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Title: **The prevalence and transmission dynamics of *Escherichia coli* ST131 among contacts of infected community and hospitalized patients**

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Abstract

Objectives: The *E. coli* O25b-associated ST131 clonal group was recently found to be prevalent in our area as a cause of community-acquired UTIs. We evaluated the transmission dynamics and longitudinal persistence of *E. coli* O25b-ST131 between patients with nosocomial and community-acquired infections and their contacts.

Methods: Prevalence and transmission of O25b/*pabB*3/$B2_3$ isolates were compared in 38 community clusters, 30 nosocomial clusters and 50 healthy volunteers. Duration of colonization was studied at 1 to 4 months and 6 to 12 months after the first sample. Isolates exhibiting a ≤ 3-band difference by PFGE were assigned to the same pulsotype.

Results: Colonization was found to be more frequent in index cases (31/68, 45.6%) than in contacts (25/118, 21.2%; p=0.0009) or volunteers (1/50, 2%; p=0.0009). Seven of 64 (11%) isolates were ESBL producers. Transmission ocurred in 61% (8/13) community clusters and in 12% (1/8) nosocomial clusters. Thirteen (56.5%) of the 23 initial carriers assessed at 1-4 months remained colonized. Only 2 (13.3%) of 15 positive patients followed for 6-12 months showed prolonged carriage, and none was ESBL producers. Six previously positive individuals acquired a different ST131 pulsotype (5/23 at sample 2 and 1/15 at sample 3) and 3 previously negative individuals became positive (2/46 at 1-4 months and 1/33 at 6-12 months).

Conclusions: Person-to-person transmission or acquisition from a common source of *E. coli* O25b-associated ST131 is more frequent in the household setting than in the nosocomial. The carrier state does not usually last beyond 4 months, with new acquisitions in certain individuals.

Introduction

The increase of resistance to fluoroquinolones and cephalosporins in *Escherichia coli* in recent years is partially due to the worldwide dissemination of a single clonal complex: *E. coli* O25b:H4/ST131.[1] Resistance traits such as quinolone resistance and CTX-M production seem to be specifically associated with the subgroup or lineage possessing the *fimH*30 allele (clade C/H30-Rx).[2] Other lineages of this clone are less prevalent.[3] *E. coli* sequence type ST131 derives from phylogenetic group B2, exhibiting virulence factors typical of extraintestinal pathogenic E. coli.[1,4,5] His antibiotic resistance pattern considerably limit the treatment of community-acquired urinary tract infections (UTIs) caused by these isolates, although invasive infections caused by this clone have also occurred.[6]

This clone has been associated with healthcare and long term facilities[7,8] and household spread has also been documented.[9] The *E. coli* ST131 clonal group was recently found to be prevalent in our area, although only 7% of those isolates were ESBL producers.[6] Because most studies have been performed on ESBL producers, the role of non-ESBL-producing *E. coli* ST131 has been underestimated. Few studies analyzing colonization with *E. coli* ST131 in healthy individuals have been performed and the duration of intestinal carriage is unknown. The aim of this study was to characterize the transmission dynamics and longitudinal persistence of *E. coli* O25b-associated ST131 in patients with nosocomial and community-acquired infections.

Methods

The study was performed between April 2011 and April 2013 in the health area (500,000 inhabitants) of the Hospital Universitario Virgen Macarena, a 900-bed tertiary hospital in the northern area of Seville.

First, a prevalence study of fecal colonization with *E. coli* ST131 was performed among the following groups of individuals: (a) patients attending the emergency room with *E. coli* ST131 isolates from clinical samples who had not been hospitalized during the previous month ("index community patients"); (b) all available adult household members of index community patients ("community contacts"); (c) admitted patients with *E. coli* ST131 isolates from a clinical sample ≥72 hours after hospital admission ("index nosocomial patients"); (d) up to 6 hospital contacts of the index nosocomial patients, defined as roommates, if any, and those admitted to the nearest rooms and attended by the same team of nurses ("nosocomial contacts"); and (e) healthy volunteers (acquaintances and relatives of the researchers without previous hospitalization or antibiotic consumption). Colonization status among index community and nosocomial patients and their contacts was evaluated within 7 days of diagnosis of infection. Second, all individuals were asked to participate in a longitudinal study of colonization status at 1 to 4 months (sample 2) and 6 to 12 months (sample 3) after the first sample. Each index case (community or nosocomial) and his/her contacts were considered a cluster.

The Hospital University Virgen Macarena Review Board approved the study; written informed consent was obtained from all participants. To avoid bias, all studied individuals as well as researchers, were blinded with regard to colonization status.

To detect the "index" patients infected with ST131 *E. coli*, all clinical *E. coli* isolates recovered from clinical samples in hospitalized patients and those attended to in the emergency room were screened for the ST131 clone using specific PCR for O25b *rfb*[4], allele 3 of the *pabB* gene[10] and for the B2 phylogroup.[11]

For fecal carriage studies, rectal swabs were inoculated onto Brilliance™ UTI agar, MacConkey agar containing 4mg/l cefotaxime, and a blood agar plate as a control. All distinct morphotypes (at least 4-5 different colonies per sample were studied from the UTI medium and all morphotypes from the selective medium) were selected for further analysis and identified using biochemical tests (positive β-galactosidase reaction and indole test). All *E. coli* identified from rectal samples were screened for O25b/*pabB*/B2. Both clinical and rectal third-generation cephalosporin-resistant isolates were screened for ESBL production by the double-disk synergy test.[12] bla_{ESBL} genes were characterized by PCR and sequencing.[13] Further antibiotic susceptibility tests were performed using broth microdilution procedures, according to CLSI recommendations and CLSI 2013 breakpoints.[12, 14] Clonal relationship was determined for all *E. coli* ST131 isolates by pulsed field gel electrophoresis (PFGE) analysis with *Xba*I (http://www.pulsenetinternational.org/protocols/pfge.asp). PFGE patterns were analyzed using Fingerprinting 3.0 software (Bio-Rad), using the Dice coefficient. Isolates exhibiting a ≤ 3-band difference were assigned to the same pulsotype (≥ 90% similarity).[14] 4-6 bands of difference were considered to be clonally related (89-80% similarity) and those with >6 bands were considered unrelated.

The prevalence of carriage was calculated as the percentage of carriers among participants in each group. For independent samples, categorical variables were

compared using the χ^2 or Fisher's exact test as appropriate, and continuous variables using the Mann–Whitney *U*-test. Data were analyzed using PASW Statistics version 18.0 (IBM SPSS Inc., Chicago).

Results

Prevalence study

The total number of patients tested during the study period is shown in Figure 1. Screening yielded 223 (14%) positive patients, 68 of whom agreed to participate: 38 index community patients, 64 household contacts (median per index case: 2; range, 1 to 4; no-contact patients were included from 4 index cases who lived alone), 30 index nosocomial patients, 54 hospital contacts (median per index case: 2; range, 1-6) and 50 healthy volunteers. Among the index community and nosocomial cases, *E. coli* ST131 was isolated from urine in 43 patients, wound exudate in 13, and blood cultures in 12 patients.

Sixty four *E. coli* ST131 isolates overall were recovered from rectal swabs from 58 individuals (6 individuals had two different *E. coli* ST131 strains). Seven isolates (7/64, 11%) were ESBL producers (harboring 5 $bla_{\text{CTX-M-15}}$ and 2 $bla_{\text{TEM-150}}$). Antimicrobial resistance analysis of ST131 isolates showed that 55 (86%) were resistant to amoxicillin/clavulanate, 44 (69%) to ciprofloxacin, 3 (4.7%) to fosfomycin, 12 (19%) to gentamycin, 22 (34%) to tobramycin and 1 (1.6%) to amikacin.

The prevalence of fecal carriage of ST131 in the first sample (within 7 days of diagnosis of infection in the index case) was 30% among index patients and their contacts (56/186) but distributed heterogeneously across subgroups (Table 1): 17/38 (44.7%) in index community cases; 14/30 (46.7%) in index

nosocomial patients; 17/64 (27%) in community contacts; and 8/54 (14.8%) in nosocomial contacts. The prevalence was 2% (1/50 person) among healthy volunteers. Overall, colonization was more frequent in index cases than in their contacts (31/68 vs. 25/118; p=0.0009), and in contacts more than in healthy volunteers (25/118 vs. 1/50, p=0.0009). The prevalence among contacts was somewhat higher in community than nosocomial contacts (p=0.08). There was a non-statistically significant trend in fecal carriage among contacts of index patients who were and were not carriers: fecal carriage was 32% (10/31) and 21% (6/21) among community contacts, and 11% (3/27) and 20% (5/25) among nosocomial contacts, respectively (p=0.3 by Fisher's test).

Clonal relatedness between the clinical and rectal isolates of the 31 index patients who were fecal carriers was analyzed (only 17 of 34 community-acquired cases and 14 of 30 hospital cases were found to be rectally colonized by ST131 strains at the time of sampling). At least one rectal isolate had the same pulsotype as its corresponding clinical isolate in 29 (16/17 community patients and 13/14 hospital patients, 94%) cases, with no differences between community and nosocomial cases. Additionally, in one case, the clinical and rectal isolates were clonally related but did not belong to the same pulsotype (4 bands of difference), and in one case they were unrelated.

With regard to the clusters, more than one member was colonized by ST131 in 13/34 (38.2%) community clusters (4 of the 38 community index cases lived alone and were excluded from the analysis) and 8/30 (26.7%) nosocomial clusters (p=0.33) (Figure 1). Based on PFGE results, transmission or common acquisition of ST131 was shown in 8/34 (23.5%) community clusters and 1/30 (3.3%) nosocomial clusters (p=0.03).

190

191 Longitudinal fecal carriage study

192 During the study period, a second sample was obtained from 69 individuals:
193 14/38 (37%) index community patients, 31/64 (48%) household contacts, 11/30
194 (37%) hospitalized index patients and 13/54 (24%) roommates. A third sample
195 was also obtained from 48 individuals: 9/38 (24%) community patients, 22/64
196 (34%) household contacts, 11/30 (37%) hospitalized patients and 6/54 (11%)
197 roommates. Volunteers were not included in the longitudinal study.

198 The overall prevalence of colonization with ST131 in the second sample was
199 27.6% (19/69) (Table 1); with respect to the first sample, prevalence had
200 decreased somewhat among the index patients but not among their contacts.
201 Globally, 13 out of 23 (57%) initial carriers remained colonized with the same
202 ST131 pulsotype. The rate of ST131 acquisition was 10.1% (7/69): 5 initially
203 ST131-positive individuals had new pulsotypes and two initially negative
204 hospitalized patients became colonized. The two hospital cases who were
205 previously non-carriers had both been roommates of an index nosocomial
206 patient and the pulsotype of the acquired ST131 was different from the index
207 case isolate.

208 With respect to sample 3, the overall prevalence of ST131 colonization was
209 8.3% (4/48). Only 2 of 15 (13.3%) previously positive patients studied showed
210 prolonged carriage. Two individuals acquired ST131: 1 (6.7%) of 15 who was
211 previously positive had a new pulsotype and 1 (3%) of 33 previous non-carriers.
212 In total, nine individuals acquired ST131 strains over the study period.

213 With respect to ESBL producers, 3 ESBL-producing ST131 isolates were
214 obtained from the second sample (Table 2) and none from the third sample.

Discussion

To the best of our knowledge, this is the first study to analyze the fecal carriage and spread of *E. coli* O25b-ST131 between patients with infection and their contacts in two different settings: hospitals and households. Within households, sharing *E. coli* ST131 strains has been documented previously; most previous reports have referred to sporadic cases[15,16] or to ST131 strains shared by companion animals and household members.[17] Other studies of *E. coli* ST131 carriers investigated isolates with resistance characteristics, which may not reflect the epidemiological behavior of all *E. coli* ST131.

The main findings of the study were: (1) the rectal colonization rate among index patients was lower than expected (around 45%); (2) the prevalence of colonization was higher among index and contact patients than among healthy volunteers; (3) sharing of specific ST131 pulsotypes was more frequent in households than in the nosocomial environment; (4) the duration of colonization was at least 1-4 months in around half the colonized patients; and (5) new ST131 isolates were occasionally acquired, most frequently among persons who had previously been carriers.

The prevalence of colonization among index patients was lower than expected. Two previous studies have investigated household members of patients with infections due to ESBL-producing *E. coli* (belonging to ST131 was not studied);[18,19] and both showed a higher proportion of colonized index patients (around 70%). Higher rates of rectal colonization with the infecting strain were also found in women with cystitis;[20] on the other hand, a similar rate to ours was found in a study of UTI in febrile men with pre-therapy urine and rectal

240 samples.[21] The reason for the lower colonization rate in our study is not clear.
241 Our detection procedure, based on direct plating on unselected medium, could
242 be less sensitive than others which included an enrichment step[18] or selective
243 media.[19] It is also unknown whether empirical treatment could have eradicated
244 colonization in more patients than in previous studies, which focused on ESBL
245 producers. The prevalence of ESBL-producing ST131 in our study was similar
246 to the rate found in a previous national study in 2009 (10%)[22] and slightly higher
247 than the one detected in a previous local study performed in 2010 (6.8%).[6]
248 We found that colonization was much more prevalent among the contacts of
249 both index community and nosocomial patients than among healthy volunteers.
250 Since sharing a common pulsotype was more common in households, and
251 longer duration of colonization was observed, our results suggest that person-
252 to-person transmission or acquisition from a common source is more frequent in
253 the household setting than in the nosocomial. This would imply that relatively
254 close contact is needed for ST131 acquisition. We hypothesize that the similar
255 prevalence of colonization among contacts of index patients not found to be
256 carriers and relatives of index patients who were carriers implies that the index
257 patients in the former group had been carriers before the sample was taken.
258 Our findings are similar to those of previously mentioned studies of ESBL-
259 producing *E. coli* carriage (irrespective of sequence type) in the community,
260 which found higher rates of colonization among household members of index
261 patients than among non-household members.[18,19] On the other hand, it seems
262 that standard precautions in hospitals prevent the transmission of ST131 in
263 most cases; this is also consistent with studies that found low rates of ESBL-
264 producing *E. coli* transmission among hospitalized patients, even when contact

265 precautions were not used.[23,24] Studies focused on ESBL-producers (including
266 isolates belonging to ST131) in nursing homes suggested that behavior was
267 more like households than hospitals.[25] A mathematical model showed that
268 avoiding person-to-person transmission was more efficacious than reducing
269 exposure to antibiotics.[26]
270 To our knowledge, longitudinal persistence of ST131 isolates has been
271 previously explored only in one household with two clinical cases of pediatric
272 UTI infection;[9] six members of a family with an index case infected with ESBL-
273 producing ST131 were followed for 19 weeks. Our study provides data obtained
274 from systematically following colonization of all types of ST131 over a long
275 period (up to 1 year). Outstanding findings are the rapid dynamics of ST131
276 with a short period of colonization (56.5% remained positive with the same
277 pulsotype after 1-4 months and 13.3% after 6-12 months) and occasional
278 acquisition of new ST131 pulsotypes. This can be compared with persistence in
279 returned travelers; in one study, fluoroquinolone-resistant *E. coli* was detected
280 after 5 months in a 6-month follow-up[27] and ESBL producers after more than 6
281 months in a 3-yr follow-up.[28] The fact that acquisition of new ST131 pulsotypes
282 was more frequent among those previously colonized is intriguing and deserves
283 further study.
284 There are several limitations to this study that should be considered: the
285 sensitivity of the techniques used for detecting carriage of ST131 was not
286 known; only a limited number of persons could be followed in the longitudinal
287 study; healthy volunteers were not properly matched with cases in order to so
288 they could serve as controls, and lack of information about other ST131 *E. coli*
289 clones not associated with serotype O25b. Comparison of carriage among the

population groups studied here may have been affected by factors not taken into consideration. These include gender, age group and any underlying illnesses. In particular, we did not have data on antibiotic treatment. Antibiotic usage in a period previous to testing would likely have affected the colonization or carriage status of both patients and contacts (but not healthy controls, who had not received antibiotics). Additionally, the study was performed in a single health area, so that our results may not extrapolate to other areas with a different ST131 epidemiology.

On the other hand, our results provide data that are helpful for deciphering the epidemiology of ST131 transmission. More studies to identify the epidemiological determinants of ST131 transmission in households (potential environmental reservoirs, hand contamination after contact, etc.) are needed.

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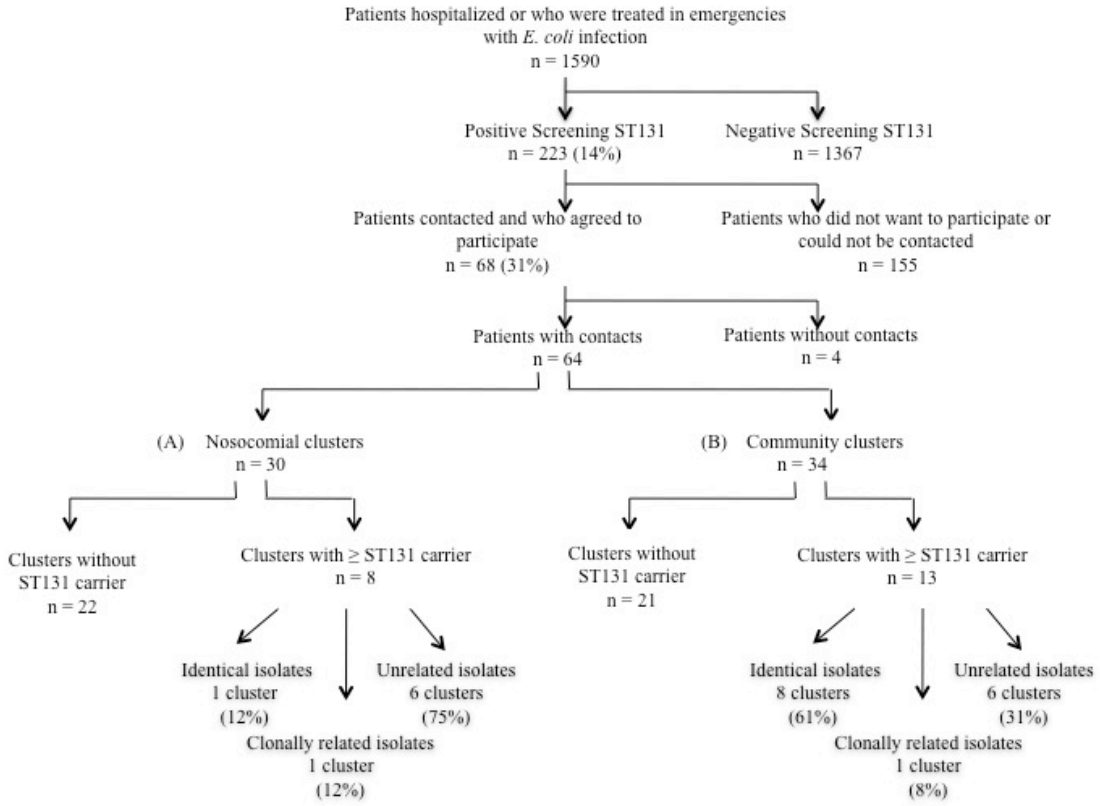
420 **Figure 1.** Workflow of patient selection and genetic relatedness by *XbaI* PFGE
421 of *E. coli* O25b/ST131 isolated from rectal swabs and clinical samples in
422 nosocomial (A) and household (B) settings (in clusters).

423



424

425 **Table 1.** Prevalence of ST131 *E. coli* carriage in index patients and their contacts at different sampling times.

	Cases				Contacts					
	Community		hospitalized		Community		Hospital		Total	
Sample 1 (0-7 days)	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**	**No.**	**(%)**
Total studied	38		30		64		54		186	
Positive	17	(44.7)	14	(46.7)	17	(26.6)	8	(14.8)	56	(30.1)
Sample 2 (1-4 months)										
Total studied	14		11		31		13		69	
Previously positive	6		6		9		2		23	
Positive sample 2	5	(83.3)	3	(50.0)	8	(88.9)	1	(23.1)	17	(73.9)
Same pulsotype as sample 1	5	(100.0)	3	(100.0)	5	(62.5)			13	(76.5)
Different pulsotype from sample 1	1*	(20.0)			3	(37.5)	1	(100.0)	5	(29.4)
Previously Negative	8		5		22		11		34	
Positive sample 2	0				0		2	(18.2)	2	(5.9)
Sample 3 (6-12 months)										
Total studied	9		11		22		6		48	
Previously positive	4		6		4		1		15	
Positive sample 3	1	(25.0)	2	(33.3)	0		0		3	(20.0)
Same pulsotype as sample 1	1	(100.0)	1	(50.0)					2	(66.7)
Different pulsotype from sample 1			1**	(50.0)					1	(33.3)
Previously negative	5				18		5		28	
Positive sample 3					1	(5.6)	0		1	(3.6)

*1 This community case was doubly colonized with the initial ST131 strain and a second different ST131 strain.

**This nosocomial patient was a ST131 carrier in the first sample, negative in the second, and was found to carry an unrelated ST131 in the third.

Table 2. Comparison of ESBL-producing *E. coli* detected in Sample 2.

	Rectal sample result		
Type of individual	**Sample 1**	**Sample 2**	**Comparison with index clinical isolate**
Cluster 11			
Hospital case	non ESBL ST131	Negative	
Roommate 1	Negative	Negative	
Roommate 2	Negative*	CTX-M-15-producing ST131	Different
Cluster 16			
Community case	Negative	Negative	
Contact 1	CTX-M-15-producing ST131	CTX-M-15-producing ST131	Different
Contact 2	non-ESBL ST131	non-ESBL ST131	Different
Cluster 27			
Hospital case	TEM-150-producing ST131	SHV-12-producing ST131	Identical
Roommate 1	Negative	Negative	
Roommate 2	Negative	Negative	

*This patient was colonized by a non-ST131 CTX-M-1-producing *E. coli* belonging to D2 group.