Risk Factors for Recovery of Ampicillin-Sulbactam-Resistant *Escherichia coli* in Hospitalized Patients

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Ampicillin-sulbactam resistance in *Escherichia coli* is an emerging problem. This study determined risk factors for the recovery of ampicillin-sulbactam-resistant *E. coli* in hospitalized patients. A case-control design was used to compare two groups of case patients with control patients. The first group of case patients consisted of patients from whom nosocomially acquired ampicillin-sulbactam-resistant *E. coli* strains were isolated, and the second group of case patients consisted of patients from whom ampicillin-sulbactam-susceptible *E. coli* strains were isolated. Control patients were a random selection among 5% of all patients admitted during the same time period. Risk factors analyzed included antimicrobial drug exposure, comorbid conditions, and demographics. Univariate and multivariate analyses were performed. Ampicillin-sulbactam-resistant *E. coli* strains were isolated from 175 patients, and ampicillin-sulbactam-susceptible *E. coli* strains were isolated from 577 patients. Nine hundred thirty-four control patients were selected. Exposure to penicillin antibiotics as a class and to amoxicillin and ampicillin-sulbactam individually were the only significant independent risk factors associated with the isolation of ampicillin-sulbactam-resistant *E. coli* (odds ratio [OR] = 2.32 [P < 0.001], OR = 3.04 [P = 0.02], and OR = 1.72 [P = 0.04], respectively), but they were not associated with the isolation of ampicillin-sulbactam-susceptible *E. coli*. Interestingly, exposure to piperacillin-tazobactam tended to protect against the isolation of *E. coli* strains resistant to ampicillin-sulbactam, but this did not reach statistical significance (OR = 0.13; P = 0.11).

Ampicillin-sulbactam is a β-lactam–β-lactamase inhibitor combination antibiotic that is frequently used in hospitals (12, 16). It has a good safety profile and provides coverage for a wide spectrum of bacterial pathogens, including aerobic gram-positive and gram-negative bacteria and anaerobic organisms. This broad coverage allows the effective use of ampicillin-sulbactam in clinical situations that might otherwise necessitate treatment with two or three antimicrobial drugs. Ampicillin-sulbactam is often used to treat polymicrobial bacterial infections. Its use, as well as the use of other β-lactam–β-lactamase inhibitor antibiotics, will likely increase in hospitals as a result of the high prevalence of antibiotic-resistant organisms. Although ampicillin-sulbactam has traditionally had good activity against *Escherichia coli* (14), an increase in the rate of resistance has been described in the United States (S. Fridkin, Centers for Disease Control and Prevention, personal communication).

The aim of the study described here was to identify risk factors for the nosocomial isolation of ampicillin-sulbactam-resistant *E. coli* from clinical specimens in a U.S. tertiary-care hospital, with a particular focus on the risk conferred by prior antimicrobial drug exposures. Risk factor analyses that involved the isolation of bacteria that are resistant to a particular antimicrobial drug have traditionally used as controls the isolation of bacteria that are susceptible to the antibiotic. Study designs that use the isolation of “susceptible organisms” as controls are potentially problematic. The control group is supposed to represent the source population from which patients infected or colonized with drug-resistant strains have emerged (13, 18). Thus, if patients from whom nosocomially acquired antibiotic-susceptible bacteria are isolated were used as a control group for patients from whom nosocomially acquired antibiotic-resistant bacteria are isolated, the inference might be that a resistant bacterial isolate in a given patient arose from a previously susceptible population of the same bacteria in that individual. In most instances, this is probably not the case. The more likely scenario is the nosocomial acquisition of a resistant strain. Therefore, patients infected with susceptible isolates represent only a portion of the source population from which the patients infected with resistant isolates arose and should not be used exclusively as controls. Furthermore, members of a control group should be selected independently of their exposure status (13, 18). By using patients infected with antibiotic-susceptible isolates as controls, the antibiotic risk factor effect estimates (or odds ratios [ORs]) might be biased, because these patients are less likely than patients infected with resistant isolates to have been exposed to an antibiotic active against the susceptible strain. In this situation, a variable identified as a risk factor might actually protect against the isolation of a susceptible organism rather than confer true risk for isolation of a resistant organism. In a meta-analysis of risk factors for the nosocomial isolation of vancomycin-resistant enterococci (VRE) reported from this laboratory (3), two control groups were studied. When patients from whom vancomycin-susceptible enterococci (VSE) were isolated were used as a control group, prior exposure to vancomycin emerged as a major risk factor. This disappeared as a risk factor when patients infected with VRE were compared to the source population from which the patients infected with VRE were derived, namely, all hospital admissions adjusted for the length of hospital stay. The erroneous identification of exposure to vancomycin as a significant risk factor for isolation of VRE probably occurred because exposure to vancomycin protected against subsequent infection with VSE, resulting in less exposure to vancomycin in the patients from whom VSE were...
isolated. Thus, the most appropriate control group was a random sample of all hospitalized patients, which represented the source population from which both the VRE and VSE patients were derived.

The present study identifies risk factors for the nosocomial isolation of ampicillin-sulbactam-resistant *E. coli*. In order to avoid the identification of biased variables as outlined above, a new study design was developed (3, 4) and was used in the study described in the present report: a case-case-control study. This study design involved two models: (i) risk factors for the isolation of ampicillin-sulbactam-resistant *E. coli* and (ii) risk factors for the isolation of ampicillin-sulbactam-susceptible *E. coli*. Both models used a random sample of hospitalized patients as controls. By comparing and contrasting these two sets of risk factors, we were able to identify variables specifically predictive of the outcome of interest, the isolation of ampicillin-sulbactam-resistant *E. coli* in the hospital.

**MATERIALS AND METHODS**

**Case definition, control definition, and study design.** A case-case-control study design was used. Two retrospective case-control studies were conducted at the Beth Israel Deaconess Medical Center West Campus. The hospital is a 320-bed tertiary-care teaching hospital in Boston, Mass., with approximately 12,000 patient admissions per year. There are no pediatric or obstetric patients. The first group of case patients was defined as patients from whom nosocomially acquired *E. coli* strains resistant to ampicillin-sulbactam were isolated. The second group of case patients was defined as patients from whom nosocomially acquired *E. coli* strains susceptible to ampicillin-sulbactam were isolated. Both ampicillin-sulbactam susceptible and ampicillin-sulbactam resistant *E. coli* strains were not recovered from any of the patients studied.

The microbiology laboratory database was searched to identify all cultures of specimens from patients admitted between October 1993 and September 1997 that were positive for *E. coli*. Patients from whom *E. coli* isolates were obtained within the first 48 h of admission were excluded. Controls were a computer-generated random selection among 5% of all patients who were admitted during the same time period, and from whom *E. coli* was not isolated during the hospital stay. Patients admitted for less than 48 h were excluded. The same control group was used for both case-control studies i.e., the same control group was used for patients from whom ampicillin-sulbactam-resistant *E. coli* strains were isolated and for case patients from whom ampicillin-sulbactam-susceptible *E. coli* strains were isolated. These patients were used as controls because, as described above, they best represented the source population from which case patients arose.

The reasoning behind a case-case-control study design was to identify risk factors for the isolation of ampicillin-sulbactam-resistant *E. coli*. It was believed that this could best be accomplished by comparing and contrasting the two multivariate models: risk factors for isolation of *E. coli* resistant to ampicillin-sulbactam and risk factors for isolation of *E. coli* susceptible to ampicillin-sulbactam. Other studies have used a similar study design (4).

**Risk factors analyzed.** Data were collected from administrative, pharmacy, and laboratory computerized databases by means of a relational database management system (Access, Microsoft, Redmond, Wash.). Variables that were explored as possible risk factors included age, sex, underlying diseases or comorbid conditions, intensive care unit (ICU) stay prior to the isolation of *E. coli* (for controls, ICU stay at any point during hospitalization), surgery during the present hospitalization, transfer from another hospital, length of hospital stay (LOS; for case patients, LOS prior to *E. coli* isolation, and for control patients, complete length of hospital stay) and treatment with antimicrobial drugs (analyzed individually and in groups; see Tables 1 and 2). The cephalosporins most commonly used at our institution are cefazolin, cefuroxime, cefotetan, ceftriaxone, and ceftazidime. For the case patients, treatment with antimicrobial drugs was included as a risk factor only when the antimicrobial drugs were given prior to the isolation of *E. coli* (i.e., prior to the outcome of interest). For the control patients, treatment with any antimicrobial drug during the hospital stay was included.

**Statistical analysis.** Statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). Univariate analysis was performed separately for each of the variables. ORs and 95% confidence intervals were calculated for the binomial variables; *P* values were calculated by Fisher’s exact test for binomial variables, the chi-square test for categorical variables with greater than two subgroups, and Student’s *t* test or the Wilcoxon rank-sum test for continuous variables.

Variables with a *P* value of <0.2 in the univariate analysis were included in a logistic regression model for multivariate analysis. A forward selection process was used. Risk factors were checked for confounding and collinearity. We included confounders in multivariate models if covariate inclusion changed the coefficient of any statistically significant variable in the logistic regression model by 10% or greater. All tests were two tailed, and a *P* value of ≤0.05 was considered significant in the multivariate model. The final regression model was analyzed for overfitting by the bootstrap method (1,000 bootstrap samples of all of the data were used).

Interaction terms among variables in the final model were evaluated. Any interaction terms that met statistical significance (*P* < 0.05) were tested for overfitting by running 1,000 bootstrap samples of all of the data.

**RESULTS**

One hundred seventy-five patients infected with ampicillin-sulbactam-resistant *E. coli* and 577 patients infected with ampicillin-sulbactam-susceptible *E. coli* were identified. These two groups of case patients were compared to 934 randomly selected control patients. The mean ages of the patients with ampicillin-sulbactam-resistant and -susceptible *E. coli* were 65.2 and 67.4 years, respectively. The mean age of the control patients was 61.3 years. Women made up 65.1 and 67.2% of patients infected with resistant and sensitive *E. coli* strains, respectively, whereas women made up 42.1% of the control patients. Ampicillin-sulbactam-resistant *E. coli* was most frequently recovered from urine (66.9%), cultures of wound specimens, (11.4%), and respiratory secretions (9.1%). Other sites of recovery included blood (4.0%), intravascular catheter tips (1.1%), tissue (1.1%), and other body fluids (6.5%). *E. coli* strains susceptible to ampicillin-sulbactam were recovered from urine (73.1%), cultures of wound specimens, (7.5%), respiratory secretions (7.5%), blood (3.8%), tissue (1.4%), intravascular catheter tips (0.2%), and other body fluids (6.6%).

The results of the univariate analysis for the recovery of *E. coli* strains resistant to ampicillin-sulbactam are displayed in Table 1. Case patients were significantly older than control patients (*P* = 0.003), and more were female (OR = 2.57; *P* < 0.001). Case patients were more likely than control patients to have had underlying hepatic disease (OR = 2.45; *P* < 0.001), an ICU stay (OR = 2.61; *P* < 0.001), and surgery (OR = 1.60; *P* < 0.001) during hospitalization and were more likely than control patients to have been transferred from another hospital (OR = 1.97; *P* < 0.001). Case patients were more likely than control patients to have received penicillin antibiotics as a group (OR = 2.58; *P*< 0.001), ampicillin (OR = 3.32; *P* = 0.008), ampicillin-sulbactam (OR = 1.82; *P* = 0.01), and aminoglycosides (OR = 2.41; *P* = 0.002). Case patients were less likely than control patients to have received cefazolin (OR = 0.45; *P* < 0.001) and cefepin antibiotics as a group (OR = 0.61; *P* = 0.005).

The results of univariate analysis for isolation of *E. coli* strains susceptible to ampicillin-sulbactam are displayed in Table 2. Case patients were older than control patients (*P* < 0.001) and were more likely to be female (OR = 2.83; *P* < 0.001). Case patients were more likely than controls to have had diabetic mellitus (OR = 2.17; *P* < 0.001) and were less likely to have had AIDS (OR = 0.19; *P* = 0.02) and diabetes mellitus (OR = 0.76; *P* = 0.01). Case patients were more likely than controls to have had an ICU stay (OR = 2.69; *P* < 0.001) and surgery (OR = 1.52; *P* < 0.001) during their hospitalization. Case patients also were more likely to have been transferred from another hospital (OR = 1.95; *P* < 0.001). Case patients were more likely than control patients to have had received ampicillin (OR = 2.89; *P* = 0.001) and aminoglycosides (OR = 1.94; *P* = 0.001). Case patients were less likely than control patients to have had received ampicillin-sulbactam (OR = 0.68; *P* = 0.001), cefazolin (OR = 0.63; *P* < 0.001), cefepin antibiotics (OR = 0.64; *P* < 0.001), and quinolones (OR = 0.45; *P* = 0.009).

The results of the multivariate analyses are shown in Table 3.

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Patients infected with resistant strains versus control patients. For the isolation of *E. coli* strains resistant to ampicillin-sulbactam, all results were adjusted for confounding covariates. Exposure to penicillin antibiotics was a significant risk factor (OR = 2.32; *P* < 0.001). Because of this strong association, the relationship between each individual penicillin antibiotic and the isolation of ampicillin-sulbactam-resistant *E. coli* was studied. Treatment with ampicillin and treatment with ampicillin-sulbactam were significant risk factors (OR = 3.04 [95% CI 2.02, 4.62] and OR = 1.72 [95% CI 0.74, 3.95], respectively). Treatment with piperacillin also tended toward being a risk factor for the isolation of ampicillin-sulbactam-resistant *E. coli* (OR = 2.55 [95% CI 0.97, 6.72]; *P* = 0.06). Of particular interest, piperacillin-tazobactam treatment tended to protect against isolation (OR = 0.75 [95% CI 0.50, 1.14]; *P* = 0.18). Neither of these associations was statistically significant.

Holding an ICU stay was a risk factor (OR = 2.29 [95% CI 1.30, 4.04]; *P* = 0.003). Treatment with Ceftriaxone and Ceftazadime was associated with a trend toward being a risk factor for the isolation of ampicillin-sulbactam-resistant *E. coli* (OR = 2.05 [95% CI 0.78, 5.38]; *P* = 0.16). Cardiac disease was protective (OR = 0.52 [95% CI 0.27, 0.99]; *P* = 0.04). Surgery increased the risk for males (OR = 2.02 [95% CI 1.20, 3.41]; *P* = 0.009). Exposure to imipenem was protective (OR = 0.62 [95% CI 0.37, 1.02]; *P* = 0.06). Other multivariate analyses, all adjusted for confounding covariates, risk factors included age (OR = 1.03; *P* < 0.001), female gender (OR = 3.14; *P* < 0.001), transfer from another institution (OR = 1.42; *P* = 0.008), hepatic disease (OR = 2.26; *P* < 0.001), surgery (OR = 1.73; *P* < 0.001), and ICU stay (OR = 2.89; *P* < 0.001). Cardiac disease was protective (OR = 0.68; *P* = 0.02), as was exposure to cefazolin (OR = 0.43; *P* < 0.001). Control patients were more likely than case patients to have received quinolones (OR = 0.22; *P* < 0.001).

### DISCUSSION

In 1998, 41% of nosocomial *E. coli* isolates recovered in 270 U.S. hospitals reporting to the National Nosocomial Infections

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**Antimicrob. Agents Chemother.**

**TABLE 1. Univariate risk factors for isolation of *E. coli* resistant to ampicillin-sulbactam**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control patients (n = 934)</th>
<th>Case patients (n = 175)</th>
<th><em>P</em> value</th>
<th>OR</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics and comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>61.3</td>
<td>65.2</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (no. [%] female)</td>
<td>393 (42.1)</td>
<td>114</td>
<td>&lt;0.001</td>
<td>2.57</td>
<td>1.84–3.60</td>
</tr>
<tr>
<td>No. [%] of subjects with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS</td>
<td>17 (1.8)</td>
<td>3 (1.7)</td>
<td>1.00</td>
<td>0.94</td>
<td>0.27–3.25</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>663 (71.0)</td>
<td>132</td>
<td>0.27</td>
<td>1.26</td>
<td>0.87–1.82</td>
</tr>
<tr>
<td>Diabetes</td>
<td>403 (43.2)</td>
<td>72 (41.1)</td>
<td>0.68</td>
<td>0.92</td>
<td>0.66–1.28</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>112 (12.0)</td>
<td>26 (14.9)</td>
<td>0.32</td>
<td>1.28</td>
<td>0.81–2.03</td>
</tr>
<tr>
<td>Malignancy disease</td>
<td>148 (15.9)</td>
<td>29 (16.6)</td>
<td>0.82</td>
<td>1.06</td>
<td>0.68–1.63</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>62 (6.6)</td>
<td>26 (14.9)</td>
<td>&lt;0.001</td>
<td>2.45</td>
<td>1.50–4.01</td>
</tr>
<tr>
<td>Renal disease</td>
<td>96 (10.3)</td>
<td>24 (13.7)</td>
<td>0.19</td>
<td>1.39</td>
<td>0.86–2.24</td>
</tr>
<tr>
<td>Transplant</td>
<td>39 (4.2)</td>
<td>6 (3.4)</td>
<td>0.84</td>
<td>0.82</td>
<td>0.34–1.96</td>
</tr>
<tr>
<td>Median no. of comorbidities</td>
<td>2</td>
<td>2</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables related to hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median LOS (days)</td>
<td>5</td>
<td>4</td>
<td>0.11^d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. [%] of patients with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU stay</td>
<td>201 (21.5)</td>
<td>73 (41.7)</td>
<td>&lt;0.001</td>
<td>2.61</td>
<td>1.86–3.66</td>
</tr>
<tr>
<td>Surgery</td>
<td>265 (28.4)</td>
<td>68 (38.9)</td>
<td>0.007</td>
<td>1.60</td>
<td>1.15–2.24</td>
</tr>
<tr>
<td>Transfer</td>
<td>245 (26.2)</td>
<td>72 (41.1)</td>
<td>&lt;0.001</td>
<td>1.97</td>
<td>1.41–2.75</td>
</tr>
<tr>
<td>Antibiotics (no. [%] of patients treated)^c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All penicillins</td>
<td>144 (15.4)</td>
<td>56 (32.0)</td>
<td>&lt;0.001</td>
<td>2.58</td>
<td>1.79–3.72</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>15 (1.6)</td>
<td>9 (5.1)</td>
<td>0.008</td>
<td>3.32</td>
<td>1.43–7.72</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>99 (10.6)</td>
<td>31 (17.7)</td>
<td>0.01</td>
<td>1.82</td>
<td>1.17–2.82</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>18 (1.93)</td>
<td>5 (2.86)</td>
<td>0.39</td>
<td>1.50</td>
<td>0.55–4.09</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>10 (1.07)</td>
<td>3 (1.67)</td>
<td>1.00</td>
<td>0.53</td>
<td>0.07–4.18</td>
</tr>
<tr>
<td>All cephalosporins</td>
<td>383 (41.8)</td>
<td>52 (29.7)</td>
<td>0.005</td>
<td>0.61</td>
<td>0.43–0.86</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>239 (25.6)</td>
<td>25 (14.3)</td>
<td>&lt;0.001</td>
<td>0.45</td>
<td>0.31–0.76</td>
</tr>
<tr>
<td>Cefuroxime and cefotetan</td>
<td>77 (8.24)</td>
<td>9 (5.14)</td>
<td>0.22</td>
<td>0.60</td>
<td>0.30–1.23</td>
</tr>
<tr>
<td>Ceftriaxone and cefazadine</td>
<td>99 (10.6)</td>
<td>24 (13.7)</td>
<td>0.24</td>
<td>1.34</td>
<td>0.83–2.16</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>50 (5.35)</td>
<td>21 (12.0)</td>
<td>0.002</td>
<td>2.41</td>
<td>1.41–4.13</td>
</tr>
<tr>
<td>Quinolones</td>
<td>46 (4.9)</td>
<td>10 (5.7)</td>
<td>0.71</td>
<td>1.17</td>
<td>0.58–2.37</td>
</tr>
<tr>
<td>Imipenem</td>
<td>16 (1.71)</td>
<td>7 (4.0)</td>
<td>0.08</td>
<td>2.39</td>
<td>0.97–5.90</td>
</tr>
</tbody>
</table>

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^a Boldface type indicates variables for which *P* is ≤0.05.

^b For OR only.

^c Solid organ only.

^d *P* value for LOS in quartiles (nonlinear relationship with outcome variable).

^e Intravenous only.

^f Includes penicillin, ampicillin, piperacillin, ampicillin-sulbactam, and piperacillin-tazobactam.

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Surveillance System, were resistant to ampicillin-sulbactam; this rate of resistance had increased since 1990, when it was 24% (Fridkin, personal communication). At our institution, the change was not as impressive; the proportion of E. coli strains not susceptible to ampicillin-sulbactam increased from 30.7% in 1994 to 33.3% in 1997.

The efficacy of β-lactam–β-lactamase inhibitor combination antibiotics in the treatment of bacterial infections is related both to the antimicrobial activity of the β-lactam antibiotic and to the activity of the β-lactamase inhibitor. The presence of plasmid-mediated TEM-1 β-lactamase mediates resistance to ampicillin in many strains of E. coli (9). Therefore, the effectiveness of ampicillin-sulbactam in the treatment of E. coli infections is largely dependent on the inhibitory activity of sulbactam. However, sulbactam is a relatively weak inhibitor of TEM-1 β-lactamase. Other mechanisms of ampicillin-sulbactam resistance include the hyperproduction of chromosomal cephalosporinase (AmpC), plasmid-borne AmpC, alteration of porin channels (9, 10, 19), and a less frequently described method of resistance, conferred by mutant TEM-1 β-lactamases. These β-lactamases, described only in Europe, have been designated Bush-Jacoby-Medeiros group 2b or inhibitor-resistant TEM (IRT) (1, 2). A limited number of nucleotide substitutions have been shown to cause resistance to β-lactamase inhibitors (8; G. Jacoby and K. Bush, http://www.lahey.org/studies/webt.htm), and significant nucleotide sequence diversity among the genes that encode IRTs has been noted, prompting the hypothesis that the mutations that lead to IRT formation are likely independent phenomena that possibly occur under selective antibiotic pressure (5, 6, 15). Antibiotic exposure might also select for the more common mechanisms of ampicillin-sulbactam resistance, such as TEM-1 β-lactamase hyperproduction.

A limitation of the present study was that we did not know the molecular mechanisms by which resistance was conferred in our study isolates. Therefore, we could not draw specific conclusions regarding the relationships among these mechanisms and the identified risk factors. Phenotypic and genotypic analyses of ampicillin-sulbactam-resistant E. coli strains would be the best way to study these relationships. Additionally, since the control patients were not screened for the presence of E. coli (e.g., with stool cultures), it is possible that some of these patients might actually have represented unrecognized case patients. However, this type of misclassification would make...
were not selected for use in the final model. For the ampicillin-sulbactam-resistant E. coli relationships among the individual penicillin antibiotics and the isolation of ampicillin-sulbactam-resistant E. coli P

ble a risk factor for the isolation of ampicillin-sulbactam-susceptible strains, surgery negated much of this protective effect. One explanation for this is that surgery increased the risk of urinary tract infections in men than in women. In patients infected with ampicillin-sulbactam-resistant E. coli strains, surgery negated much of this protective effect. One explanation for this is that surgery increases the risk of urinary tract infections, and surgery catheters had been placed in most men who underwent surgery. Surgery was also a risk factor for the isolation of ampicillin-sulbactam-susceptible E. coli. ICU stay during hospitalization was a risk factor for the isolation of both ampicillin-sulbactam-resistant and ampicillin-sulbactam-susceptible E. coli. This increased risk likely reflects the increased morbidity of ICU patients, the presence of indwelling devices, the use of mechanical ventilation, and longer hospital stays. The increased prevalence of surgery and ICU stays among case patients than among control patients might also reflect an increased severity of illness. Quinolones protected against the isolation of E. coli strains susceptible to ampicillin-sulbactam but did not have a significant effect on the isolation of E. coli strains resistant to ampicillin-sulbactam. The reason for this difference might be related in part to an observed increased incidence of quinolone resistance in ampicillin-sulbactam-resistant E. coli strains than in ampicillin-sulbactam-susceptible E. coli strains in this study (3.2 versus 1.0%; \( P = 0.09 \); data not shown). Cefazolin protected against the isolation of both ampicillin-sulbactam-resistant and ampicillin-sulbactam-susceptible E. coli strains. The explanation for this protective effect is unclear.

We used a new study design, the case-case-control study, to examine specifically the roles of various antimicrobial agent exposures as risk factors for the isolation of ampicillin-sulbactam-resistant E. coli. When the two models are compared (Table 3), what is most striking is the fact that exposure to penicillin antibiotics was associated only with the isolation of ampicillin-sulbactam-resistant E. coli. Because of this strong association, the relationship between exposure to each of the individual penicillin antibiotics and the isolation of ampicillin-sulbactam-resistant E. coli was studied. Exposures to ampicillin and ampicillin-sulbactam were significant risk factors. Exposure to piperacillin tended toward being a risk factor for isolation of ampicillin-sulbactam-resistant E. coli, and exposure to piperacillin-tazobactam tended to protect against this isolation. Neither of the latter two associations was statistically significant. These results suggest that exposure to ampicillin and ampicillin-sulbactam (and probably piperacillin) is important in the isolation of resistant E. coli strains. It should be noted that since many patients were not exposed to penicillin antibiotics prior to the nosocomial isolation of ampicillin-sulbactam-resistant E. coli, and many patients were not exposed to penicillin antibiotics prior to the nosocomial isolation of ampicillin-sulbactam-resistant E. coli, the penicillin class was removed, and each individual penicillin antibiotic was studied in the model individually. Boldface type indicates variables for which \( P \) is <0.05.

\[ \text{Exposure to all penicillins} <0.001 \ 2.32 (1.54–3.51) \]
\[ \text{Ampicillin}^a 0.02 \ 3.04 (1.22–7.58) \]
\[ \text{Ampicillin-sulbactam}^b 0.04 \ 1.72 (1.03–2.85) \]
\[ \text{Piperacillin}^b 0.15 \ 2.55 (0.71–9.25) \]
\[ \text{Piperacillin-tazobactam}^b 0.11 \ 0.13 (0.01–1.60) \]

\[ \text{ICU stay} <0.001 \ 2.47 (1.64–3.72) \]
\[ \text{Cefazolin exposure} <0.001 \ 0.35 (0.20–0.59) \]

\[ \text{Gender (female)} \]
\[ \text{Surgical patients}^c 0.20 \ 1.46 (0.82–2.61) \]
\[ \text{Nonsurgical patients}^d <0.001 \ 5.14 (3.14–8.43) \]

\[ \text{Surgery}^e \]
\[ \text{Male}^e <0.001 \ 3.96 (2.17–7.24) \]
\[ \text{Female}^e 0.67 \ 1.13 (0.65–1.94) \]

\[ \text{Age}^f <0.001 \ 1.05 (1.02–1.08) \]
\[ \text{Transfer} 0.008 \ 1.22 (1.09–1.84) \]
\[ \text{Hepatic disease} <0.001 \ 2.26 (1.50–3.39) \]
\[ \text{Cardiac disease} 0.02 \ 0.68 (0.51–0.92) \]

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TABLE 3. Multivariate analysis of risk factors for isolation of E. coli

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ampicillin-sulbactam-resistant E. coli</th>
<th>Ampicillin-sulbactam-susceptible E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to all penicillins</td>
<td>(&lt;0.001)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Ampicillin(^a)</td>
<td>0.02</td>
<td>0.22 (0.11–0.46)</td>
</tr>
<tr>
<td>Ampicillin-sulbactam(^b)</td>
<td>0.04</td>
<td>1.72 (1.03–2.85)</td>
</tr>
<tr>
<td>Piperacillin(^b)</td>
<td>0.15</td>
<td>2.55 (0.71–9.25)</td>
</tr>
<tr>
<td>Piperacillin-tazobactam(^b)</td>
<td>0.11</td>
<td>0.13 (0.01–1.60)</td>
</tr>
<tr>
<td>ICU stay</td>
<td>(&lt;0.001)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Cefazolin exposure</td>
<td>(&lt;0.001)</td>
<td>0.43 (0.31–0.60)</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>(&lt;0.001)</td>
<td>3.14 (2.47–4.00)</td>
</tr>
<tr>
<td>Surgical patients(^c)</td>
<td>0.20</td>
<td>1.46 (0.82–2.61)</td>
</tr>
<tr>
<td>Nonsurgical patients(^d)</td>
<td>(&lt;0.001)</td>
<td>5.14 (3.14–8.43)</td>
</tr>
<tr>
<td>Surgery(^e)</td>
<td>(&lt;0.001)</td>
<td>1.73 (1.30–2.32)</td>
</tr>
<tr>
<td>Male(^e)</td>
<td>(&lt;0.001)</td>
<td>3.96 (2.17–7.24)</td>
</tr>
<tr>
<td>Female(^e)</td>
<td>0.67</td>
<td>1.13 (0.65–1.94)</td>
</tr>
<tr>
<td>Age(^f)</td>
<td>(&lt;0.001)</td>
<td>1.03 (1.02–1.04)</td>
</tr>
<tr>
<td>Transfer</td>
<td>0.008</td>
<td>1.22 (1.09–1.84)</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>(&lt;0.001)</td>
<td>2.26 (1.50–3.39)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>0.02</td>
<td>0.68 (0.51–0.92)</td>
</tr>
</tbody>
</table>

\(^a\) This table shows two multivariate models. Variables were selected by a forward selection process, and confounding variables were added back to the models. Several associations that were significantly associated with the recovery of E. coli by univariate analysis were no longer statistically significant by multivariate analysis, and thus were not selected for use in the final model. For the ampicillin-sulbactam-resistant E. coli model, penicillin antibiotics as a class were selected. In order to study the relationships among the individual penicillin antibiotics and the isolation of ampicillin-sulbactam-resistant E. coli, the penicillin class was removed, and each individual penicillin antibiotic was studied in the model individually. Boldface type indicates variables for which \( P \) is <0.05.

\(^b\) OR and \( P \) value when penicillin class is removed from the model.

\(^c\) Effect of female gender in surgical patients.

\(^d\) Effect of female gender in nonsurgical patients.

\(^e\) Effect of surgery in male patients.

\(^f\) Effect of surgery in female patients.

\(^g\) Risk is per year.
bactam-resistant *E. coli*, other demographic and hospital-related risk factors discussed above were probably important risk factors as well.

Our results suggest that piperacillin-tazobactam might protect against the isolation of *E. coli* strains resistant to ampicillin-sulbactam. This protective effect is likely related to the relatively high degree of susceptibility of *E. coli* to piperacillin-tazobactam (7, 9). Because piperacillin is a weaker substrate than ampicillin for TEM-1 and because tazobactam is a stronger inhibitor of TEM-1 β-lactamase than sulbactam, piperacillin-tazobactam is much more active than ampicillin-sulbactam against *E. coli* strains that produce TEM-1 (9, 11, 17). These associations among the penicillin antibiotics and the isolation of ampicillin-sulbactam-resistant *E. coli* merit further investigation.

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