CLINICAL AND EPIDEMIOLOGICAL STUDY

Extended-spectrum *β*-lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy

S. Meier · R. Weber · R. Zbinden · C. Ruef · B. Hasse

Abstract

Background Extended-spectrum *β*-lactamases (ESBLs) are an increasing challenge in the treatment of urinary tract infections (UTIs), and also in the community. We aimed to investigate the characteristics of patients with UTIs due to ESBL-producing *Escherichia coli* and to assess the risk factors for ESBLs in community-acquired isolates.
Methods We performed a retrospective study from January 1, 2007 to December 31, 2009 at a tertiary care teaching hospital in Switzerland, comparing patients with community-acquired versus healthcare-associated UTIs due to ESBL-producing *E. coli*. Additionally, we investigated the antimicrobial susceptibility of these isolates.
Results A total of 123 patients were studied, of whom 79 (64%) had community-acquired and 44 (36%) had healthcare-associated UTIs. Community-acquired isolates were associated with acute uncomplicated UTIs (odds ratio [OR] 6.62, 95% confidence interval [CI] 1.83–36.5, *P* < 0.001). Risk factors were recurrent UTI (OR 3.04, 95% CI 1.14–9.14, *P* = 0.022) and female sex (OR 2.46, 95% CI 1.01–6.08). Community-acquired ESBL-producing *E. coli* urinary isolates showed high resistance rates to most of the currently used oral antimicrobial agents, including *β*-lactam antibiotics (amoxicillin–clavulanic acid, 69.6% resistance), quinolones (ciprofloxacin, 84.8% resistance; norfloxacin, 83.9% resistance), and trimethoprim–sulfamethoxazole (75.9% resistance), except for nitrofurantoin (15% resistance) and fosfomycin (0% resistance).
Conclusion UTI due to ESBL-producing *E. coli* are emerging, and also in a country with low antibiotic use. Because of increasing antibiotic resistance rates of *E. coli* to current standard therapy and because of the resistance patterns of ESBL-producing *E. coli*, guidelines for the management of UTIs must be revised. Fosfomycin or nitrofurantoin are recommended for the first-line empirical oral treatment of community-acquired uncomplicated UTIs.

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Introduction

Frequent or inappropriate use of antibiotics in humans and animals led to an increasing resistance rate of Gram-negative bacteria in recent years. Consequently, the treatment of urinary tract infections (UTIs) has become more complex, not only because of an increasing bacterial resistance to fluoroquinolones, trimethoprim–sulfamethoxazole, or other standard antibiotics [1, 2], but also because of the emergence of extended-spectrum *β*-lactamases (ESBLs) in *Enterobacteriaceae* [3–6]. ESBLs are *β*-lactamases which

confer bacterial resistance to β-lactam antibiotics and aztreonam [7]. *Escherichia coli* are the most common cause of acute uncomplicated UTI, and reports of community-acquired UTI with ESBL-producing *E. coli* have accumulated in recent years [8–10].

The identification of risk factors for antimicrobial resistance may contribute to the improved empirical treatment of UTIs. Reported risk factors for developing a UTI with a community-acquired ESBL-producing *E. coli* are older age, female sex, diabetes mellitus, recurrent UTI, invasive urological procedures, and prior use of antibiotics such as aminopenicillins, cephalosporins, or fluoroquinolones [9, 11–15]. In a recent case–control study about risk factors for infections with ESBL-producing *E. coli* and *Klebsiella pneumoniae*, we observed ten patients with non-healthcare-associated UTIs due to ESBL-producing *E. coli* in the time period from July 2005 to June 2007 [16]. The aim of the present study was to continue the surveillance of these pathogens at our institution, to characterize patients with urinary samples positive for ESBL-producing *E. coli*, to identify risk factors for community-acquired UTIs, and to assess antibiotic resistance patterns.

Methods

Setting

This is a retrospective study conducted at the University Hospital in Zurich, Switzerland, a tertiary care teaching hospital. The computerized database of the Institute of Medical Microbiology, University of Zurich, where all microbiological samples of the University Hospital are processed, was used to identify patients with the detection of ESBL-producing *E. coli* ($>10^4$ colony forming units per milliliter) in urinary samples from January 1, 2007 to December 31, 2009.

Data collection and definitions

Clinical data from outpatients and inpatients of the Departments of Urology, Gynaecology/Obstetrics, and Internal Medicine were retrieved from patient charts. Women were classified to have acute uncomplicated UTI if they had a structurally normal urinary tract and symptoms of cystitis. If women had an infection of the renal pelvis without structural anomalies, they were classified to have acute uncomplicated pyelonephritis. Men with UTIs in the setting of a structurally normal urinary tract were assigned to have complicated UTI. All patients with structural abnormalities and signs of symptomatic cystitis or pyelonephritis were assigned to have complicated UTI. Asymptomatic patients with positive urine cultures (also

those with an indwelling catheter) were classified as having asymptomatic bacteriuria. Infections were rated as community-acquired if they did not fulfill any of the following criteria: (1) patient received intravenous therapy or specialized wound care at home; (2) patient received hemodialysis treatment or antineoplastic chemotherapy in the 30 days before the infection; (3) patient was hospitalized in an acute care center 2 days in the 90 days before infection; (4) patient resided in a nursing home or long-term care facility [17].

A structured questionnaire was used to collect the following variables: age, gender, clinical symptoms of UTI, previous urological operations, obstructive diseases of the urinary tract, history of recurrent UTI, hospitalizations in the previous year (and the reasons for the hospitalization), residency in a nursing home, antibiotic treatment during the previous year, and immunosuppressive medication (including steroids). The severity of comorbidity was assessed using the Charlson comorbidity index [18].

Microbiological analysis

Antimicrobial susceptibility testing and screening for ESBLs was performed according to the Clinical and Laboratory Standards Institute (CLSI) recommendations. In brief, the initial screen test to indicate ESBL production was a diameter of the inhibition zone of ceftazidime ≤22 mm or of cefotaxime ≤27 mm. Furthermore, 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 an indication for the organism to be tested by a phenotypic confirmatory test. A greater than twofold concentration decrease in the minimum inhibitory concentration (MIC) for ceftazidime or cefepime or cefotaxime tested in combination with clavulanic acid versus its MIC when tested alone was confirmatory for ESBL production. In accordance with the CLSI 2008 guidelines, all ESBL-producing *E. coli* strains were classified as resistant to all penicillins, cephalosporins, and aztreonam, regardless of the MICs determined for these drugs [19].

Statistical analysis

We used EpiData (version 3.1, Jan 2008) for the statistical analyses. Categorical data were analyzed using the Fisher's exact test and continuous data were analyzed by the Kruskal–Wallis test. We used logistic regression analyses for the univariable 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

Approval by the Research Ethics Board of the Canton of Zurich, Switzerland (address: Kantonale Ethikkommission Zürich, Sonneggstrasse 12, CH-8091 Zürich, Switzerland), was obtained. The ethics committee decided that patients' informed consent was not required because this study was a retrospective quality control project by infectious diseases physicians directly involved in patient care.

Results

In the reference period, 5,694 urine samples were positive for *E. coli*, and, among those, 123 (2.16%) were ESBL-producers. A total of 40 patients were treated in the Department of Urology, 51 patients in the Department of Internal Medicine, and 32 in the Department of Gynae-cology/Obstetrics.

Patient characteristics

The characteristics of the 123 patients with ESBL-producing *E. coli* UTIs are shown in Table 1. The median age was 48 years (interquartile range [IQR] 34–68 years). Seventy-nine (64.3%) patients had a community-acquired and 44 (35.8%) a healthcare-associated infection. Of 79 patients with community-acquired infections 63 (79.7%) patients and 27/44 (61.4%) patients with healthcare-associated infections were female. Comorbidities were equally distributed in both groups, except for non-urological malignancies (1.3 vs. 11.4%, $P = 0.022$). Previous hospitalizations in the preceding year was noted in 36 (45.6%) patients with community-acquired infection and in 32

Table 1 Baseline characteristics and clinical presentation of 123 individuals with extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* in urinary samples, stratified by the location of acquisition

Characteristics	Community-acquired UTI	Healthcare-associated UTI	*P*-value
Number of patients (%)	79 (100)	44 (100)	
Female, *n* (%)	63 (79.7)	27 (61.4)	0.035
Age (years), median (IQR)	48 (33–66)	52 (37–70)	0.284
Resident in a nursing home, *n* (%)	0 (0)	6 (13.6)	–
Hospital stay in the previous year, *n* (%)	36 (45.6)	32 (72.7)	0.002
Intensive care stay in the previous year, *n* (%)	8 (10.1)	2 (4.6)	0.492
Charlson comorbidity index (IQR)	0 (0–1)	0 (0–2)	0.009
Comorbidities, *n* (%)			
Renal insufficiency	10 (12.8)	10 (22.7)	0.203
Diabetes mellitus	8 (10.1)	8 (18.2)	0.264
Immunosuppression	12 (15.2)	8 (18.2)	0.799
Non-urological neoplasia	1 (1.3)	5 (11.4)	0.022
Antibiotic use in the previous year, *n* (%)	52 (65.8)	28 (63.6)	0.845
Duration of antibiotic treatment (days), median (IQR)	3 (0–11)	1 (0–19.5)	0.837
Urological history and morbidity, *n* (%)			
Previous urological operations	23 (29.1)	18 (40.9)	0.232
Anomaly of the urinary tract	32 (40.5)	28 (63.6)	0.016
Prostata hyperplasia	4 (5.1)	1 (2.3)	0.654
Urolithiasis	1 (1.3)	4 (9.1)	0.055
Ureteral stenosis	1 (1.3)	4 (9.1)	0.055
Urological neoplasia	1 (1.3)	3 (6.8)	0.130
Incontinence	10 (12.7)	7 (15.9)	0.599
Neurological impairment of the bladder	7 (8.9)	6 (13.6)	0.542
Self-catheterism	2 (2.5)	5 (11.4)	0.100
Foreign material in the urinary tract	4 (5.1)	15 (34.1)	<0.001
Clinical presentation, *n* (%)			
Asymptomatic bacteriuria	24 (30.4)	25 (56.8)	0.007
Uncomplicated lower UTI	26 (32.9)	3 (6.8)	<0.001
Uncomplicated upper UTI	5 (6.3)	3 (6.8)	1.000
Complicated UTI	24 (30.4)	13 (29.5)	1.000

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(72.7%) healthcare-associated UTIs. Urinary tract anomalies (63.6 vs. 40.5%, $P = 0.016$) and foreign material in the urinary tract (34.1 vs. 5.1%, $P < 0.001$) were found more frequently in patients with healthcare-associated infections, and there was also a trend for a higher rate of urolithiasis (9.1 vs. 1.3%, $P = 0.055$) and ureteral stenosis (9.1 vs. 1.3%, $P = 0.055$). Patients with community-acquired infections presented more frequently with uncomplicated lower UTI (32.9 vs. 6.8%, $P < 0.001$), whereas patients with healthcare-associated infections more likely had asymptomatic bacteriuria (30.4 vs. 56.8%, $P = 0.007$).

Empirical antimicrobial therapy

A proportion of 90/123 patients received antibiotic prescriptions. For empirical antibiotic therapy, quinolones were used in 44 of 90 (48.8%) patients, penicillins in 25.5%, cephalosporins in 5.6%, carbapenems in 12.2%, and trimethoprim–sulfamethoxazole in 10.0%. Community-acquired UTIs were treated empirically with quinolones (31/55 prescriptions, 56.3%), penicillins (29.1%), or trimethoprim–sulfamethoxazole (14.5%). Empirical treatment with nitrofurantoin was prescribed in 2 (3.6%) and with fosfomycin in 1.5% of cases.

Acute uncomplicated UTI

All of the 26 patients presenting with acute uncomplicated UTI caused by community-acquired ESBL-producing *E. coli* isolates were women. The median age was 38 years (IQR 17–80) and the median Charlson comorbidity index was 0 (0–1). Three patients (11.5%) had been hospitalized in the previous years (one patient received mechanical ventilation), none had indwelling urological foreign material, and 9/26 (34.6%) experienced recurrent UTI. A proportion of 11/26 (42.3%) had received antibiotic treatment, of whom eight had received fluoroquinolones, one amoxicillin–clavulanic acid, and two trimethoprim–sulfamethoxazole. Of the 26 ESBL-producing *E. coli* urinary isolates from acute uncomplicated UTI, 20 (76.9%) were resistant to ciprofloxacin, 69.2% to norfloxacin, 57.7% to amoxicillin–clavulanic acid, and 69.2% to trimethoprim–sulfamethoxazole. All isolates were susceptible to nitrofurantoin, fosfomycin, and ertapenem.

Risks for ESBL-producing *E. coli* in community-acquired UTI

Univariable analyses of risk factors for ESBL-producing *E. coli* in community-acquired UTI are shown in Table 2. There was an association of community-acquired isolates with acute uncomplicated UTI (OR 6.62, 95% CI 1.83–36.5, $P < 0.001$), recurrent UTI (OR 3.04, 95%

CI 1.14–9.14, $P = 0.022$), and female sex (OR 2.46, 95% CI 1.01–6.08, $P = 0.035$). There was evidence of a negative association with previous hospitalizations (OR 0.290, 95% CI 0.120–0.690, $P = 0.002$), beginning of symptoms abroad (OR 0.00, 0.00–0.57, $P < 0.005$), indwelling foreign material (OR 0.110, 95% CI 0.020–0.370, $P < 0.001$), non-urological neoplasia (OR 0.100, 95% CI 0.000–0.970, $P = 0.0227$), and previous treatment with a cephalosporin (OR 0.160, 95% CI 0.060-0.490, $P < 0.001$).

Resistance of ESBL-producing *E. coli* to other antibiotics

The rates of resistance to antimicrobial agents in *E. coli* urinary isolates are shown in Table 3. The rates of ciprofloxacin resistance among the community-acquired UTI were 84.8% and 77.3% in the healthcare-associated group. The corresponding values for amoxicillin–clavulanic acid were 69.6 and 77.3%, for piperacillin–tazobactam 25.3 and 27.3%, for trimethoprim–sulfamethoxazole 75.9 and 75.0%, for nitrofurantoin 15.4 and 33.3%, and for fosfomycin 0 and 0%, respectively. The resistance rates for the different antimicrobial agents did not differ among groups with community-acquired versus healthcare-associated isolates (all $P > 0.05$).

Outcome

The outcome of 123 patients with ESBL-producing *E. coli* urinary isolates is shown in Table 4. The median time of follow up was 166 days (IQR 26-490). Nine patients died, one thereof attributable to infection. All deaths occurred in the healthcare-associated group, and, also, rehospitalization rates were higher in the healthcare-associated group. New infection rates were not significantly different between the two groups.

Discussion

We retrospectively assessed the resistance rates of ESBL-producing *E. coli* urinary isolates at our tertiary referral center and characterized the corresponding patients with resistant isolates. Within a 3-year period, 123 patients with UTI were followed, 79 (64.2%) with community-acquired and 44 (35.8%) with healthcare-associated ESBL-producing *E. coli* isolates. Patients with community-acquired isolates were more likely to be women ($P = 0.035$), presenting with acute uncomplicated UTI ($P < 0.001$). Risk factors for community-acquired isolates were female sex and recurrent UTI. Rates of resistance to most currently used antimicrobial agents were high, and did not differ between

Table 2 Univariate analyses of risk factors for community-acquired UTIs with ESBL-producing *E. coli*

Variables, *n* (%)	Total UTI	Community-acquired UTI	OR (95% CI)	*P*-value
Number of patients	123 (100)	79 (100)		
Age < 50 years	65 (52.8)	44 (55.7)	1.37 (0.620–3.08)	0.453
Female gender	90 (73.2)	63 (79.7)	2.46 (1.01–6.08)	0.035
Hospital stay in the previous year	68 (55.7)	36 (45.6)	0.290 (0.120–0.69)	0.002
Repeated outpatient visits	82 (66.7)	51 (64.6)	0.770 (0.310–1.80)	0.554
Beginning of symptoms abroad	5 (4.1)	0 (0)	0.00 (0.00-0.570)	0.005
Asymptomatic bacteriuria	49 (39.8)	24 (30.4)	0.330 (0.14-0.76)	0.007
Uncomplicated UTI	29 (23.6)	26 (32.9)	6.62 (1.83–36.5)	<0.001
Uncomplicated pyelonephritis	8 (6.5)	5 (6.3)	0.92 (0.17–6.25)	1.000
Complicated UTI	37 (30.1)	24 (30.4)	1.04 (0.44–2.56)	1.000
Anomaly of the urinary tract	60 (46.8)	32 (40.5)	0.390 (0.170–0.89)	0.016
Previous urological operation	41 (33.3)	23 (29.1)	0.600 (0.260–1.39)	0.232
Foreign material in the urinary tract	19 (15.4)	4 (5.1)	0.110 (0.020–0.370)	<0.001
Recurrent UTI	36 (29.2)	29 (36.7)	3.04 (1.14-9.14)	0.022
Non-urological neoplasia	6 (4.9)	1 (1.3)	0.100 (0.000–0.970)	0.023
Diabetes mellitus	16 (13.0)	8 (10.1)	0.510 (0.150-2.70)	0.264
Immunosuppression	23 (18.7)	14 (17.7)	0.840 (0.300–2.53)	0.810
Antibiotic use in the previous year, any	80 (65.0)	52 (65.8)	1.10 (0.470–2.54)	0.845
Cephalosporins	21 (17.1)	6 (7.6)	0.160 (0.060–0.490)	<0.001
Quinolones	56 (45.5)	38 (48.1)	1.54 (0.69–3.53)	0.265

OR, odds ratio, *CI* confidence interval, *UTI* urinary tract infection

Table 3 Rates of resistance in ESBL-producing *E. coli* isolates, stratified by the mode of acquisition of UTI

Antimicrobial agent	Community-acquired UTI		Healthcare-associated UTI		*P*-value
	Number of isolates analyzed, *n* (%)	Number of isolates resistant, *n* (%)	Number of isolates analyzed, *n* (%)	Number of isolates resistant, *n* (%)	
Ampicillin	79 (100)	78 (98.7)	44 (100)	43 (97.7)	0.361
Amoxicillin–clavulanic acid	79 (100)	55 (69.6)	44 (100)	34 (77.3)	0.526
Amikacin	68 (100)	6 (8.80)	37 (100)	1 (2.70)	0.417
Gentamycin	79 (100)	40 (51.3)	44 (100)	26 (59.1)	0.453
Tobramycin	77 (100)	53 (68.8)	42 (100)	28 (66.7)	0.839
Piperacillin–tazobactam	79 (100)	20 (25.3)	44 (100)	12 (27.3)	0.834
Trimethoprim–sulfamethoxazole	79 (100)	60 (75.9)	44 (100)	33 (75.0)	0.828
Ciprofloxacin	79 (100)	6 (84.8)	44 (100)	34 (77.3)	0.318
Norfloxacin	62 (100)	52 (83.9)	34 (100)	29 (85.3)	1.000
Ertapenem	50 (100)	1 (2.0)	24 (100)	0 (0)	1.000
Meropenem	74 (100)	2 (2.7)	40 (100)	1 (2.5)	1.000
Impipenem	75 (100)	2 (2.7)	42 (100)	0 (0)	0.536
Fosfomycin	23 (100)	0 (0)	11 (100)	0 (0)	–
Nitrofurantoin	26 (100)	4 (15.4)	12 (100)	4 (33.3)	0.232

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community-acquired versus healthcare-associated ESBL-producing *E. coli* isolates.

In recent years, several studies showed that multiresistant pathogens like ESBL-producing *E. coli* are responsible

not only for healthcare-associated [20] but also for community-acquired UTI [8, 9, 11–14, 21]. We observed a similar epidemiology at our institution (Fig. 1), although Switzerland is still regarded as a country with a low

Table 4 Outcome of 123 individuals with extended-spectrum β-lactamase-producing *E. coli* in urinary samples, stratified by mode of acquisition of UTI

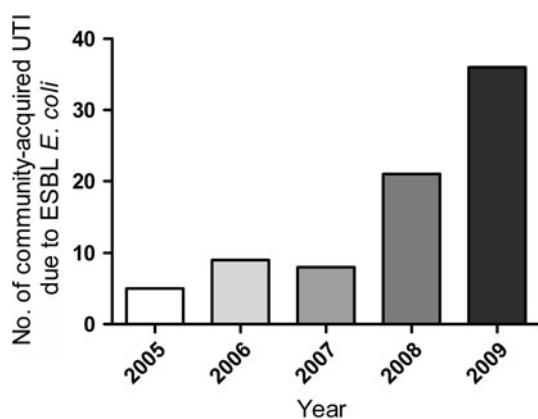| Outcome	Community-acquired UTI, $n = 79$ (%)	Healthcare-associated UTI, $n = 44$ (%)	*P*-value
Death, *n* (%)	0 (0)	9 (20.5)	<0.001
Readmission, *n* (%)	23 (29.1)	24 (54.5)	0.007
Relapse or reinfection	31 (39.2)	19 (43.2)	0.700

Fig. 1 Acute uncomplicated urinary tract infections (UTIs) with community-acquired *Escherichia coli* extended-spectrum β-lactamases (ESBLs) treated at the University Hospital of Zurich, Switzerland

prevalence of ESBL production [22] and low antibiotic use. The results of our study confirm published risk factors for community-acquired UTI with ESBL-producing *E. coli*, namely, recurrent UTI and female sex being the most commonly reported factors [9, 11–13, 15]. Other studies found associations with the use of quinolones [9, 12, 15], aminopenicillins [9], penicillins [12], cephalosporins [9], β-lactam antibiotics [13], diabetes mellitus [15], and prostatic disease [13, 15], whereas we did not observe these factors. In contrast, we found negative associations for community-acquired ESBL-producing *E. coli* with the use of cephalosporins, previous hospital stay, beginning of symptoms abroad, non-urological malignancies, anomaly of the urinary tract, and foreign material in the urinary tract. Differences between our results and other reports are explained by the different study designs. Previous studies assessed risk factors for community-acquired ESBL-positivity by comparing outpatients with ESBL-producing *E. coli*-positive urinary samples with control patients with non-ESBL-producing *E. coli* isolates [9, 11–13, 15], whereas we compared exclusively the isolates of ESBL-producing *E. coli* stratified by the location of acquisition of UTI, i.e., community versus healthcare infection.

One may expect that community-acquired *E. coli* isolates would express less resistance to antimicrobial agents than healthcare-associated isolates, which would translate into better treatment outcome. However, epidemiologic results indicate that ESBL-producing *E. coli* UTI is rather community-acquired—possibly a food-borne disease—and probably less as a consequence of antibiotic pressure in healthcare settings, nosocomial transmission, or repeated antibiotic therapy of outpatients with urological morbidity, particularly obstruction of the urinary tract [4]. *E. coli* that produce CTX-M β-lactamases seem to be true community ESBL-producers with a different epidemiology than TEM- or SHV-derived ESBL, which are typically healthcare- or hospital-associated [23]. We, therefore, compared patient characteristics, the clinical course of UTI, and susceptibility patterns of ESBL-producing *E. coli* in community-acquired and healthcare-associated isolates, whereas previous studies were content with comparing antibiotic resistance rates exclusively in ESBL-positive and ESBL-negative isolates [9, 13]. We found that neither resistance nor cure rates were different in community-acquired versus healthcare-associated ESBL-producing *E. coli* UTI. The resistance rates of community-acquired ESBL-producing *E. coli* for cephalosporins, trimethoprim–sulfamethoxazole, ciprofloxacin, amoxicillin–clavulanic acid, carbapenems, and gentamycin in our study were similar to those reported by a tertiary referral center in Turkey [13]. ESBL-producing *E. coli* exhibited a 100% susceptibility to fosfomycin, but the resistance rates of nitrofurantoin were higher at our institution than those reported by other studies [9, 13, 21]. This is particularly worrisome because treatment options for ESBL-producing *E. coli* are limited, but when exclusively considering isolates from acute uncomplicated UTI, no resistance for nitrofurantoin was detected.

Previous studies on community-acquired UTI did often not account for risk factors for antibiotic resistance, such as home intravenous therapy, specialized wound care at home, hemodialysis, antineoplastic chemotherapy, and residence in a nursing home or long-term facility. By using the criteria of Friedmann et al. [17], we had a standardized tool to separate community-acquired from healthcare-associated cases. Nevertheless, the differentiation of community versus healthcare versus nosocomial infection may be particularly difficult in comorbid or multimorbid patients with symptomatic or asymptomatic bacteriuria who have frequent contacts with hospital-based outpatient clinics or other healthcare institutions. Also, some other limitations of our (and other studies) should be noted. Demographic and clinical data were retrieved from patient charts, and available information on outpatients is usually not as detailed as for hospitalized patients, thus, potentially leading to a measurement bias. We tried to preclude this bias by using a structured questionnaire. Antimicrobial

therapy for UTI in outpatients is usually started empirically, and urinary cultures are only performed if patients do not respond to treatment or have complicated or recurrent UTI [24]. Thus, a selection bias may have been introduced by overestimating the resistance rates in the community. However, we believe that this was a minor source of bias, since the resistance rates of community-acquired and healthcare-associated ESBL-producing *E. coli* isolates were virtually the same. The results of resistance tests to fosfomycin and nitrofurantoin deserve careful evaluation, because routine testing for these antimicrobial agents in ESBL-positive urinary samples was introduced at our institution only in 2009. The retrospective design of our study may complicate outcome analyses, especially in patients with community-acquired isolates, and generalization may be diminished because our data were collected at a single hospital.

Until recently, local and many other guidelines recommended the use of a 3-day course of trimethoprim–sulfamethoxazole or norfloxacin for acute uncomplicated UTI. Because of the increasing resistance rate of these substances, the emergence of community-acquired ESBL-producing *E. coli*, and because of the high rates of resistance to other antimicrobials, these recommendations can no longer be substantiated. Treatment with amoxicillin–clavulanic acid, as proposed by Rodríguez-Baño et al. [9], does not seem to be applicable because of high resistance rates in non-ESBL- and ESBL-producing *E. coli*, and ertapenem, which would be suited for an outpatient intravenous therapy, should be used with caution in order to prevent further spread of carbapenemase-producing *Enterobacteriaceae* [25]. The need for a revision of empirical treatment guidelines for UTIs is also substantiated by the inappropriate high use of quinolones—quinolones themselves being a risk factor for the development of ESBL. As a consequence, the Infectious Disease Society of America (ISDA) and the European Society of Clinical Microbiology and Infectious Disease (ESCMID) issued on March 1, 2011 new treatment guidelines for UTIs considering a 5-day course of nitrofurantoin or a single dose of fosfomycin, which are appropriate choices for the treatment of acute uncomplicated urinary tract infections [26]. The use of trimethoprim–sulfamethoxazole is discouraged in case resistance prevalence would exceed 20%, and the use of quinolones and β-lactams for the treatment of acute uncomplicated cystitis is no longer recommended.

In conclusion, we found an increasing prevalence of ESBL-producing *E. coli* in community-acquired UTI. These isolates showed high resistance rates for β-lactam antibiotics, quinolones, and trimethoprim–sulfamethoxazole—whereas the susceptibility to nitrofurantoin and fosfomycin was excellent. Therefore, these antimicrobial agents appear to be the empirical treatment of choice for

community-acquired UTI at present. However, an increasing use of these substances may also result in antibiotic resistance, and, thus, only prudent use of all antimicrobials may prevent selection pressure and avoid clinical situations with no further treatment options.

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