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The Effect of a Hospital-Wide Urine Culture Screening Intervention on the Incidence of Extended-Spectrum β-Lactamase-Producing *Escherichia coli* and *Klebsiella* Species

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Abstract

OBJECTIVE—Optimal strategies for limiting the transmission of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp (ESBL-EK) in the hospital setting remain unclear. The objective of this study was to evaluate the impact of a urine culture screening strategy on the incidence of ESBL-EK.

DESIGN—Prospective quasi-experimental study.

SETTING—Two intervention hospitals and one control hospital within a university health system from 2005 to 2009.

PATIENTS AND INTERVENTION—All clinical urine cultures with *E. coli* or *Klebsiella* spp were screened for ESBL-EK. Patients determined to be colonized or infected with ESBL-EK were placed in a private room with contact precautions. The primary outcome of interest was

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nosocomial ESBL-EK incidence in nonurinary clinical cultures (cases occurring more than 48 hours after admission). Changes in monthly ESBL-EK incidence rates were evaluated with mixed-effects Poisson regression models, with adjustment for institution-level characteristics (eg, total admissions).

RESULTS—The overall incidence of ESBL-EK increased from 1.42/10,000 patient-days to 2.16/10,000 patient-days during the study period. The incidence of community-acquired ESBL-EK increased nearly 3-fold, from 0.33/10,000 patient-days to 0.92/10,000 patient-days ($P < .001$). On multivariable analysis, the intervention was not significantly associated with a reduction in nosocomial ESBL-EK incidence (incidence rate ratio, 1.38 [95% confidence interval, 0.83–2.31]; $P = .21$).

CONCLUSIONS—Universal screening of clinical urine cultures for ESBL-EK did not result in a reduction in nosocomial ESBL-EK incidence rates, most likely because of increases in importation of ESBL-EK cases from the community. Further studies are needed on elucidating optimal infection control interventions to limit spread of ESBL-producing organisms in the hospital setting.

Extended-spectrum β-lactamase (ESBL)-producing Entero-bacteriaceae have rapidly emerged as an important cause of nosocomial and community infections worldwide.[1,2] Infections due to ESBL-producing Enterobacteriaceae, most commonly *Escherichia coli* and *Klebsiella* spp (ESBL-EK), have been associated with increased mortality, length of hospital stay, and healthcare costs.[3–5] However, despite the increasing prevalence of these pathogens, optimal strategies for control of ESBL-EK infection in acute care hospitals remain unclear, particularly in the absence of an outbreak. Indeed, a recent systematic review on the efficacy of infection control interventions for decreasing ESBL-producing Enterobacteriaceae in the nonoutbreak setting (eg, active surveillance, educational campaigns) identified only 4 studies,[6] all of which had significant limitations (eg, limited sample size, retrospective study design, lack of control groups).

Recommendations from the Centers for Disease Control and Prevention (CDC) for the prevention of transmission of multidrug-resistant organisms (MDROs) include judicious use of antibiotics, surveillance measures, and education of healthcare personnel.[7] Contact precautions are also recommended in the case of specific MDROs that are locally important, clinically or epidemiologically. Consequently, comprehensive detection of patients colonized or infected with ESBL-EK is critical for the prompt application of infection control measures (eg, contact precautions) designed to prevent transmission of ESBL-EK within the hospital setting.

One such potential strategy for detection of ESBL-EK is screening of all clinical *E. coli* and *Klebsiella* spp in urine cultures for ESBL-EK. Clinical and Laboratory Standards Institute (CLSI) guidelines currently do not recommend universal screening of clinical urine specimens for ESBL-producing organisms.[8] However, the impact of such screening on the increased detection of ESBL-EK is unknown. Therefore, we conducted this study to evaluate the impact of a comprehensive urine screening strategy on the incidence of ESBL-EK. The hypothesis was that enhanced detection would be associated with decreased ESBL-EK transmission, and therefore decreased ESBL-EK incidence, in the hospital setting.

SUBJECTS AND METHODS

Study Design and Setting

This multihospital study was a prospective quasi-experimental study[9,10] designed to assess the effect of a urine culture screening intervention on the incidence of ESBL-EK. Three hospitals within the University of Pennsylvania Health System were included in this study, with 2 designated as intervention hospitals and one designated as a control hospital. A control hospital was included in order to allow for assessment of temporal changes in regional ESBL-EK prevalence in the absence of the intervention. Intervention hospital 1 was a 772-bed academic tertiary care medical center, and intervention hospital 2 was a 331-bed urban community hospital. The control hospital was a 150-bed acute care urban hospital.

Study Intervention

In accordance with CLSI guidelines, screening of clinical urine specimens for ESBL-producing organisms was not routinely performed at the study institutions in the preintervention time period. The urine culture screening intervention for our study involved testing all clinical urine cultures with *E. coli* and/or *Klebsiella* spp for ESBL production. All isolates meeting CLSI criteria for ESBL-EK were subsequently reported to the primary team caring for the patient as well as to the infection control personnel of the respective intervention hospital. Contact precautions were then initiated for the patient and were maintained throughout the patient's hospital course. Contact precautions for ESBL-producing organisms consisted of gown and glove use for all entry into the patient room, as well as placement in a private room. In addition, the patient's medical record was flagged such that contact precautions were initiated for any hospital readmission. The intervention was implemented hospital-wide (ie, all floors and units) on January 1, 2006, at the 2 intervention hospitals. The preintervention period was January 1–December 31, 2005, and the postintervention period was January 1, 2006–February 28, 2009. Notably, there were no other new infection control interventions implemented at either of the intervention hospitals during the study period. However, active surveillance screening for methicillin-resistant *Staphylococcus aureus* (MRSA) via cultures of nares swab specimens upon admission was implemented at the control hospital on January 1, 2007. The study was reviewed and approved by the institutional review board of the University of Pennsylvania.

Microbiologic Methods

ESBL-EK urinary isolates were recovered from plating on 2 MacConkey agar plates, one supplemented with 1 μg/mL ceftazidime and the other with 1 μg/mL cefotaxime, and incubated for 48 hours.[11] Colonies suspected of being *E. coli* or *Klebsiella* spp were subcultured to blood agar plates (trypticase soy agar with 10% sheep blood) and MacConkey agar without antibiotics. Subsequently, all oxidase-negative colonies with the appropriate colony morphology were definitively identified with the semiautomated Vitek 2 identification and susceptibility system (bioMérieux).[12] Confirmatory testing for ESBL production was performed according to CLSI guidelines with the double disk confirmation test method.[13] Clinical nonurinary cultures were screened for ESBL-EK and results were confirmed with these same methods during the study period.

Data Collection

The primary outcome of interest was nosocomial ESBL-EK incidence in nonurinary clinical cultures (standardized per 10,000 patient-days), defined as those cases with a positive result from a culture sample collected more than 48 hours after admission. Nosocomial ESBL-EK was selected as the primary outcome, given that such cases were most likely to reflect acquisition in the hospital (ie, the target of the intervention) versus importation from the community at the time of admission. A secondary outcome of interest was overall ESBL-EK incidence in nonurinary clinical cultures (ie, including both nosocomial and community acquisition). Urine cultures were not included in the outcome, given that screening for ESBL-EK in clinical urine cultures was the focus of the intervention. As a result, no ESBL-EK would have been identified in urine cultures prior to the intervention, thus falsely elevating the incidence of ESBL-EK in clinical urine cultures following implementation of the intervention. Only the first nonurinary clinical culture positive for ESBL-EK was included for each patient in the calculation of the outcome for each study month.

Data were collected on institution-level variables (using monthly intervals) that could potentially affect the incidence of ESBL-EK, as follows: average daily census, total number of admissions, and average length of stay. Data on monthly institutional antimicrobial use was also ascertained for intervention hospital 1, in defined daily doses. Finally, monthly prevalence of fluoroquinolone-resistant *E. coli* (FQREC) in clinical cultures was selected as a nonequivalent dependent variable. A nonequivalent dependent variable was assessed in order to evaluate the possibility that factors other than the intervention might have influenced ESBL-EK incidence. Specifically, a nonequivalent dependent variable should have potential causal and confounding variables similar to those of the primary dependent variable (ie, ESBL-EK incidence) except for the effect of the intervention.[9,10] While ESBL-EK and FQREC may both be affected by such factors as antimicrobial use and patient census, there is less evidence of patient-to-patient transmission of FQREC.[14,15] Thus, in contrast to ESBL-EK, it is considered unlikely that enhanced infection control interventions would have an appreciable effect on FQREC prevalence.

Statistical Analysis

The effect of the urine culture screening intervention was assessed with segmented regression analysis,[16] which estimates both changes in the outcome when comparing the preintervention and postintervention periods and the slope of change in the outcome across these 2 time periods. The analysis included 12 data points for the preintervention period and 38 data points for the postintervention period. A mixed-effects Poisson regression model was developed to estimate the incidence rate ratio (IRR) associated with the intervention, with random effects for hospital and time after the intervention (in months), inclusion of a hospital × time interaction term, and adjustment for institution-level variables as noted (eg, monthly average daily census, monthly average length of stay). The natural logarithm of the total number of patient-days was used as an offset in the regression model, allowing for the modeling of rates rather than numbers of events. A secondary analysis was also performed with the nonequivalent dependent variable (ie, monthly FQREC prevalence) as the outcome of interest. Finally, in the case of intervention hospital 1, for which these data were

available, institutional antimicrobial use (by both agent and class) was also evaluated for inclusion in the final multivariable model.

For all calculations, a 2-tailed *P* value of less than .05 was considered significant. All statistical calculations were performed with commercially available software (STATA v11.0; StataCorp).

RESULTS

Over the approximately 4-year study period, the overall university health system–wide clinical incidence of ESBL-EK in nonurine clinical cultures increased from 1.42 cases/10,000 patient-days in the preintervention period to 2.16 cases/10,000 patient-days in the postintervention period ($P = .006$). Figure 1 demonstrates monthly trends in ESBL-EK incidence per 10,000 patient-days, stratified by intervention versus control hospitals.

Notably, there was no significant change in the incidence of nosocomial ESBL-EK (isolates obtained more than 48 hours after admission) from the pre- to the postintervention study period (from 1.08 to 1.23 cases/10,000 patient-days; $P = .51$). However, there was a significant increase in the incidence of community-acquired ESBL-EK (isolates obtained up to 48 hours after admission), from 0.33 cases/10,000 patient-days in the preintervention period to 0.92 cases/10,000 patient-days in the postintervention period ($P < .001$). Figure 2 demonstrates the monthly incidence rates of community-acquired ESBL-EK cases at the 2 intervention hospitals.

The mixed-effects Poisson regression model for the primary outcome of nosocomially acquired ESBL-EK (Table 1) demonstrated no significant association between the intervention and ESBL-EK incidence (IRR, 1.38 [95% confidence interval (CI), 0.83–2.31]; $P = .21$). On secondary-outcome analysis (Table 2), there was a significant association between the urine culture screening intervention and ESBL-EK incidence rates (IRR 1.67 [95% CI, 1.11–2.53]; $P = .02$). In addition, there were no significant changes in these multivariable models with the inclusion of changes in antibiotic use data from intervention hospital 1 (data not shown). Finally, on analysis evaluating the nonequivalent dependent variable, the intervention was associated with a significant increase in FQREC prevalence rates (IRR, 1.24 [95% CI, 1.11–1.38]; $P < .001$) at the 2 intervention hospitals.

DISCUSSION

In this 4-year multihospital study, we found that the implementation of a hospital-wide intervention involving screening of clinical *E. coli* and *Klebsiella* spp urine isolates for ESBL-EK did not lead to a decrease in nosocomial ESBL-EK incidence. Furthermore, the results of our study demonstrated a significant increase in rates of community-acquired ESBL-EK from the pre- to the postintervention study period. This increase in ESBL-EK was mirrored by an increase in the non-equivalent dependent variable (ie, monthly prevalence of FQREC), suggesting that antibiotic resistance overall rose significantly during the 4-year study period.

Despite the increasing global prevalence of ESBL-EK, there are limited data on optimal infection control strategies for controlling ESBL-EK transmission in acute care hospitals, particularly in the nonoutbreak setting. Previous studies in this area have had significant limitations,[6,17–20] including lack of control groups, small sample sizes, lack of multivariable analysis, and assessment of multiple interventions (eg, antimicrobial restriction, educational initiatives), making it difficult to evaluate the contribution of infection control measures alone. Our study is novel in that it evaluated the impact of a urine culture screening strategy on the incidence of ESBL-EK cases in the hospital setting. The results of our study are strengthened by use of segmented regression analysis, adjustment for potential confounders that could have changed over time (eg, total admissions, average length of stay), assessment of a nonequivalent dependent variable, inclusion of a prolonged baseline period, and use of a control hospital from the same health system and region as that of the intervention hospitals.

Notably, on analysis evaluating the impact of the urine culture screening intervention on the outcome of all ESBL-EK cases (ie, community and hospital acquired), the intervention was associated with an increased incidence of ESBL-EK. This demonstrated association was most likely attributable to the increasing prevalence of ESBL-EK in the community over time, leading to greater importation of ESBL-EK into the hospital during the postintervention period (2006–2009). Indeed, the intervention had no significant effect on the primary outcome of nosocomial ESBL-EK incidence rates (cases occurring in patients more than 48 hours after hospital admission), for which active identification and implementation of contact precautions would be expected to have the most effect.

Particularly with the increasing importance of ESBL-EK as community-associated pathogens, including in the United States,[21–23] these findings suggest that a more regional approach to control of ESBL-EK may be needed. Given that an increasing proportion of ESBL-EK cases are imported from the community, the implementation of contact precautions for cases detected via clinical cultures during hospitalization may be ineffective, especially in patients who are asymptomatically colonized. Active surveillance of patients on admission, including screening for asymptomatic colonization, may be a more effective infection control measure in this case, but further research is needed to clarify the appropriate target population as well as the cost-effectiveness of this strategy. Nevertheless, these findings emphasize the importance of accounting for the increasing community burden of ESBL cases in the development of optimal strategies for the control of ESBL-EK in acute care hospitals.

There are several potential reasons why screening of urine cultures for ESBL-EK had no effect on reducing the nosocomial incidence of ESBL-EK. While no other infection control–associated interventions were implemented during the study period, (eg, educational campaigns), it is possible that there may have been unmeasured changes in adherence to other infection control–related activities, such as hand hygiene and gown and glove use. A number of antibiotic agents and classes have been implicated as risk factors for ESBL-EK, and it is possible that changes in antibiotic selection pressure may have led to an increase in the incidence of ESBL-EK that offset the effect of the intervention. However, controlling for changes in monthly antibiotic use for the larger intervention hospital did not change this lack of association. Furthermore, there were no changes in antimicrobial stewardship policies

(eg, restriction of specific agents or classes) during the study period. Finally, given significant increases in colonization pressure over the study period, specifically in the intervention hospitals (ie, community-acquired ESBL-EK), it is possible that the urine screening intervention may have attenuated concomitant increases in nosocomially acquired ESBL-EK rates and resulted in a smaller increase in the primary outcome than would have occurred had the intervention not been implemented.

Alternatively, some studies suggest that patient-to-patient transmission may not be an important determinant of emergence of ESBL-producing Enterobacteriaceae in the hospital setting, particularly in comparison to colonization and antibiotic selection pressures.[24,25] For example, a study performed at a university hospital[25] demonstrated that transmission, as confirmed by pulsed-field gel electrophoresis, occurred in only 1.5% of patients who had been hospitalized in the same room as a patient colonized or infected with ESBL-producing Enterobacteriaceae. It is also possible that patient-to-patient transmission may be more important in acquisition of ESBL-producing *Klebsiella* spp specifically,[26,27] and indeed, in our study, the proportion of community-acquired ESBL-producing *Klebsiella* spp isolates at the intervention hospitals increased significantly over the study period. Thus, while the hospital-wide urine culture screening intervention in our study may have led to enhanced identification of patients colonized or infected with ESBL-EK, subsequent initiation of contact precautions and presumably decreased opportunities for patient-to-patient transmission may not have had a significant impact on overall ESBL-EK incidence.

Finally, in association with the increasing prevalence of ESBL-positive Enterobacteriaceae from the community, there has been a shift in the distribution of ESBL types. Specifically, ESBLs associated with community-acquired infections have predominantly been of the CTX-M type, as opposed to the TEM and SHV types more typically associated with nosocomial infections.[23,28] A growing body of data demonstrates that CTX-M-producing isolates differ in regard to epidemiologic characteristics from those producing SHV-TEM group ESBLs,[23,28] and further research is needed on potential differences in transmissibility and optimal infection control measures based on ESBL type.

There are potential limitations of our study. While there were no new infection control initiatives during the study period at the intervention hospitals, we were unable to systematically collect data on adherence to infection control measures that may have affected the outcome, including hand hygiene and contact precautions. In addition, antibiotic use data was available for only one of the intervention hospitals. Finally, our study was conducted in an academic tertiary care medical system, and these results may not be generalizable to other institutions.

In conclusion, the results of our study demonstrate that the implementation of a hospital-wide intervention for screening clinical urine cultures for ESBL-EK did not significantly reduce nosocomial ESBL-EK incidence rates. Furthermore, the proportion of community-acquired ESBL-EK isolates significantly increased over time, which may have important implications for potential targeted surveillance screening in hospitals with a high prevalence of ESBL-EK. Finally, ESBL-EK emergence in the hospital setting is complex, and further studies are needed on elucidating optimal interventions to limit spread of ESBL-producing

organisms in acute care hospitals, including the relative importance of contact precautions, hand hygiene adherence, and effective antimicrobial stewardship.

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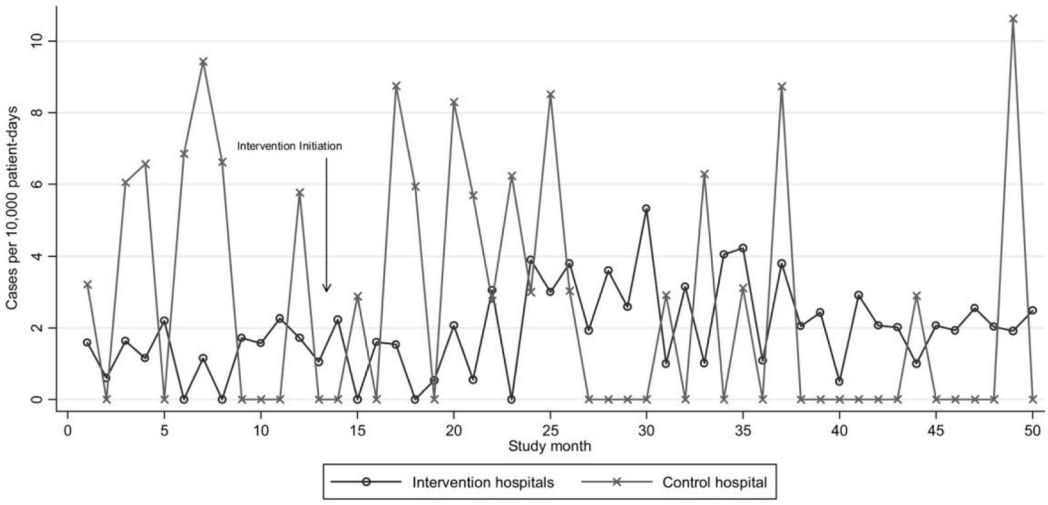

FIGURE 1.

Incident nonurinary source extended-spectrum *β*-lactamase-producing *Escherichia coli* and *Klebsiella* cases per month from January 2005 to February 2009.

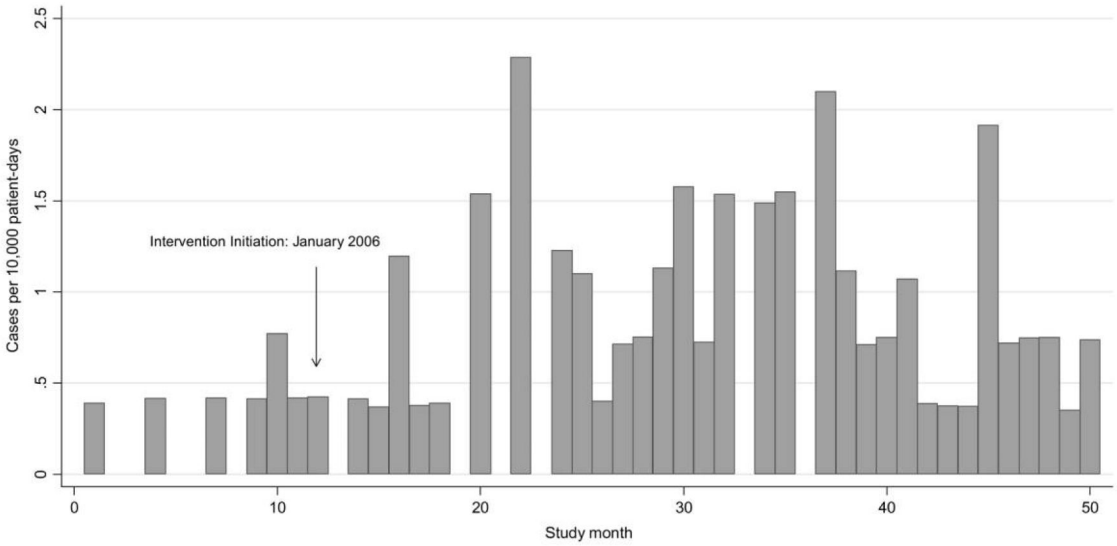

FIGURE 2.

Incident nonurinary-source community-acquired extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* cases per month from January 2005 to February 2009 for intervention hospitals.

TABLE 1

Associations from Poisson Mixed-Effects Model for Nosocomial ESBL-EK Incidence

Variable	IRR (95% CI)	*P* value
Urine culture screening intervention	1.38 (0.83–2.31)	.21
Time[a]	1.01 (0.99–1.03)	.29
Hospital[b]		
Intervention hospital 2	0.44 (0.02–10.7)	.04[c]
Control hospital	3.12 (0.05–203.3)	
Average daily census	1.00 (0.99–1.01)	.85
Average number of admissions	1.00 (0.998–1.001)	.88
Average length of stay	0.65 (0.35–1.21)	.17
Hospital × time[d]		
Intervention hospital 2 × time	0.97 (0.94–1.01)	.008[e]
Control hospital × time	0.93 (0.89–0.98)	

NOTE. CI, confidence interval; ESBL-EK, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp; IRR, incidence rate ratio.

[a] In months following the initiation of the intervention.

[b] Reference category is intervention hospital 1.

[c] Wald test of hospital terms in the final model (ie, nosocomial ESBL-EK incidence differed significantly between the hospitals).

[d] Reference category is intervention hospital 1 × time.

[e] Wald test for all hospital × time terms in the final model (ie, the change in nosocomial ESBL-EK incidence over time differed significantly between the hospitals).

TABLE 2

Associations from Poisson Mixed-Effects Model for Overall ESBL-EK Incidence

Variable	IRR (95% CI)	*P* value
Urine culture screening intervention	1.67 (1.11–2.53)	.02
Time[a]	1.01 (0.99–1.03)	.25
Hospital[b]		
Intervention hospital 2	0.81 (0.06–10.3)	.21[c]
Control hospital	2.38 (0.08–69.6)	
Average daily census	1.00 (0.99–1.004)	.38
Average number of admissions	1.00 (0.99–1.002)	.37
Average length of stay	0.95 (0.62–1.47)	.82
Hospital × time[d]		
Intervention hospital 2 × time	0.98 (0.96–1.01)	.01[e]
Control hospital × time	0.96 (0.93–0.99)	

NOTE. CI, confidence interval; ESBL-EK, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* spp; IRR, incidence rate ratio.

[a] In months following the initiation of the intervention.

[b] Reference category is intervention hospital 1.

[c] Wald test of hospital terms in the final model.

[d] Reference category is intervention hospital 1 × time.

[e] Wald test for all hospital × time terms in the final model (ie, the change in overall ESBL-EK incidence over time differed significantly between the hospitals).