Risks Factors for Infections with Extended-Spectrum Beta-Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae* at a Tertiary Care University Hospital in Switzerland

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Abstract

Background: There are considerable geographical differences in the occurrence of extended-spectrum beta-lactamase (ESBL)-producing bacteria, both in the community and in the hospital setting. Our aim was to assess risk factors for bloodstream, urinary tract, and vascular catheter-associated infections with ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* at a tertiary care hospital in a low-prevalence country.

Methods: We performed a case–control study comparing 58 patients with infections due to ESBL-producing *E. coli* or *K. pneumoniae* vs 116 controls with infections due to non-ESBL producing organisms at the University Hospital Zurich, Switzerland, between 1 July 2005 and 30 June 2007.

Results: Cases included 15 outpatients and 43 inpatients. Multivariable analyses found three risk factors for ESBL-producing isolates: begin of symptoms or recent antibiotic pre-treatment in a foreign country (odds ratio [OR] 27.01, 95% confidence interval [CI] 2.38–1,733.28], p = 0.042), antibiotic therapy within the year preceding the isolation of the ESBL-producing strain (OR 2.88, 95% CI 1.13–8.49, p = 0.025), and mechanical ventilation (OR 10.56, 95% CI 1.06–579.10, p = 0.042).

Conclusions: The major risk factors for infections due to ESBL-producing bacteria were travel in high-prevalence countries, prior antibiotic use, and mechanical ventilation during a stay in the intensive care unit. Community-acquired infections were documented in 17% of the patients. An early identification of risk factors is crucial to providing the patients an optimal empiric antibiotic therapy and to keep the use of carbapenems to a minimum.

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Introduction

Extended-spectrum beta-lactamases (ESBL) are beta-lactamases that confer bacterial resistance to all penicillins, first-, second- and third-generation cephalosporins, and aztreonam through their enzymatic hydrolysis of the four-atom ring (beta-lactam) of these antibiotics. They are most often found in strains of *Escherichia coli* and *Klebsiella pneumoniae* [1, 2]. While ESBLs can be inhibited by beta-lactamase inhibitors, such as clavulanic acid, treating infections due to ESBL-producing Gram-negative bacteria is challenging due to the limited availability of antibiotics that are not susceptible to hydrolysis by ESBLs. In addition, the use of beta-lactams in combination with beta-lactamase inhibitor agents for the treatment of serious infections with ESBL-producing bacteria is still a matter of debate [3]. Therefore, some experts recommend the use of a carbapenem antibiotic for all cases of serious infection with ESBL-producing bacteria [4].

Infections with ESBL-producing *Enterobacteriaceae* originally emerged primarily in the hospital setting. Patients at high risk for developing colonization or infection with ESBL-producing organisms are often seriously ill, have (had) a prolonged hospital stay, or are in need of invasive medical devices [1, 2, 5–9]. Several studies have found a relationship between third-generation cephalosporin use and colonization or infections with an ESBL-producing strain [10]. Since 2001 [11], reports of community-acquired infections of ESBL have emerged, which makes the epidemiology of ESBL-producing bacteria yet more complex [12]. *E. coli* is the most common cause of community-acquired urinary tract infections, and ESBL-producing isolates of *E. coli* are frequently resistant to many of the antimicrobial agents recommended for the treatment of such infections. The presence of community-acquired

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ESBL-producers plus the potential for plasmid-mediated resistance to quinolone and carbapenem antibiotics will undoubtably create significant therapeutic problems in the future [13, 14].

There are considerable geographical differences in the occurrence of ESBLs, both in the community and in the hospital setting. Even though Switzerland is a country with a relatively low prevalence rate, community-acquired ESBLs have already emerged [15]. Given this new ESBL-epidemiology, there is a need to re-evaluate established risk factors.

The objective of this study was to assess risk factors for bloodstream, urinary tract, and catheter-associated infections with ESBL-producing *E. coli* and *K. pneumoniae* in a low-prevalence country.

Patients and Methods

Setting

We performed a case–control study at the University Hospital Zurich, an 800-bed tertiary care teaching hospital that covers all specialties except for pediatrics and orthopedics. Six intensive care units (ICUs) provide a full range of clinical services in different departments of surgery and internal medicine.

The computerized database of the Institute of Medical Microbiology, University of Zurich, which compiles and processes all microbiological samples of the University Hospital Zurich, was used to identify patients with *E. coli* or *K. pneumoniae* detected in blood cultures, cultures from vascular catheters, and cultures from urine in the time period from 1 July 2005 through to 30 June 2007. As most infections due to ESBL-producing *E. coli* and *K. pneumoniae* occurred and were treated in the departments of Internal Medicine, Surgery, Gynecology and Obstetrics, and Urology, only patients treated in these departments were included in this analysis. Other clinical samples as well as surveillance swabs yielding ESBL-producing *E. coli* and *K. pneumoniae* and infections due to other ESBL-producing *Enterobacteriaceae* were not included in this analysis.

Case and Control Patients

Case patients were defined as patients presenting with bloodstream infections (systemic inflammatory response syndrome and blood cultures positive for an ESBL-producing strain of *E. coli* or *K. pneumoniae* [16]), those with local or systemic signs of infection from an intravascular catheter with a positive catheter tip culture (> 5 cfu/ml [17]) with an ESBL-producing *E. coli* or *K. pneumoniae*, and those with asymptomatic bacteriuria or symptomatic urinary tract infection (e.g., fever, dysuria, urgency, frequency, suprapubic tenderness, or flank pain) with documentation of an ESBL-producing *E. coli* or *Klebsiella pneumoniae* ($\geq 10^4$ cfu/ml) in the urine. Symptomatic case patients with pyelonephritis, indwelling urinary catheters, or urinary tract obstruction were assigned to have a complicated urinary tract infection. Asymptomatic patients with positive urine cultures, including those with indwelling bladder catheters, were considered to have asymptomatic bacteriuria.

Control patients were defined as patients presenting with the same types of infections as those of the case patients, but with infections due to non-ESBL-producing *E. coli* or *K. pneumoniae*. Two controls were matched with every case patient. The matching priorities in decreasing order were: bacterial isolate, specimen, department, age (± 5 years), and gender.

Data Collection and Definitions

Clinical and demographic data of cases and controls were collected from patients' charts. The variables evaluated as possible risk factors were: nosocomial onset of infection, ICU stay, mechanical ventilation, central venous catheter, urinary catheter or pigtail catheter in the urinary tract at the time of infection, hospitalization within the preceding 365 or 30 days, urological or general surgery within the preceding 365 or 30 days, prior antibiotic use within the year preceding the infection, documented urinary tract anomaly, recurrent urinary tract infections according to anamnestic information, renal insufficiency, prior renal transplantation, hemodialysis, malignoma, diabetes, HIV infection, neutropenia (< 500 neutrophils/μl), immunosuppressive medication (corticosteroids and other immunsuppressants), and travel history. We used the ''Chronic Disease Score'' to assess the comorbidity of hospitalized patients [18, 19].

The administration of antibiotics within 1 year prior to the diagnosis of infection was assessed. One antibiotic course was defined as the administration of at least one dose of any antibacterial agent. A time interval of > 24 h between the administration of two doses was defined to separate one course from another, unless certain conditions (e.g., renal insufficiency) justified a dose interval of < 24 h.

Infections were considered to be nosocomial if the patient was hospitalized in an acute care center for > 24 h prior to sample collection. Surgical site infections were rated as nosocomial if the infection was related to a surgical procedure performed in the preceding year [20]. Non-nosocomial infections were either community-acquired or health care-associated. They were rated as health care associated if they fulfilled any of the following criteria (adapted from [21]): (1) Patient received iv therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends; had self-administered iv medical therapy in the 30 days before the infection (patients whose only home therapy was oxygen use were excluded); (2) patient attended a hospital or hemodialysis clinic or received iv antineoplastic chemotherapy in the 30 days before the infection; (3) patient was hospitalized in an acute care hospital for ≥ 2 days in the 90 days before the infection; (4) patient resided in a nursing home or long-term care facility.

Microbiological Analysis

Antimicrobial susceptibility testing and screening for ESBL was performed according to Clinical and Laboratory Standards Institute recommendations [22]. In brief, the initial screen test to indicate ESBL production was a ceftazidime inhibition zone with a diameter ≤ 22 mm or a cefotaxime inhibition zone ≤ 27 mm. Any synergy between amoxicillin/clavulanic acid and ceftazidime or cefepime (double disk method) or between piperacillin/tazobactam and cefotaxime in the disk diffusion test was also taken to be an indication for the organism to be tested by a phenotypic confirmatory test. A greater than twofold concentration decrease in an MIC for ceftazidime or cefepime or for cefotaxime tested in combination with clavulanic acid versus its MIC when tested alone was confirmatory for ESBL. In accordance with the CLSI guidelines, all ESBL-producing *E. coli* strains were classified as resistant to all penicillins, cephalosporins, aztreonam irregardless of the MICs determined for these drugs [22].

Table 1
Patient characteristics of cases and controls.

Patient characteristics	ESBL group n (%)	Non-ESBL group n (%)	p-value
Number of patients	58 (100)	116 (100)	
Male	25 (43.1)	48 (41.4)	0.871
Age, years (mean ± SD)	52.6 ± 19.2	54.0 ± 18.2	0.637
Outpatients	15 (25.9)	30 (25.9)	1.000
Inpatients	43 (74.1)	86 (74.1)	1.000
Duration of hospital stay, days (mean ± SD)	35.4 ± 39.2	24.4 ± 23.4	0.177
Intensive care stay, days	21 (36.2)	38 (32.8)	0.734
Duration of intensive care stay, days (mean ± SD)	14.2 ± 15.8	9.9 ± 9.4	0.573
Duration of hospital stay before first isolate, days (mean ± SD)	12.2 ± 18.5	8.5 ± 10.0	0.466
Chronic Disease Score (mean ± SD)	6.0 ± 2.6	5.3 ± 2.3	0.136
Nosocomial onset of infection	26 (44.8)	53 (45.7)	1.000
Non-nosocomial onset of infection	32 (55.2)	63 (54.3)	1.000
Health care-associated	22 (37.9)	30 (25.9)	0.080
Community-acquired	10 (17.2)	33 (28.4)	0.080
Comorbidity			
Urinary tract anomaly	18 (31.0)	31 (26.7)	0.594
Malignoma	14 (24.1)	24 (20.7)	0.698
Renal insufficiency	6 (10.3)	17 (14.7)	0.486
Hemodialysis	4 (6.9)	3 (2.6)	0.224
Diabetes	8 (13.8)	12 (10.3)	0.615
Sites of infection			
Urinary tract infections	48 (82.8)	96 (82.8)	1.000
Asymptomatic bacteriuria	22 (37.9)	46 (39.7)	0.870
Acute uncomplicated urinary tract infection	10 (17.2)	7 (6.0)	0.028
Acute uncomplicated pyelonephritis	0 (0)	10 (8.6)	0.032
Complicated urinary tract infection	16 (27.6)	28 (24.1)	0.712
Other or unclear diagnosis	0 (0)	5 (4.3)	0.176
Bacteremia	5 (8.6)	15 (12.9)	0.461
Peritonitis	2 (3.4)	4 (3.4)	1.000
Urosepsis	2 (3.4)	4 (3.4)	1.000
Burns	1 (1.7)	2 (1.7)	1.000
Septic abortion	0 (0)	1 (0.9)	1.000
Perinephritic abscess	0 (0)	1 (0.9)	1.000
Unknown focus	0 (0)	3 (2.6)	0.552
Vascular catheter-associated infection	5 (8.6)	5 (4.3)	0.304

ESBL: Extended-spectrum beta-lactamase; SD: standard deviation

Statistical Analysis

All statistical analyses were performed using Intercooled Stata Software Version 10 for Windows (Stata Corp, College Station, TX). Categorical data were analyzed using the two-tailed χ^2 test or Fisher's exact test, and continuous data were analyzed by the Wilcoxon rank-sum test. We used conditional logistic regression analysis for the univariable and multivariable calculation of risk factors and odds ratios (OR) with 95% confidence intervals (CI). A two-tailed test of significance with a p-value < 0.05 was considered to be statistically significant.

Ethical Approval

The study protocol was approved by the local ethics committee.

Results

Patient characteristics

A total of 174 patients (58 cases and 116 controls) were included in the analysis (Table 1). 73 (42.0%) patients were male, of whom 25 (43.1% of case patients) were in the ESBL group and 48 (41.4% of control patients) in the non-ESBL group. The mean age (± standard deviation [SD]) was 52.6 years (± 19.17 years) for cases and 53.51 years (± 18.48 years) for controls. 25.9% of all patients in each group were treated as outpatients, while 48 patients (27.6%) were treated in the Department of Surgery, 60 (34.5%) in the Department of Internal Medicine, 45 (25.9%) in the Department of Urology, and 21 (12.1%) in the Department of Gynecology and Obstetrics. *E. coli* could be cultured in 153 (87.9%) patients, and *K. pneumoniae* in 21 (12.1%). The mean duration of hospital stay was 35.4 days (± 39.2 days) for cases and 24.4 days (± 23.4 days) for controls.

48 (82.8%) patients with infections due to ESBL-producing *E. coli* or *K. pneumoniae* suffered from urinary tract infections, five (8.6%) suffered from bloodstream

infections, and five (8.6%) had vascular catheter-associated infections. In the ESBL group, 26 (44.8%) patients had a nosocomial infection: Ten (17.2%) had acquired their infection in the community, whereas in 22 (37.9%) patients, the infection was rated as health care-associated.

The ten patients with non-health care-associated infections were assessed individually (Table 2). Six of these patients had been pre-treated with antibiotics during the preceding year, two of whom had been hospitalized during this same period. Two of the remaining patients had a history of urological disease (recurrent urinary tract infections or benign prostatic hyperplasia), one was pregnant at the time of the first positive culture, and one patient had no history of any disease.

96 (82.8%) control patients had an infection with *E. coli* or *K. pneumoniae* related to the urinary tract, 15 (12.9%) had a bacteremia, and five (4.3%) had a vascular catheter-associated infection. 53 (45.7%) infections in control patients were rated as nosocomial, 30 (25.9%) were rated as health care-associated, and 33 (28.4%) were rated as community-acquired.

Co-morbidities and characteristics according to the duration of hospitalization and ICU stay were equally distributed among the two groups. Patients from the ESBL group had significantly more acute uncomplicated urinary tract infections than control patients (17.2% vs 6.0%, $p = 0.028$). A tendency in case patients to have more health care-associated infections than control patients was observed; however, the trend did not reach statistical significance (37.9% vs 25.9%, $p = 0.080$).

Risk Factors for Infections due to ESBL-producing Organisms

The risk factors for bacteremia, urinary, or vascular catheter-associated infections with ESBL-producing *E. coli* or *K. pneumoniae* derived from the univariable and multivariable analysis are shown in table 3. The univariable analysis revealed that the begin of symptoms or recent treatment in a foreign country was strongly associated with infections with ESBL-producing strains (OR 16.96, 95% CI 2.49–788.96, $p < 0.001$). Another risk factor was antibiotic therapy within the year preceding the isolation of the ESBL-producing strain (OR 3.03, 95% CI 1.33–7.68, $p = 0.006$). Mechanical ventilation (OR 6.27, 95% CI 1.30–63.48, $p = 0.017$) increased the risk of infections due to ESBL-producing *E. coli* or *K. pneumoniae*, especially if the duration of ventilation exceeded 14 days. Stay in the ICU itself was not associated with a significantly increased risk. However, an increasing risk was found with increasing length of ICU stay. These three risk factors were identified in both the univariable and multivariable model.

Prior hospitalization in Switzerland or any kind of surgery did not enhance the risk for infections due to ESBL-producing *E. coli* or *K. pneumoniae*. Other factors not associated with an increased risk for such an infection were nosocomial onset of infection, urinary tract anomalies, urinary tract devices, such as urinary catheters or pigtail catheters, central venous catheters, and/or co-morbidities, such as renal insufficiency, hemodialysis, malignomas, diabetes, HIV infection, neutropenia and/or immunosuppressive medication.

Prior Antibiotic Use

The upper part of table 4 depicts the antibiotic treatment history of the cases and controls within 1 year preceding the first isolate in terms of the number of antibiotic courses received. Only 15 (25.9%) case patients were not pretreated with antibiotics in the observation period, whereas 54 (46.6%) control patients had an uneventful treatment history. Patients who received none or only one course of antibiotics within the preceding year were significantly less often infected with an ESBL-producing strain (43.1% [cases] vs 71.6% [controls], $p < 0.001$). Pretreatment with three or more courses of any antibiotic resulted in a marked increase of the risk for infection with an ESBL-producing strain (41.4% [cases] vs 19.8% [controls], $p = 0.004$).

The lower part of table 4 shows the distribution of antibiotics used for pre-treatment. A significant increase in the number of infections due to ESBL-producing bacteria was found in patients with a history of previous treatment with cephalosporins (27.6% vs 9.5%, $p = 0.003$), carbapenems (13.8% vs 4.3%, $p = 0.033$), quinolones (55.2% vs 21.6%, $p < 0.001$), or aminoglycosides (8.6% vs 0.9%, $p = 0.016$).

Discussion

Our case–control study of 58 patients with ESBL and 116 controls with non-ESBL-producing *E. coli* and *K. pneumonia* infections, performed at a tertiary care university hospital in a low-prevalence country, identified three major risk factors: Mechanical ventilation, prior antibiotic use, and onset of symptoms and/or start of treatment abroad. Two factors in particular were found to increase the risk for infections with these multi-resistant organisms: Prior exposure to cephalosporins, carbapenems, quinolones, and aminoglycosides and exposure to three or more courses of antibiotic therapy within the preceding year. Only two case patients with community-acquired infections were not pre-treated with any antibiotics within the preceding year and did not have any underlying urinary tract disorder.

Exposure to antibiotics reduces the drug-susceptible normal flora and enhances the vulnerability of the patient to colonization by resistant organisms. In addition, organisms that are resistant to several drugs are more likely to be selected by the use of one of these antibiotics. Prior antibiotic use, especially of beta-lactams, is a well-recognized risk factor for infection with ESBL-producing organisms [1, 2, 6, 7]. The results of our study confirm the increase of risk of infection after prior exposure to ceph-

Table 2
Characteristics of the ten case patients with non-health care-associated infections due to ESBL-producing *E. coli*.

Patient number	Diagnosis	Age (years)	Sex	History	Antibiotics within last year	Hospitalization within last year	Foreign material in urinary tract	Onset of symptoms abroad	Mechanical ventilation
1	Asymptomatic bacteriuria	62	Male	Cauda equina syndrome Intermittent self-catheterization	Yes	Yes	No	No	No
2	Asymptomatic bacteriuria	76	Male	Ruptured aneurysm of iliac artery Hydronephrosis due to hematoma Benign prostatic hyperplasia	No	No	No	No	No
3	Asymptomatic bacteriuria	36	Male	Acute gastroenteritis Hemophilia A HIV	Yes	No	No	No	No
4	Asymptomatic bacteriuria	70	Female	Recurrent urinary tract infections Overactive bladder syndrome	Yes	Yes	No	No	No
5	Acute uncomplicated urinary tract infection	37	Female	Pregnancy	No	No	No	No	No
6	Acute uncomplicated urinary tract infection	44	Female	Recurrent urinary tract infections	Yes	No	No	No	No
7	Acute uncomplicated urinary tract infection	70	Female	Recurrent urinary tract infections	No	No	No	No	No
8	Acute uncomplicated urinary tract infection	24	Female	None	No	No	No	No	No
9	Acute uncomplicated urinary tract infection	39	Female	Recurrent urinary tract infections	Yes	No	No	No	No
10	Complicated urinary tract infection	63	Male	Secondary urethral stricture	Yes	No	No	No	No

Table 3
Univariable and multivariable conditional logistic regression analysis of risk factors for infections with extended-spectrum beta-lactamase-producing *E. coli* and *K. pneumoniae*.

Variable	ESBL group, n (%)	Non-ESBL group, n (%)	Univariable analysis		Multivariable analysis	
			p-value	OR (95% CI)	p-value	OR (95% CI)
Nosocomial onset of infection	26 (44.8)	53 (45.7)	1.000	0.93 (0.34–2.64)		
ICU stay	21 (36.2)	38 (32.8)	0.606	1.64 (0.42–7.05)		
Duration of ICU stay between 1 and 6 days	8 (13.8)	16 (13.8)	0.869	1.36 (0.31–6.19)		
Duration of ICU stay between 7 and 13 days	5 (8.6)	15 (12.9)	0.657	2.24 (0.26–22.82)		
Duration of ICU stay 14 or more days	8 (13.8)	7 (6.0)	0.151	6.88 (0.61–111.12)		
Central venous catheter	18 (31.0)	34 (29.3)	0.681	1.40 (0.47–4.55)		
Mechanical ventilation	15 (25.9)	17 (14.7)	0.017	6.27 (1.30–63.48)	0.042	10.56 (1.06–579.10)
Duration of ventilation between 1 and 6 days	4 (6.9)	4 (3.4)	0.202	3.97 (0.57–45.68)		
Duration of ventilation between 7 and 13 days	3 (5.2)	9 (7.8)	0.761	2.68 (0.13–56.37)		
Duration of ventilation 14 or more days	8 (13.8)	4 (3.4)	0.008	16.95 (1.74–956.72)		
Pigtail catheters in urinary tract	5 (8.6)	13 (11.2)	0.787	0.73 (0.18–2.55)		
Urinary catheter	30 (51.7)	52 (44.8)	0.400	1.48 (0.65–3.41)		
Hospitalization within last 30 days	18 (31.0)	34 (29.3)	0.944	1.09 (0.50–2.35)		
Hospitalization within last year	32 (55.2)	64 (55.2)	0.952	1.08 (0.53–2.19)		
Surgery within last 30 days	12 (20.7)	22 (19.0)	0.938	1.12 (0.45–2.73)		
Surgery within last year	19 (32.8)	39 (33.6)	1.000	0.96 (0.45–1.99)		
Prior antibiotic use within last year	43 (74.1)	62 (53.4)	0.006	3.03 (1.33–7.68)	0.025	2.88 (1.13–8.49)
Urinary tract anomaly	18 (31.0)	31 (26.7)	0.628	1.33 (0.54–3.39)		
Recurrent urinary tract infections	16 (27.6)	21 (18.1)	0.125	2.25 (0.82–6.61)		
Renal insufficiency	6 (10.3)	17 (14.7)	0.601	0.69 (0.21–1.91)		
Renal transplantation	1 (1.7)	11 (9.5)	0.093	0.17 (0.00–1.20)		
Hemodialysis	4 (6.9)	3 (2.6)	0.263	5.09 (0.46–275.59)		
Malignoma	14 (24.1)	24 (20.7)	0.691	1.33 (0.48–3.57)		
Diabetes mellitus	8 (13.8)	12 (10.3)	0.664	1.39 (0.46–3.97)		
HIV infection	1 (1.7)	3 (2.6)	1.000	0.60 (0.01–13.40)		
Neutropenia (< 500/mm^3)	2 (3.4)	7 (6.0)	0.783	0.60 (0.06–3.17)		
Immunosuppressive medication	16 (27.6)	33 (28.4)	1.000	0.96 (0.41–2.14)		
Onset of symptoms abroad	9 (15.5)	1 (0.9)	0.0007	16.96 (2.49–788.96)	0.042	27.01 (2.38–1,733.28)

OR: Odds ratio; CI: confidence interval; ICU: intensive care unit

alosporins and quinolones. We also found that carbapenems and aminoglycosides were statistically associated with an increased risk, but the relevance of these findings remains unclear because of the low number of patients who were treated with these antibiotics. Different study designs and definitions as well as new mechanisms of resistance to fluoroquinolones and aminoglycosides may be reasons why other trials were unable to demonstrate an association with the previous use of these antibiotics [23–25]. The finding that quinolones are a risk factor is particularly worrisome as the use of these antibiotics in the community has been increasing over time [26].

Switzerland is currently regarded a country with a low prevalence of ESBL-producing bacteria [27], with an estimated prevalence rate of 0.7% [15]. The fact that the start of symptoms and/or therapy abroad is strongly associated with ESBL production may reflect the higher prevalence of such bacteria in other countries. Prophylactic infection control measures are routinely performed in our hospital in patients who are relocated from hospitals abroad. The impact of community-acquired infections due to ESBL-producing bacteria may warrant a change in infection control measures for tourists in the future.

Cordery et al. [5] evaluated risk factors for the acquisition of ESBL-producing organisms in ICUs and were unable to identify any individual risk factor. However, we were able to demonstrate that mechanical ventilation itself and the length of mechanical ventilation were both strongly associated with an increased risk for infection with ESBL-producing *E. coli* and *K. pneumoniae*. A stay in the ICU itself was not associated with an increased risk.

The limitations of our study include the inherent weaknesses of case–control studies. As such, the selection of matching criteria may mask certain risk factors. In our study, for example, the selection of age as a matching criterion may have concealed the increasing risk of infections from ESBL-producing bacteria with increasing age [1]. Furthermore, with increasing matching of the criteria selected, there is a decrease in the number of risk factors that can be detected because the patients become more similar. However, a strict matching strategy results in similar medical histories of cases and controls and

Table 4
History of antibiotic use prior to the onset of infection.

Antibiotic use	ESBL group, n (%)	Non-ESBL group, n (%)	p-value
Antibiotic courses (patients can be included in only one category)			
0-1	25 (43.1)	83 (71.6)	< 0.001
2	9 (15.5)	10 (8.6)	0.200
≥ 3	24 (41.4)	23 (19.8)	0.004
Antibiotic classes (patients can be included in more than one category)			
Penicillins	24 (41.4)	36 (31.0)	0.181
Cephalosporins	16 (27.6)	11 (9.5)	0.003
Carbapenems	8 (13.8)	5 (4.3)	0.033
Quinolones	32 (55.2)	25 (21.6)	< 0.001
Sulfonamides	4 (6.9)	8 (6.9)	1.000
Imidazole derivatives	10 (17.2)	9 (7.8)	0.073
Aminoglycosides	5 (8.6)	1 (0.9)	0.016
Glycopeptides	6 (10.3)	9 (7.8)	0.576
Macrolides	5 (8.6)	3 (2.6)	0.119
Tetracyclines	2 (3.4)	1 (0.9)	0.258
Others	3 (5.2)	4 (3.4)	0.687

Data are for the 58 cases and 116 controls during the year immediately preceding the isolation of the first isolate. The upper part of the table shows the distribution of patients according to number of antibiotic courses; the lower part depicts the distribution of patients according to antibiotic classes.

lowers the risk of selection bias. Previous antimicrobial use may be overestimated in case–control studies that investigate risk factors for infections if controls are selected among patients with an susceptible organism [7]. Finally, the retrospective design of our study did not allow an appropriate outcome analysis. Due to the large proportion of asymptomatic urinary tract infections among our case patients, there was no follow-up data available for a significant number of patients. In-hospital deaths did not differ between the two groups: three (5.2%) case patients died during hospitalization, one of which was attributable to infection. In the control group, seven (6.0%) deaths (two attributable to infection) were detected. Antibiotic treatment in these patients appeared to be appropriate.

There are only a few published studies in which attempts were made to identify the risk factors for infections with ESBL-producing bacteria. In their 2006 case–control study, *Tumbarello* et al. [1] identified age, length of hospital stay, and previous antibiotic therapy as significant risk factors. The cases included two groups: One group with an ESBL-positive specimen of *K. pneumoniae* and one group with an ESBL-negative specimen of this organism. The control group had no microbiological specimen. The differences in their patient selection may thus partly explain their results. In the 2005 study of *Peña* et al. [2], female gender, nasogastric tube, and prior antibiotic use were identified as independent risk factors for the acquisition of ESBL-producing *E. coli*. As in the prior study, there were no strict matching criteria, and the matching ratio was 1:1. In contrast to other studies [2, 8], we did not perform molecular epidemiology and characterization of ESBL types, but epidemiological findings and antimicrobial susceptibility patterns of the isolates did not indicate clonal or plasmid spread.

Future epidemiological studies need to focus on mechanisms for the spread of multidrug-resistant Gram-negative bacteria in the community as these mechanisms are currently not understood. Although many patients have risk factors for infections with ESBL-producing bacteria, no risk factor can be identified in some patients. In particular, the emergence of community-acquired infections due to ESBL-producing bacteria, including analysis of risk factors, appropriateness of treatment, and outcome, need to be further evaluated. Our finding that not only cephalosporins and quinolones but also carbapenems and aminoglycosides were statistically significant risk factors for ESBL infections requires confirmation in larger studies.

In conclusion, the emergence of ESBL-producing organisms highlights the importance of concepts for the rational use of antibiotics as well as for infection control measures. Our study confirms the major risk factors for infections due to ESBL-producing bacteria, namely prior and repeated antibiotic use, and raises concerns about the emergence of these bacteria in the non-nosocomial and non-health care-associated setting. The early identification of risk factors for antibiotic resistance is crucial to providing optimal empiric antibiotic therapy to individual patients before the microbiology results are available. In addition, the use of carbapenems in hospitals must be kept to a minimum in order to lower the antibiotic selection pressure on recently emerging carbapenemase-producing bacteria. Because many infections due to ESBL-producing isolates occur in patients with recurrent urinary tract infections, the rationale use of antibiotics has particularly to be promoted in primary care where quinolones are overused in many countries. As fosfomycin and nitrofurantoin are frequently active against ESBL-producing isolates at the present time, a change in guidelines on the treatment of urinary tract infections may be an important approach.

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