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BRIEF REPORT

Characterization of third generation cephalosporin-resistant *Escherichia coli* clinical isolates from Ushuaia, Argentina

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KEYWORDS

Extended-spectrum beta-lactamase; *Escherichia coli*; Third-generation cephalosporin; ST131

Abstract *Escherichia coli* is one of the main human pathogens causing different hospital- and community-acquired infections. During the period from January 2013 to March 2015, 1.96% (32/1632) of *E. coli* isolates recovered at the Hospital Regional de Ushuaia, Tierra del Fuego province, were resistant to third-generation cephalosporins (TGCs). These isolates were resistant to cefotaxime (91%) and/or ceftazidime (28%). No resistance to carbapenems was detected. Twenty-six isolates were positive for *bla*_{CTX-M} gene, grouped as CTX-M-1/15 (54%); CTX-M-9/14 (25%); CTX-M-2 (17%); and CTX-M-1/15 plus CTX-M-9/14 (4%). Five TGC-resistant strains were positive for *bla*_{CMY} gene, while one strain harbored TEM-19 ESBL. Twelve isolates were identified as ST131 *E. coli* hyperepidemic clone, and one as ST69. Genome sequence analysis of seven *bla*_{CTX-M-15} *E. coli* selected isolates confirm the circulation of ST131, ST617 and ST405 international high-risk clones in the city of Ushuaia.

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PALABRAS CLAVE

Betalactamasa de espectro extendido; *Escherichia coli*; Cefalosporina de tercera generación; ST131

Caracterización de aislamientos clínicos de *Escherichia coli* resistente a cefalosporinas de tercera generación de Ushuaia, Argentina

Resumen *Escherichia coli* es uno de los principales patógenos humanos causantes de diferentes infecciones de inicio hospitalario y comunitario. Se determinó que el 1,96% (32/1.632) de los aislamientos de *E. coli* recuperados entre enero de 2013 y marzo de 2015 en el Hospital Regional de Ushuaia, provincia de Tierra del Fuego, fueron resistentes a cefalosporinas

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de tercera generación (CTG). Estos aislamientos fueron resistentes a cefotaxima (91%) y/o a ceftazidima (28%). No se detectó resistencia a los carbapenemes. Veintiséis aislamientos fueron positivos para el gen *bla*_{CTX-M}, agrupados como CTX-M-1/15 (54%), CTX-M-9/14 (25%), CTX-M-2 (17%) y CTX-M-1/15 más CTX-M-9/14 (4%). Cinco cepas resistentes a CTG dieron positivo para el gen *bla*_{CMY}, mientras que un aislamiento presentó la BLEE TEM-19. Doce aislamientos se identificaron como clon hiperepidémico *E. coli* ST131 y uno como ST69. El análisis de las secuencias del genoma de siete aislamientos seleccionados de *E. coli* *bla*_{CTX-M-15} confirmó la circulación de los clones internacionales de alto riesgo ST131, ST617 y ST405 en la ciudad de Ushuaia.

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Escherichia coli is one of the main human pathogens causing both hospital- and community-acquired infections. *E. coli* mostly cause uncomplicated urinary tract infections (UTIs), however some of them evolve to complicated infections such as upper UTI, sepsis or meningitis. Globally, the SMART study points to *E. coli* as the gram negative bacilli most frequently implicated in intra-abdominal infections and urinary tract infections.¹² In Latin America, the SENTRY study reports *E. coli* in cases of sepsis and soft skin infections with a prevalence of 19% and 19.7% respectively.⁷

E. coli resistant to β -lactams, particularly to third-generation cephalosporins (TGCs), represent a major global public health concern. TGCs are used to treat *E. coli* causing UTIs, bloodstream infections and intra-abdominal infections. In many cases resistance to TGCs is accompanied by resistance to other antimicrobials used for therapy leaving few treatment options. Resistance to TGCs in *E. coli* can be mediated by different mechanisms, including chromosomally encoded AmpC β -lactamase hyperproduction, increased efflux or reduced outer membrane permeability, however the two main relevant mechanisms are plasmid-mediated extended-spectrum β -lactamases (ESBLs) or plasmid-mediated AmpCs enzymes.¹³ There are currently a large number of ESBLs described among *E. coli* isolates, being CTX-M the most detected family. More than 230 CTX-M variants have been reported, nevertheless CTX-M-2, CTX-M-9, CTX-M-14 and CTX-M-15 are the most frequently described enzymes among *Enterobacterales*¹³ (<https://www.ncbi.nlm.nih.gov/pathogens/refgene/-ctx-m>; last accession 04.19.22).

E. coli sequence type 131 (ST131) is a globally disseminated multidrug-resistant (MDR) clone responsible for different human infections including UTI and bloodstream infections.¹⁴ This clone belongs to phylogroup B2 and was successfully spread worldwide. Its main characteristics include the expression of resistance determinants to multiple drugs, including the production of CTX-M-15 ESBL and resistance to fluoroquinolones by chromosomal mutations, and the acquisition of virulence genes, where the possession of the type 1 fimbriae FimH30 allele is common.¹⁴ In addition to *E. coli* ST131, other relevant ESBL-producing *E. coli* clones, such as ST10, ST38, ST405, and ST648, were associated with human infections.^{2,13}

In Argentina, Marchisio et al. analyzed 71 *Enterobacterales* recovered from outpatient urine cultures in two health institutions from Santa Fe city during July 2010.¹⁰ Among 63 *E. coli* isolates, only one (1.6%) showed resistance to TGC mediated by CMY-2 plasmidic-AmpC. In another study carried out during October 2010 in 15 hospitals from three regions of Argentina, a total of 1120 *E. coli* clinical isolates were analyzed, detecting resistance to TGC in 64 strains (5.7%).¹⁵ Among 13 selected *E. coli* isolates, 7 harbored *bla*_{CTX-M-15}, 3 of them *bla*_{CTX-M-2}, and the remaining 3 encoded *bla*_{CTX-M-14}.¹⁵ In an additional study performed between November 2012 and April 2013, a total of 3105 community urine samples from adult male patients from a health care institution were analyzed.¹⁷ A total of 374 *E. coli* isolates were recovered and a frequency of 15.2% of ESBL-producing strains was detected, although no molecular characterization was performed to describe the genes involved.¹⁷ Additionally, according to the WHONET-Argentina network, the national rate of resistance to TGCs among community-onset *E. coli* infections for the year 2015 was 5.3%.⁹

The city of Ushuaia is located in the Isla Grande archipelago, a very important tourist spot. In 2015, Ushuaia had a stable population of <70 000 people and received around 400 000 national and international tourists (<https://turismoushuaia.com/wp-content/uploads/2018/05/sintesis-2015.pdf>). A lack of information and studies about the epidemiology of TGC resistance in this city was observed. Therefore, the objective of the present work was to characterize and describe TGC-resistant *E. coli* clinical isolates in the southernmost city of Argentina.

A prospective, descriptive study was performed at the Microbiology Laboratory of Hospital Regional Ushuaia between January 2013 and March 2015. All *E. coli* isolates were obtained from non-repetitive cultures from inpatients and outpatients. The isolates were recovered from urine, blood, respiratory materials, skin and soft tissue, puncture fluids and prosthetic material. Screening cultures were excluded from the study. Epidemiological data, age and sex were analyzed. Species identification was performed by conventional biochemical methods in accordance to the Manual of Clinical Microbiology. Antimicrobial susceptibility was evaluated by the Kirby-Bauer agar diffusion method, according to CLSI guidelines M100-S23.¹

The antimicrobials tested were defined by the WHONET Argentina Network protocol. Isolates were classified as suspicious of ESBL-production, displaying inhibition halos ≤ 27 mm to cefotaxime and/or ≤ 22 mm to ceftazidime, and were selected for further characterization. Phenotypic ESBL production was confirmed when there was a positive synergistic effect between discs of amoxicillin-clavulanic acid (10/20 μ g) and cefotaxime (30 μ g), or ceftazidime (30 μ g). PCR was performed to detect the following genes: *bla*_{CTX-M}, *bla*_{PER-2}, *bla*_{TEM}, *bla*_{SHV} and *bla*_{CMY}.⁵ *bla*_{CTX-M} genes were classified using PCR to differentiate among the following CTX-M groups: *bla*_{CTX-M-2}, *bla*_{CTX-M-1/15}, *bla*_{CTX-M-8/25}, and *bla*_{CTX-M-9/14}.⁵ *bla*_{TEM} gene was amplified and sequenced using the Sanger sequencing method. The presence of clinically relevant *E. coli* clones from humans was evaluated by multiplex PCR to detect ST69, ST73, ST95, and ST131 clones.³ Whole-genome sequencing of selected strains was performed, using DNA extracted with QIAcube, using the QIAamp1 DNA Mini Kit (Qiagen) and sequenced on an Illumina-MiSeq sequencer. Paired-end reads were trimmed with Trim Galore (V.0.6.3) and analyzed for quality with FASTQC (V.0.11.5). Kraken2 (V.2.0.7-beta) was used to confirm the species. Reads were de novo assembled with Spades assembler running under Unicycler (v0.4.8-beta) and its quality was evaluated with QUAST (V.5.0.2). The annotation of the genomes was done with Prokka (V.1.14.0). ARIBA was run to determine resistance genes (ResFinder, V.2.14.4). Sequence types (Achtman scheme) for each genome was determined by running ARIBA sequence type (MLST, V.2.14.6) and clonal complexes (CC) were obtained by submitting trimmed reads to Enterobase. The *fimH* gene, encoding the type 1 fimbriae adhesin, was characterized using fimTyper from the Center of Genomic Epidemiology (<http://www.genomicsepidemiology.org/>). The phylogroup assignment was performed in silico according to the Clermont PCR method using the command line tool.¹⁶

During the period from January 2013 to March 2015 a total of 1632 *E. coli* isolates were recovered at the Hospital Regional de Ushuaia, Tierra del Fuego province. Nearly two percent (32/1632; 1.96%) of the isolates were resistant to TGC and suspected to be ESBL producers. Most suspected isolates were recovered from urine (31/32: 97%), and one from the peritoneal cavity. The age of the patients ranged from 5 and 84 years, and 87% of them were women. Twenty-seven (84%) isolates were from outpatients while five patients had over 48 h of hospitalization at the time of sampling.

Among the 32 *E. coli* isolates, 91% showed resistance to cefotaxime and 28% to ceftazidime. Twenty-seven (84%) *E. coli* were phenotypically confirmed as ESBL-producers, therefore the rate of ESBL-producing *E. coli* from Ushuaia reached 1.65%. The five ESBL-negative *E. coli* isolates were positive for the plasmid-borne *bla*_{CMY} gene. Among the 27 ESBL-producer isolates, 26 were positive for *bla*_{CTX-M} gene and one was only positive for *bla*_{TEM} gene. *bla*_{CTX-M} genes were grouped according to their nucleotide sequence similarity as follows: CTX-M-1/15 (n: 13; 54%); CTX-M-9/14 (n: 6; 25%); CTX-M-2 (n: 4; 17%); and CTX-M-1/15 plus CTX-M-9/14 (n: 1; 4%), while two isolates were not viable for further studies. The dissociated TGC phenotype, displaying resistance to cefotaxime and susceptibility to ceftazidime, is related to the strong cefotaximase activity of CTX-M family ESBLs, as previously described.¹¹ The TEM-producer *E. coli*

isolate showed a low-level ESBL activity profile and was confirmed by sequencing as ESBL TEM-19. Additional resistance to ampicillin-sulbactam (78%), ciprofloxacin (75%), trimethoprim-sulfomethoxazole (65%), cefoxitin (22%), and nitrofurantoin (19%) were also observed. No resistance to carbapenems was observed.

Among the 30 available isolates, 12 (40%) were identified as ST131 and one as ST69. Nine out of twelve (75%) *E. coli* ST131 isolates were positive for the *bla*_{CTX-M-1/15} group, one for *bla*_{CTX-M-2}, one for *bla*_{CTX-M-9/14}, and one for ESBL *bla*_{TEM-19}. The ST69 isolate was positive for the *bla*_{CTX-M-2} group.

Considering that the CTX-M-1/15-group was the most prevalent ESBL, seven *bla*_{CTX-M-1/15}-positive *E. coli* isolates (ECO1 to ECO7) were selected for the whole-genome sequencing analysis (Table 1). Four of these strains were confirmed as ST131 (ECO3, ECO4, ECO6 and ECO7), two isolates (ECO1 and ECO2) were typed as ST617 (clonal complex 10) and one (ECO5) as ST405 (CC405). The *bla*_{CTX-M-15} allele was confirmed by sequencing in all seven isolates. The four ST131-CTX-M-15 producing *E. coli* isolates harbored additional resistance genes: *bla*_{OXA-1}, *mph(A)*, *aac(6')-Ib-cr*, *tetA*, *catB3*, *sul1* and *qacE* (Table 1). Further resistance genes were found in some of the four ST131 isolates (n): *aadA5* (3), *dfrA17* (3), *aac(3)-IIa* (3), *aadA1* (1), *ant(2'')-Ia* (1), *cmlA1* (1) (Table 1). All these four ST131-CTX-M-15 producing isolates exhibited the same mutations at the quinolone-resistance determining regions (QRDRs): Ser83Leu and Asp87Asn of *gyrA* gene, plus Ser80Ile and Glu84Val of *parC* gene, and Ile529Leu of *parE* gene. Additionally, these four ST131 isolates were *in silico* serotyped as O25:H4 and three of them were typed as fimH30, while the remaining one was 98.65% related to fimH1516⁸(Table 1).

The two *bla*_{CTX-M-15}-producing ST617 *E. coli* isolates harbored the following acquired resistance genes, *bla*_{OXA-1}, *mph(A)*, *aac(6')-Ib-cr*, *aadA5*, *tetB*, *catB3*, *dfrA17*, *sul1* and *qacE* genes, while ECO2 isolate additionally harbored *tetA*, *aac(3)-IIa*, *aph(3'')-Ib*, *aph(6)-Id* and *sul2* genes (Table 1). These isolates showed the following QRDR mutations: Ser83Leu and Asp87Asn of *gyrA* gene, Ser80Ile of *parC* gene, and Ser458Ala of *parE* gene. These two strains, ECO1 and ECO2, were serotyped as O101:H10 but with an untyped *fim* gene. The ECO5 (ST405) isolate harbored *bla*_{CTX-M-15}, *mph(A)*, *tetB*, *aadA5*, *aac(3)-IIa*, *dfrA17*, *sul1* and *qacE* genes, and showed the same mutations in the QRDR as ST617 strains (Table 1). This strain was serotyped as O102:H6 and showed the fimH27 allele. Additionally, according to the phylogroup analysis, all four *E. coli* ST131 (CC131) isolates belonged to phylogroup B2, while both ST617 (CC10) belonged to phylogroup A, and *E. coli* ST405 (CC405) to phylogroup D.

Resistance to TGCs and carbapenems in *E. coli* is a global public health concern, therefore the prompt detection and characterization of mechanisms involved and the clones associated with the dissemination is essential. Global, regional and local studies are necessary to increase the information about this pathogen. During the period January 2013 to March 2015, 1.96% of *E. coli* clinical isolates, mainly recovered from urine samples of outpatients in Ushuaia, showed resistance to TGCs. This rate was quite lower than that of other contemporary reports^{10,16,17} and the results of the National surveillance (WHONET-Argentina network) for the year 2015, where the percentage of resistance to TGCs among community-onset *E. coli* infections was 5.3%.⁹

Table 1 Epidemiological and genomic results of five selected TGC-resistant *E. coli* isolates.

Strain	ECO1	ECO2	ECO5	ECO3	ECO4	ECO6	ECO7
Age (years)	70	39	62	25	55	62	30
Sex	F	F	M	F	F	M	F
Sample	Urine	Urine	Urine	Urine	Urine	Urine	Urine
Community/Hospital onset	Community	Community	Community	Community	Community	Hospital	Community
Antimicrobial resistance profile	AMP, FGC, TGC, FOX, CIP	AMP, AMC, FGC, TGC, PTZ, FEP, CIP, TMS, AKN, GEN, TET	AMP, FGC, TGC, FEP, FOX, CIP, TMS, TET	AMP, FGC, TGC, FEP, CIP, TMS	AMP, FGC, TGC, PTZ, FEP, CIP, TMS, AKN	AMP, FGC, TGC, PTZ, FEP, CIP	AMP, FGC, TGC, FEP, CIP, TMS
Sample date	4-15-14	2-4-15	10-1-14	7-19-13	NA	11-20-14	3-16-15
Sequence type (CC)	ST617 (CC10)	ST617(CC10)	ST405 (CC405)	ST131 (CC131)	ST131 (CC131)	ST131 (CC131)	ST131 (CC131)
Acquired resistance genes	<i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-1} , <i>mdf(A)</i> , <i>mph(A)</i> , <i>tetB</i> , <i>aac(6')-Ib-cr</i> , <i>aadA5</i> , <i>dfrA17</i> , <i>catB3</i> , <i>qacE</i> , <i>sul1</i>	<i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-1} , <i>mdf(A)</i> , <i>mph(A)</i> , <i>tetB</i> , <i>tetA</i> , <i>aac(6')-Ib-cr</i> , <i>aadA5</i> , <i>aac(3)-IIa</i> , <i>aph(3'')-Ib</i> , <i>aph(6)-Id</i> , <i>dfrA17</i> , <i>catB3</i> , <i>qacE</i> , <i>sul1</i> , <i>sul2</i>	<i>bla</i> _{CTX-M-15} , <i>mdf(A)</i> , <i>mph(A)</i> , <i>tetB</i> , <i>aadA5</i> , <i>aac(3)-IIa</i> , <i>dfrA17</i> , <i>qacE</i> , <i>sul1</i>	<i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-1} , <i>mdf(A)</i> , <i>mph(A)</i> , <i>tetA</i> , <i>aac(6')-Ib-cr</i> , <i>aadA5</i> , <i>catB3</i> , <i>dfrA17</i> , <i>qacE</i> , <i>sul1</i>	<i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-1} , <i>mdf(A)</i> , <i>mph(A)</i> , <i>tetA</i> , <i>aac(6')-Ib-cr</i> , <i>aadA5</i> , <i>aac(3)-IIa</i> , <i>catB3</i> , <i>dfrA17</i> , <i>qacE</i> , <i>sul1</i>	<i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-1} , <i>mdf(A)</i> , <i>mph(A)</i> , <i>tetA</i> , <i>aac(6')-Ib-cr</i> , <i>aadA1</i> , <i>aac(3)-IIa</i> , <i>ant(2'')-Ia</i> , <i>catB3</i> , <i>sul1</i> , <i>qacE</i> , <i>cmlA1</i>	<i>bla</i> _{CTX-M-15} , <i>bla</i> _{OXA-1} , <i>mdf(A)</i> , <i>mph(A)</i> , <i>tetA</i> , <i>aac(6')-Ib-cr</i> , <i>aadA5</i> , <i>aac(3)-IIa</i> , <i>dfrA17</i> , <i>catB3</i> , <i>qacE</i> , <i>sul1</i>
Chromosomal mutations associated with fluoroquinolone resistance	<i>gyrA</i> (S83L; D87N), <i>parC</i> (S80I), <i>parE</i> (S458A)	<i>gyrA</i> (S83L; D87N), <i>parC</i> (S80I), <i>parE</i> (S458A)	<i>gyrA</i> (S83L; D87N), <i>parC</i> (S80I), <i>parE</i> (S458A)	<i>gyrA</i> (S83L; D87N), <i>parC</i> (S80I; E84V), <i>parE</i> (I529L)	<i>gyrA</i> (S83L; D87N), <i>parC</i> (S80I; E84V), <i>parE</i> (I529L)	<i>gyrA</i> (S83L; D87N), <i>parC</i> (S80I; E84V), <i>parE</i> (I529L)	<i>gyrA</i> (S83L; D87N), <i>parC</i> (S80I; E84V), <i>parE</i> (I529L)
Plasmidic incompatibility groups	Col(MG828), <i>IncFIA</i> , <i>IncFIB</i> , <i>IncFII</i>	Col156, <i>IncFIA</i> , <i>IncFIB</i> , <i>IncFII</i>	Col156, <i>IncFIB</i> , <i>IncFII</i>	Col(MG828), Col156, <i>IncFIA</i> , <i>IncFII</i> , <i>IncY</i>	Col(MG828), <i>IncFIA</i> , <i>IncFII</i>	Col(MG828), Col156, <i>IncFIA</i> , <i>IncFII</i>	<i>IncFIA</i> , <i>IncFIB</i> , <i>IncFII</i>
SerotypeFinder	O101, H10	O101, H10	O102, H6	O25, H4	O25, H4	O25, H4	O25, H4
fimTyper	Unknown	Unknown	fimH27	fimH30	fimH1516-like	fimH30	fimH30

AMP: ampicillin; AMC: amoxicillin-clavulanate; FGC: first generation cephalosporins; TGC: third generation cephalosporins; FOX: cefoxitin; PTZ: piperacillin-tazobactam; FEP: cefepime; CIP: ciprofloxacin; TMS: trimethoprim-sulfamethoxazole; AKN: amikacin; GEN: gentamicin; TET: tetracycline. NA: not available.

The main mechanism of resistance to TGC was mediated by ESBL production, particularly CTX-M. The CTX-M-1/15 group was the most commonly detected followed by the CTX-M-9/14 and CTX-M-2 groups. The proportion among the CTX-M-groups was similar to a previous report from Argentina, where CTX-M-1/15 enzymes represented >50% of ESBL-producing *E. coli* isolates.¹⁵ In Ushuaia, urinary tract infections by ESBL-producer organisms are treated with piperacillin-tazobactam or carbapenems.

Plasmid-borne *bla*_{CMY} gene, which was detected in five ESBL-negative TGC-resistant *E. coli* isolates, is the second mechanism involved in resistance to TGC. TEM-19 variant, which was also previously described in our country,⁴ was detected in only one isolate showing marginal ESBL activity. The above information highlights the usefulness of phenotypic assays to confirm even weak ESBL-producers and defines an optimal antimicrobial therapy in infected patients.

There is scarce information from our country about the circulation of the MDR ST131 *E. coli* clone. The present work analyzes TGC-R *E. coli* clinical isolates mainly recovered from urine samples and a high proportion (40%) of them were classified as ST131 *E. coli* clone. A deep analysis by whole-genome sequencing of some of these strains confirmed the main characteristics of this international high-risk clone, such as the MDR phenotype, including resistance to fluoroquinolones and TGC, serotype O25:H4, fimbriae FimH30, and grouping into the phylogroup B2. This information confirms the circulation of this international clone in Ushuaia and contributes to a better understanding of its spread throughout our country. Similarly, the finding of the other two ESBL-producing international high-risk clones, ST617 (CC10) and ST405, highlights a concerning scenario.^{6,13}

The present study was conducted in Ushuaia, the southernmost city of Argentina located in the Isla Grande archipelago and could forecast a different behavior of antimicrobial resistance dissemination compared to continental cities. The following were some limitations of our work: (i) it was not possible to analyze if patients were residents or visitors to Ushuaia city, which could have an important effect on the incidence of antimicrobial resistance; ii) the number of fully sequenced isolates was limited; and iii) a complete characterization of *bla*_{CTX-M}-carrying plasmids was not performed.

Nevertheless, the information presented in this manuscript contributes to a better understanding of the dissemination of antimicrobial resistance among *E. coli* in our country, and alerts about the spread of *E. coli* ST131, ST617 and ST405 pandemic clones even in remote cities.

Conflict of interest

The authors declare that they have no conflicts of interest.

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