported; however, an earlier study suggested that the sensitivity and specificity of perianal cultures for detecting colonization with fluoroquinolone-resistant *Escherichia coli* were 90% and 100%, respectively.[13] Clinical cultures were collected as medically indicated from patients exhibiting signs or symptoms of an infection.

Study Population

The study population consisted of all adult (18 years of age or older) patients admitted to the MICU or SICU during the study period who had no previous ESBL-positive clinical cultures obtained at the index admission, had an ESBL-negative perianal surveillance culture at ICU admission, and had an ICU length of stay of at least 48 hours. Our primary exposure of interest was admission to an ICU room whose immediate prior occupant had an ESBL-positive surveillance or clinical culture. The primary outcome of interest was acquisition of

an ESBL-producing bacteria, defined as having an ESBL-positive perianal or clinical culture during the ICU stay. For patients who acquired an ESBL-producing pathogen, only data associated with the first ESBL-positive surveillance culture were included in the analysis. Patients with multiple admissions to the ICU during the study period were allowed to enter the cohort of at-risk patients multiple times so long as they had negative culture results at the time of the index ICU admission. Previous occupants of the patient's room were not required to have a minimum length of stay. Terminal cleaning (disinfection and cleaning of hospital room surfaces after patient discharge) was performed by the hospitals' hospitality services using a quaternary germicidal cleaner, SaniMaster IV (Ecolab), in accordance with Centers for Disease Control and Prevention guidelines.[14] Infection control policies during the study period included MRSA nasal and VRE perianal screening at ICU admission, weekly, and at ICU discharge; use of contact isolation for patients colonized or infected by MRSA, VRE, and other multidrug-resistant organisms (including ESBL-producing bacteria); and universal glove and gown use for all patient contacts (regardless of colonization or infection status) beginning in June 2007.

Data Sources and Variable Definitions

Patient-level data were collected retrospectively from the UMMC Central Data Repository (CDR). The UMMC CDR is a relational database containing patient administrative, pharmacy, admission, discharge, transfer, and clinical data. A random sample of the data from the UMMC CDR was validated against patients' paper medical records for this study and previous studies, and the CDR data had positive and negative predictive values greater than 98%.[15–17] Patient characteristics collected included age, sex, total length of stay in the ICU, ICU time at risk, length of stay in the ICU of the prior room occupant, ICU antibiotic use, individual comorbid illnesses, aggregate comorbidity indices, and colonization pressure. ICU time at risk was defined as the number of days from ICU admission to ESBL-positive perianal or clinical culture or discharge. ICU antibiotic exposure was defined as antibiotics ordered during the ICU time at risk. Individual comorbid illnesses were determined by the International Classification of Diseases, Ninth Revision (*ICD-9*), at ICU discharge. Aggregate comorbidity was measured using the Charlson Comorbidity Index (CCI) and calculated using the discharge *ICD-9* codes for comorbid conditions.[18] ICU chronic disease score (CDS) was calculated as an aggregate comorbidity measure on the basis of medication use at the time of ICU admission.[15] For each patient, colonization pressure was calculated as the mean of the daily proportion of patients positive for an ESBL-producing bacteria during the time at risk.[19] Patients who were ESBL positive at ICU admission and patients who acquired an ESBL-producing bacteria during their ICU stay both contributed to colonization pressure. Patients who were ESBL positive at ICU admission were assumed to be positive throughout their ICU stay, and patients who acquired an ESBL-producing bacteria during their ICU stay were assumed to be ESBL positive from the day of positive culture collection until ICU discharge.

Microbiology and Molecular Testing

The ESBL-positive status of patients admitted to the ICU during the study period was determined by microbiological testing. Briefly, perianal surveillance culture specimens were inoculated onto MacConkey agar plates (Remel) containing 1 μg/mL ceftazidime and incubated at 37°C for 24–48 hours. Lactose-fermenting colonies were identified using API 20E identification strips or VITEK II (bioMériuex). ESBL testing of *Klebsiella* species and *E. coli* was performed using the Kirby-Bauer disk diffusion test method using 30 μg of ceftazidime and 30 μg of cefotaxime with and without 10 μg of clavulanic acid, as recommended by the Clinical and Laboratory Standards Institute (CLSI). ESBL-positive clinical cultures were determined by the UMMC microbiology laboratory, and susceptibility testing was performed following CLSI guidelines.[20] Polymerase chain reaction (PCR) was

performed to determine which family of β-lactamase-derived gene (ie, TEM, SHV, or CTX-M) was present in the ESBL-positive bacterial isolates. Pulsed-field gel electrophoresis (PFGE) was performed as described elsewhere to determine the extent of genetic similarity between acquired ESBL-producing bacterial isolates obtained from patients whose prior room occupants were colonized or infected with ESBL-producing bacteria of the same species (ie, *Klebsiella* or *E. coli*).[21] Isolates with at least 80% similarity in PFGE band pattern were considered similar and isolates with 100% similarity in PFGE band pattern were considered identical according to Tenover criteria.[22]

Statistical Analysis

Univariate analysis was performed to evaluate the distributions of all study variables. Bivariate analysis was performed to determine the variables associated with acquisition of an ESBL-producing bacteria. Continuous variables were compared using Student *t* test or Wilcoxon rank-sum test as appropriate. Categorical variables were compared using the Pearson χ^2 test or Fisher exact test as appropriate. Stratified analysis was performed to determine whether any variable modified the association between the prior room occupant's ESBL status and acquisition of ESBL-producing bacteria. Statistical testing was performed using 2-tailed tests.

Logistic regression was used to quantify the association between the prior room occupant's ESBL status and acquisition of an ESBL-producing bacteria adjusting for potential confounding variables. All variables associated with acquisition of ESBLs in the bivariate analysis and any identified effect modifiers were included in the initial (full) model. Variables that were not statistically associated with the outcome (P .05) were sequentially removed from the model, starting with the variable with the largest P value. Variables whose removal resulted in a 10% change in the regression coefficient of the prior room occupant were identified as confounders and retained in the model. Because patients were allowed to enter the study multiple times, we used the robust sandwich variance estimator to account for the correlated error structure that resulted from repeated admissions.[23] Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated on the basis of the final multivariate regression model.

RESULTS

There were 18,175 admissions to the MICU and SICU during the study period. Approximately 48% of admissions were excluded for the following reasons: 1,786 (10%) of the admissions did not have an admission perianal surveillance culture, 5,597 (31%) involved an ICU stay of less than 48 hours, 786 (4%) were for patients colonized with an ESBL-producing bacteria at ICU admission, and 635 (3%) were missing information on the prior room occupant's ESBL status. The final sample size was 9,371 admissions of 7,651 unique patients at risk for acquiring an ESBL-producing bacteria during the study period.

Approximately 84% of patients had a single admission during the study period. Mean age (± standard deviation [SD]) was 55.7 ± 15.6 years, 55% were male, and 51% of the admissions were to the MICU. The median ICU length of stay was 4 days (interquartile range [IQR], 2–8 days), and the median ICU time at risk was 4 days (IQR, 2–8 days). Approximately 2,557 patients (27%) had cancer, 2,063 patients (22%) had diabetes, 1,213 patients (13%) had renal disease, and 449 patients (5%) were positive for human immunodeficiency virus. The median colonization pressure was 0.07 (IQR, 0.01–0.15); in other words, the mean daily proportion of patients positive for ESBL-producing bacteria during patient time at risk was less than 7% in 50% of the ICU patient population.

Approximately 648 admissions (7%) were to rooms in which the prior occupant was positive for an ESBL-producing bacteria. Of these, 32 (5%) acquired an ESBL-producing bacteria, compared with 235 (3%) of 8,723 admissions to rooms whose prior room occupant was ESBL negative. Thus, although this suggests an increased risk of 67%, the absolute risk difference is only 2%. Among all 267 admissions of patients who acquired an ESBL-producing bacteria, 236 (88%) were detected by surveillance cultures only, 20 (8%) were detected by both surveillance and clinical cultures, and 11 (4%) were detected by clinical cultures only. Ninety-four (35%) of the ESBL-producing bacteria acquired were *E. coli*, 167 (63%) were *Klebsiella pneumoniae*, and 6 (2%) were *Klebsiella oxytoca*.

The associations between patient characteristics and acquisition of an ESBL-producing bacteria are displayed in Table 1. The unadjusted odds ratio for acquiring an ESBL was 1.88 (95% CI, 1.29–2.74), which suggests that patients admitted to a room whose prior occupant was ESBL positive had almost 2 times the odds of acquiring an ESBL-producing bacteria. However, after adjusting for other variables, the association between the prior room occupant's ESBL status and acquisition of an ESBL-producing bacteria was attenuated and was no longer statistically significant (adjusted OR, 1.39 [95% CI, 0.94–2.08]; Table 2). ICU time at risk and colonization pressure were positively correlated ($r = 0.95$), and ICU time at risk was removed from the multivariable analysis. Independent risk factors for acquisition of ESBL-producing bacteria in the ICU were colonization pressure, renal disease, anti-MRSA therapy, and antipseudomonal β-lactam therapy received during the time at risk in the ICU (Table 2). Patients with colonization pressure greater than 7% were twice as likely to acquire an ESBL, compared with patients with colonization pressure less than 7%.

Among the 32 admissions of patients who acquired an ESBL-producing bacteria and had resided in a room in which the prior room occupant was ESBL positive, 17 (53%) were of patients colonized with the same bacterial species as that found in the prior room occupant. Among these 17 patients, 8 (47%) had isolates that carried the same family of ESBL genes as the isolates obtained from the prior room occupant. PCR did not detect any ESBL genes in 2 of the patient pairs, possibly because our primers were not specific enough for the ESBL genes. PFGE performed on isolates obtained from the 17 patients suggested that 3 patients (18%) acquired the same bacterial strain as that found in the prior room occupant, whereas 3 patients (18%) acquired a bacterial strain that was closely related to that of the prior room occupant. The PFGE pattern did not indicate evidence of clustering or a predominant ESBL-positive bacterial strain in this ICU patient population.

DISCUSSION

Earlier studies have suggested that patients colonized or infected with ESBL-producing bacteria often contaminate their immediate environmental surfaces.[9,10,24] However, these studies were predominately conducted in outbreak settings and did not demonstrate an epidemiological link between the environmental and clinical strains. Our study improved on earlier studies by assessing the risk of acquiring ESBL-producing bacteria from prior room occupants positive for ESBL-producing bacteria in a large of sample of ICU patients during a nonoutbreak period, and we used molecular typing to compare bacterial strains. Despite these improvements over previous studies, our study results did not suggest a statistically significant increased risk of acquiring ESBL-producing bacteria among patients admitted to rooms previously occupied by patients positive for ESBL-producing pathogens. In addition, the relatively low prevalence of exposure (7%) and absolute risk difference of only 2% reinforce that environmental contamination may have only a minor impact on acquisition of ESBL-producing bacteria in our patient population. Our study results are consistent with those of a similar but smaller study conducted in France.[6]

Colonization pressure, renal disease, and several antibiotic exposures were identified as independent risk factors for acquisition of ESBL-producing bacteria in ICU patients. These results are also consistent with previous findings.[25–31] Colonization pressure, which is an important infection control metric, has previously been shown to be associated with acquisition of MRSA, VRE, and *C. difficile* in ICU patients.[32] To our knowledge, this is the first study to identify colonization pressure as an independent risk factor for acquiring ESBL-producing bacteria.

Possible reasons for our study results include that patients colonized or infected with ESBL-producing bacteria may not shed sufficient inoculum into the environment to be transmitted to subsequent room occupants or that the terminal cleaning performed at UMMC may effectively eradicate ESBL-producing pathogens from the environmental surfaces. Unfortunately, our retrospective study design did not allow for culturing of hospital room surfaces, and thus we were not able to test these hypotheses. Another potential limitation is that our lengthy study period allowed for variation in infection control policies, hand hygiene compliance, thoroughness of terminal cleaning, and education of healthcare workers. We were unable to control for these variables in our analysis, which may have biased our results. However, despite this limitation, the lengthy study period was a strength of our study, which focused on endemic ESBL-producing bacteria colonization and thus was not biased by a single epidemic strain.

In conclusion, this study suggests that environmental contamination may not play a significant role in the transmission of ESBL-producing bacteria among ICU patients. Intensifying environmental decontamination may be less effective in preventing ESBL transmission than other interventions. Other infection prevention efforts, including antibiotic stewardship, contact isolation, and hand hygiene, may have a greater effect on the transmission of ESBL-producing bacteria in this patient population.

Acknowledgments

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TABLE 1

Association between Patient Characteristics and Acquisition of Extended-Spectrum β-Lactamase (ESBL)–Producing Bacteria

Patient characteristic	Acquired ESBL-producing bacteria ($n = 267$)	Did not acquire ESBL-producing bacteria ($n = 9,104$)	P
Prior room occupant positive for ESBL-producing			
Klebsiella species or *Escherichia coli*	32 (4.9)	235 (2.7)	<.01
Age, mean years (± SD)	57.1 (15.2)	55.6 (15.6)	.11
Male sex	161 (60.3)	5,033 (55.3)	.10
Admission to the MICU	175 (65.5)	4,619 (50.7)	<.01
ICU total length of stay, median days (IQR)	11 (5–24)	4 (2–8)	<.01
ICU time at risk, median days (IQR)	8 (4–15)	4 (2–8)	<.01
Prior room occupant length of stay, median days (IQR)	3 (1–5)	2 (1–5)	.85
Colonization pressure, median value (IQR)	0.13 (0.06–0.13)	0.07 (0.01–0.14)	<.01
Comorbidity			
AIDS	10 (3.8)	439 (4.8)	.42
Malignancy	35 (13.1)	1,998 (21.9)	<.01
Cerebrovascular disease	18 (6.7)	1,170 (12.8)	<.01
Chronic pulmonary disease	49 (18.4)	1,920 (21.1)	.28
Diabetes	47 (17.6)	1,964 (21.6)	.12
Cardiovascular disease	68 (25.5)	2,337 (25.7)	.94
Liver disease	29 (10.9)	887 (9.7)	.54
Renal disease	65 (24.3)	1,148 (12.6)	<.01
Charlson comorbidity index, mean (IQR)	2 (1–3)	2 (1–4)	.11
ICU chronic disease score, mean (± SD)	8.9 (3.9)	8.6 (4.2)	.23
ICU antibiotic use			
Any antibiotic exposure	259 (97.0)	7,713 (84.2)	<.01
Piperacillin-tazobactam	158 (59.2)	3,536 (38.8)	<.01
First-generation cephalosporins	28 (10.5)	1,316 (14.9)	.07
Second-generation cephalosporins	6 (2.3)	313 (3.4)	.29
Third-generation cephalosporins	23 (8.6)	1,031 (11.2)	.17
Cefepime	52 (19.5)	724 (7.9)	<.01
Antifungal therapy	85 (31.8)	2,188 (20.0)	<.01
Antipseudomonal β-lactam	232 (86.7)	5,107 (56.1)	<.01
Macrolides	33 (12.4)	900 (9.9)	.18
Quinolones	66 (24.7)	1,910 (20.9)	.14
Anti-MRSA therapy	189 (70.8)	3,447 (37.9)	<.01

NOTE. Data are no. (%) of patients, unless otherwise indicated. Antimicrobial drug exposure was defined as antibiotic therapy ordered during the period between ICU admission and ICU discharge for patients who did not acquire an ESBL-producing pathogen and between ICU admission and date on which a positive culture specimen was collected for patients who acquired an ESBL-producing pathogen. Colonization pressure was defined as the daily proportion of patients positive for an ESBL-producing pathogen. For each patient, colonization pressure was calculated as the average of the daily proportion of patients positive for an ESBL-producing pathogen during their time at risk. ICU, intensive care unit; IQR, interquartile range; MICU, medical ICU; MRSA, methicillin-resistant *Staphylococcus aureusr*, SD, standard deviation.

TABLE 2

Independent Risk Factors for Intensive Care Unit–Acquired Extended-Spectrum β-Lactamase (ESBL)–Producing *Klebsiella* Species or *Escherichia coli*

Study variable	Adjusted odds ratio (95% confidence interval)	P
ESBL-positive prior room occupant[a]	1.39 (0.94–2.08)	.10
Colonization pressure (>7%)[b]	2.17 (1.59–2.96)	<.01
Renal disease	1.68 (1.20–2.35)	<.01
Anti-MRSA therapy[c]	1.72 (1.25–2.37)	<.01
Antipseudomonal β-lactam therapy[c]	2.17 (1.43–3.30)	<.01

NOTE. ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* OR, odds ratio; CI, confidence interval.

[a] Crude odds ratio (95% confidence interval) was 1.88 (1.29–2.74), with *P* < .01.

[b] These variables were dichotomized at the median, because variables were not normally distributed.

[c] Antimicrobial drug exposure was defined as antibiotic therapy ordered during the period between ICU admission and ICU discharge for patients who did not acquire an ESBL-producing pathogen and between ICU admission and the date on which a positive culture specimen was collected for patients who acquired an ESBL-producing pathogen. Colonization pressure was defined as the daily proportion of patients positive for ESBL-producing pathogens. For each patient, colonization pressure was calculated as the average of the daily proportion of patients positive for an ESBL-producing pathogen during their time at risk. A median colonization of 7% indicates that, in 50% of the patient population, colonization pressure was less than 7%.