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Escherichia coli belonging to the worldwide emerging epidemic clonal group O25b/ST131: risk factors and clinical implications

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Objectives: *Escherichia coli* belonging to clonal group ST131 has emerged as a significant contributor to infection caused by antibiotic-resistant *E. coli* worldwide. We investigated the risk factors for infections caused by ST131 *E. coli* and their clinical implications.

Methods: One thousand and seventy-seven *E. coli* isolates were screened for ST131 by molecular methods. Risk factors for ST131 were investigated separately for patients with *E. coli* producing and not producing extended-spectrum β-lactamases (ESBLs) in the Seville area, Spain. Multivariate analysis using logistic regression was performed. Patients with infections caused by ST131 and non-ST131 isolates were prospectively followed.

Results: Independent risk factors for non-ESBL-producing ST131 were female gender (OR: 1.94; 95% CI: 1.07–3.51), diabetes mellitus (OR: 2.17; 95% CI: 1.29–3.67), bedridden status (OR: 7.75; 95% CI: 0.70–85.07) and exposure to amoxicillin/clavulanate (OR: 2.07; 95% CI: 1.08–3.96) or fluoroquinolones (OR: 2.48; 95% CI: 1.41–4.34). For ESBL-producing ST131, male gender was an independent risk factor (OR: 2.20; 95% CI: 0.94–5.11), while healthcare-related acquisition and exposure to any previous antibiotic were protective (OR: 0.30; 95% CI: 0.13–0.71; and OR: 0.43; 95% CI: 0.19–1.00, respectively). Overall, the severity of sepsis, bacteraemia and mortality were similar among ST131 and non-ST131 groups. The presence of typical factors predisposing to *E. coli* infection was more frequent in non-ESBL-producing ST131 than in controls (76% versus 57.2%, $P=0.005$).

Conclusions: Previous use of antibiotics selecting for ST131 isolates was the main modifiable risk factor for infections caused by these isolates. Our results also suggest that the clinical virulence of ST131 is not higher than that of other common *E. coli* causing infections.

Keywords: antimicrobial resistance, extended-spectrum β-lactamases, clinical outcomes

Introduction

Escherichia coli belonging to clonal group ST131 has emerged as an important human pathogen worldwide.[1,2] In recent multicentre studies, ST131 accounted for 17% of selected *E. coli* isolates in the USA[3] and 12% of unselected isolates in Spain.[4] ST131 isolates are frequently associated with fluoroquinolone resistance[3] and a subset also harbours extended-spectrum β-lactamases (ESBLs), particularly CTX-M-15;[3,4] also, these isolates exhibit the usual virulence factors associated with extraintestinal pathogenic *E. coli* strains belonging to phylogroup B2.[1] Therefore, ST131 is important because of its combination of successful spread, antibiotic resistance and virulence.

Although critical to the design of prevention strategies, there are considerable gaps in our knowledge of the epidemiology of ST131 *E. coli*. The most important reservoirs and mechanisms of transmission have not been clearly delimited. Although ST131 isolates have been found in non-human sources,[5–7] molecular data suggest that humans would be the main reservoir and that person-to-person would be the usual mode of transmission.[2]

However, to our knowledge, the individual risk factors and outcomes for such infections have only been investigated in one study.[8]

The objectives of our study were to investigate the risk factors for colonization or infection by *E. coli* ST131 producing and not producing ESBLs, and to provide information about the clinical implications of infections caused by these isolates.

Methods

Study design, setting and participants

The population base of the study comprised all residents >14 years old in two healthcare areas in Seville, Spain (1.2 million population) attending any public healthcare centre (including primary care), from whom *E. coli* was isolated in any clinical sample (surveillance samples were excluded).

The analysis of risk factors was performed separately for non-ESBL and ESBL producers using case–control designs. For non-ESBL producers, a case patient was defined as a resident from whom non-ESBL-producing ST131 *E. coli* was isolated. All patients from whom non-ESBL-producing non-ST131 *E. coli* was isolated were eligible as controls. Up to three controls per each ST131 group case were randomly chosen using a computerized method from among those eligible per week and hospital. Because of the intensive work required for screening tasks, the screening process was performed 2 days per week over 30 weeks in 2010. For ESBL producers, all patients with ESBL-producing ST131 *E. coli* were compared with those with ESBL-producing non-ST131 *E. coli* in the same time periods. The inclusion of 110 patients with non-ESBL-producing ST131 was planned according to the sample size of a previous study, which provided enough power to detect some relevant risk factors for ESBL-producing *E. coli*.[9]

For the study of clinical outcomes, all patients studied were prospectively followed for 30 days.

Variables, collection of data and definitions

The following data were collected: age, gender, acquisition (nosocomial, community or healthcare associated, according to previously used criteria[9]), sample, chronic underlying conditions and severity according to the Charlson index,[10] antibiotic use in the previous 2 months, infection (instead of colonization), type of infection, bacteraemia, occurrence of severe sepsis or shock[11] and all-cause 30 day mortality.

Data were collected from electronic charts and personal interviews with attending doctors and nurses and with the patients or their closest relatives. A previously used questionnaire[9] was employed. Investigators collecting the data were blinded to the groups of patients.

CDC criteria were used to differentiate infection from colonization (asymptomatic bacteriuria was not considered an infection) and to define the type of infection.[12] Any functional or anatomical defect and any invasive procedure performed on the site/tract of infection were considered to be local factors predisposing to *E. coli* infection. Diabetes mellitus, liver cirrhosis, chronic renal insufficiency, receipt of immunosuppressive therapy, neutropenia and organ transplantation were considered to be systemic factors predisposing to *E. coli* infection.

The study was approved by the institutional review board of Hospital Universitario Virgen Macarena, which waived the need to obtain written informed consent.

Microbiological studies

All isolates were screened for the O25b:H4/ST131 clonal group using PCR with primers for O25b *rfb* and allele 3 of the *pabB* gene[13] and multiplex PCR for phylogroup B23 typing with two different sets of primers.[14,15] Methods for isolate characterization and typing have been previously described.[16] Specifically, ESBL production was screened in all isolates showing cefotaxime or ceftazidime MICs ≥1 mg/L; ESBLs were characterized by PCR and sequencing. Antibiotic susceptibility was studied according to the Clinical and Laboratory Standards Institute recommendations.[17]

Statistical analysis

Univariate comparisons of proportions were performed using the χ^2 test or Fisher's exact test as appropriate and the Mann–Whitney *U*-test for continuous variables. Multivariate analyses were performed by logistic regression. Variables with a *P* value of ≤0.2 in the univariate analysis and interactions of interest were introduced into the models. Variables were selected using a stepwise backward process; those with a *P* value <0.1 were kept in the models. Adjusted ORs with 95% CIs were calculated. The models were evaluated using the Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic (ROC) curve. The analyses were performed with the statistical software package SPSS v19.

Results

Overall, *E. coli* was isolated from 1077 patients over the study period; 928 were not ESBL producers. Among these, 114 belonged

Table 1. Susceptibility data of *E. coli* isolates

	Non-ESBL producers			ESBL producers		
	ST131, *n*=110	non-ST131, *n*=288	*P* value	ST131, *n*=34	non-ST131, *n*=112	*P* value
Ampicillin	23 (20.9)	117 (40.6)	<0.001	0	0	1.0
Amoxicillin/clavulanate	75 (68.1)	219 (76)	0.1	7 (20.6)	45 (40.1)	0.04
Piperacillin/tazobactam	104 (94.5)	272 (94.4)	1.0	31 (91.2)	105 (93.7)	0.6
Cefotaxime	110 (100)	273 (94.7)	0.01	0	1 (0.8)	1.0
Ceftazidime	110 (100)	270 (93.7)	0.005	1 (2.9)	3 (2.6)	1.0
Ciprofloxacin	32 (29.1)	192 (66.7)	<0.001	3 (8.8)	16 (14.2)	0.5
Gentamicin	95 (86.4)	258 (89.5)	0.3	33 (97.1)	83 (74.1)	0.002
Tobramycin	93 (84.5)	258 (89.5)	0.1	7 (20.6)	79 (70.5)	<0.001
Amikacin	107 (97.2)	286 (99.3)	0.6	27 (79.4)	107 (95.5)	0.006
Trimethoprim/sulfamethoxazole	78 (70.9)	205 (71.2)	1.0	9 (26.5)	50 (44.6)	0.07
Fosfomycin	110 (100)	285 (99.9)	0.5	34 (100)	112 (100)	1.0

Data are shown as number of susceptible isolates (percentage).

to ST131 and formed the non-ESBL case group; 292 controls were chosen among the 814 patients with non-ESBL-producing non-ST131 isolates. Because data were unavailable from 4 cases and controls, the final numbers were 110 cases and 288 controls. Among the 149 ESBL producers, 35 belonged to ST131 and 114 did not (one and two patients, respectively, were excluded because of missing data). Overall, *E. coli* were isolated from urine samples (81.9%), blood cultures (6%) and other samples (12.1%); the distribution of samples was similar in all groups ($P=0.06$).

Microbiological data

The susceptibility data are shown in Table 1. Among non-ESBL producers, ST131 isolates were less frequently susceptible to ampicillin and ciprofloxacin, but more frequently susceptible to cefotaxime and ceftazidime than non-ST131 isolates. Among ESBL producers, ST131 isolates were less frequently susceptible to amoxicillin/clavulanate, tobramycin and amikacin, but more frequently susceptible to gentamicin.

Among the 25 isolates selected from the control group, 5 (20%) belonged to phylogroup A, 3 (12%) to B1, 9 (36%) to B2 and 8 (32%) to D. Of the ESBL-producing non-ST131 group isolates, 38 (33.9%) belonged to phylogroup A, the same number to B1, 15 (13.4%) to B2 and 19 (17%) to D; the phylogroup could not be studied in 2 isolates. By definition, all ST131 isolates belonged to phylogroup B2.

As regards the ESBLs, 33 (97.1%) of ESBL-producing ST131 group isolates produced enzymes from the CTX-M-1 group (31 were CTX-M-15) and 1 produced CTX-M-14. Among the ESBL-producing non-ST131 group, only 26 (23.3%) produced CTX-M-1 group enzymes ($P<0.001$), 16 of which were

Table 2. Univariate analysis of risk factors for colonization/infection by ST131 *E. coli*

	Non-ESBL producers			ESBL producers		
	ST131, $n=110$	non-ST131, $n=288$	*P* value	ST131, $n=34$	non-ST131, $n=112$	*P* value
Age in years, median (IQR)	67 (53–78)	61 (43–75)	0.04	74 (57–85)	68 (59–78)	0.2
Male gender	24 (21.8)	82 (28.5)	0.2	19 (55.9)	32 (28.6)	0.09
Nosocomial acquisition	26 (23.6)	50 (17.4)	0.2	8 (23.5)	20 (17.9)	0.5
Healthcare related	37 (33.6)	103 (35.8)	0.6	10 (20.4)	64 (57.1)	0.006
Community acquired	47 (43.1)	135 (46.9)	0.4	16 (47.4)	28 (25)	0.01
Nursing home resident	4 (3.6)	5 (1.7)	0.2	1 (2.9)	0	0.2
Previous hospital admission	9 (8.2)	35 (12.2)	0.2	3 (8.8)	20 (17.9)	0.2
Haemodialysis	2 (1.8)	3 (1)	0.6	1 (2.9)	3 (2.7)	1.0
Attended day hospital	7 (6.4)	24 (8.3)	0.5	2 (5.9)	23 (20.5)	0.05
Any chronic underlying disease	34 (38.8)	113 (40.1)	0.9	45 (58.3)	64 (57.1)	0.8
Charlson index, median (IQR)	0 (0–1)	0 (0–1)	0.8	0 (0–2)	1 (0–2)	0.6
Diabetes mellitus	36 (32.7)	56 (19.4)	0.005	6 (17.6)	34 (30.4)	0.1
Chronic pulmonary disease	5 (4.5)	17 (5.9)	0.5	6 (17.6)	11 (9.8)	0.2
Cancer	6 (5.5)	27 (9.4)	0.2	5 (14.7)	12 (10.7)	0.5
Liver cirrhosis	2 (1.8)	4 (1.4)	0.6	0	4 (3.6)	0.5
Chronic renal insufficiency	6 (5.5)	29 (10.1)	0.1	5 (14.7)	16 (14.3)	1.0
Organ transplantation	5 (4.5)	12 (4.2)	0.7	2 (5.9)	8 (7.1)	1.0
Recurrent urinary tract infections	32 (29.1)	61 (21.2)	0.09	10 (29.4)	46 (41.1)	0.2
Bedridden	3 (2.7)	1 (0.3)	0.06	0	5 (4.5)	0.5
Dependent for basic activities	11 (10)	14 (4.9)	0.05	5 (14.7)	12 (10.7)	0.5
Any invasive procedure	24 (21.8)	47 (16.3)	0.2	7 (20.6)	28 (25)	0.5
Urinary catheter	15 (13.6)	36 (12.5)	0.7	6 (17.6)	21 (18.8)	1.0
Central venous catheter	8 (7.3)	15 (5.2)	0.4	0	12 (10.7)	0.06
Mechanical ventilation	1 (0.9)	5 (1.7)	1.0	0	3 (2.7)	1.0
Surgery	12 (10.9)	27 (9.4)	0.6	2 (5.9)	8 (7.1)	1.0
Previous antibiotics	69 (59.1)	110 (38.2)	<0.001	17 (50)	72 (64.3)	0.1
aminopenicillin	1 (0.9)	10 (3.5)	0.3	0	7 (6.3)	0.3
amoxicillin/clavulanate	21 (19.1)	32 (11.5)	0.04	3 (8.8)	11 (9.8)	1.0
piperacillin/tazobactam	5 (4.5)	2 (2.4)	0.3	3 (8.8)	6 (5.4)	0.4
second-generation cephalosporin	4 (3.6)	10 (3.5)	1.0	1 (2.9)	12 (10.7)	0.3
third-generation cephalosporin	4 (3.6)	3 (1)	0.09	0	4 (3.6)	0.5
carbapenem	0	6 (2.1)	0.1	2 (5.9)	5 (4.5)	1.0
fluoroquinolone	31 (28.2)	41 (14.2)	0.001	14 (41.2)	40 (35.7)	0.5
aminoglycoside	2 (1.8)	3 (1)	0.6	0	5 (4.5)	0.5

Data are shown as number of cases per group (percentage), except where specified.

CTX-M-15, and 45 (40.2%) produced CTX-M-9 group ESBLs (39 were CTX-M-14), 26 (23.3%) CTX-M-1 group (16 were CTX-M-15) and 39 (34.8%) SHV group (38 were SHV-12); the ESBL type could not be studied in 2 isolates.

Risk factors

Exposures to potential predisposing factors are shown in Table 2. Multivariate analyses are shown in Table 3. The independent risk factors for colonization/infection due to *E. coli* ST131 among non-ESBL producers were female gender, diabetes mellitus, bedridden status and previous receipt of amoxicillin/clavulanate or fluoroquinolones. Among ESBL producers, male gender increased the risk of harbouring ST131 isolates, while healthcare-related acquisition and previous receipt of any antibiotic were protective. The *P* values of the Hosmer–Lemeshow goodness-of-fit test for the two models were 0.8 and 0.9 and the areas under the ROC curves were 0.68 and 0.70, respectively.

Table 3. Multivariate analyses of risk factors for colonization/infection by ST131 *E. coli*

	OR (95% CI)	*P* value
Non-ESBL producers		
female gender	1.94 (1.07–3.51)	0.02
diabetes mellitus	2.17 (1.29–3.67)	0.003
bedridden	7.75 (0.70–85.07)	0.09
amoxicillin/clavulanate use	2.07 (1.08–3.96)	0.02
fluoroquinolone use	2.48 (1.41–4.34)	0.001
ESBL producers		
male gender	2.20 (0.94–5.11)	0.06
healthcare-related acquisition	0.30 (0.13–0.71)	0.006
previous antibiotics	0.43 (0.19–1.00)	0.05

Clinical impact

Among non-ESBL producers, 75 (68.2%) of the ST131 group and 187 (64.9%) of the non-ST131 group had an infection ($P=0.5$); the figures among ESBL producers were 21 (61.8%) in the ST131 group and 64 (57.1%) in the non-ST131 group ($P=0.6$). As shown in Table 4, the presence of typical factors predisposing to *E. coli* infections was less frequent among patients with infections caused by non-ESBL-producing non-ST131 isolates than among those with non-ESBL-producing ST131 isolates. The source of infection, bacteraemia, severe sepsis or shock or mortality showed no significant differences between ST131 and non-ST131 groups.

Discussion

Our study provides information about the risk factors for ST131 *E. coli* and showed that the features of infections were similar to those caused by non-ST131 isolates; furthermore, contrary to what we expected, patients with infections caused by ST131 were more frequently exposed to factors predisposing to infection.

ST131 was initially described as CTX-M-15-producing, multidrug-resistant *E. coli* in different parts of the world.[18,19] It was subsequently found that ST131 isolates were more frequently non-ESBL producers; in fact, non-ESBL-producing ST131 lineages were frequently found to be colonizers of the human gut[20] as well as causes of infection.[3,4,16,21] However, most of the epidemiological and clinical studies performed to date on ST131 refer to selected isolates, such as ESBL producers.[22,23]

Although the oldest ST131 isolates detected date from 1967,[2] the recent spread of particular ST131 lineages seems to have occurred at specific sources[2] and, in the case of ESBL producers, with the acquisition of diverse multidrug-resistant IncFII plasmids.[24] ST131 isolates have been found in the environment, food products and livestock;[5–7] however, when ST131 lineages were studied in detail, little commonality was observed between humans and other sources, so that direct or indirect person-to-person transmission was hypothesized as the main method of transmission.[2] This was reinforced by the fact that ESBL-producing ST131 isolates have frequently been found in nursing home patients[25] and that ST131

Table 4. Types of infection caused by ST131 and non-ST131 *E. coli* producing and not producing ESBLs

	Non-ESBL producers			ESBL producers		
	ST131, $n=75$	non-ST131, $n=187$	*P* value	ST131, $n=21$	non-ST131, $n=64$	*P* value
Presence of predisposing factors						
local factors	40 (53.3)	83 (44.3)	0.1	16 (76.2)	41 (64.1)	0.2
systemic factors	31 (41.3)	49 (26.2)	0.01	6 (28.6)	26 (40.6)	0.3
local and systemic factors	57 (76)	107 (57.2)	0.005	19 (91.5)	48 (75)	0.2
Type of infection						
urinary tract infection	55 (73.3)	151 (80.7)	0.1	18 (85.7)	48 (75)	0.3
intra-abdominal infection	8 (10.7)	16 (8.6)	0.5	2 (9.5)	7 (10.9)	1.0
soft tissue infection	7 (9.3)	16 (8.6)	0.8	1 (4.8)	7 (10.9)	0.4
others	5 (6.6)	4 (2.1)	0.2	0	2 (3.1)	1.0
Bacteraemia	5 (6.7)	16 (8.6)	0.6	0	9 (14.1)	0.1
Severe sepsis or shock	0 (1.3)	6 (3.4)	0.6	0	3 (4.7)	1.0
Mortality	1 (1.3)	4 (2.1)	1.0	0	5 (7.8)	0.3

Patients without criteria for infection (colonized) were excluded. Data are shown as number of cases per group (percentage).

producing CTX-M-27 was among the most frequently transmitted *E. coli* clonal groups in two geriatric rehabilitation wards in Israel.[23]

To the best of our knowledge, only one previous study investigated the risk factors for colonization or infection caused by isolates from ST131 *E. coli*;[8] Banerjee *et al.*[8] used a retrospective cohort collected over 2 months in Minnesota, USA and found age, long-term care facility residency, urinary tract infection in the previous 30 days, complex infection and previous receipt of extended-spectrum cephalosporins and macrolides or fluoroquinolones to be risk factors for ST131. Because some 11% of ST131 isolates were resistant to cephalosporins, some of these risk factors may partly be related to ESBL production.[9,26] With the aim of identifying specific risk factors for ST131, we performed a separate analysis for ST131 producing and not producing ESBLs.

Female gender, diabetes mellitus, bedridden status and previous use of amoxicillin/clavulanate or fluoroquinolones were associated with ST131 among non-ESBL-producing *E. coli*. Some of these have also been frequently found as risk factors for ESBL-producing *E. coli*,[9,26] with the exception of exposure to amoxicillin/clavulanate. Although limited by lower numbers, we were surprised to see that the risk factors for ST131 among ESBL producers were very different; our interpretation is that the patients with ESBL-producing *E. coli* represent a markedly different population.

As regards the clinical implications of infections caused by ST131 isolates, previous data were similarly scarce. ST131 isolates were not found to increase mortality in a mouse model when compared with non-ST131 isolates.[27] Also, ST131 isolates were not associated with increased mortality among bacteraemic infections caused by ESBL producers.[22,28] ST131 isolates were over-represented among patients with *E. coli* bacteraemia occurring after a transrectal ultrasound-guided prostate biopsy,[29] probably in relation to the use of fluoroquinolones for prophylaxis. Finally, ST131 were associated with persistent or recurrent symptoms in the Minnesota study,[8] but again the potential impact of ESBL production was not considered. In our study, the frequencies of infection, type of infection, bacteraemia and severe sepsis were similar between ST131 and non-ST131. Furthermore, predisposing factors were more frequent among patients with non-ESBL-producing ST131. All these data strongly suggest that ST131 is not more clinically virulent than other *E. coli* counterparts.

Our study has some limitations. The results may only be applicable to areas with a similar epidemiology and there may not have been enough cases to detect some risk factors. Although highly specific and sensitive, some ST131 isolates belonging to different serotypes, such as O16, may not have been detected by the screening methodology used.[30]

In conclusion, we described the epidemiological and clinical features of infections caused by ESBL-producing and non-ESBL-producing isolates of *E. coli* ST131. Previous use of antibiotics selecting for ST131 isolates was the main modifiable risk factor caused by non-ESBL-producing ST131; infections and their severity were similar to those caused by non-ST131 isolates, although patients with ST131 were more frequently predisposed to developing *E. coli* infection.

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J. M. C. has served as a speaker for Merck, Pfizer, Novartis and Astellas. A. P. has been a consultant for Merck and Pfizer, has served as a speaker for Astra-Zeneca, Merck and Pfizer, and has received research support from Merck and Pfizer. J. R.-B. has been a consultant for Merck, Pfizer and Roche, has served as a speaker for Merck, Pfizer, Astra-Zeneca and Astellas, and has received research support from Merck and Pfizer. All other authors: none to declare.

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