

Extended-spectrum cephalosporin-resistant *Escherichia coli* in community, specialized outpatient clinic and hospital settings in Switzerland

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Objectives: Resistance to extended-spectrum cephalosporins (ESCs) in *Escherichia coli* can be due to the production of ESBLs, plasmid-mediated AmpCs (pAmpCs) or chromosomal AmpCs (cAmpCs). Information regarding type and prevalence of β -lactamases, clonal relations and plasmids associated with the *bla* genes for ESC-R *E. coli* (ESC-R-*Ec*) detected in Switzerland is lacking. Moreover, data focusing on patients referred to the specialized outpatient clinics (SOCs) are needed.

Methods: We analysed 611 unique *E. coli* isolated during September–December 2011. ESC-R-*Ec* were studied with microarrays, PCR/DNA sequencing for *bla*_{ESBLs}, *bla*_{pAmpCs}, promoter region of *bla*_{cAmpC}, IS elements, plasmid incompatibility group, and also implementing transformation, aIEF, rep-PCR and MLST.

Results: The highest resistance rates were observed in the SOCs, whereas those in the hospital and community were lower (e.g. quinolone resistance of 22.6%, 17.2% and 9.0%, respectively; $P=0.003$ for SOCs versus community). The prevalence of ESC-R-*Ec* in the three settings was 5.3% ($n=11$), 7.8% ($n=22$) and 5.7% ($n=7$), respectively. Thirty isolates produced CTX-M ESBLs (14 were CTX-M-15), 5 produced CMY-2 pAmpC and 5 hyper-expressed cAmpCs due to promoter mutations. Fourteen isolates were of sequence type 131 (ST131; 10 with CTX-M-15). *bla*_{CTX-M} and *bla*_{CMY-2} were associated with an intact or truncated *ISEcp1* and were mainly carried by IncF, IncFII and IncI1 plasmids.

Conclusions: ST131 producing CTX-M-15 is the predominant clone. The prevalence of ESC-R-*Ec* (overall 6.5%) is low, but an unusual relatively high frequency of AmpC producers (25%) was noted. The presence of ESC-R-*Ec* in the SOCs and their potential ability to be exchanged between hospital and community should be taken into serious consideration.

Keywords: ESBL, AmpC, CMY, CTX-M, ST131

Introduction

Extended-spectrum cephalosporin-resistant *Escherichia coli* (ESC-R-*Ec*) isolates are dramatically increasing worldwide. This phenomenon is usually due to the production of extended-spectrum β -lactamases (ESBLs), plasmid-mediated AmpC (pAmpCs) or, more rarely, chromosomal AmpC (cAmpC).¹

Several sequence types (STs) of ESC-R-*Ec* (e.g. ST131 producing the CTX-M-15 ESBL) have shown the ability to cause severe infections in both hospitalized and community patients.^{1–3} However, data describing the rates and characteristics of ESC-R-*Ec* in the community are still limited and, more importantly, those

specifically focusing on the subgroup of patients referring to the specialized outpatient clinics (SOCs) are almost lacking.^{2,4,5} In Switzerland, several works have described the prevalence and molecular characteristics of ESC-R-*Ec* detected in healthy people, food and animals.^{1,6,7} However, there is a lack of contemporary data regarding the ESC-R-*Ec* causing infections in humans.⁸

Materials and methods

Clinical isolates and definitions

All *E. coli* identified at the Laboratory of Clinical Microbiology of the University of Bern (Switzerland) between 1 September and 31 December 2011 were

analysed. The laboratory receives samples from outpatients and those hospitalized at the University Hospital of Bern (Inselspital). Data regarding outpatients were further stratified as 'community'—patients referring to primary care general physicians (GPs) and emergency departments (ERs)—and 'SOCs'—patients referring to the specialized departments of Inselspital. We defined 'community acquired' (CA) and 'healthcare associated infections' (HCA) according to the current CDC criteria.⁹

Species identification and antimicrobial susceptibility tests (ASTs)

Species identification was achieved by implementing standard biochemical tests. ASTs were routinely assessed using the disc diffusion method and results were interpreted according to the CLSI criteria.¹⁰ The MICs for different antibiotics were obtained in Mueller–Hinton II broth (BBL, Becton Dickinson) using the microdilution Sensititre ESB1F plates (Trek Diagnostics) only for the ESC-R-Ec (Table S1, available as Supplementary data at JAC Online).

Characterization of β -lactamases

The CT103 microarray (Check-Points) was used to screen the ESC-R-Ec for the presence of β -lactamase genes. PCR/DNA sequence analyses for the *bla* genes found with the microarray were performed as previously reported.¹¹ *Bla*_{OXA-types}, the promoter region of *bla*_{CampC} and the presence of *ISEcp1*-like and *ISCR1* genes were also analysed.^{8,12,13} Production of β -lactamases was determined using analytical isoelectric focusing (aIEF).⁶

Analysis of clonality

The ST was obtained using multilocus sequence typing (MLST) Achtman scheme (<http://mlst.ucc.ie/mlst/dbs/Ecoli>). Repetitive extragenic palindromic PCR (rep-PCR) and phylogenetic group characterization were also implemented.^{6,11}

Plasmid analysis

The incompatibility group (Inc) of the plasmid(s) was characterized using a multiplex PCR (PBRT Kit, Diatheva). Plasmid extract was electroporated into ElectroMAX *E. coli* DH10B (Invitrogen) and cells were selected on Luria–Bertani plates with ampicillin (20 mg/L) or cefotaxime (1 mg/L) (Sigma).

Results and discussion

Six-hundred-and-eleven unique *E. coli* were analysed. The overall resistance rates to trimethoprim/sulfamethoxazole, quinolones, gentamicin and amoxicillin/clavulanate were 31.5%, 17.4%, 19% and 31.5%, respectively (Table S2, available as Supplementary data at JAC Online).

The highest resistance rates were observed in the SOCs, whereas those recorded in hospital and community settings were lower. For instance, rates to quinolones were 22.6%, 17.2% and 9.0%, respectively ($P=0.003$ for SOCs versus community), whereas those for amoxicillin/clavulanate were 35.1%, 32.3% and 23.8%, respectively ($P=0.04$ for SOCs versus community) (Table S3, available as Supplementary data at JAC Online). Thus, the resistance rates in SOCs are more similar to those observed in hospital rather than in the community. The specific use of antibiotics in this setting may be one of the reasons related to this phenomenon. Unfortunately, in most institutions like ours, statistics regarding the consumption of antimicrobials in SOCs are merged with those of the corresponding hospital wards, making their interpretation in a context of antibiotic resistance difficult. However, we note that 8 of 11 ESC-R-Ec found in

SOCs were from patients referring to nephrology or urology SOCs (Figure 1). During the same period of our analysis, these two wards showed the highest consumption of quinolones [10.7 and 13.3 defined daily doses (DDD)/100 occupied bed-days (BDs), respectively] (Table S4, available as Supplementary data at JAC Online), a recognized risk factor responsible for selection of ESC-R-Ec.^{2,3,14}

Impact of ESC-R-Ec in the different settings

The overall prevalence of ESC-R-Ec ($n=40$; 6.5%) recorded in our area suggests that the impact of such pathogens is still small compared with other countries.¹⁵ However, the analogous prevalence of ESC-R-Ec observed in the community ($n=7$; 5.7%), SOCs ($n=11$; 5.3%) and hospital ($n=22$; 7.8%) settings drives further conclusions (Table S2, available as Supplementary data at JAC Online).

The relatively low hospital prevalence observed may be justified by the different standards of hospital infection control programmes in Switzerland. In contrast, available studies with which to compare our results about the community and SOCs are scarce. In fact, most surveys considered invasive nosocomial infections, whereas studies regarding non-hospitalized patients are limited.^{3,4,15} A general prevalence of 1%–4% among outpatients was recorded, but only a few analyses addressed the specific impact of ESC-R-Ec among GP and ER patients.^{5,16,17} The prevalence of ESC-R-Ec in women with urinary tract infections (UTIs) referring to GPs was 1% in the Netherlands (2009) and 10% in China (2004), whereas one study from the USA (2008) reported a frequency of ~1% among ER patients.^{5,18,19} In our area (2008–09), ESC-R-Ec represented 1.7% of UTIs due to *E. coli* in community.²⁰ Therefore, the prevalence recorded in the present study (4.2% in urine in 2011; Table S2, available as Supplementary data at JAC Online) indicates that there may be a more significant expansion of ESC-R-Ec in the community than in hospital.

Data about ESC-R-Ec in the SOC setting are essentially unavailable because results are frequently merged with those of GPs and/or ERs.^{3,14} However, Qi *et al.*⁵ reported ESBL-producing *E. coli* (ESBL-Ec) in ~1% of urine samples collected in SOCs, whereas Doi *et al.*² noted that 33.6% of CA and 22.8% of HCA infections due to ESC-R-Ec occurred in this setting. In this pilot work we explored this location, suggesting its possible key role in the spread of ESC-R-Ec. As shown in Figure 1, 10 of 11 SOC patients (mean age 53.5 years) had a CA infection usually involving the genitourinary tract (these subjects were referring to the ambulatories of urology, nephrology or gynaecology). Of note, seven patients had been hospitalized during the previous year. Moreover, most of them were referred to the SOCs for many years and had clinical samples positive for ESC-R-Ec for long periods previously and/or later than those analysed in the present study (data not shown). Overall, these figures indicate that SOC patients may serve as a source amplifying the spread of ESC-R-Ec between hospital and community settings. In this context, we note that transmission of ESC-R-Ec from colonized people previously hospitalized to healthy subjects can occur in the community.¹¹

Molecular characteristics of the ESC-R-Ec

Thirty (75%) ESC-R-Ec were CTX-M-15 ($n=14$), CTX-M-27 ($n=7$), CTX-M-1 ($n=5$), CTX-M-14 ($n=3$) or CTX-M-79-like ($n=1$) producers. The *bla*_{CTX-M} were carried by IncF/II plasmids and were

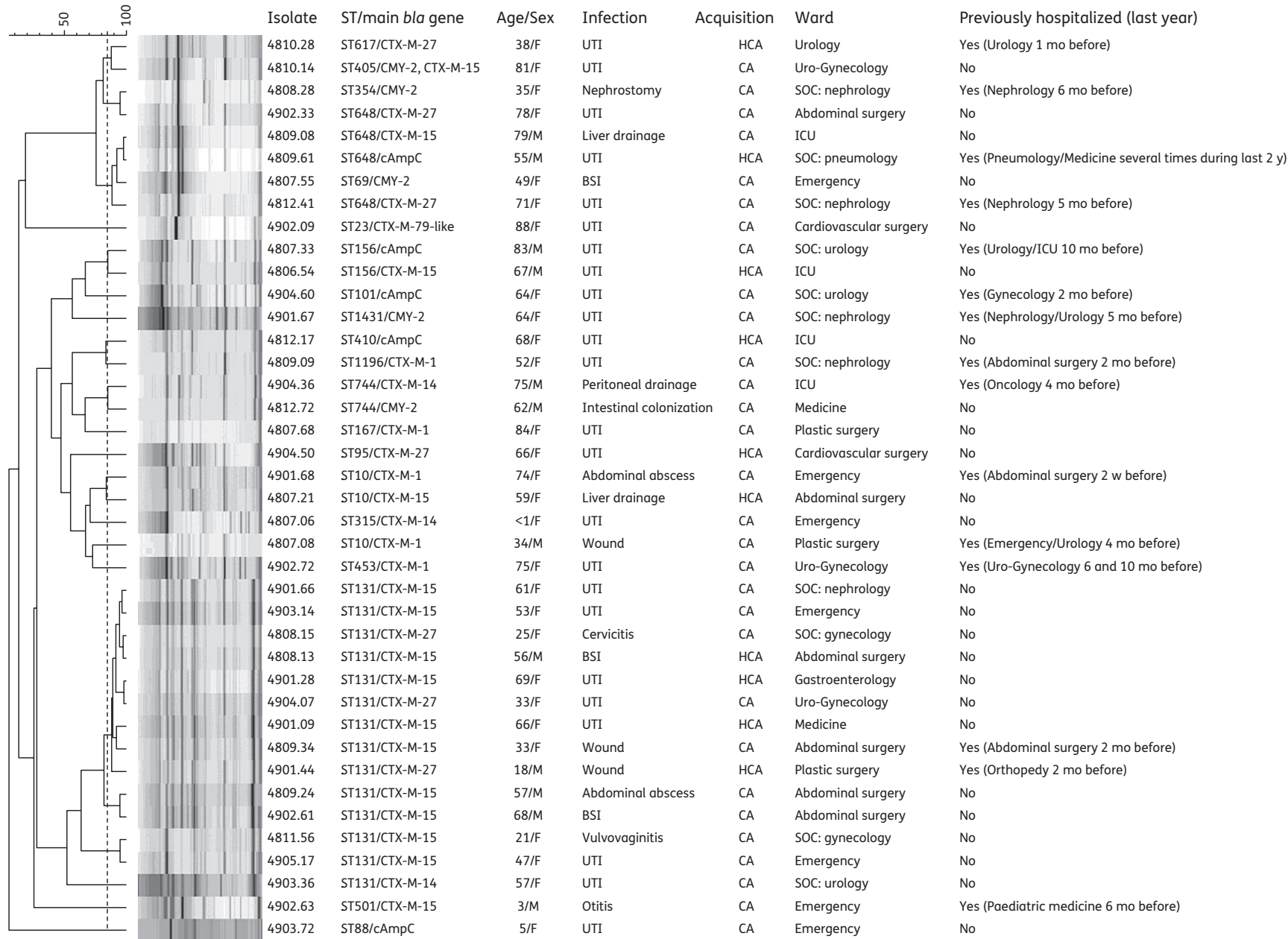


Figure 1. Results of rep-PCR and MLST analyses presented along with demographic and clinical data of patients with infection due to ESC-R-Ec ($n=40$). ST, sequence type; cAmpC, chromosomal AmpC; CA, community acquired; HCA, healthcare associated; UTI, urinary tract infection; BSI, bloodstream infection; SOC, specialized outpatient clinic; y, years; mo, months; w, weeks. The dotted line indicates the cut-off value of $\geq 85\%$ determining clonality between the isolates. The isolates were mainly responsible for CA UTIs ($n=17$) and the major clones were represented by ST131 ($n=14$), ST648 ($n=3$) and ST10 ($n=3$). Notably, 11 of 40 ESC-R-Ec were detected in SOC patients (of which 8 were referred to nephrology or urology). Notably, two further patients referred to the emergency room (4807.55 and 4903.72) were actually SOC patients (nephrology).

Table 1. Molecular characteristics of the 40 ESC-R-*Ec* isolates detected during the study period

Isolate	CT103 microarray ^a	Molecular characterization (PCR/DNA sequencing) ^{b,c,d}	aIEF (±0.2)	Plasmid Inc group(s)	Phylo group	MLST	Plasmid Inc group for transformant
4810.28	CTX-M-gr-9, TEMall	CTX-M-27, TEM-1, OXA-1-like, Δ ISEcp1 3' end	8.3, 6.0, 5.4	F, FII	A	ST617	NP
4810.14	CMY-II, CTX-M-gr-1, TEMall	CMY-2, CTX-M-15, TEM-1, OXA-1-like, ISEcp1 (for both <i>bla</i> genes)	8.9, 6.0, 5.4	F, FII, I1, X1	D	ST405	F, FII, I1 ^e
4808.28	CMY-II	CMY-2, OXA-1-like, ISEcp1	9.0, 7.0, 6.2	F, FII, I1, X1	D	ST354	F, FII, I1, X1
4902.33	CTX-M-gr-9, TEMall	CTX-M-27, TEM-1, OXA-1-like, Δ ISEcp1 3' end	8.6, 8.1, 5.4	F, FII, X1	D	ST648	F, FII
4809.08	CTX-M-gr-I	CTX-M-15, OXA-1-like, Δ ISEcp1 3' end	8.9	F, FII, N, Y	D	ST648	NP
4809.61	—	OXA-1-like, [T/A at -32, G/A at -28, G/A at +34, C/T at +58]	8.6	F, FII, I1, HI2	D	ST648	NP
4807.55	CMY-II, TEMall	CMY-2, TEM-1, OXA-1-like, Δ ISEcp1 3' end	9.0, 6.2, 5.4	F, I2, N, P, X1	D	ST69	TNO
4812.41	CTX-M-gr-9, TEMall	CTX-M-27, TEM-1, OXA-1-like, Δ ISEcp1 3' end	8.5, 6.2, 5.4	F, FII, N, X1	D	ST648	F, FII
4902.09	CTX-M-gr-I	CTX-M-79-like, OXA-1-like, ISEcp1	9.0	F, FII, I1	A	ST23	F, FII, I1
4807.33	—	OXA-1-like, [C/T at -42, G/A at -18, C/T at -1, C/T at +58]	9.0	B/O, F, FII, I1, P	B1	ST156	NP
4806.54	CTX-M-gr-I, TEMall	CTX-M-15, TEM-1, OXA-1-like, Δ ISEcp1 3' end	8.9, 6.0, 5.4	I2	B1	ST156	NP
4904.60	—	OXA-1-like, [C/T -42, G/A -18, C/T -1, C/A +24, A/G +49, C/T +58]	8.6	—	B1	ST101	NP
4901.67	CMY-II, TEMall	CMY-2, TEM-1, OXA-1-like, ISEcp1	9.0, 6.0, 5.4	B/O, F, FII, K	B1	ST1431	F, FII, K
4812.17	—	OXA-1-like, [C/T at -42, G/A at -18, C/T at -1, C/T at +58]	9.0, 6.0	F, FII	A	ST410	NP
4809.09	CTX-M-gr-I, TEMall	CTX-M-1, TEM-1, OXA-1-like, Δ ISEcp1 3' end	8.5, 8.1, 6.0, 5.4	F, FII, I1, P, R	B1	ST1196	FII, I1
4904.36	CTX-M-gr-9, TEMall	CTX-M-14, TEM-1, OXA-1-like, ISEcp1	8.1, 6.0, 5.4	F, FII, I2, X1	A	ST744	TNO
4812.72	CMY-II, TEMall	CMY-2, TEM-1, OXA-1-like, Δ ISEcp1 3' end	9.0, 6.0, 5.4	F, FII, I1, X1	A	ST744	F, FII, I1, X1
4807.68	CTX-M-gr-I, TEMall	CTX-M-1, TEM-1, OXA-1-like, Δ ISEcp1 3' end	8.9, 6.2, 5.4	F, FII, N, X1	A	ST167	F, FII
4904.50	CTX-M-gr-9	CTX-M-27, OXA-1-like, Δ ISEcp1 3' end	8.4	F, FII, X1	B2	ST95	NP
4901.68	CTX-M-gr-I, TEMall	CTX-M-1, TEM-1, OXA-1-like, ISEcp1	8.6, 6.0, 5.4	F, FII, I1, X1	A	ST10	TNO
4807.21	CTX-M-gr-I	CTX-M-15, OXA-1-like, Δ ISEcp1 3' end	8.9, 7.9, 6.0	F, FII	A	ST10	F, FII
4807.06	CTX-M-gr-9, TEMall	CTX-M-14, TEM-1, OXA-1-like, ISEcp1	8.1, 7.9, 5.4	F, FII	D	ST315	NP
4807.08	CTX-M-gr-I, TEMall	CTX-M-1, TEM-1, OXA-1-like, ISEcp1	8.4, 6.0	F, FII, I2, X1	A	ST10	TNO
4902.72	CTXM-gr-1, TEMall	CTXM-gr-1, TEMall, TEM-164R CTX-M-1, TEM-1, OXA-1-like, Δ ISEcp1 3' end	5.4	F, FII, N	B1	ST453	TNO
4901.66	CTX-M-gr-I, TEMall	CTX-M-15, TEM-1, OXA-1-like, ISEcp1	8.6, 5.4	F, FII	B2	ST131	NP
4903.14	CTX-M-gr-I, TEMall	CTX-M-15, TEM-1, OXA-1-like, ISEcp1	8.9, 5.4	F, FII, I2	B2	ST131	TNO
4808.15	CTX-M-gr-9	CTX-M-27, OXA-1-like, Δ ISEcp1 3' end	8.2, 6.0	B/O, F, FII	B2	ST131	NP
4808.13	CTX-M-gr-I	CTX-M-15, OXA-1-like, ISEcp1	8.6, 6.0	B/O, F, FII, X1	B2	ST131	NP
4901.28	CTX-M-gr-I	CTX-M-15, OXA-1-like, ND	8.9, 7.6, 6.0	F, FII	B2	ST131	NP
4904.07	CTX-M-gr-9	CTX-M-27, OXA-1-like, ND	8.6	F, FII	B2	ST131	NP
4901.09	CTX-M-gr-I, TEMall	CTX-M-15, TEM-1, OXA-1-like, ISEcp1	8.9, 6.2, 5.4	F, FII, N, Y	B2	ST131	NP
4809.34	CTX-M-gr-1	CTX-M-15, OXA-1-like, ISEcp1	9.0, 7.6	F, FII	B2	ST131	NP
4901.44	CTX-M-gr-9	CTX-M-27, OXA-1-like, ND	8.2	F, FII	B2	ST131	F, FII
4809.24	CTX-M-gr-I	CTX-M-15, OXA-1-like, Δ ISEcp1 3' end	8.9, 7.2, 6.2	F, FII	B2	ST131	NP
4902.61	CTX-M-gr-I	CTX-M-15, OXA-1-like, Δ ISEcp1 3' end	8.9, 7.2, 6.2	F, FII, I1	B2	ST131	NP
4811.56	CTX-M-gr-I	CTX-M-15, OXA-1-like, ISEcp1	8.9	F, FII	B2	ST131	NP
4905.17	CTX-M-gr-1, TEMall	CTX-M-15, TEM-1, OXA-1-like, ISEcp1	8.9, 5.4	F, FII, I1	B2	ST131	NP
4903.36	CTX-M-gr-9, TEMall	CTX-M-14, TEM-1, OXA-1-like, ISEcp1	8.1, 7.9, 5.4	F, FII, N	B2	ST131	F, FII
4902.63	CTX-M-gr-I, TEMall	CTX-M-15, TEM-1, OXA-1-like, ISEcp1	8.6, 5.4	B/O, F	D	ST501	F
4903.72	TEMall	TEM-1, OXA-1-like, [C/T at -42, G/A at -18, C/T at -1, C/T at +58]	9.0, 6.0, 5.4	F, FII, HI2	A	ST88	NP

NP, transformation in DH10B *E. coli* strain not performed; TNO, transformants not obtained; -, negative.

^aTEMall indicates narrow-spectrum enzymes (e.g. TEM-1/-2) and that TEM-type ESBLs were not present.

^bData in square brackets indicate the nucleotide mutations found in the promoter region of the *bla*_{CampC}; results for this analysis are not shown when the promoter region has a wild-type pattern.

^cThe *bla*_{OXA} gene was only partially sequenced (~200 bp).

^dISEcp1, the element was upstream of the *bla* gene; Δ ISEcp1 3' end, the element was upstream of the *bla* but partially truncated in its 3' end (isolates with Δ ISEcp1 5' were not found); ND, not determined (i.e. an intact ISEcp1 was detected but its position was undetermined).

^eFor strain 4810.14, the obtained transformant carried both *bla*_{CTX-M-15} and *bla*_{CMY-2}.

associated with an intact or truncated *ISEcp1* (Table 1). *Bla*_{CTX-M-15/-14/-27} are the most reported *bla*_{ESBLs} among humans and their association with *ISEcp1* and *IncF/FII* plasmids is also common. In contrast, *bla*_{CTX-M-1} is frequent in animals and food products.¹ Since this specific *bla* has been recurrently recorded in Swiss livestock and in the intestinal tract of healthy people, further analyses to confirm its possible transmission between animals and humans should be made.^{1,6}

MLST indicated that ST131, ST648 and ST10 were the most preponderant among the ESBL-*Ec*. In particular, ST131 isolates (10 producing CTX-M-15) were found in community (*n*=2), hospital (*n*=8) and SOC (*n*=4) settings (Figure 1). These pandemic clones were responsible for CA infections in all settings, indicating possible exchange and/or common sources among the different patient populations.¹

Five (12.5%) ESC-R-*Ec* possessed the *bla*_{CMY-2} associated with an intact or truncated *ISEcp1* (Table 1). These *E. coli* are important human pathogens in both community and hospital settings.²¹ Recently, we also recorded a high prevalence of *bla*_{CMY-2} in poultry and pigs.^{6,7} In such analyses, this gene was associated to *Inc11* plasmids, whereas in the present study further *Inc* groups (*IncF/FII*) were also observed. As for *bla*_{CTX-M-1}, this may indicate that human and animal isolates partially share the same plasmids.¹ The remaining five isolates were cAmpC hyperproducers due to mutations (at -32 or -42) located within the promoter region. These strains are occasionally reported in humans and animals.^{1,12} However, most previous studies implemented methods to detect only the ESBL-*Ec*, probably underestimating the impact of these specific ESC-R-*Ec*.^{5,8,14}

CMY-2- or cAmpC-producing isolates were not clonally related to each other (Figure 1). However, some of these strains were from STs also present among the ESBL-*Ec* (ST648, ST156, ST744). Therefore, identical genotypes have the ability to acquire different genetic backgrounds of resistance and have the potential for dissemination. Indeed, several of them (ST648, ST405, ST410) are well recognized pandemic clones that usually carry CTX-M-15.¹

More surprising is the fact that most of the AmpC producers were responsible for infection in SOC patients (Figure 1). It is probable that in this population there are some factors that contribute to their emergence. For example, in the urology of our institution there is the highest use of β-lactam/β-lactamase inhibitor combinations (70.0 DDD/100 BDs; Table S4, available as Supplementary data at JAC Online); moreover, in our region amoxicillin/clavulanate is more frequently implemented than in other areas.²² These treatments might have some effect in the selection of non-susceptible strains, such as those producing AmpCs.

Conclusions

This is the first Swiss study analysing contemporary ESC-R-*Ec* causing infection in humans. Most ESBL-*Ec* shared common characteristics with those described in other countries (e.g. high prevalence of ST131 producing CTX-M-15). More intriguing is the observation that common clusters of ESC-R-*Ec* have spread transversally among different settings. In particular, the SOCs may play an important role in the expansion of these pathogens because it involves increasing numbers of at-risk outpatients who are constantly referred to healthcare institutions. Since SOC patients may serve as a 'bridge' that favours the spread of ESC-R-*Ec* between the hospital and community (or vice versa), larger

epidemiological studies should be planned to better understand the impact of such pathogens in this setting.¹¹

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Transparency declarations

None to declare.

Supplementary data

Tables S1–S4 are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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