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Epidemiology, risk factors and comorbidity for urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing enterobacteria

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SUMMARY

Aim: Urinary tract infection (UTI) caused by resistant bacteria is becoming more prevalent. We investigate characteristics and associated risk factors for UTIs resulting from extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. **Methods:** Retrospective study of urinary tract isolates of ESBL-producing enterobacteria in adults (2009 and 2010). We included 400 patients and 103 controls (UTI caused by non-ESBL *Escherichia coli*). Clinical and demographic information was obtained from medical records. Comorbidity was evaluated using Charlson Index (CI). Strains were identified using VITEK 2 system. **Results:** A total of 400 isolates were obtained (93% *E. coli* and 7% *Klebsiella spp*). In 2009, 6% of cultures were ESBL-producing *E. coli* and 7% in 2010. 37% of patients were men and 81% were aged ≥ 60 years. CI was 2.3 ± 1.8 (high comorbidity: 42.8%). 41.5% of strains were susceptible to amoxicillin-clavulanate, 85.8% to fosfomycin and 15.5% to ciprofloxacin. The total number of ESBL *E. coli* positive urine cultures during hospital admission was 97 and, compared with 103 controls, risk factors for UTI caused by ESBL- *E. coli* strains in hospitalised patients were nursing home residence ($p < 0.001$), diabetes ($p = 0.032$), recurrent UTI ($p = 0.032$) and high comorbidity ($p = 0.002$). In addition, these infections were associated with more symptoms ($p < 0.001$) and longer admission ($p = 0.004$). **Conclusions:** Urinary tract infection caused by ESBL are a serious problem and identifying risk factors facilitates early detection and improved prognosis. Male sex, hospitalisation, institutionalisation, diabetes, recurrent UTI and comorbidity were risk factors and were associated with more symptoms and longer hospital stay.

What's known

- Urinary tract infections (UTI) are the second most prevalent cause of community-acquired infection and nosocomial infection most prevalent in our setting.
- The prevalence of ESBL-producing bacteria is not known, although its incidence is increasing progressively around the world.
- Today they are a frequent cause of healthcare-related and hospital-acquired infections but few studies have assessed the specific risk of UTI caused by ESBL-producing gram-negative bacilli.

What's new

- Epidemiology in our region
- Male sex, hospitalisation, living at nursing home, diabetes mellitus, recurrent UTI and comorbidity are risk factors in our HealthCare Area.
- Risk factors are associated with a greater number of symptoms and increased hospital stay as long as frequent use of health resources.
- Carbapenem and fosfomycin are the treatment of choice for these infections resulting from high resistance to quinolones (ciprofloxacin) in our region.

Introduction

Urinary tract infections (UTI) are the second cause of community-acquired infection and nosocomial infection most prevalent in our setting being gram-negative bacilli (GNB) pathogens the most frequently implicated, particularly *Escherichia coli* (1).

Extended-spectrum beta-lactamases (ESBL) are enzymes produced by GNB (mainly *E. coli* and *Klebsiella pneumoniae* but also *K. oxytoca, Proteus spp, Acinetobacter spp,* and others) responsible for resistance against penicillins, cephalosporins and aztreonam (2). The spread of ESBL-producing bacteria worldwide has become a serious public health being a frequent cause of infection in healthcare centres and in the community: it is estimated that around 50% affect non-hospitalised patients although it may be difficult to establish boundaries between community and nosocomial cases (2–4). Risk factors for such infection include comorbidity, frequent use of health resources, prior use of antibiotics, recurrent UTI, older age and male sex (4–10). This is of clinical importance because these patients are at risk of receiving inappropriate empirical therapy, resulting in increased morbidity and mortality (8,11).

Few studies have assessed the specific risk of UTI caused by ESBL-producing GNB. The aim of this study was to describe the characteristics of UTI resulting from ESBL-producing bacteria in our HealthCare Area and to identify the risk factors associated with isolations of *E. coli* carrying ESBL in urine samples from hospitalised patients and to compare them with non-ESBL-carrying strains.

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Disclosure
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Materials and methods

We retrospectively studied all isolates of ESBL in urine during 2009 and 2010 (except paediatric samples) in the Valladolid-West Health Area whose reference centre is the Rio Hortega University Hospital, serving a population of approximately 250000. We collected 423 cases (186 in 2009 and 237 in 2010). Of these, 23 were excluded attributable to a lack of clinical and demographic data in the hospital medical record. Patients with multiple isolates were deeply investigated. Each episode was considered a truly individual UTI if isolates were separated more than 3 months, antibiogram was different than previous and a control urine culture post treatment was negative.

Sociodemographic and clinical information obtained from medical records and included: age, gender, residence (family home vs. nursing home), diabetes mellitus (DM), chronic renal failure (CRF), solid tumour, benign prostate hyperplasia (BPH) in men, carriers of indwelling urinary catheter, hospitalisation in the month prior to the isolation of ESBL-producing GNB and recurrent UTI (≥ 3 episodes per year).

A total of 103 hospitalised patients with UTI caused by non-ESBL-producing *E. coli* were randomly selected as control group to carry out a comparative case-control analysis with 97 hospitalised patients infected by ESBL-producing *E. coli* in the same period.

The original version of the Charlson Index (CI) was used to assess comorbidity. The CI consists of 19 items corresponding to co-morbid conditions which, attributable to their severity, may increase mortality. Each item is assigned a score and the sum of all item scores is a predictor of mortality: 0–1 points signifies no comorbidity, 2 points low comorbidity and > 3 points high comorbidity. This provides a prediction of the mortality rate (short-term follow up < 3 years): 0: 12% mortality/year; 1–2: 26%; 3–4: 52%; > 5: 85% (12).

We also collected data on variables related to infection: ESBL-producing GNB detected and antibiogram. In patients with isolations made during hospitalisation, we collected data on accompanying symptoms, blood cultures (or not) and microorganism found, empiric treatment used and its duration, specific treatment and its duration, final diagnosis and final outcome (discharge or death).

The strains were identified and antimicrobial sensitivity determined using the automated VITEK 2 system (bioMerieux, Lyon, France) according to Clinical and Laboratory Standards Institute (CLSI) recommended methods (13). When results were inconsistent, we used agar diffusion with strips of Etest® (AB Biodisk, Solna, Sweden). Therapeutic corrections for cephalosporins were applied.

We made a descriptive analysis of the study sample expressed as means ± standard deviation, frequencies and percentages. Associations between variables were analysed using the chi-square test and differences between means were assessed using the Student's *t*-test and ANOVA. Data were analysed using the SPSS v15.0 statistical package (SPSS Inc®, Chicago, IL, USA). The level of statistical significance was established as $p \leq 0.05$.

Results

In 2009, 23,839 urine samples were processed in the Microbiology Service of Rio Hortega University Hospital (Valladolid, Spain) of which 4522 were positive. *E. coli* was isolated in 60% ($N = 2725$), of which 6% ($N = 162$) were ESBL-producing strains. In 2010, 30,438 cultures were processed of which 5062 were positive. *E. coli* was isolated in 59.4% ($N = 3007$), of which 7% ($N = 210$) were ESBL-producing strains. We finally included 400 isolates positive for ESBL-producing GNB, which came from 312 patients (one patient with seven different episodes, 5 with 5, 2 with 4, 10 with 3, 36 with 2 and 258 patients with one episode). Of the 312 patients, 63% were women, the mean age was 72 ± 18 years (range 16–103) and 81% were aged ≥ 60 years. Sociodemographic, epidemiological and clinical patient characteristics are shown in Table 1.

Of the 400 isolates, 93% ($N = 372$) were *E. coli* and 7% ($N = 28$) *Klebsiella spp.* Antibiotic resistance is shown in Table 2. A total of 60.3% ($N = 241$) of requests for urine cultures were made from the primary healthcare centre, 17.3% ($N = 69$) from the internal medicine ward, 7.8% from the urology clinic ($N = 31$), 3.3% ($N = 13$) from the nephrology clinic, 5.3% ($N = 21$) from other medical areas including oncology, neurology, pulmonology, gastroenterology and haematology and 3.8% ($N = 15$) from surgical services.

A total of 101 isolates of ESBL-producing GNB came from hospitalised patients, who had a mean hospital stay of 14.5 ± 11.6 days (range 2–57). Associated bacteraemia (blood culture with positive isolation of bacteria) was found in 15.8% ($N = 16$) of these patients, compared with 31.7% ($N = 32$) in whom blood cultures were negative and 52.5% ($N = 53$) patients in whom blood cultures were not made. The most-frequent associated symptoms in hospitalised patients were non-focal febrile syndrome (40.4%, $N = 41$), micturition syndrome (16.7%,

Table 1 Sociodemographic, epidemiological and clinical characteristics of the study sample

Characteristics of all patients	*N* (%)
Gender Male	148 (37)
Mean age (SD), years	72 ± 18
Age ≥ 60 years	325 (81)
Normal residence	
Family home	277 (69.2)
Nursing home	123 (30.8)
Risk factors	
DM	88 (22)
CRF	94 (23.5)
Recurrent UTI	138 (34.5)
Indwelling urinary catheter	47 (11.8)
BPH (male only)	52 (35)
Solid neoplasia	72 (18)
Hospitalisation in previous month	66 (16.5)
Charlson Index (mean score, SD)	2.3 ± 1.8
No comorbidity	141 (35.3)
Low Comorbidity (2 points)	88 (22)
High comorbidity (> 2 points)	171 (42.8)
Prediction of mortality rate by CI	
Index 0 (12% mortality/year)	83 (20.8)
Index 1–2 (26% mortality/year)	146 (36.4)
Index 3–4 (54% mortality/year)	135 (33.8)
Index ≥ 5 (85% mortality/year)	36 (9)

BPH, benign prostatic hyperplasia; CI, Charlson Index; CRF, chronic renal failure; DM, diabetes mellitus; SD, standard deviation; UTI, urinary tract infection.

N = 17) and sepsis (15%, *N* = 15). Only 12.9% (*N* = 13) of patients were asymptomatic.

Empirical treatment was used for a mean of 6 ± 2.7 days: empirical treatment was incorrect in 61.3% of patients, and correct in 27.7%, whereas 11% of patients did not receive empirical antibiotic therapy. Treatment was changed according to the antibiogram in 44.2% of cases compared with 25.8% of cases in which incorrect treatment was not changed. The duration of therapy according to the antibiogram was 7.6 ± 3 days. The final discharge diagnosis was non-specific UTI in 73.2% (*N* = 74) of patients, sepsis in 13.9% (*N* = 14), UTI in catheterised patients in 7.9% (*N* = 8) and the remainder (5%) were classified as nosocomial UTI. Overall hospital mortality of patients with UTI caused by ESBL-producing GNB (with or without other conditions) was 18.8% (*N* = 19), which rose to 37.5% (*N* = 6) in patients with associated bacteraemia.

Ninety-six per cent (*N* = 97) of isolates of ESBL-producing GNB in hospitalised patients were *E. coli*. Table 3 compares these patients with the control group of hospitalised cases urinary isolates of non-ESBL-producing *E. coli*. Most patients with isolates of ESBL-producing *E. coli* were men (45.4% vs. 31.1%), whereas patients with isolates of non-ESBL-producing *E. coli* were significantly more-often women (54.6% vs. 68.9%) (p = 0.037). Isolates of ESBL-producing *E. coli* were more frequent in elderly (90.7% vs. 89.3%) and institutionalised patients (52.6% vs. 26.2%), whereas isolates of non-ESBL-producing *E. coli* were more frequent in patients living at home (47.4% vs. 73.8%) (p = 0.001). In addition, diabetes and recurrent UTI (p = 0.032 for both) were identified as additional risk factors for UTI resulting from ESBL-producing *E. coli*.

ESBL-producing *E. coli* infections were significantly associated with comorbidity measured by the CI (p = 0.0029) and the CI prediction of mortality rate (p = 0.019). Comparing the clinical characteristics at admission, we found that infection-related symptoms were significantly more frequent (p < 0.001) in cases of ESBL-producing *E. coli* (febrile syndrome: 39.2% vs. 27.2%; micturition syndrome: 16.5% vs. 7.8%; sepsis: 15.5% vs.. 5.8%). Associated bacteraemia was more frequent in patients with ESBL-producing strains (15.5% vs. 10.6%, p < 0.001). In respect of final diagnosis, sepsis was significantly more frequent in cases of ESBL-producing *E. coli* (13.4% vs. 6.9%) and non-specific UTI was more frequent in cases of non-ESBL-producing *E. coli* (73.2% vs. 90.2%) (p = 0.003). No association was found with respect to the discharge status (discharge vs. death).

Discussion

ESBL-producing *E. coli* has increased significantly in recent years, especially in the community, and is an important cause of invasive infections (8,14).

In our series, 6% of urinary isolates of *E. coli* in 2009 and 7% in 2010 were ESBL-producing strains, thus suggesting a substantially lower prevalence than that found for the whole of Spain (15–17) but higher than that reported in older studies (6,18,19), showing an increasing trend over time. In Spain, according to data from the 2006 GEIH-BLEE study, the percentage of ESBL-producing strains among isolates of *E. coli* and *K. pneumoniae* was 4.04% and 5.04% respectively (15) which, when compared with the prevalence of 0.5% and 2.7%, respectively, found in a study carried out in 2000, implies a significant increase (18). The SMART (Study for Monitoring Antimicrobial Resistance Trends) study conducted in 2008 and 2009 found a frequency of isolations of ESBL-producing *E. coli* of 11% in Europe and 8% in Spain (17). Latest data from the European Antimicrobial Surveillance System

Table 2 Description of antibiotic resistance*

	ESBL *E. coli* (*N* = 372)		ESBL *Klebsiella spp.* (*N* = 28)		MIC interpretive standard (μg/ml)	
	S	R	S	R	S	R
Amoxycillin/clavulanic acid	41.7	30.9	39	39	≤ 8/4	≥ 32/16
Carbapenems†	97.8	2.2	89	3	≤ 4‡ ≤ 2§	≥ 16‡ ≥ 8§
Gentamicin	88.3	11.4	61	39	≤ 4	≥ 16
Amikacin	96.2	3	100	–	≤ 16	≥ 64
Trimethoprim-sulphamethoxazole	39.5	60.5	54	46	≤ 2/38	≥ 4/76
Fosfomycin	88.7	11.3	46	54	≤ 64	≥ 256
Ciprofloxacin	15.6	83.3	14	64	≤ 1	≥ 4
Nitrofurantoin	83.3	6.5	25	54	≤ 32	≥ 128
Nalidixic acid	8.7	91.3	11	89	≤ 16	≥ 32

*Data are expressed as percentages. S, sensitive; R, resistant; MIC, minimum inhibitory concentration. †Includes imipemen, ertapenem and meropenem. ‡MIC for imipenem and meropenem. §MIC for ertapenem.

(EARSS) show a progressive increase in detection of such strains. In 2010, the prevalence of ESBL-producing *E. coli* in Europe ranged from 2.6% in Sweden to 24.8% in Bulgaria, with a prevalence of 12% in Spain (20).

The profile of our study population was closely related to the demographic pattern of our Health-Care Area. With respect to the presence of risk factors for infection by ESBL-producing GNB, we found that prevalence of diabetes, CRF and recurrent UTI was lower than that found by other studies (7,10) but similar to the results found by Rodríguez Baño et al. (9) and Yang et al. (4). The prevalence of other risk factors (neoplasia, previous hospital admission and carriage of an indwelling urinary catheter) was similar to findings by other groups (7,9,10,21). CI-comorbidity, rarely reported in this patients, was greater than findings by Rodríguez Baño et al. (9) and Calbo et al. (6).

Reports suggest that associated bacteraemia occurs in 15–20% of UTI caused by ESBL-producing *E. coli* (8,10,21,22): the prevalence in our study was at the lower end of this range, although blood cultures were not made in around 50% of our patients, either because they were outpatients or because there was no clinical bacteraemia.

The ESBL-producing *E. coli* antibiogram showed some variations with respect to other studies. Resistance to amoxicillin-clavulanate was similar to other studies (5,9,10,22), but resistance to ciprofloxacin was high and similar to findings by Velasco et al. (10), although lower rates were reported (3,5,9,17,22). Rate of resistance to trimethoprim-sulphamethoxazole was also high and similar to findings by Rodriguez-Baño et al. (9). The high rate of sensitivity to carbapenem and fosfomycin is similar to other studies (3,5,9,10,22) as these drugs remain the treatment of choice for such infections (1,23–25). We found that in around 25% of hospitalised patients with urinary isolation of these strains, the antibiotic used was not appropriate neither modified according to antibiogram: this is a mortality risk factor (11,26) since correct empirical treatment improves prognosis (2,8).

The case-control analysis found a significant association between UTI resulting from ESBL-producing *E. coli* and male sex, nursing home residence, diabetes mellitus, recurrent UTI and a high CI. Gender, institutionalisation and indwelling urinary catheters are widely reported risk factors (5,7,9,10) although there is controversy regarding age and diabetes (4,6,21). However, there are few reports on comorbidity as a risk factor (9). In respect of clinical features, we found that hospitalised patients with isolates of ESBL- producing *E. coli* in urine had significantly more symptoms, associated bacteraemia and longer hospital stay. Yang et al. (4) found no association between ESBL-producing enterobacteria and symptoms: however, they found that these bacteria were associated with longer hospital stay, as did Colodner et al. (7). Calbo et al. (6) found no link between UTI caused by ESBL-producing GNB and associated bacteraemia, although we found no recent studies evaluating both these aspects. Finally, we found no differences in mortality, as did another study (4), although there are few reports on this aspect.

Our study has some limitations, as it was a retrospective analysis, some data may have been missing from the medical records. However, our series is one

Table 3 Sociodemographic, epidemiological and clinical characteristics of hospitalised patients with isolates of ESBL-producing *Escherichia coli* vs. patients with non-ESBL-producing *E. coli* (control group)

Patient characteristics	ESBL *E. coli* N = 97 (%)	Non-ESBL *E. coli* N = 103 (%)	p-value
Gender Male	44 (45.4)	32 (31.1)	**0.037**
Mean age (SD), years	78 ± 14	77 ± 13	0.427
Age ≥ 60 years	88 (90.7)	92 (89.3)	0.741
Normal residence			
Nursing home	51 (52.6)	27 (26.2)	**< 0.001**
Risk factors			
DM	35 (36.1)	23 (22.3)	**0.032**
CRF	20 (20.6)	27 (26.2)	0.351
Recurrent UTI	26 (26.8)	15 (14.6)	**0.032**
Indwelling urinary catheter	15 (15.5)	10 (9.7)	0.219
BPH (male only)	14 (31.8)	8.25	0.419
Solid neoplasia	18 (18.6)	17 (16.5)	0.422
Hospitalisation in previous month	26 (26.8)	18 (17.5)	0.111
Charlson Index (mean score, SD)	3 ± 1.7	2.4 ± 1.9	**0.005**
Charlson Index (group)			**0.002**
No comorbidity	18 (18.6)	41 (39.8)	
Low Comorbidity (2 points)	22 (22.7)	24 (23.3)	
High comorbidity (> 2 points)	57 (58.7)	38 (36.9)	
Prediction of mortality rate by CI			**0.019**
Index 0 (12% mortality/year)	7 (7.2)	11 (10.7)	
Index 1–2 (26% mortality/year)	33 (34)	54 (52.4)	
Index 3–4 (54% mortality/year)	41 (42.3)	25 (24.3)	
Index ≥ 5 (85% mortality/year)	16 (16.5)	13 (12.6)	
Symptoms			**< 0.001**
Asymptomatic	13 (13.4)	31 (30.1)	
Febrile syndrome	38 (39.1)	28 (27.2)	
Micturition syndrome	16 (16.5)	8 (7.8)	
Sepsis	15 (15.5)	6 (5.8)	
Others	15 (15.5)	30 (29.1)	
Blood culture			**< 0.001**
Positive ESBL *E. coli**	11 (11.4)	0.0%	
Positive for another microorganism*	4 (4.1)	11 (10.6)	
Negative	30 (30.9)	27 (26.2)	
Not made	52 (53.6)	65 (63.2)	
Final diagnosis			**0.003**
Sepsis	13 (13.4)	7 (6.9)	
UTI in catheterised patient	8 (8.2)	3 (2.9)	
Nosocomial UTI	5 (5.2)	0.0%	
Non-specific UTI	71 (73.2)	93 (90.2)	
Length of stay (days)	17.7 ± 11.8	13.83 ± 11	**0.004**
Outcome at discharge			0.494
Discharge	79 (81.4)	85 (82.5)	
Death	18 (18.6)	18 (17.5)	

*Associated bacteraemia. BPH, benign prostatic hyperplasia; CI, Charlson Index; CRF, chronic Renal failure; DM, diabetes mellitus; ESBL, extended-spectrum beta-lactamase; SD, standard deviation; UTI, urinary tract infection. Bold values indicate statistical significance.

of the largest reported, and provides data not reported before in our HealthCare Area, such as risk factors for UTI caused by ESBL-producing GNB. These factors are associated with a greater number of symptoms and frequent use of health resources, although additional studies are needed to establish a predictive model for our setting. Suspected infection resulting from ESBL-producing GNB should be thoroughly investigated since treatment can play an important role in the prognosis.

Author contributions

Laisa Socorro Briongos Figuero: concept and design the study, data collection, data analysis and interpretation, drafting article, critical revision and approval. In coordination with other authors. Tamara Gómez-Traveso: concept and design the study, data collection, data analysis and interpretation, drafting article, critical revision and approval. Pablo Bachiller-Luque: concept and design the study, data analysis and interpretation, critical revision and approval. Marta Domínguez-Gil González: concept and design the study, data collection, drafting article, critical revision and approval. Amelia Gómez-Nieto: concept and design the study, data collection, critical revision and approval. Teresa Palacios-Martín: concept and design the study, data analysis and interpretation, critical revision and approval. Manuel González-Sagrado: statistics, design and data analysis and interpretation, critical revision and approval. Antonio Dueñas-Laita: drafting article, data analysis and interpretation, critical revision and approval. José Luis Pérez-Castrillón: concept and design the study, data collection, data analysis and interpretation, drafting article, critical revision and approval. In coordination with other authors.

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