



Published in final edited form as:

Infect Control Hosp Epidemiol. 2012 December ; 33(12): 1242–1245. doi:10.1086/668443.

Risk Factors for Gastrointestinal Tract Colonization with Extended-Spectrum β -Lactamase (ESBL)–Producing *Escherichia coli* and *Klebsiella* Species in Hospitalized Patients

Jennifer H. Han, MD, MSCE¹, Irving Nachamkin, DrPH, MPH², Theoklis E. Zaoutis, MD, MSCE^{3,4}, Susan E. Coffin, MD, MPH^{3,4}, Darren R. Linkin, MD, MSCE^{1,3,5}, Neil O. Fishman, MD¹, Mark G. Weiner, MD⁶, Baofeng Hu, MD², Pam Tolomeo, MPH^{3,7}, and Ebbing Lautenbach, MD, MPH, MSCE^{1,3,7}

¹Division of Infectious Diseases, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

²Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

³Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

⁴Division of Infectious Diseases, and Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

⁵Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania

⁶Division of General Internal Medicine, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

⁷Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

We describe the prevalence of and risk factors for colonization with extended-spectrum β -lactamase (ESBL)–producing *Escherichia coli* and *Klebsiella* species (ESBL-EK) in hospitalized patients. The prevalence of colonization with ESBL-EK was 2.6%. Colonization was associated with cirrhosis, longer duration of hospital stay prior to surveillance, and prior exposure to clindamycin or meropenem.

Infections owing to extended-spectrum β -lactamase (ESBL)–producing *Enterobacteriaceae*, most commonly *Escherichia coli* and *Klebsiella* species (EK), are associated with increased morbidity and mortality.¹ Asymptomatically colonized patients may contribute to the reservoir in the hospital setting and increase the risk of patient-to-patient transmission. While several studies have evaluated risk factors for colonization with ESBL-producing *Enterobacteriaceae*,^{2–6} these have been limited to specific patient populations (eg, intensive

© 2012 by The Society for Healthcare Epidemiology of America. All rights reserved.

Address correspondence to Jennifer Han, MD, MSCE, Division of Infectious Diseases, Department of Medicine, Hospital of the University of Pennsylvania, 3400 Spruce Street, 3rd Floor, Silverstein Building, Suite E, Philadelphia, PA 19104 (jennifer.han@uphs.upenn.edu).

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

care unit [ICU] patients). Therefore, we conducted this study to determine the prevalence of, and risk factors for, colonization with ESBL-EK in a hospital-wide patient population.

METHODS

This case-control study was conducted at the Hospital of the University of Pennsylvania, a 725-bed academic tertiary care medical center. A total of 4 hospital-wide fecal surveillance surveys were performed every 4–8 months from April 23, 2007, to March 17, 2009. All patient care units were included (ie, all hospital floors or ICUs). All subjects were considered eligible and were approached for informed consent, with each patient included only once per survey. Once consent was obtained, a perirectal swab was collected for processing.

Identification of *E. coli* and *Klebsiella* species and antimicrobial susceptibility testing were performed and interpreted in accordance with Clinical and Laboratory Standards Institute (CLSI) criteria using the semiautomated Vitek 2 identification and susceptibility system (bioMérieux).⁷ Confirmatory testing for ESBL production was performed using the double-disk confirmation method.⁷ Isolates were tested for the presence of ESBLs (ie, *K. pneumoniae* carbapenemase [KPC], TEM, SHV, and CTX-M enzymes) using real-time polymerase chain reaction.⁸ Cases and controls were defined solely on the isolation of ESBL-EK from the surveillance culture, with case patients designated as those who were ESBL-EK-positive, and control patients as those who were ESBL-EK-negative.

Data were abstracted from the Pennsylvania Integrated Clinical and Administrative Research Database, which includes demographic, laboratory, and pharmacy information. Information was collected on baseline demographics, origin at the time of admission, hospital location, and length of stay prior to sampling. Comorbid conditions were documented, including diabetes mellitus, cirrhosis, renal insufficiency, malignancy, infection with human immunodeficiency virus, neutropenia, and transplant. Data were collected on all antimicrobial and immunosuppressive agents administered during the 30 days prior to sampling. Chart review was performed to ascertain the presence of any positive clinical cultures for ESBL-EK following the surveillance culture date to discharge or death.

Cases and controls were characterized by potential risk factors, including demographics, comorbidities, and prior antimicrobial use. Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using Fisher exact test. Bivariable analyses were performed to determine the association between potential risk factors and ESBL-EK colonization. An odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association. Given the small number of cases, multivariable analyses were not performed. For all calculations, a 2-tailed *P* value of less than .05 was considered significant. All statistical calculations were performed using STATA software ver. 11.0 (StataCorp). This study was reviewed and approved by the institutional review board of the University of Pennsylvania.

RESULTS

Over the 2-year study period, study personnel approached a total of 992 patients, of which 437 provided informed consent. Of these, 389 patients subsequently had perirectal swabs obtained. The median age of patients was 59 years (interquartile range [IQR], 48–68 years) and 171 (44.0%) were female. Furthermore, 232 (59.6%) were white, 108 (27.8%) were black, 11 (2.8%) were Hispanic, and 38 (9.8%) were self-identified as “other.”

Among the 389 patients, 10 (2.6%) were colonized with ESBL-EK. Of these, 4 isolates were *E. coli*, and 6 were *K. pneumoniae*. Two of the *K. pneumoniae* isolates were KPC-positive. All 4 of the *E. coli* isolates were CTX-M-positive. The proportion of ESBL-EK isolates did not vary significantly across study year (3.2% in 2007, 2.6% in 2008, and 1.7% in 2009; $P = .86$).

Results of bivariable analyses are shown in Table 1. Case patients had a significantly longer duration of hospitalization prior to sampling compared to control patients (mean, 28.9 days vs 7.8 days, respectively; $P < .001$). The presence of cirrhosis ($P = .006$) and prior receipt of either meropenem ($P = .01$) or clindamycin ($P = .04$) were significantly associated with ESBL-EK colonization.

Of the 10 patients with ESBL-EK colonization, there were 3 groups of case patients with overlapping dates of hospitalization. However, patients within each group were not located on the same unit. Four (40%) patients with ESBL-EK colonization had subsequent clinical cultures that tested positive for ESBL-EK, compared to 1 (0.3%) control patient ($P < .001$). Notably, these patients had positive clinical cultures a mean of 8.8 days after the surveillance culture date. None of the patients had positive ESBL-EK clinical cultures prior to the sampling date.

DISCUSSION

In this 2-year hospital-wide study, we found that the prevalence of gastrointestinal colonization with ESBL-EK was 2.6%. Previous studies evaluating colonization with ESBL-producing Enterobacteriaceae in hospitalized patients²⁻⁶ have demonstrated a wide range of prevalence rates from ~1% to 38% in an outbreak setting. The prevalence of ESBL-EK colonization in the present study was comparable to those reported from studies performed in academic tertiary care centers in the United States,^{5,6} although these were focused on ICU and high-risk populations.

We found that ESBL-EK colonization was associated with the recent use of clindamycin or meropenem. Antimicrobial use induces emergence of resistant organisms through pressure on endogenous flora, and it is likely that various antimicrobials identified as risk factors across studies^{4,6} are institution-dependent. Therefore, interventions to decrease ESBL spread in the hospital setting should focus on appropriate use of antimicrobials overall rather than restriction of specific classes. Alternatively, infection control interventions (eg, barrier precautions) may be more important for control of ESBL-EK in the hospital setting, and further research is needed on evaluating strategies to this effect.

Furthermore, 40% of patients in our study that were colonized with ESBL-EK had a subsequent positive clinical culture for ESBL-EK during hospitalization. Given that receipt of inappropriate antimicrobial therapy is associated with increased mortality in patients with infections due to ESBL-producing organisms,⁹ knowledge of ESBL-EK colonization status may help guide empiric antimicrobial therapy for nosocomial infections (eg, carbapenems). Notably, 60% of patients in our study who were colonized with ESBL-EK did not have positive clinical cultures and were never placed on barrier precautions. Asymptomatically colonized patients may act as a reservoir for persistence of ESBL-EK in the hospital setting, and this may provide further rationale for routine surveillance screening in high-risk populations.

Our study demonstrated an increased risk for colonization with ESBL-EK in patients with cirrhosis. This association is of particular concern given studies reporting an increased risk of infection with ESBL-EK in this patient population.¹⁰ Further work is needed to elucidate

mechanisms leading to ESBL-EK colonization and subsequent infection in patients with cirrhosis.

Potential limitations of our study include selection bias as only ~44% of eligible subjects were enrolled. Misclassification bias is a concern in case-control studies. However, testing for ESBL-production was performed prior to data collection, and cases and controls were drawn from the same population and classified solely based on ESBL positivity. Finally, the present study was conducted in an academic medical system, and these results may not be generalizable to other settings.

In conclusion, our study demonstrates a hospital-wide prevalence rate of 2.6% for ESBL-EK colonization. Future studies should focus on elucidating optimal infection prevention interventions to limit spread of ESBL-producing organisms in the hospital setting, including the role of routine surveillance screening in specific target populations.

Acknowledgments

Financial support. This work was supported by the Centers for Disease Control and Prevention (R01-CI000389) to E.L. This study was also supported, in part, by the CDC Prevention Epicenters Program (grant U54-CK000163 to E.L.), the National Institutes of Health (grant K24 AI080942 to E.L.), and a Commonwealth Universal Research Enhancement Program grant from the Pennsylvania State Department of Health (to E.L.).

References

- Schwaber MJ, Navon-Venezia S, Kaye KS, Ben-Ami R, Schwartz D, Carmeli Y. Clinical and economic impact of bacteremia with extended-spectrum- β -lactamase-producing *Enterobacteriaceae*. *Antimicrob Agents Chemother*. 2006; 50:1257–1262. [PubMed: 16569837]
- Pena C, Pujol M, Ricart A, et al. Risk factors for faecal carriage of *Klebsiella pneumoniae* producing extended spectrum β -lactamase (ESBL-KP) in the intensive care unit. *J Hosp Infect*. 1997; 35:9–16. [PubMed: 9032631]
- Thouverez M, Talon D, Bertrand X. Control of *Enterobacteriaceae* producing extended-spectrum beta-lactamase in intensive care units: rectal screening may not be needed in non-epidemic situations. *Infect Control Hosp Epidemiol*. 2004; 25:838–841. [PubMed: 15518025]
- Friedmann R, Raveh D, Zartzer E, et al. Prospective evaluation of colonization with extended-spectrum β -lactamase (ESBL)-producing *Enterobacteriaceae* among patients at hospital admission and of subsequent colonization with ESBL-producing *Enterobacteriaceae* among patients during hospitalization. *Infect Control Hosp Epidemiol*. 2009; 30:534–542. [PubMed: 19419270]
- Reddy P, Malczynski M, Obias A, et al. Screening for extended-spectrum β -lactamase-producing *Enterobacteriaceae* among high-risk patients and rates of subsequent bacteremia. *Clin Infect Dis*. 2007; 45:846–852. [PubMed: 17806048]
- Harris AD, McGregor JC, Johnson JA, et al. Risk factors for colonization with extended-spectrum β -lactamase-producing bacteria and intensive care unit admission. *Emerg Infect Dis*. 2007; 13:1144–1149. [PubMed: 17953083]
- Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. Wayne, PA: CLSI; 2010. CLSI document M100-S20
- McGettigan SE, Hu B, Andreatchio K, Nachamkin I, Edelstein PH. Prevalence of CTX-M β -lactamases in Philadelphia, Pennsylvania. *J Clin Microbiol*. 2009; 47:2970–2974. [PubMed: 19587301]
- Tumbarello M, Sanguinetti M, Montuori E, et al. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum- β -lactamase-producing *Enterobacteriaceae*: importance of inadequate initial antimicrobial treatment. *Antimicrob Agents Chemother*. 2007; 51:1987–1994. [PubMed: 17387156]
- Song KH, Jeon JH, Park WB, et al. Clinical outcomes of spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species: a retrospective matched case-control study. *BMC Infect Dis*. 2009; 9:41. [PubMed: 19361340]

TABLE 1

Bivariable Analyses of Risk Factors for Colonization with ESBL-Producing *E. coli* or *Klebsiella* Species in Hospitalized Patients

Variable	Cases (n = 10)	Controls (n = 379)	OR (95% CI)	P value
Age, mean years (SD)	61.0 (10.4)	57.5 (15.4)45
Female sex	8 (80.0)	163 (43.0)	5.30 (1.03–51.7)	.03
Nonwhite race	3 (30.0)	154 (40.6)	0.63 (0.10–2.80)	.75
Duration of hospitalization prior to culture date, mean days (SD)	28.9 (38.9)	7.8 (10.5)001
Admitted as a transfer	1 (10.0)	75 (19.8)	0.45 (0.01–3.43)	.69
Admitted through the ED	7 (70.0)	184 (48.6)	2.47 (0.55–15.0)	.21
Prior hospitalization in UPHS 30 days before culture date	4 (40.0)	51 (13.5)	4.29 (0.85–18.7)	.05
Year of sampling				
2007	5 (50.0)	151 (39.8)		
2008	3 (30.0)	113 (29.8)86
2009	2 (20.0)	115 (30.4)		
Congestive heart failure	3 (30.0)	82 (21.6)	1.55 (0.25–6.98)	.46
Diabetes mellitus	1 (10.0)	125 (33.0)	0.23 (0.01–1.67)	.18
HIV	0 (0.0)	8 (2.1)	...	>.99
Malignancy	4 (40.0)	129 (34.0)	1.29 (0.26–5.56)	.74
Cirrhosis	3 (30.0)	13 (3.4)	12.1 (1.78–59.9)	.006
Transplant	1 (10.0)	55 (14.5)	0.65 (0.01–4.89)	>.99
Renal insufficiency ^a	4 (40.0)	75 (19.8)	2.70 (0.55–11.7)	.12
Neutropenia	1 (10.0)	42 (11.1)	0.89 (0.02–6.72)	>.99
Mean Charlson score (SD)	3.7 (3.1)	3.5 (3.5)64
Receipt of any immunosuppression 30 days prior to culture date	4 (40.0)	129 (34.0)	1.29 (0.26–5.56)	.74
Receipt of corticosteroids 30 days prior to culture date	4 (40.0)	124 (32.7)	1.37 (0.28–5.90)	.74
ICU location on culture date	3 (30.0)	48 (12.7)	2.96 (0.48–13.4)	.13
Receipt of antimicrobial therapy 30 days prior to culture date ^b				
Amikacin	1 (10.0)	7 (1.9)	5.90 (0.12–54.5)	.19
Clindamycin	2 (20.0)	11 (2.9)	8.36 (0.77–48.9)	.04
Gentamicin	2 (20.0)	22 (5.8)	4.06 (0.39–22.0)	.12
Meropenem	3 (30.0)	16 (4.2)	9.72 (1.47–47.2)	.01
Aminoglycoside	3 (30.0)	33 (8.7)	4.49 (0.71–20.7)	.06

NOTE. Data are presented as no. (%), unless otherwise indicated. CI, confidence interval; ED, emergency department; ESBL, extended-spectrum β -lactamase; HIV, human immunodeficiency virus; ICU, intensive care unit; OR, odds ratio; SD, standard deviation; UPHS, University of Pennsylvania Health System.

^a Creatinine ≥ 2.0 mg/dL or requirement for dialysis.

^b Only antimicrobial agents with $P < .20$ are shown.