Received: 13 March 2017 | Accepted: 8 August 2017

DOI: 10.1111/ijcp.13001

ORIGINAL PAPER

WILEY THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Prospective cohort study of risk factors for extended-spectrum ß-lactamase-producing *Escherichia coli* urinary tract infections in elderly patients admitted to hospital

Arturo Artero[1] | Ana Esparcia[2] | Juan Alberola[3] | Manuel Madrazo[2] | José M. Nogueira[3] | José M. Eiros[4]

[1]Department of Internal Medicine, Hospital Universitario Dr. Peset, Universitat de València, València, Spain

[2]Department of Internal Medicine, Hospital Universitario Dr. Peset, València, Spain

[3]Department of Microbiology, Hospital Universitario Dr. Peset, Universitat de València, València, Spain

[4]School of Medicine, Universidad de Valladolid, Valladolid, Spain

Correspondence
Arturo Artero, Hospital Universitario Dr. Peset, Valencia, Spain.
Email: arturo.artero@uv.es

Summary

Background: Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* are currently common in community-onset infections, limiting therapeutic options. In this work we aim to identify the prevalence of and risk factors for ESBL-producing *E. coli* in elderly patients with urinary tract infections (UTI) admitted to hospital.

Methods: Prospective cohort study on elderly patients with *E. coli* UTI admitted to a university hospital in Spain, from January 2013 to December 2015. Clinical features, microbiology and outcomes were recorded from the electronic medical records and reviewed by two researchers. Cases were segregated according to ESBL-producing *E. coli*. Risk factors for ESBL-producing *E. coli* were analysed by multivariate analysis.

Results: The prevalence of ESBL-producing *E. coli* was 27.4% (85/310). Healthcare-associated UTI was the only risk factor for ESBL-producing *E. coli* (OR 6.79; 95% CI 3.22-14.31, $P < .001$) by multivariate analysis. ESBL-producing *E. coli* was 43.9% in the healthcare-associated UTI group and 8.9% in the community-acquired UTI group ($P < .001$). Inadequate empirical antibiotic therapy and length of stay in hospital were higher in the ESBL-producing *E. coli* group than in the non-ESBL-producing *E. coli* group (62.3% vs 5.3% and 6.60 ± 3.69 days vs 5.61 ± 3.16 days, respectively). Mortality was not significantly different between groups (13% in ESBL-producing *E. coli* group vs 7.5% in non-ESBL-producing *E. coli* group, $P = .140$).

Conclusions: Healthcare-associated UTI was a risk factor for ESBL-producing *E. coli* in elderly patients with UTI admitted to hospital. Our results might help clinicians in choosing empirical antibiotics in an overall high rate setting of ESBL-producing *E. coli*.

1 | INTRODUCTION

Urinary tract infections (UTI) are the most common cause of bacterial infection in elderly people, causing significant morbidity and mortality, particularly in hospitals.[1,2] *Escherchia coli* is the main cause of UTI, especially among young women but is also the most common pathogen in elderly people. Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* infections were found first in hospital.[3] In the last couple of decades, ESBL-producing *E. coli* has spread across different regions in the world, causing infections both in hospital and community settings.[4-8] Although ESBL-producing *E. coli* can cause a variety of infections, UTI are the most commonly encountered infections.[9]

ESBL-producing *E. coli* are resistant to most beta-lactams and often co-resistant to other classes of antibiotics.[3] Treatment with imipenem or meropenem has been associated with the best outcomes in severe ESBL-producing *E. coli* infections but there is no randomised controlled clinical trial for UTI caused by ESBL-producing *E. coli*.[9] Carbapenems are the surest agents for therapy of these infections but

the variety of beta-lactamases that confer resistance to carbapenems is increasing, and overuse of any single class of antibiotic is likely to be followed by the selection of pathogens resistant to that agent.[10,11]

To our knowledge, no study so far has prospectively studied risk factors of ESBL-producing *E. coli* in elderly patients admitted to hospital with community-acquired UTI. We think that even in a high rate setting of ESBL-producing *E. coli* it would be possible to identify patients with different risk for ESBL-producing *E. coli* based on their epidemiological and clinical characteristics, thus allowing a better use of empirical antibiotics. The aim of this study was to identify clinical factors to predict ESBL-producing *E. coli* among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-producing *E. coli*. This might help us to reduce the use of carbapenems as empirical antibiotic treatment for patients without these risk factors.

What's known

- Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* is a common cause of urinary tract infection (UTI) both in hospital and community settings.
- ESBL-producing *E. coli* are resistant to most beta-lactams and often co-resistant to other antibiotics.
- Risk factors for ESBL-producing *E. coli* UTI in elderly patients admitted to hospital so far have not been prospectively studied.

What's new

- Healthcare-associated UTI is a risk factor for ESBL-producing *E. coli* UTI in elderly patients admitted to hospital.
- Community-acquired UTIs in elderly patients with and without healthcare-associated criteria have very different risk for ESBL-producing *E. coli*. These results could be useful in the selection of the empirical therapy for UTI in clinical practice and suggest that carbapenems could be reserved for healthcare-associated UTI, at least in less severe cases.

2 | METHODS

2.1 | Design and setting

Prospective cohort study of consecutive patients with community-onset UTI admitted to a teaching tertiary hospital over a 3-year period (from January 2013 to December 2015). All patients admitted to the Department of Internal Medicine with a diagnosis of pyelonephritis or urinary sepsis in the emergency department were considered for inclusion to the study. Patients >65 years were finally included in the study if *Escherichia coli* was isolated from a urine culture and a diagnosis of acute pyelonephritis or sepsis, severe sepsis or septic shock of urinary origin were established and there was no other apparent source of infection (see Figure 1).

This study was carried out in the Department of Internal Medicine of the University Hospital Dr. Peset in Valencia, Spain. The Department of Internal Medicine accounts for 50 beds of the total of 549 beds in the hospital.

2.2 | Data collection

Epidemiological, clinical and microbiological data were collected from the electronic medical records of the patients. Clinical manifestations of UTI were reviewed in every case by two researchers for inclusion in the study. Cases were segregated according to the presence or not of ESBL-producing *E. coli* to identify clinical factors to predict ESBL-producing *E. coli*. Independent variables analysed as possible risk factors were age, sex, healthcare-associated UTI, comorbidities, APACHE II, septic shock, fever and bacteraemia. Outcome variables studied were inadequate empirical antibiotic treatment (IEAT), length of stay in hospital and in-hospital mortality.

2.3 | Definitions

Healthcare-associated (HA) UTI was defined by the presence of any of the following conditions: Hospitalisation in the past 3 months, nursing home residence or prior antibiotic use in the past 3 months. Community-acquired UTI was defined when a case of UTI did not meet HA-UTI criteria.[12] Pyelonephritis was diagnosed if a patient had the following symptoms: temperature of 38°C, flank pain or costovertebral angle tenderness or all of these. Sepsis, severe sepsis and septic shock were defined following the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[13] Empirical antimicrobial therapy was considered inappropriate when the causative microorganism was reported as non-susceptible to the antimicrobial agent.[14]

2.4 | Microbiological methods

Urine samples were transported from the emergency department to the laboratory of microbiology at University Hospital Dr. Peset and processed following the standard procedures at any time of the day. For the identification and study of the sensitivity of the isolated organism, a semi-automated system (MicroScan; Beckman Coulter Inc.: L'Hospitalet de Llobregat, Barcelona, Spain) was used. For the purposes of analysis, intermediate and resistant isolates were combined and classified as "non-susceptible".[15] Those isolates whose results were positive for ESBL (generally those with reduced sensitivity to one or more of the following antibiotics: cefpodoxime, ceftazidime, cefotaxime, ceftriaxone and aztreonam) were confirmed by the double disc synergy test (DDST). This test consists of comparing the inhibition halos of a third-generation cephalosporin alone and with clavulanic acid incorporated into the discs. The increased activity of cephalosporin in the presence of clavulanic acid indicates the production of ESBL in Gram negative bacilli, according to the CLSI (National Committee for Clinical Laboratory Standards)

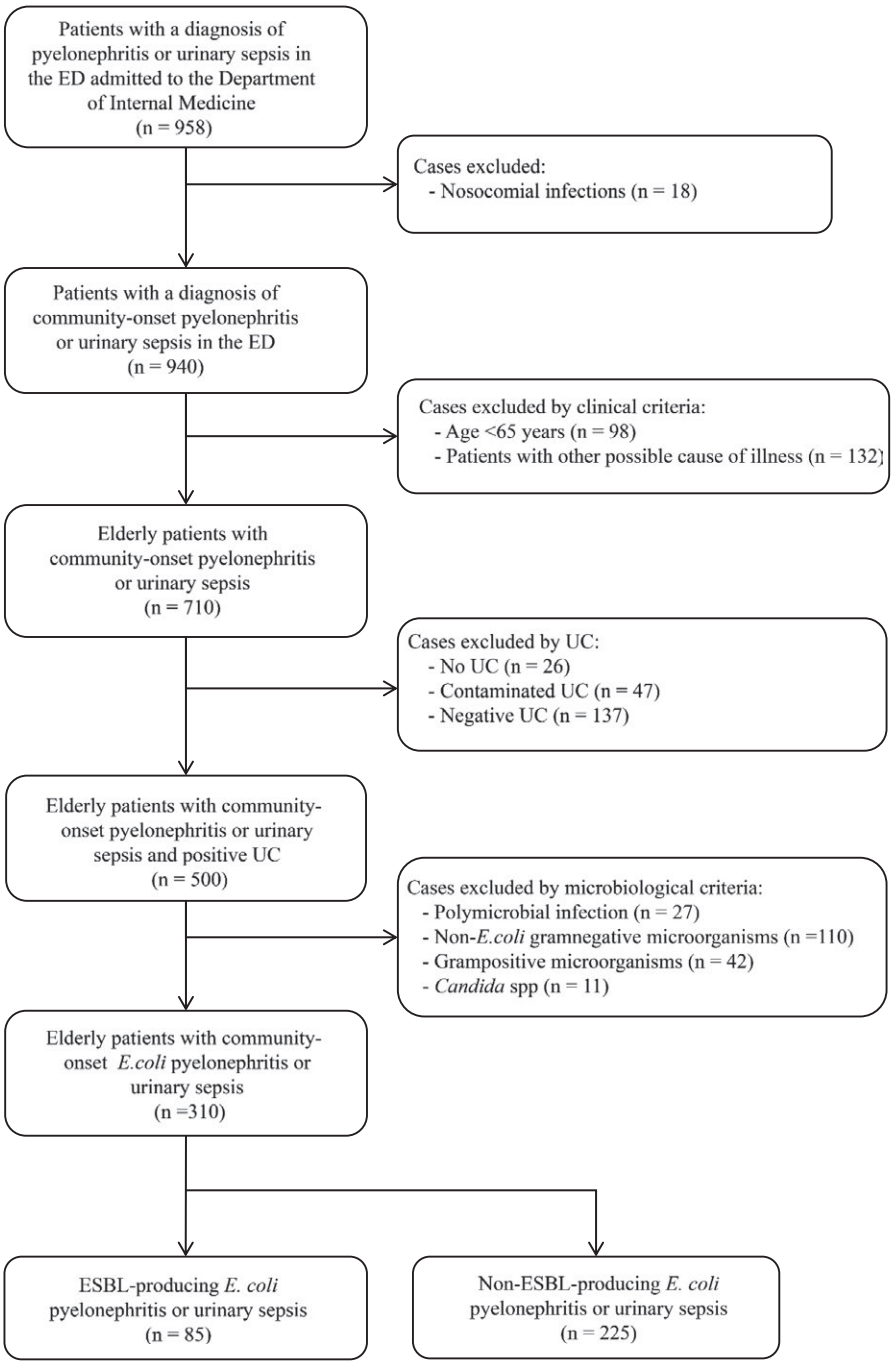

FIGURE 1 Flow of patients included in the study. Abbreviations: ICU, intensive care unit; UC, urinary culture; *E. coli*, *Escherichia coli*; ESBL, extended-spectrum beta-lactamase

guidelines. A phenotypic confirmation test was also performed on those isolates suspected of having AmpC beta-lactamases (mainly resistance to third-generation cephalosporins that have a confirmatory ESBL negative test or have intermediate sensitivity or resistance to amoxicillin with clavulanic acid and third-generation cephalosporins).

2.5 | Statistical analysis

Categorical variables were compared by using the chi-squared test or Fisher's exact test when appropriate. For the comparison of continuous variables, we used the Student's *t* test. A *P* value of <.05 was considered significant. Logistic regression analysis was used to determine independent predictors of ESBL-producing *E. coli*. All statistical analyses were performed by using the statistical pack SPSS 22.0 (SPSS, Inc., Chicago,IL).

This study was approved by the hospital's Clinical Investigation Ethics Committee and complies with ethical standards. The Committee waived the need to obtain informed consent because of the fact that it was a non-interventional study and that all data were kept confidential and information identifying patients were removed.

3 | RESULTS

From January 2013 to December 2015, a total of 958 patients were admitted to the Department of Internal Medicine with a diagnosis of UTI in the emergency department. A total of 310 of the 958 patients were finally included in the study (see Figure 1). All patients included were aged >65 years with community-onset *E. coli* UTI.

The main demographic and clinical characteristics of the patients are provided in Table 1. Most of the patients were very old with a mean age of 82.05 ± 7.33 years, two-thirds were older than 80 years, and 64% were women. Just over half of the cases were healthcare-associated UTI and most of the patients had one or more comorbidities. Septic shock was present in 17.4%.

In 85 (27.4%) of the 310 cases, UTI was caused by ESBL-producing *E. coli*. Healthcare-associated UTI and recurrent urinary infection were more prevalent in the ESBL-producing *E. coli* group than in the non-ESBL-producing *E. coli* group (84.7% vs 40.9% and 53% vs 23%, respectively). Inadequate empirical antibiotic treatment and length of stay in hospital were significantly higher in the ESBL-producing *E. coli* group than in the non-ESBL-producing *E. coli* group (62.3% vs 5.3% and 6.60 ± 3.69 days vs 5.61 ± 3.16 days, respectively). The in-hospital mortality was 9%. There was no significant difference between the groups in the number of deaths in the hospital (13% in ESBL-producing *E. coli* group vs 7.5% in non-ESBL-producing *E. coli* group, *P* = .140).

The empirical antibiotics used for the treatment of our patients were: ceftriaxone 170 (54.8%) cases, 24.1% were IEAT and 75.9% appropriate empirical antimicrobial therapy (AEAT); meropenem 85 (27.4%), 1.2% IEAT and 98.8% AEAT; levofloxacin 20 (6.5%), 70% IEAT and 30% AEAT; amoxicillin-clavulanic acid 16 (5.2%), 31.3% IEAT and 68.8% AEAT; aztreonam 5 (1.6%), 0% IEAT and 100% AEAT; ertapenem 4 (1.3%), 0% IEAT and 100% AEAT; others 10 (3.1%), 30% IEAT and 70% AEAT.

TABLE 1 Patient characteristics and comparison between ESBL-producing *Escherichia coli* UTI and non-ESBL-producing *E. coli* UTI groups

	All N = 310	ESBL *E. coli* UTIN = 85 (27.4%)	Non-ESBL *E. coli* UTIN = 225 (72.6%)	*P* value
Age y, mean±SD	82.05 ± 7.33	82.55 ± 6.97	81.86 ± 7.47	.457
Age >80 y	205 (66.1)	59 (69.4)	146 (64.9)	.453
Male sex, no. (%)	112 (36)	32 (37.6)	80 (35.5)	.732
Healthcare-associated UTI, no. (%)	164 (52.9)	72 (84.7)	92 (40.9)	**<.001**
Hospitalisation in the past 3 months	101 (32.5)	42 (49.4)	59 (26.2)	**<.001**
Nursing home residence	33 (10.6)	18 (21)	15 (6.6)	**<.001**
Prior antibiotic use (3 months)	134 (43.2)	61 (71.7)	73 (32.4)	**<.001**
Comorbidities, no. (%)				
Diabetes mellitus	83 (26.8)	27 (32)	56 (24.8)	.231
Chronic respiratory disease	47 (15.2)	19 (22.3)	28 (12.4)	.081
Dementia	134 (43.2)	44 (51.7)	90 (40)	.153
Immunosuppression	13 (4.2)	4 (4.7)	9 (4)	.782
Liver failure or cirrhosis	9 (3)	0	9 (4)	.142
Malignancy	32 (10.3)	12 (14)	20 (8.8)	.338
Chronic kidney disease	39 (12.6)	13 (15.3)	26 (11.5)	.566
Recurrent urinary infection (≥3 episodes/year)	97 (31.3)	45 (53)	52 (23)	**<.001**
Urological procedure	9 (3)	4 (4.7)	5 (2.2)	.245
Catheter-associated UTI	32 (10.3)	8 (9.4)	24 (10.6)	.746
Fever > 38° C no. (%)	150 (48.4)	35 (41)	115 (51)	.118
Heart rate, bpm, mean±SD	93.96 ± 21.8	90.81 ± 25.41	95.15 ± 20	.118
Mean blood pressure, mm Hg, mean±SD	74.82 ± 18.74	74.52 ± 17.7	74.93 ± 19.14	.862
White blood cell count >12 000 $\times 10^9$/L, n (%)	84 (27)	22 (25.8)	62 (28.8)	.767
Bacteraemia, no. (%)[a]	72 (41.6)	21/45 (46.6)	51/128 (39.8)	.424
Septic shock, n (%)	54 (17.4)	17 (20)	37 (16.4)	.462
IEAT, no. (%)	65 (21)	53 (62.3)	12 (5.3)	**<.001**
Length of stay in hospital, days, mean ± SD	5.88 ± 3.34	6.60 ± 3.69	5.61 ± 3.16	**.020**
Mortality, no. (%)	28 (9)	11 (13)	17 (7.5)	.140

ESBL *E. coli*, extended-spectrum beta-lactamase-producing *Escherichia coli*; UTI, urinary tract infection; IEAT, inadequate empirical antibiotic treatment. Results with significant differences are indicated in boldface.

[a]Blood cultures were taken in 173 patients.

TABLE 2 Antimicrobial non-susceptibility pattern of *Escherichia coli* isolate from the urine of elderly patients with UTI admitted to the hospital

Criteria	Ampicillin	Amoxicillin-clavulanic acid	TMP-SMX	Ciprofloxacin	Cefotaxime	Piperacillin tazobactam	Gentamicin	Imipenem
All patients	224/309 72%	74/308 24%	85/306 27.7%	134/301 43.2%	88/310 28%	13/306 4.2%	53/309 17%	3/310 0.9%
ESBL-producing *Escherichia coli*[a]	*P* < .001	*P* < .001	*P* = .001	*P* < .001	*P* < .001	*P* = .004	*P* = .001	*P* = .818
Yes	84/84 100%	46/83 54.7%	36/84 42.8%	69/84 82%	82/85 96.4%	9/83 10.8%	26/85 30.5%	1/85 1.2%
No	140/225 62.2%	28/225 12.4%	49/222 22%	65/217 30%	6/225 2.6%	4/223 1.7%	27/224 12%	2/225 0.9%
Healthcare-associated UTI[a]	*P* < .001	*P* < .001	*P* = .009	*P* < .001	*P* < .001	*P* = .136	*P* = .008	*P* = .631
Yes	136/164 83%	59/163 36%	57/163 35%	98/159 61.6%	75/164 45.7%	11/162 6.8% 2/144 1.3%	36/163 22%	2/164 1.2%
No	88/145 60%	15/145 10.3%	28/144 20%	36/142 24.6%	13/146 9%		17/146 10.4%	1/146 0.6%
Recurrent urinary infection[a]	*P* = .005	*P* = .002	*P* = .001	*P* = .001	*P* < .001	*P* = .806	*P* = .041	*P* = .939
Yes	82/96 85%	35/96 36.4%	40/96 41.6%	65/94 69%	46/97 47.4%	4/95 4.2%	23/96 24%	1/97 1%
No	142/213 66.6%	39/212 18.4%	45/210 21.4%	69/207 33.3%	40/211 19%	9/211 4.2%	30/213 14%	2/213 0.9%

UTI, urinary tract infection.
[a]Statistically significant differences in antimicrobial susceptibility, *P* < .05.

TABLE 3 Multivariate analysis of ESBL-producing *Escherichia coli* among UTI in elderly patients

	Odds ratio	95% confidence interval	*P* value
Healthcare-associated UTI[a]	6.79	3.22-14.31	**<.001**[b]
Recurrent urinary infection (≥3 episodes/year)	1.32	0.70-2.47	.308

UTI, urinary tract infection.
[a]Healthcare-associated UTI is defined by the presence of any of the following conditions: Hospitalisation in the past 3 months, nursing home residence or prior antibiotic use (3 months).
[b]Statistically significant differences at P<.05

Antimicrobial non-susceptibility pattern of *E. coli* is shown in Table 2. Piperacillin tazobactam, gentamicin and imipenem were the only antibiotics which had <20% of non-susceptibility in the total of the series. Ampicillin-clavulanic acid, cefotaxime and gentamicin had statistically significant differences in percentages of <20% non-susceptibility when the series was analysed according to the presence of ESBL-producing *E. coli*, healthcare-associated UTI and recurrent urinary infection. Ampicillin, TMP-SMX and ciprofloxacin had percentages of non-susceptibility >20% for every group of patients analysed, ranging from 20.5% to 100%.

Healthcare-associated UTI was a predictor of ESBL-producing *E. coli* (OR 6.79, 95% CI 3.22-14.31) by multivariate analysis. However, recurrent urinary infection was not a predictor (OR 1.32, 95% CI 0.70-2.47), see Table 3. The percentage of ESBL-producing *E. coli* was 43.9% in healthcare-associated UTI group and 8.9% in the community-acquired UTI group (*P* < .001).

4 | DISCUSSION

In this study, we found that elderly patients admitted to hospital with community-onset *E. coli* UTI could be classified into two groups according to the presence or not of healthcare-associated criteria with varying risk of infection by ESBL-producing *E. coli*.

Knowing the risk factors for ESBL-producing *E. coli* is important in order to choose the appropriate empirical antibiotic therapy in *E. coli* infections. In this regard, carbapenems have become the antibiotics of choice for therapy of serious ESBL-producing *E. coli* infections[16,17] and by contrast other antibiotics, mainly cephalosporins or ß-lactam/ß-lactamase inhibitors, could be appropriate for non-ESBL-producing *E. coli* infections. Particularly, in settings where the trimethoprim/sulfamethoxazole and fluoroquinolones resistance rates are higher than 20%.[18,19]

Previous studies have shown several risk factors for ESBL-producing *E. coli* community-acquired UTI; such as older age, previous use of antibiotics, recurrent UTI, previous UTI caused by ESBL-producing *E. coli*, female, nursing home residency, nasogastric tube placement and diabetes mellitus.[20-28] These studies have included asymptomatic bacteriuria,[23,28] outpatients,[21,26,28] cystitis,[27,28] other Enterobacteriaceae[25] or cases identified through records of clinical microbiology laboratory.[22,24,26,28] In this study, a series of consecutively elderly patients admitted to hospital with community-onset *E. coli* UTI is analysed for risk factors for ESBL-producing *E. coli* UTI. We found quite a high global percentage of ESBL-producing *E. coli* UTI (27.3%). However, we found that healthcare-associated UTI allows segregating our series into two groups with very different rates of ESBL-producing *E. coli* UTI: 43.9% in healthcare-associated UTI and 8.9% in community-acquired UTI. Therefore, we suggest that elderly patients without any of the criteria of healthcare-associated UTI (hospitalisation in the past 3 months, nursing home residence or prior antibiotic use in the past 3 months) might be empirically treated with cephalosporins even in an overall high rate setting of ESBL-producing *E. coli* UTI.

ESBL-producing *E. coli* are resistant to most beta-lactams and often co-resistant to other classes of antibiotics (fluoroquinolones, sulfonamides and aminoglycosides) which limits therapeutic options and often leads to failed empirical therapy.[29,30]We found a great difference in IEAT between ESBL-producing and non-ESBL-producing *E. coli* groups (62.3% vs 5.3%, respectively). This could be the reason for the higher length of hospital stay observed in patients with ESBL-producing *E. coli* UTI. This detrimental effect on length of hospital stay has been previously described by MacVane in ESBL-producing *E. coli* and *Klebsiella* UTI.[28] ESBL-producing *E. coli* has been shown to be associated with an increase in mortality in blood stream infections[31-33] but the effect on mortality in UTI is not clear.[27] We have not found any effect on mortality in this series. This might be because of the relatively low rate of mortality of patients with UTI admitted to general wards, 13% in ESBL-producing UTI and 7.5% in non-ESBL-producing UTI in our series.

This study has limitations. First, the study has been carried out in a single hospital and our results need to be corroborated in other settings. Second, identify ESBL-producing *E. coli* is not easy in the laboratory and some cases could have been misclassified because of the fact that molecular testing was not used.[34] Third, there may be other risk factors for ESBL-producing *E. coli* that have not been analysed in this study. Four, we could not assure that some elderly patients with asymptomatic bacteriuria and sepsis of other unidentified sources had been misclassified as urinary sepsis. Fifth, some cases identified as urinary sepsis in this study by the criteria of sepsis of Bone et al.[13] might not have had sepsis according to the 2016 consensus definition of sepsis.[35] Identification of these cases is important in order not to over-treat patients, which is also inappropriate therapy. However, the study has some strengths: The selection of cases was rigorous and the study was carried out in conditions of clinical practice, which clinicians might find useful.

In conclusion, this study shows that the prevalence of ESBL-producing *E. coli* significantly varies between healthcare-associated UTI and community-acquired UTI in an overall rate setting of ESBL-producing *E. coli*. Our results suggest that elderly patients with *E. coli* community-acquired UTI admitted to a hospital with similar characteristics to ours might be empirically treated with cephalosporins or ß-lactam/ß-lactamase inhibitors, at least in less severe cases, reserving carbapenems for healthcare-associated UTI.

DISCLOSURE

None.

ORCID

Arturo Artero http://orcid.org/0000-0002-7479-3408

REFERENCES

1. Liang SY, Mackowiack PA. Infections in the elderly. *Clin Geriatr Med*. 2007;23:441-456. https://doi.org/10.1016/j.cger.2007.01.010
2. Nicolle LE. Urinary Tract Infections in the Older Adult. *Clin Geriatr Med*. 2016;32:523-538. https://doi.org/10.1016/j.cger.2016.03.002. Epub 2016 Apr 18.
3. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. *Clin Microbiol Rev*. 2005;18:657-686. https://doi.org/10.1128/CMR.18.4.657-686.2005
4. Pitout JDD, Nordmann P, Laupland KB, Poirel L. Emergence of Enterobacteriaceae producing extended-spectrum ß-lactamases (ESBLs) in the community. *J Antimicrob Chemother*. 2005;56:52-59. https://doi.org/10.1093/jac/dki166. Epub 2005 May 25.
5. Cantón R, Novais A, Valverde A, et al. Prevalence and spread of extended-spectrum beta-lactamase-producing Enterobacteriaceae in Europe. *Clin Microbiol Infect*. 2008;14(Suppl 1):144-153. https://doi.org/10.1111/j.1469-0691.2007.01850.x.
6. Tansarli GS, Poulikakos P, Kapaskelis A, Falagas ME. Proportion of extended-spectrum β-lactamase (ESBL)-producing isolates among Enterobacteriaceae in Africa: evaluation of the evidence–systematic review. *J Antimicrob Chemother*. 2014;69:1177-1184. https://doi.org/10.1093/jac/dkt500. Epub 2014 Jan 6.
7. Kim B, Kim J, Seo MR, et al. Clinical characteristics of community-acquired acute pyelonephritis caused by ESBL-producing pathogens in South Korea. *Infection*. 2013;41:603-612. https://doi.org/10.1007/s15010-013-0441-z.
8. Rodriguez-Baño J, Paterson DL. A change in the epidemiology of infections due to extended-spectrum beta-lactamaseproducing organisms. *Clin Infect Dis*. 2006;42:935-937. https://doi.org/10.1086/500945. Epub 2006 Feb 27.
9. Boyle DP, Zembower TR. Epidemiology and management of emerging drug-resistant gram-negative bacteria: extended-spectrum β-lactamases and beyond. *Urol Clin North Am*. 2015;42:493-505. https://doi.org/10.1016/j.ucl.2015.05.005. Epub 2015 Jul 15.
10. Jacoby GA, Munoz-Price LS. The new beta-lactamases. *N Engl J Med*. 2005;352:380-391. https://doi.org/10.1056/NEJMra041359.
11. Bader MS1, Hawboldt J, Brooks A. Management of complicated urinary tract infections in the era of antimicrobial resistance. *Postgrad Med*. 2010;122:7-15. https://doi.org/10.3810/pgm.2010.11.2217.
12. Friedman ND, Kaye HS, Stout JE, et al. Health care associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137:791-797.
13. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The

ACCP/SCCM Consensus Conference Committee American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644-1655.
14. Shaw E, Benito N, Rodríguez-Baño J, et al. Risk factors for severe sepsis in community-onset bacteraemic urinary tract infection: impact of antimicrobial resistance in a large hospitalised cohort. *J Infect*. 2015;70:247-254. https://doi.org/10.1016/j.jinf.2014.09.011. Epub 2014 Oct 12.
15. Campbell JD, Lewis JS, McElmeel ML, Fulcher LC, Jorgensen JH. Detection of favorable oral cephalosporin-clavulanate interactions by in vitro disk approximation susceptibility testing of extended-spectrum-beta-lactamase-producing members of the enterobacteriaceae. *J Clin Microbiol*. 2012;50:1023-1026. https://doi.org/10.1128/JCM.06248-11. Epub 2011 Dec 14.
16. Bou-Antoun S, Davies J, Guy R, Johnson AP, Sheridan EA, Hope RJ. Descriptive epidemiology of *Escherichia coli* bacteraemia in England, April 2012 to March 2014. *Euro Surveill*. 2016;21:1-9. https://doi.org/10.2807/1560-7917.es.2016.21.35.30329.
17. Hoban DJ, Nicolle LE, Hawser S, Bouchillon S, Badal R. Antimicrobial susceptibility of global inpatient urinary tract isolates of *Escherichia coli*: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program: 2009–2010. *Diagn Microbiol Infect Dis*. 2011;70:507-511. https://doi.org/10.1016/j.diagmicrobio.2011.03.021.
18. Sanchez GV, Master RN, Karlowsky JA, Bordon JM. In vitro antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. *Antimicrob Agents Chemother*. 2012;56:2181-2183. https://doi.org/10.1128/aac.06060-11. Epub 2012 Jan 17.
19. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. *Infect Control Hosp Epidemiol*. 2013;34:1-14. https://doi.org/10.1086/668770. Epub 2012 Nov 27.
20. Savatmongkorngul S, Poowarattanawiwit P, Sawanyawisuth K, Sittichanbuncha Y. Factors associated with extended spectrum b-lactamase producing *Escherichia coli* in community-acquired urinary tract infection at hospital emergency department, Bangkok, Thailand. *Southeast Asian J Trop Med Public Health*. 2016;47:227-233.
21. Rodríguez-Baño J, Alcalá JC, Cisneros JM, et al. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med*. 2008;168:1897-1902. https://doi.org/10.1001/archinte.168.17.1897.
22. Calbo E, Romaní V, Xercavins M, et al. Risk factors for community-onset urinary tract infections due to *Escherichia coli* harbouring extended-spectrum ß-lactamases. *J Antimicrob Chemother*. 2006;57:780-783. https://doi.org/10.1093/jac/dkl035. Epub 2006 Feb 21.
23. Ena J, Arjona F, Martínez-Peinado C, López-Perezagua MM, Amador C. Epidemiology of urinary tract infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Urology*. 2006;68:1169-1174. https://doi.org/10.1016/j.urology.2006.08.1075.
24. Moor CT, Roberts SA, Simmons G, et al. Extended-spectrum b-lactamase (ESBL)-producing enterobacteria: factors associated with infection in the community setting, Auckland, New Zealand. *J Hosp Infect*. 2008;68:355-362. https://doi.org/10.1016/j.jhin.2008.02.003. Epub 2008 Mar 19.
25. Kung CH, Ku WW, Lee CH, et al. Epidemiology and risk factors of community onset urinary tract infection caused by extended-spectrum b-lactamase-producing Enterobacteriaceae in a medical center in Taiwan: a prospective cohort study. *J Microbiol Immnunol Infect* 2015;48:168-174. https://doi.org/10.1016/j.jmii.2013.08.006. Epub 2013 Sep 21.
26. Martin D, Fougnot S, Grobost F, et al. ; ONERBA-ville network. Prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in community-onset urinary tract infections in France in 2013. *J Infect*. 2016;72:201-206. https://doi.org/10.1016/j.jinf.2015.11.009. Epub 2015 Dec 15.
27. Azap OK, Arslan H, Serefhanoglu KS, et al. Risk factors for extended-spectrum-lactamase positivity in uropathogenic *Escherichia coli* isolated from community-acquired urinary tract infections. *Clin Microbiol Infect*. 2010;16:147-151. https://doi.org/10.1111/j.1469-0691.2009.02941.x. Epub 2009 Aug 18.
28. Osthoff M, Sarah L, McGuinnessa SL, Wagena AZ, Eisen DP. Urinary tract infections due to extended-spectrum beta-lactamase-producing Gram-negative bacteria: identification of risk factors and outcome predictors in an Australian tertiary referral hospital. *Int J Infect Dis*. 2015;34:79-83. https://doi.org/10.1016/j.ijid.2015.03.006. Epub 2015 Mar 11.
29. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum β-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. *J Hosp Med*. 2014;9:232-238. https://doi.org/10.1002/jhm.2157. Epub 2014 Jan 24.
30. Schwaber MJ, Navon-Venezia S, Schwartz D, Carmeli Y. High levels of antimicrobial coresistance among extended-spectrum-b-lactamase producing Enterobacteriaceae. *Antimicrob Agents Chemother*. 2005;49:2137-2139. https://doi.org/10.1128/AAC.49.5.2137-2139.2005.
31. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by *Escherichia coli* and influence of extended-spectrum-b-lactamase production and inadequate initial antibiotic therapy. *Antimicrob Agents Chemother*. 2010;54:4085-4091. https://doi.org/10.1128/AAC.00143-10. Epub 2010 Jul 26.
32. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2007;60:913-920. Epub 2007 Sep 11.
33. Esteve-Palau E, Solande G, Sánchez F, et al. Clinical and economic impact of urinary tract infections caused by ESBL-producing *Escherichia coli* requiring hospitalization: a matched cohort study. *J Infect*. 2015;71:667-674. https://doi.org/10.1016/j.jinf.2015.08.012. Epub 2015 Sep 14.
34. Schmitt J, Jacobs E, Schmidt H. Molecular characterization of extended-spectrum beta-lactamases in Enterobacteriaceae from patients of two hospital in Saxony, Germany. *J Med Microbiol*. 2007;56:241-249. https://doi.org/10.1099/jmm.0.46670-0.
35. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:762-774. https://doi.org/10.1001/jama.2016.0288.

How to cite this article: Artero A, Esparcia A, Alberola J, Madrazo M, Nogueira JM, Eiros JM. Prospective cohort study of risk factors for extended-spectrum ß-lactamase-producing *Escherichia coli* urinary tract infections in elderly patients admitted to hospital. *Int J Clin Pract*. 2017;71:e13001. https://doi.org/10.1111/ijcp.13001