Infection and Drug Resistance

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ORIGINAL RESEARCH

Risk factors for infections with extended-spectrum beta-lactamase-producing *Escherichia coli* in a county of Southern Sweden

This article was published in the following Dove Press journal:
Infection and Drug Resistance
18 September 2013
Number of times this article has been viewed

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Background: It is important to identify patients who are at risk for infections with extended-spectrum β-lactamase (ESBL)-producing bacteria in order to reduce mortality, to avoid spread of resistant bacteria in hospitals, and to minimize the number of patients receiving unnecessary treatment with broad-spectrum antibiotics. A case-control survey among Swedish patients was performed at Skåne University Hospital to identify risk factors for developing an infection with ESBL-producing *Escherichia coli* in a low endemic country.

Methods: We used a computerized database to identify patients with growth of ESBL-producing *E. coli* (n = 109) in urine or blood cultures and an equal number of controls matched for age and gender with non ESBL-producing *E. coli* in urine and blood diagnosed between January and October 2008. We used unadjusted *P*-values.

Results: Patients with ESBL-producing *E. coli* had a significantly ($P < 0.05$) higher likelihood of having traveled to Asia including Turkey and the Middle East including Egypt (14/58) than the non-ESBL-positive group (4/53). Hospital stay during the previous year ($P < 0.04$), especially for more than one month, was another significant ($P = 0.01$) risk factor for infection with ESBL-producing *E. coli* (8/58). A stay in the surgical department was a further risk factor ($P < 0.01$).

Conclusion: In this study, we identified 22 of 58 (38%) patients with ESBL-producing *E. coli* by considered significant risk factors before starting antibiotics.

Keywords: extended-spectrum β-lactamase, Enterobacteriaceae, resistant bacteria, risk factors, *Escherichia coli*

Introduction

The incidence of infections due to extended-spectrum β-lactamase (ESBL)-producing bacteria has increased rapidly in recent years and poses a worldwide threat to health care. The close relationship between ESBL production and multidrug resistance leaves only a few treatment options for infections commonly caused by Enterobacteriaceae.[1] Patients with an infection caused by ESBL-producing bacteria are at risk for therapeutic failure or even death because there is often a delay before the correct antibiotic treatment is given.[2] In international comparisons, there have so far been only a few nosocomial outbreaks of plasmid-mediated ESBL-producing bacteria in Sweden.[3,4] Further, compared with other European countries, the prevalence of ESBL in bacterial isolates from feces and blood has long been relatively low in Sweden, found in less than 3% of *Escherichia coli*, although this proportion is increasing.[5,6] Poor hand hygiene and lack of food hygiene facilitates the spread of ESBL-producing Enterobacteriaceae.[7–10] Known risk factors for colonization or onset of infection with

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ESBL-producing Enterobacteriaceae from different studies are antibiotic use, prolonged and/or recent hospital stay, severe illness, recent surgery, bladder catheterization or other invasive medical devices, residence in a long-term care facility, international travel, and age 65 years and older.[1,4,11–14] However, the positive predictive value of these risk factors is low.[15] It is important to identify patients who are at risk for infection with ESBL-producing bacteria, especially in low endemic countries, in order to reduce mortality, to avoid spread of resistant bacteria in hospitals, and to minimize the number of patients receiving unnecessary treatment with broad-spectrum antibiotics.[2]

The aim of this study was to perform a case-control survey of Swedish patients to identify risk factors for developing an infection with ESBL-producing *E. coli* in a low endemic country.

Materials and methods

Study design and setting

We performed a case-control survey in the department of medical microbiology laboratory at Skåne University Hospital, Malmö, Sweden, that serves a population of about 470,000 people. We used a computerized database to identify patients with growth of ESBL-producing *E. coli* in urine or blood cultures and an equal number of controls matched for age and gender with non-ESBL-producing *E. coli* in urine and blood cultures diagnosed between January and October 2008. The study investigators developed the questionnaire used in this study. Both groups were asked the same questions regarding risk factors, including stomach problems, urinary catheter, endoscopic procedures, recurrent urinary infections, medication for stomach ulcers, hospital stay, length of hospital stay, antibiotic consumption, comorbid conditions, occupation, visiting abroad, and finally, if the patient thought that they had received adequate information about ESBL when infected (Table 1).

Microbiology

Urine and blood samples were examined for *E. coli* using phenotyping tests according to national guidelines.[16,17] The *E. coli* strains were screened for cephalosporin resistance using a cefadroxil disk. *E. coli* strains resistant to cefadroxil were analyzed for ESBL production by inoculation on agar plates with medium selective for cephalosporin resistance (ChromID™ ESBL, BioMerieux Clinical Diagnostics, Marcy-l'Étoile, France) and synergy testing with discs containing ceftazidime, cefotaxime, and amoxicillin-clavulanic acid.[16,18]

Statistical analysis

Statistical methods included analysis of a contingency table (Fisher's exact test), odds ratios (OR), and calculation of 95% confidence intervals (CI) for the parameters, computed using the method of Clopper and Pearson for binomial data and Mann–Whitney–Wilcoxon for continuous data (age). Using statistical power calculations, we concluded that a study population of just over 100 participants (including those who did not answer) should be enough to obtain significant results. Subject characteristics at baseline were summarized using medians, ranges, and frequencies. The prevalence of risk factors was calculated as the percentage of risk factors among patients in each group. Odds ratios and 95% CI were calculated to evaluate the strength of any association that emerged. An unadjusted P-value <0.05 was considered to be statistically significant. Analysis was performed using Graph Pad software (Graph Pad Software, Inc., La Jolla, CA, USA) and the responses from the returned questionnaires were compiled in Excel. Ethical approval for the study was obtained from the research ethics committee at the University of Lund.

Results

During the study period, 109 patients of median age 65 (range 2–95) years suffering from urinary tract infection or bacteremia with ESBL-producing *E. coli* and 109 controls of median age 65 (2–95) years, with non-ESBL-producing *E. coli* in urine or blood were included. Of these 218 patients, six had moved out from the county and five had died. No significant difference in response rates were seen between the groups, ie, 53% (n = 58) in the ESBL group and 49% (n = 53) in the control group. The cases and controls who replied to the survey were well matched for age and gender (Table 1). Patients with ESBL-producing *E. coli* had a significantly ($P < 0.05$) higher rate of travel to Asia including Turkey and the Middle East including Egypt (14/58) than the non-ESBL-positive group (4/53).

A hospital stay during the previous year ($P < 0.04$) and especially for more than one month ($P = 0.01$) was a risk factor for infection with ESBL-producing *E. coli* (8/58). Notable was that three of these eight patients had also received treatment with quinolones. No patient in the ESBL-negative group had stayed in hospital for more than one month. A stay in the surgical department was also a risk factor ($P < 0.01$). Treatment with antibiotics in general during the previous year was more common ($P = 0.09$) and with quinolones in particular ($P = 0.06$) in cases than in controls. We could not

Table 1 Results of a survey of different risk factors of developing an infection with ESBL-producing *Escherichia coli,* including for ESBL-positive versus ESBL-negative cases

Covariate	All	ESBL-positive	ESBL-negative	OR (95% CI)	*P*-value
Response rate, n (%)	111/218 (51%)	58/109 (53%)	53/109 (49%)		
Demographic characteristics					
Median age, years	65	65	65		
Range, years	2–95	2–95	2–95		
Female gender, n (%)	85 (77)	45 (77)	40 (75)		
Occupation					
Health care	14	7	7		>0.3
Restaurant	3	2	1		>0.3
Office	13	6	7		>0.3
Kindergarten/school	10	8	2	4 (0.8–20.2)	0.0970
Comorbidity disease					
Gastrointestinal	12	6	6		>0.3
Ear nose and throat	5	3	2		>0.3
Urinary tract (including renal disease)	31	18	13		>0.3
Heart	22	13	9		>0.3
Liver	2	2	0		>0.3
Lung	11	7	4		>0.3
Diabetes	10	6	4		>0.3
Cancer	7	4	3		>0.3
Miscellaneous	15	8	7		>0.3
Endoscopy	49	29	20	1.65 (0.8–3.5)	0.25
Urinary tract catheter (including chronic)	29	16	13		>0.3
Recurrent UTI	41	23	18		>0.3
Antiulcer medication (eg, omeprazole)	42	24	18		>0.3
Staying at nursery home	5	4	1		
Hospital stay in previous year	49	31	18	2.2 (1.0–4.8)	0.04
Medical department	20	12	8		>0.3
Surgical department	17	14	3	5.3 (1.4–19.7)	0.01
Department of infectious diseases	11	7	4		>0.3
ICU	2	0	2		>0.3
Length of stay at hospital					
<1 week	26	18	8	2.5 (1.0–6.4)	0.07
>1 week and <4 weeks	16	6	10		>0.3
>4 weeks	8	8	0		0.01
Antibiotic treatment in previous year	62	37	25	2.0 (0.9–4.2)	0.09
Treatment with quinolones	5	5	0		0.06
Foreign travel					
High-risk areas (Middle East and Asia)	18	14	4	3.9 (1.2–12.7)	0.02
Europe	32	16	16		>0.3
Both Europe and others	9	6	3		>0.3
Miscellaneous	4	1	3		>0.3
Travelers' diarrhea	10	7	3	2.3 (0.56–9.3)	>0.3
Adequate information, n (%)			22/56 (39)		

Abbreviations: ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; UTI, urinary tract infection.

find any other statistically significant differences between the groups regarding civil status, accommodation, comorbid conditions (including urinary tract problems), intubation, endoscopies, catheterization, medication other than antibiotics, relatives who had been abroad, or history of travelers' diarrhea. In the ESBL group, 34 of 58 (39%) thought that the information given by their physician about their ESBL colonization was inadequate.

Discussion

In this case-control study, we found that travelling to countries in which ESBL is high endemic, such as Asia, the Middle East, and Turkey, was a significant risk factor (with an unadjusted P-value < 0.05) for contracting a urinary tract or bloodstream infection with ESBL-producing *E. coli*. We also found that a hospital stay longer than one month and especially in a surgical ward could be a risk factor for

acquiring ESBL-producing *E. coli* infections. However, because many of these patients had also received antibiotic treatment with quinolones we could not determine if it was the hospital stay or the antibiotic treatment that was the cause for acquiring ESBL-producing *E. coli*.

Our study has some limitations. The first is that we used unadjusted *P*-values. However, in this explorative phase, it was more important to identify possible predictors than to rule out false ones. Second, different *E. coli* strains could be influenced by different risk factors, but because this was a retrospective study and several isolates were not available for examination, we could not perform multilocus sequence typing or use polymerase chain reaction methods to investigate the molecular epidemiology of the different *E. coli* strains and we could not characterize the ESBL enzymes. Further, the matching criteria selected in this case-control study were age and gender, which could conceal age and gender as potentially significant risk factors.

The results of this study correspond well with the results of other published studies reporting a high rate of fecal colonization of ESBL-producing *E. coli* after international travel to countries outside Europe, especially to the Middle East and Asian countries which have a much higher prevalence of ESBL-producing Enterobacteriaceae.[19–22] In a study from Sweden, Tängden et al showed a high rate of ESBL-producing bacteria in fecal flora, mostly from patients having travelers' diarrhea, who were cultured before and after international travel.[13] In another study, we found a very high rate of ESBL-producing *E. coli* in patients with travelers' diarrhea who had traveled outside Europe (36%) and especially to Asia (41%) and the Middle East (50%).[12] Notably, this is not the same as acquiring an infection caused by ESBL-producing bacteria because they could be normal inhabitants of the gastrointestinal tract and could stay there as a subdominant population. Laupland et al performed a case-control study published in 2008 which identified that foreign travel was an important risk factor for developing community-onset ESBL-producing *E. coli* infections in Calgary, Canada, especially if patients had travelled to India or to the Middle East.[23] Our results from this Swedish case-control study match the results reported by Laupland et al, ie, the acquisition of ESBL-producing bacteria is also a risk for becoming infected with these bacteria.

Like Lautenbach et al, we also found that a long hospital stay could be a significant risk factor for infection with ESBL-producing bacteria, but we could not determine if the patients had acquired the ESBL-producing *E. coli* during their hospital stay.[24] A possibility is that the patients had been unrecognized carriers before admission to hospital and due to selective pressure (antibiotic consumption), ESBL-producing *E. coli* had appeared. In another study, we investigated the prevalence of ESBL-producing bacteria in hospitalized patients and patients from primary health care centers in 2008 and 2010. The prevalence of ESBL-producing bacteria increased in both groups during the study period, but we did not notice any hospital spread or outbreaks during this time, indicating that the patients had acquired their ESBL-producing *E. coli* in the community.[5] Having invasive medical devices was not a risk factor in our study, but this could be of more importance in patients with ESBL-producing Klebsiella species than in ESBL-producing *E. coli*.[25]

To prescribe correct empiric antibiotic treatment in patients with severe septicemia/septic shock is of great importance for survival.[2,26] In this study, we would have identified 22 of 58 (38%) patients with ESBL-producing *E. coli* if we had considered the significant risk factors that we found in our study before giving antibiotics. However, the majority of patients with ESBL-producing *E. coli* would not have been detected if only addressing these risk factors. Only a few patients in our study, ie, four of 53 (8%), with non-ESBL-producing *E. coli* would have received an unnecessary broad-spectrum antibiotic.

Conclusion

A long stay in hospital (for more than one month) or asking the patient about international travel to the Middle East or Asia are important factors to consider when predicting if a patient would be at risk of having an infection with ESBL-producing *E. coli* or not. Rapid microbiologic diagnostic tests and high clinical suspicion with careful evaluation are currently the only instruments we have to identify these patients. The need for new antibiotics is urgent. Disciplined antibiotic stewardship, adherence with hand hygiene routines, and infection control methods in hospitals are vital. The incidence of ESBL-producing bacteria in hospitals should be carefully monitored in the future and patients with ESBL-producing bacteria should receive better information.

Acknowledgment

This research was funded by the Swedish Strategic Programme Against Antibiotic Resistance from Region Skåne, Sweden.

Disclosure

The authors report no conflicts of interest in this work.

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