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ORIGINAL ARTICLE

Increasing prevalence of ciprofloxacin resistance in extended-spectrum-β-lactamase-producing *Escherichia coli* urinary isolates

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Abstract
Purpose To describe the incidence and drug susceptibility profiles of uropathogenic extended-spectrum-β-lactamase-producing *Escherichia coli* (ESBL-EC) during a 10-year period and to identify differences in resistance patterns between urological and non-urological ESBL-EC isolates.
Methods Retrospective analysis of 191,564 urine samples obtained during 2001 to 2010 at the University Hospital Basel, Switzerland. The computerized database of the Clinical Microbiology Laboratory and the Division of Infectious Diseases and Hospital Epidemiology was used to identify ESBL-EC positive urine samples. ESBL-EC isolates were stratified according their origin into two groups: Urology and non-Urology isolates.
Results The rate of ESBL-EC positive urine samples increased significantly during the study period (3 in 2001 compared to 55 in 2010, $p < 0.05$). The most active agents were imipenem, meropenem, and fosfomycin (100 %), followed by amikacin (99.1 %) and nitrofurantoin (84 %). The least active substances were ampicillin-clavulanate (20 %), sulfamethoxazole (28 %), and ciprofloxacin (29.6 %). ESBL-EC isolates from urological and non-urological patients showed similar susceptibility profiles. However, ESBL-EC isolates from urological patients were significantly less susceptible to ciprofloxacin compared to non-urological isolates (14.7 vs. 32.7 %, $p < 0.05$).
Conclusions The rate of urinary ESBL-EC isolates is increasing. Their susceptibility to nitrofurantoin, fosfomycin, and carbapenems is excellent, whereas ampicillin-clavulanate, sulfamethoxazole, and ciprofloxacin demonstrate only low susceptibility. In particular, the use of ciprofloxacin should be strictly avoided in urologic patients with suspicion for an ESBL-EC urinary tract infection as well as routine antibiotic prophylaxis prior to urological interventions if not explicit indicated by current international guidelines or local resistance patterns.

Keywords Epidemiology · ESBL · *Escherichia coli* · Urinary tract infection · Urology

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Introduction

The microbial etiology of urinary tract infections (UTI) has been regarded as well-established and reasonably consistent over the past decades [1]. The majority of cases are caused by *Escherichia coli* (EC) that accounts for 70–90 % of uncomplicated and 50–60 % for recurrent or complicated cases [2, 3]. These infections received little attention in the past since their treatment was straightforward. However, the emergence of extended-spectrum-β-

lactamase-producing *Escherichia coli* (ESBL-EC) challenges this statement. Today, up to 50 % of the healthy population is colonized with ESBL-EC, whereas it was very uncommon in the past [4, 5]. Treatment options for infections due to these multidrug-resistant organisms are limited. Empirical therapy may be inappropriate for ESBL-EC, resulting in a delay in effective therapy, a longer hospital stay, and higher costs compared with non-ESBL infections [6, 7]. A report from the Infectious Diseases Society of America (IDSA) listed ESBL-EC among the six drug resistant microbes to which new therapies are urgently needed [8]. ESBL-EC is most frequently found in urine samples, challenging commonly used concepts for standard treatment of UTIs with quinolones or trimethoprim/sulfamethoxazole (TMP/SMX). Therefore, microbiologic surveillance data and rates of resistance developing over time are essential to (1) allow evaluation of appropriate antimicrobial agents, (2) to improve infection control policies, and (3) to develop strategies to limit outbreaks of these infections. However, such long term data are scant in the literature. The aim of the present study was to describe the epidemiology of ESBL-EC positive urine samples in the last decade at our institution, to assess current antibiotic susceptibility patterns as well as to identify differences in resistance patterns between urological and non-urological isolates. In addition recommendations for the treatment of infections caused by ESBL-EC according to recent guidelines [9, 10] were discussed.

Materials and methods

Setting

The University Hospital Basel is a tertiary care center with 780 beds serving approximately 27,000 admissions annually. The computerized database of the microbiology laboratory and the Division of Infectious Diseases and Hospital Epidemiology was used to identify urinary samples with ESBL-EC from January 1, 2001 to December 31, 2010. The study was approved by the local ethics committee.

Data collection and definitions

A total of 191,564 urine samples from 35,946 patients were submitted to the microbiology laboratory during the study period. We identified all *Escherichia coli* ($n = 14\ 648$) positive samples of which 423 were ESBL-EC positive. As only the first isolate ESBL-EC positive sample per year from any one patient was considered, 196 isolates were included to final analysis (Table 1). Clinical data from outpatients ($n = 61$) and inpatients ($n = 117$) were retrieved from patient charts. The study population was divided into two subgroups to identify differences in resistance patterns between urological ($n = 34$) and non-urological isolates (n = 162).

Microbiological analysis

Urine samples were assessed by using CHROMagar orientation medium (Becton–Dickinson BBL Diagnostics, Sparks, MD, USA). For microbiological detection of ESBL, standard culture methods were performed in accordance with the guidelines of the Clinical and Laboratory Standards Institute [11]. Routine susceptibility testing was performed using microbroth dilution (Micronaut-S, Merlin) with the following compounds for ESBL screening: cefpodoxime, ceftriaxone, ceftazidime, and aztreonam. If the screening test yielded any positive result, confirmation testing was performed using Etest strips (AB Biodisk [now, bioMérieux]) containing cefotaxime or ceftazidime, each tested with and without clavulanic acid. All ESBL-isolates were confirmed by PCR as described recently [12].

Table 1 Case characteristics

	ESBL-EC[a]	Urology samples	Control group	*p* value
Urine samples	196 (100 %)	34 (17.3 %)	162 (82.7 %)	n.a.
Patients	178 (100 %)	28 (15.7 %)	150 (84.3 %)	n.a.
Median age (range)	63 (18–96)	68 (28–88)	62 (18–96)	0.159
Sex				
Male	65 (36.5 %)	20 (71.4 %)	45 (30 %)	<0.05
Female	113 (63.5 %)	8 (28.6 %)	105 (70 %)	
Collecting technique				
Foley catheter	43 (22 %)	10 (29.4 %)	33 (20.4 %)	0.103
Single straight catheterization	17 (8.6 %)	5 (14.7 %)	12 (7.4 %)	
Clean catch technique	122 (62.2 %)	15 (44 %)	107 (66 %)	
Unknown	14 (7.2 %)	4 (11.8 %)	10 (6.2 %)	

[a] *ESBL-EC* extended-spectrum-β-lactamase-producing *Escherichia coli*, *n.a.* statistical analysis not applicable

Statistical analysis

Statistical analysis was computed on Statistical Package for Social Sciences (SPSS, version 20.00; Chicago, IL, USA) for Windows ™. The comparison of categorical data was performed using Chi square tests and continuous variables were compared with Mann–Whitney *U* tests. A p value of less than 0.05 was considered to indicate statistical significance. The probability density function was computed with R (R Foundation for Statistical Computing).

Results

General characteristics

Data of 191,564 urine samples from 35,946 patients were analyzed. *E. coli* was identified in 7.6 %. ($n = 14\ 449$). Four hundred twenty-three (2.9 %) *Escherichia coli* isolates were ESBL-EC. Finally, 196 ESBL-EC isolates from 178 patients were included in further analysis. The median age of the patients was 63 years (range 18-96). The probability to find an ESBL-EC sample for at a given age is represented in Fig. 1 for the different subpopulations. Additional case characteristics are summarized in Table 1.

Trend analysis

The overall proportion of ESBL-EC positive urine samples increased significantly during the study period ($p < 0.05$). In this context, only three ESBL-EC positive urine samples were isolated in 2001 compared to 55 in 2010. The increase in numbers was significant in both populations (urological vs. non-urological), respectively (Fig. 2).

Antibiotic susceptibility profiles

The antimicrobial susceptibility profiles are shown in Table 2. Overall, the most active agents were imipenem, meropenem, and fosfomycin (100 %), followed by amikacin (99.1 %) and nitrofurantoin (83.8 %). The least active substances were ampicillin/clavulanate (20 %), sulfamethoxazole (28 %), ciprofloxacin (29.6 %), doxycycline (31.8 %), and levofloxacin (32 %). Urological ESBL-EC isolates were significant ($p < 0.05$) less susceptible to ciprofloxacin compared to the control group (14.7 vs. 32.7 %). In addition, a significant ($p < 0.05$) difference regarding the ciprofloxacin resistance over the study period was observed in the study population. However, this difference did not reached statistical significance considering urological samples ($p = 0.818$) or non-urological samples ($p = 0.074$) only.

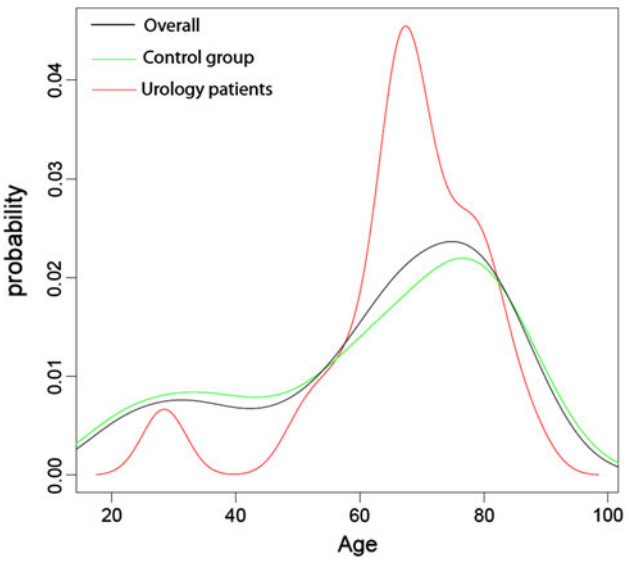

Fig. 1 Probability density plot of ESBL-EC positive samples according to age and subpopulation*. *Each *curve* (i.e., a probability density function) represents the relative likelihood for an ESBL-EC positive samples to take on a given age value

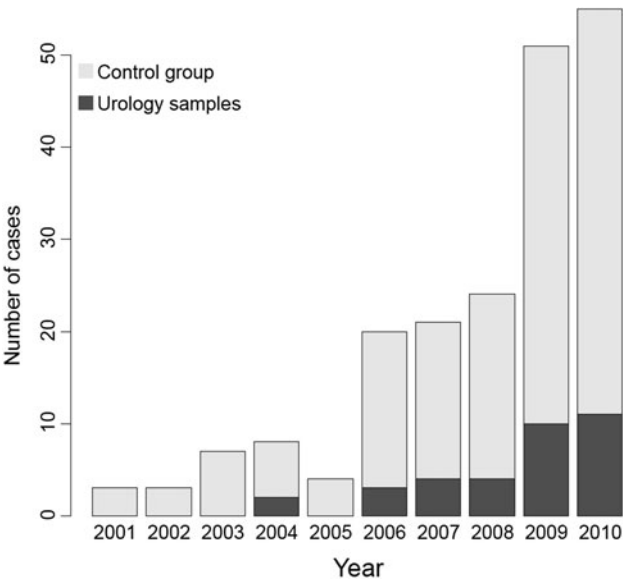

Fig. 2 Overall incidence of ESBL-EC positive urine samples between 2001 and 2010. Only the first isolate ESBL-EC positive sample per year from any one patient was considered

Origin of ESBL-EC positive urine samples

Of the 196 ESBL-EC positive urine cultures, 64 (32.65 %) were obtained in the outpatient setting, whereas 132 cultures (67.35 %) were obtained from inpatients. The rate of ciprofloxacin resistance showed no statistically significant difference (outpatients: 73.4 %, inpatients: 69 %, $p = 0.581$).

Table 2 Overall antimicrobial susceptibility profile of urinary ESBL-EC isolates

Antimicrobial class/agent	ST[a]	Overall% susc.	US[b]% susc.	CG[c]% susc.	*p* value
Carbapenems					
Imipenem	196	100	100	100	n.a.
Meropenem	196	100	100	100	n.a.
Other β-lactams					
Ampicillin/clavulanate	155	20	20.7	23	0.787
Piperacillin/tazobactam	141	55.4	57.2	54.7	0.828
Fluoroquinolones					
Ciprofloxacin	196	29.6	14.7	32.7	<0.05
Levofloxacin	191	32	20.6	34.4	0.117
Aminoglycosides					
Gentamicin	84	65.5	64.8	65.7	0.940
Amikacin	112	99.1	94.2	100	n.a.
Others					
Sulfamethoxazole	125	28	16	31	0.212
Doxycycline	107	31.8	25	33	0.528
Fosfomycin	83	100	100	100	n.a.
Nitrofurantoin	191	83.8	79.5	84.8	0.447

[a] *ST* samples tested

[b] *US* urology group

[c] *CG* control group), *susc.* susceptibility, *n.a.* statistical analysis not applicable

Discussion

Urinary tract infection (UTI) is among the most common bacterial illnesses occurring in adults. The clinical presentation varies from asymptomatic bacteriuria (ASB) to life-threatening urosepsis. Acute uncomplicated UTI occur in healthy women, while complicated UTI occurs in men or women with underlying functional or structural genitourinary abnormalities. The majority of cases are caused by a limited number of bacterial genera. Among both outpatients and inpatients, *E. coli* is the most important UTI pathogen. Antimicrobial resistance among *E. coli* is a major concern, and in particular, the emergence and spread of ESBL-EC. ESBLs are plasmid encoded enzymes which confer resistance against all β-lactam antibiotics except carbapenems and cephamycins [6]. ESBL frequently bear resistance genes for additional antibiotic classes, such as sulfonamides, aminoglycosides, and fluoroquinolones [13]. ESBL-EC strains are frequently isolated from both community onset uncomplicated UTI and nosocomial UTI. To guide future recommendations to reduce transmission of ESBL-EC analysis of such data is of major concern. We observed a higher rate of ESBL-EC in inpatients compared to outpatients. However, this observation should be interpreted with precaution. First, increasing evidence suggests that the spread of ESBL-EC is more related to the food chain than to nosocomial transmission. In this context, very high rates (up to >90 %) of ESBL-EC contaminated chicken and pork meat were reported [4, 14]. Second, a recent study could demonstrate a low rate of ESBL-EC transmission in our institution [12]. Finally, we had only limited access to microbiological outpatient records of ESBL-EC positive inpatients prior to hospitalization and not all of these patients were initially screened for ESBL-EC. Therefore, it is possible that ESBL-EC positive inpatients might be ESBL-EC positive prior to hospitalization. Studies exploring risk factors associated with urinary isolation of these pathogens consistently identified complicated UTI as a major risk factor. Rodriguez-Bano et al. [13] reported independent predictors of ESBL-EC UTI, namely age >60 years, female sex, diabetes mellitus, recurrent UTI, healthcare-associated infection, and previous antimicrobial use. Due to the emergence of ESBL-EC and high rates of cross-resistances recommendations to treat uncomplicated UTI were revised [9, 10, 15, 16]. In our study ciprofloxacin, levofloxacin, amoxicillin-clavulanate acid, gentamicin, doxycycline, and sulfamethoxazole did not show reliable in vitro coverage for ESBL-EC isolates. In addition, we observed a significant difference between samples derived from the Department of Urology and the control group regarding the susceptibility of ESBL-EC to ciprofloxacin. This may be explained by (1) the commonly increased age of urological patients with a history of ciprofloxacin treatment, (2) the widespread use of ciprofloxacin in males with only complicated UTIs by definition resulting in fluorochinolone therapy, and (3) the frequent use of ciprofloxacin for antibiotic prophylaxis in standard urological procedures [17, 18]. Therefore, we would not recommend ciprofloxacin in accordance with current guidelines in cases where ESBL-EC UTIs are suspected as well as for standard perioperative prophylaxis [9, 10]. The only oral agents with reliable in vitro activity against ESBL-EC detected in our study and reported in the literature are fosfomycin and nitrofurantoin. Fosfomycin is a phosphoric acid derivative produced by *Streptomyces* spp. which inhibits bacterial cell wall synthesis and decreases the adherence to the urothelium. It can be orally administered as fosfomycin trometamol with a single-dose of 3 g [19] and is well tolerated with neglectable side effects [20, 21]. The observed high in vitro activity of fosfomycin highlights this substance as an oral treatment option in UTI associated with ESBL-EC [22, 23]. However, it has to keep in mind that the widespread use of fosfomycin might trigger fosfomycin resistance as reported recently [24, 25]. Nitrofurantoin, a bactericidal drug, is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules.

A 7-day twice-daily administration of 100 mg nitrofurantoin macrocrystal is recommended. The ARESC study reported a high in vitro activity (94.9 %) of fosfomycin to *E. coli* isolates [3]. Our overall data could confirm this result in ESBL-EC positive urine samples. However, it has to keep in mind that both fosfomycin and nitrofurantoin are not currently licensed for treatment of complicated UTI, and the optimal dose and duration of therapy for this indication have not been evaluated in clinical trials. Therefore, fosfomycin, as well as nitrofurantoin, should be reserved for treatment of uncomplicated UTI [16]. None of the ESBL-EC isolates tested exhibited an in vitro resistance against meropenem and imipenem. These data are congruent with data from Mody et al. Tamayo et al. and Alhambra et al. which reported no resistance of ESBL-EC to another carbapenem, namely ertapenem [26–28]. The option of using this β-lactam antibiotic once a day makes it a useful parenteral antimicrobial agent for the treatment of serious UTI in nursing homes and outpatient clinics. However, an increasing use of carbapenems may also result in antibiotic resistance, and thus, only the prudent use of these substances may prevent selection pressure and avoid clinical situations with no further treatment options. In such context, the further spread of the "real threat" carbapenemase-producing *Enterobacteriaceae* is of major concern [29]. Piperacillin/tazobactam showed likewise good in vitro against ESBL-EC. However, this is contributed to the so called inoculum effect [30]. Therefore, we insistently advise against to the uncritical use of piperacillin/tazobactam in severe disease caused by ESBL producing organisms. The strengths of our study include the large sample size used, the long observation period as well as the broadly distributed and systematically collected isolates. Limitations were (1) inclusion of *E. coli* only and (2) the absence of clinical and outcome data describing the types and severity of the UTI from which the isolates were derived.

Conclusion

In conclusion, we found an increasing prevalence of ESBL-EC in the last decade at our institution. ESBL-EC isolates showed high resistance rates to quinolones and sulfamethoxazole. In contrast, the susceptibility of ESBL-EC to carbapenems and fosfomycin was excellent. ESBL-EC isolates from urological patients were significant less susceptible to ciprofloxacin compared to non-urological isolates. Therefore, the use of ciprofloxacin should strictly be avoided in urologic patients with suspicion for an ESBL-EC UTI.

Conflict of interest None of the contributing authors has any conflict of interest relevant to the subject matter or materials discussed in the manuscript. No funding or other financial support was received.

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