ESBL-producing *Escherichia coli* ST131 versus non-ST131: evolution and risk factors of carriage among French children in the community between 2010 and 2015

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**Objectives:** The objective of this study was to evaluate the evolution and risk factors of ESBL-producing *Enterobacteriaceae* (ESBL-E) carriage in children in the community for a long period distinguishing ST131 and non-ST131 *Escherichia coli*.

**Patients and methods:** In this prospective study, rectal samples were obtained from children aged 6–24 months by community paediatricians between 2010 and 2015. Demographic characteristics and risk factors for ESBL-E carriage were collected. Distribution of β-lactamase genes, phylogenetic groups, ST131 and virulence factors of resistant *E. coli* was determined.

**Results:** We enrolled 1886 children; 144 (7.6%) harboured ESBL-E, and this rate increased from 4.8% to 10.2% between 2010 and 2015. Risk factors for ESBL-E carriage were being cared for at home (adjusted OR (aOR) = 1.8, 95% CI = 1.1–2.9), recent antibiotic use (aOR = 1.5, 95% CI = 1.0–2.1) and travel history (aOR = 1.7, 95% CI = 1.1–2.6). Among patients carrying ESBL, *E. coli* (98%) and CTX-M type (90%) predominated and PapGII adhesin, characteristic of pyelonephritogenic *E. coli* strains, was rare (7%). In 2015, *E. coli* isolates frequently belonged to the phylogenetic group B2 (48%), and 37% were ST131 compared with 5% in 2010. Compared with non-ESBL-producing strains, ST131 carriage was associated with hospitalization in the last 6 months (aOR = 3.5, 95% CI = 1.4–8.8).

**Conclusions:** Between 2010 and 2015, the carriage of ESBL-E in community children doubled because of the massive expansion of the *E. coli* ST131 clonal group. The risk for carrying ST131 was associated with previous hospitalization, but not, contrary to the counterpart, antibiotic treatment, daycare attendance or travel history.

**Introduction**

In the past decade, the emergence of ESBL-producing *Enterobacteriaceae* (ESBL-E), both in nosocomial and community settings, has been one of the most concerning epidemiologic changes in infectious diseases. Carriage of ESBL-producing isolates in the gut flora may serve as a reservoir of resistance genes and has been associated with a high risk for infection caused by ESBL producers.¹ Among Enterobacteriaceae, *Escherichia coli* is becoming the most important species implicated in both community-onset and hospital-associated infections on a global scale.²,³

ESBL genes are spreading rapidly due to the combined expansion of mobile genetic elements and clonal dissemination. They are frequently accompanied by genes encoding resistance to various antibiotic groups, such as aminoglycosides, fluoroquinolones or sulphonamides, which leaves few treatment options. The best example of antibiotic resistance spread is *E. coli* ST131, an MDR clonal group disseminated worldwide. This clonal group has contributed to the dissemination of highly efficient resistance to third-generation cephalosporins because of the *bla<sub>CTX-M-15</sub>* gene and is associated with fluoroquinolone resistance, which explains in part the rapid increase in prevalence of antimicrobial resistance in *E. coli*.⁴,⁵

The rate of faecal carriage of ESBL-E has mainly been investigated in nosocomial outbreaks, in traveller adult patients or in children attending daycare centres; few studies have evaluated...
intestinal carriage in children in the community. In a preliminary study of this issue, we showed that between October 2010 and June 2011, faecal carriage of ESBL-E was 4.6% and was mainly associated with the use of third-generation oral cephalosporins.10 The aim of this study was to investigate for a longer period (2010–15) the evolution in prevalence and the risk factors of community-acquired ESBL-E in microbiota of children aged 6–24 months. The rate of ST131 carriage, phenotypic resistance patterns and the genetic characteristics of ESBL-producing E. coli were also investigated.

Methods

Participants

Between October 2010 and June 2015, 18 French paediatricians located in three regions (Ile de France, Lorraine and Provence–Alpes–Côte d’Azur) took part in this prospective study. A rectal sample was obtained from children aged 6–24 months during routine check-ups with normal findings or when they presented with acute otitis media. This work was an ancillary study of the French nasopharyngeal carriage study performed by ACTIV, a paediatric research network.7,8 The exclusion criteria were antibiotic treatment within 7 days before enrolment and severe underlying disease. Once written informed consent had been obtained, we queried the parents or guardians about the child’s demographics and risk factors for carriage of resistant bacteria, including use of any antibiotics (between 7 days to 3 months before enrolment), daycare attendancemodality, premature birth or caesarean birth, any siblings, previous hospitalization (during the previous 6 months and since birth), travel history and geographical areas visited in the last 6 months.

Ethics

The study was approved by the Saint Germain en Laye Hospital Ethics Committee (10/10/2010–CPP06063). Written informed consent from parents or guardians was obtained.

Microbiology investigations and genetic characterization

On inclusion, rectal samples were taken using a flexible, sterile, soft rayon swab tip. After sampling, the swabs were immediately inoculated in transport medium (Copan, Brescia, Italy) at room temperature and sent within 48 h to the E. coli National Reference Centre-associated laboratory at Robert Debré Hospital, Paris. The rectal swabs were spread on ChromID Enterobacteriaceae (bioMérieux, La Balme-les-Grottes, France).

One colony of each morphological type growing on the medium was identified using the API20E system (bioMérieux, Marcy-l’Etoile, France) (2010–14) and then with the Bruker Biotyper matrix-assisted laser desorption ionization–time of flight mass spectrometer (2014–15). Antibiotic susceptibility was determined using the disc diffusion method on Mueller–Hinton agar and interpreted as specified by EUCAST (http://eucast.org/). Possible evidence of ESBL production was defined as synergy between clavulanic acid and at least one of the extended-spectrum cephalosporins (ceftazidime, cefotaxime or cefepime) or aztreonam.

Multiplex PCR was used to characterize β-lactamase genes (including blaCTX-M, blaVIM, blaTEM, and blaOXA-1) with previously described methods and primers.13 Nucleotide sequences obtained were aligned with GenBank reference sequences by using ClustalX within BioEdit v7.0.5.3 and compared with published sequences in the Lahey database (http://www.lahey.org/studies/). Clonal relationships among E. coli isolates were identified by semi-automated rep-PCR (Diversilab; bioMérieux, Marcy-l’Etoile, France).15 The clonal group ST131 was identified by using DiversiLab as described previously,13,15 with the ST131 strain S242 as a control.13 On B2 strains, we also did allele-specific PCR confirmation of the pabB and trpA alleles to detect those belonging to the pandemic clone O25b-ST131 and used a specific PCR-based method to detect the O16-ST131 clade and to distinguish it from the O25b-ST131 subset.14,15 On isolates belonging to the ST131 clonal group, we amplified and sequenced the fimH allele as previously described.16 Sequences were analysed using BioEdit software using ECOR strains’ sequences as references, which was sufficient to determine all H types.17

Strains were assigned to one of the E. coli phylogenetic groups (A, B1, B2, C, D, E and F)18 or phylogenetic subgroup B2,18 by using a previously described multiplex PCR-based method.19 A PCR-based method was used to screen the strains for 11 genes encoding the following putative virulence factors: fyuA, yersiniabactin; hly, haemolisys; sci/foc, S or F1C fimbriae; papC, P fimbriae; iucC, aerobactin; papG (II and III alleles), P fimbriae adhesins; cnf1, cytotoxic necrotizing factor; iron, salmonchelin; ibeA, invasin; and hra, heat-resistant agglutinigen.

Study groups and statistical analyses

Data were double-entered by using 4D software v12 and analysed by using Stata/SE 13.1 (StataCorp, College Station, TX, USA). Trend tests involved the Cuzick test. The χ2 test was used in univariate analysis to identify potential factors (P<0.2) to be included in multivariate models. Then, we used a logistic regression model, computing ORs and 95% CI, to identify risk factors associated with ESBL-E, ST131 and non-ST131 carriage. Data for travel history were available since 2012. Countries visited were grouped into four geographical regions: African/Mediterranean region (including Algeria, Morocco, Tunisia, African countries, Greece, Croatia, Spain, Portugal, Israel, Italy and Turkey), America, Asia/Oceania and western/northern Europe. When several countries were visited, the longest stay was selected. Children who had not travelled were grouped with western/northern Europe. To analyse the evolution of ESBL carriage, we distinguished five periods: period 1, October 2010–June 2011; period 2, October 2011–June 2012; period 3, October 2012–June 2013; period 4, October 2013–June 2014; and period 5, October 2014–June 2015.

Results

Global results

ESBL carriage was assessed in 1886 children. The mean age was 13.3±5.2 months and 880 (46.7%) were between 6 and 12 months old. The sex ratio was 1.17 (male/female). Overall, 41.9% of the children attended daycare centres, and 30.5% and 27.6% were cared for by a child minder and at home, respectively. In all, 29.6% (362 of 1221) had travelled and 38.2% received antibiotics within 7 days to 3 months before enrolment. Details of geographical regions and antibiotic treatments are in Table 1.

ESBL-E were found in 144 patients (7.6%). Evolution of ESBL carriage by year is shown in Figure 1, increasing from 4.8% (95% CI = 2.9–7.3) to 10.2% (95% CI = 7.5–13.5) from period 1 to period 5, respectively. ESBL-producing E. coli was found in 142 patients (98.6%); 12 patients harboured 2 different strains of ESBL-producing E. coli and 6 a strain of ESBL-producing E. coli and another Enterobacteriaceae species (4 Citrobacter sp., 1 Enterobacter asburiae and 1 Leclercia sp.). Two patients carried only an ESBL-producing Klebsiella pneumoniae strain. We isolated 162 ESBL-E, including 154 E. coli.

Among these 162 isolates, the activity of trimethoprim/sulfamethoxazole and fluoroquinolones was severely compromised, with 54.3% and 36.4% of isolates showing resistance. Resistance to aminoglycosides was 14.8% and 3.7% for gentamicin and amikacin, respectively. Overall, 22.9% were resistant to both trimethoprim/sulfamethoxazole and ciprofloxacin. All isolates were susceptible to imipenem and ertapenem.
Table 1. Analysis of risk factors associated with ESBL-E carriage; overall subjects N=1886 and carriage of ESBL N=144

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Table 1. Analysis of risk factors associated with ESBL-E carriage; overall subjects N=1886 and carriage of ESBL N=144

The ESBL-producing ST131 isolates

Semi-automated rep-PCR analysis (DiversiLab; bioMérieux, Marcy-l’Etoile, France) easily identified isolates belonging to the clonal group ST131, which were closely related to the ST131 control strain S242 (>95% similarity). These results were confirmed using specific PCR methods.14,15 We found a high level of genomic diversity for the 112 non-ST131 isolates because distinct clonal groups (strains sharing >95% similarity) contained no more
than four isolates (Figure S1, available as Supplementary data at JAC Online).

Clonal group ST131 was found in 25.8% (39 of 151) of ESBL-producing E. coli isolates from 2010 to 2015, ranging from 5.0% in period 1 (only 1 of 20 isolates) to 37% in period 5 (Figure 4). Among these, 30 (77%) belonged to the O25b subgroup and 9 (23%) to the O16 subgroup. Regarding \textit{fimH} alleles, all O25b-ST131 isolates contained \textit{fimH}30 except one with a single locus variant of \textit{fimH}30 and all O16-ST131 isolates contained \textit{fimH}41 except one with a single locus variant of \textit{fimH}41. Results of the resistance of isolates belonging to the clonal group ST131 are depicted in Table 2. Of note, ciprofloxacin resistance was found in 100% of O25b-ST131 isolates, whereas only 33% of the O16-ST131 were resistant.

The four major ESBL variants among the ST131 clonal group were CTX-M-1 (10.3%), CTX-M-14 (12.8%), CTX-M-15 (30.8%) and CTX-M-27 (41%). For ST131 strains, the most prevalent virulence genes were \textit{fyuA} (100%) and \textit{iucC} (95%); all other virulence genes were present in 15% of the strains.

On multivariate analysis comparing carriage of non-ST131-ESBL-producing and non-ESBL-producing strains, risk factors identified were children cared for at home (aOR = 1.9, 95% CI = 1.1 – 3.2, \( P = 0.02 \)), travel history (aOR = 2.0, 95% CI = 1.2 – 3.2, \( P = 0.008 \)) and recent use of oral third-generation cephalosporins (aOR 2.3, 95% CI = 1.1 – 4.8, \( P = 0.021 \)). The risk of carrying ST131-ESBL-producing compared with non-ST131-ESBL-producing strains was strongly associated with hospitalization in the last 6 months (aOR = 10.6, 95% CI = 2.0 – 55.7, \( P = 0.005 \)).

Discussion

In the community, faecal carriage of ESBL-E in children in industrialized countries has been rarely reported. The few studies focusing on this problem have been limited in time, geographical region or associated risk factors. Here, we report one of the largest cohorts exhibiting evolution in carriage over a 5 year period, the risk factors and molecular epidemiology of community-acquired ESBL Enterobacteriaceae in infants.

In Europe, in 2010, a Swedish study found a community carriage rate of 2.9% (313 stool specimens) in healthy preschool children.\textsuperscript{21} In 2012, a French study reported a 6.7% carriage rate (28 of 419) in daycare centres.\textsuperscript{22} This rate is similar to the 6.9%
we found for the same year. A 2014 publication from northern Spain reported a 24% carriage rate (30 of 125) in healthy children.\(^5\) In our longitudinal study, we confirmed the gradual increase in carriage of ESBL-E mainly due to \textit{E. coli} in the community.

As expected, we observed that \textit{E. coli} was the Enterobacteriaceae species most prone to harbour ESBL genes, of which the CTX-M types predominated. CTX-M-1, CTX-M-15 and CTX-M-14 were the most prevalent enzymes, which agrees with previous reports.\(^{23,24}\) However, we observed a high increase in prevalence of the CTX-M-27 enzyme. In a recent longitudinal Japanese study, CTX-M-27 was not present in 2005, but represented \(>50\)% of the CTX-M alleles in 2011–12.\(^{25}\) A high proportion of CTX-M-27 has been also reported in different countries.\(^{26,27}\) Among all our ESBL-producing strains, 80\% (16 of 20) of the CTX-M-27 type belonged to the ST131 clonal group. A similar high rate was noted by Matsumura \textit{et al.}\(^{25}\) Therefore, this clonal group may be responsible for the increasing prevalence of CTX-M-27.

Genotyping characterization of our ESBL-producing \textit{E. coli} isolates revealed all phylogenetic groups featuring this mechanism of resistance. As well, we observed high genomic diversity of isolates not belonging to the ST131 clonal groups (found on rep-PCR, DiversiLab), which clearly demonstrates the high capacity for spread of ESBL, particularly CTX-M genes, among different genetic backgrounds. However, the major highly virulent phylogenetic subgroup B2\(_1\) corresponding to ST95 still exceptionally featured this resistance mechanism.\(^{28}\)

To understand better the diffusion of ESBL-producing strains, factors affecting the emergence or evolution of ESBL-E should be identified. In our global analysis, we found three factors significantly associated with increased prevalence of carriage of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Distribution of \textit{E. coli} phylogenetic groups between 2010 and 2015, and details for each period.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Evolution of the distribution of phylogenetic-group B2 isolates and ST131 among ESBL-producing \textit{E. coli}.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Antibiotic & Resistant isolates according to the O group, n (%) & & & \\
\hline
 & O25b (\(N=30\)) & O16 (\(N=9\)) & & \\
\hline
Amikacin & 3 (10) & 0 & & \\
Gentamicin & 8 (26.5) & 0 & & \\
Co-trimoxazole & 16 (53) & 4 (44.5) & & \\
Nalidixic acid & 30 (100) & 7 (77.5) & & \\
Ciprofloxacin & 30 (100) & 3 (33) & & \\
\hline
\end{tabular}
\caption{Antimicrobial resistance of isolates belonging to the ST131 clonal group}
\end{table}
ESBL-E. One factor was travel history in the last 6 months. Countries were grouped into geographical regions. Because the group sizes were heterogeneous, we found no significant association between regions and ESBL carriage. However, carriage was highest for children who had travelled in Asia/Oceania (35.7%; 5 of 14) and the African/Mediterranean region (11.1%; 31 of 279). These results agreed with those found in a recent study focusing on adult travellers returning from tropical regions and acquisition of multiresistant Enterobacteriaceae. Globally, 31.1% (57 of 183), 47.7% (93 of 195) and 72.4% (142 of 196) of travellers returning from Latin America, sub-Saharan Africa and Asia areas, respectively, had acquired ESBL-producing bacteria.29 These high rates of travel acquisition suggest a high prevalence of ESBL-E faecal carriage in southern countries and is corroborated by several studies identifying 23%–64% of children carrying ESBL-producing bacteria in community settings in non-industrialized countries.30,31

Another factor associated with ESBL-E carriage was children cared for at home. This surprising result agrees with a recent study from Spain, finding that children not attending a nursery school had the highest rate of ESBL carriage,5 but disagrees with findings from an older European study.21 One possible hypothesis is that children in contact with other children could have more chance of renewing their intestinal flora with interpersonal and interchildren contacts and thus more chance of exchanging their ESBL-producing strains for susceptible strains. This renewal of the microbiota is less likely to occur in children cared for at home, who are in contact with only their parents or siblings, particularly if family contacts may also carry resistant strains (particularly travellers). Moreover, intra-family spread of ESBL-E has been reported previously.12

A final factor associated with ESBL-E carriage was antibiotic use in the previous 3 months. In our previous study (2010–11), risk of ESBL carriage was associated with recent use of oral third-generation cephalosporins.6 The French recommendations for acute otitis media treatment changed at the end of 2011.53 Since then, amoxicillin has become the first-choice treatment and use of oral third-generation cephalosporin concomitantly decreased, from 33% in 2010 to 5% at the end of 2012.34 The major modification of types of antibiotics prescribed may explain in part the decrease in ESBL carriage between period 2 and period 3 in our study. However, the potential beneficial effect was transient, and the proportion of ESBL carriers increased between the last two periods of the study. Finally, carriage of ST131 strains, not associated with antibiotic use and that predominated during the last period, may explain the re-ascent of carriage of ESBL-producing strains.

The clonal group ST131 represented 25.8% of the ESBL-producing E. coli from 2010 to 2015, with a high increase in this rate leading to 37% carriage (17 isolates) in 2015. The ST131 clonal group is an efficient colonizer,35 so antibiotic selective pressure may not be essential to favour its implantation and dissemination. Of interest a very recent study found that excretion of ciprofloxacin-resistant E. coli in stool specimens of twins and their mothers (mainly ST131 E. coli) was not associated with previous antibiotic use.36 In contrast to carriage of their counterpart, that of ST131-ESBL-producing E. coli was significantly associated with previous hospitalization, which suggests that this clonal group is actively disseminated in the hospital environment. A previous study found a higher nosocomial transmission rate of CTX-M-27- than CTX-M-15-producing ST131 strains in a rehabilitation ward.26 Other paediatric studies reported various proportions of ST131 carriage. In 2012, a French study conducted in the south of France in childcare centres reported 44% (12 of 27) of ST131-ESBL-producing E. coli in intestinal colonization, but this finding was mainly due to local dissemination in one centre.22 Indeed, without this local dissemination, the rate of ST131-ESBL-producing E. coli in this population was 28%, a rate similar to our study.

ST131-ESBL-producing E. coli may be responsible for infections. For example, in Taiwan, up to 65% of the 111 isolates found in community-acquired urinary tract infections in children caused by ESBL-producing E. coli between 2009 and 2012 were of the ST131 group,37 but this rate was 33% between 2008 and 2012 in a French study.38 As in other studies, our ST131 strains harboured few virulence factors. In particular, no strains contained the PapGII adhesin. Fortunately, this adhesin is also rare in other ESBL-producing E. coli and may explain why urinary tract infections due to ESBL-producing E. coli are still rare in children without urinary tract abnormalities. Among this collection of ST131-ESBL-producing E. coli, the majority belonged to the O25b subgroup with 100% of isolates resistant to fluoroquinolones and 53% to co-trimoxazole, which is consistent with previous studies.15,39 Surprisingly, we also found 23% of the isolates to be O16-ST131. This O16 subset is broadly distributed, but occasionally described producing ESBL.15,39

Our study has some limitations. The travel countries were grouped to have a substantial number of children in each group, which decreased the information for individual countries. Only children between 6 and 24 months old were included, and no samples were taken from other family members. Finally, sampling involved a rectal swab, which only allowed for detection of the dominant clone, so we may have missed minority clones.

In conclusion, this large and timely extended multicentre study of children in a community setting identified a 2-fold increase in ESBL-E carriage in 5 years, in France. Several changes during the study period were observed: the distribution of the CTX-M-variant, phylogenetic group distribution between E. coli and an increase in ST131-ESBL-producing E. coli strains. Moreover, the risk factors associated with ST131 carriage were not identical to that of non-ST131 resistant strains, which suggests that infection control measures may be adapted to the genetic background of the strain.

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Transparency declarations
None to declare.

Supplementary data
Figure S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References

ESBL carriage in children 2010–15

JAC

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