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Prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in community-onset urinary tract infections in France in 2013

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Running title: ESBL-positive *E. coli* in UTI in France

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Abstract

Objectives. We sought to assess the importance of extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae in urinary tract infections in outpatients in France.

Methods. Retrospective laboratory based survey analysing susceptibility patterns of *Escherichia coli* and *Klebsiella pneumoniae* isolates providing from urines collected from outpatients during three months in 2013.

Results. 499 laboratories collected data on 51,643 *E. coli* and 3,495 *K. pneumoniae* isolates. The overall proportion of ESBL-producing *E. coli* was 3.3%. The proportion was higher for males (4.8%) than for females (3.0%) and increased with age: 2% for patients <20 years to 5.4% for those aged >80 years. More than 95% of isolates we susceptible to cefixime, fosfomycin, and nitrofurantoin. In nursing homes, the ESBL-producing *E. coli* proportion was 12.1%. For *K. pneumoniae*, the proportion of ESBL-positive isolates was 6.6%, and this proportion increased with age. Data from 2010 collected from a subset of the network showed that the ESBL-producing *E. coli* proportion was 2.0%.

Conclusion. ESBL-producing isolates were rather frequent in urines in French outpatients in 2013. Males and persons residing in nursing homes were at higher risk of ESBL-positive infection. Despite the increase in ESBL-positive isolates, the susceptibility to antibiotics used to treat cystitis remains high.

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Introduction

The worldwide rise of antimicrobial resistance conducted many countries to develop national plans to control this public health threat.[1,2] After promising results of its first plans, France is currently in the middle of its third antibiotic sparing plan.[3] In a majority of these plans, surveillance of antibiotic resistance is recognised as a core issue. The goals for such surveillance have been listed elsewhere. [4] In particular, surveillance data should help in establishing guidelines for empirical treatment when antibiotic susceptibility tests results are not yet available or will not be performed. In addition, up-to-date data are of interest to assess the accuracy of already published guidelines.

Urinary tract infections (UTI) are among the most common bacterial infections that are treated in the community by an empirical antibiotic treatment regimen. In many countries, it is currently not recommended to perform urinalysis for cystitis before treatment, and the choice of the antibiotic regimen relies on the epidemiology of antibiotic resistance. *Escherichia coli*, which is a commensal species of the digestive tract, is the most common bacterial species isolated in UTI. The increase in resistance of *E. coli* to extended-spectrum cephalosporins (ESC) is now well documented, and is mainly due to the production of extended-spectrum beta-lactamase (ESBL) in the hospital setting as well as in the community.[1,5] In France for instance, there has been a 10-fold increase in the digestive carriage of ESBL-producing *E. coli* in the community in the last years.[6] The increase in ESBL-producing *E. coli* makes the treatment of community-onset UTI more complex because such isolates are usually multidrug-resistant, which increases the risk of treatment failure.[1,2,7] In addition, treating ESBL-positive infection is more costly that treating their susceptible counterpart.[7] Therefore, it is of interest to gather up-to-date data on the prevalence of antibiotic resistance of *E. coli* isolated from UTIs in the community.

Our main objective was to assess the prevalence of ESBL-producing *E. coli* amongst all *E. coli* isolated from urine samples in the community in ambulatory care in 2013. Data on

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Klebsiella pneumoniae the second most frequent Enterobacteriaceae isolated in community-acquired UTIs and data from patients in nursing homes were also collected for comparison purposes.

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Materials and methods

Laboratories

Private practice laboratories participating in one of the three pre-existing networks (Epiville, MedQual-ville, Aforcopi-Bio) of the national observatory for epidemiology of bacterial resistance to antibiotics (ONERBA), and to a fourth network previously set-up for other purposes than surveillance of bacterial resistance (BPR network) were asked to participate on a voluntary basis. A special attention has been paid to national coverage of the network. A total of 499 private practice laboratories distributed throughout metropolitan France, and that referred urines clinical samples to 43 bacteriological centres participated into the network.

Bacteriology

Laboratories participating in this new network called « ONERBA-Ville » complied with national recommendations regarding antibiotic susceptibility testing (www.sfm-microbiologie.org), which are very similar to EUCAST recommendations (http://www.eucast.org/ast_of_bacteria), derived from ONERBA's recommendations for surveillance of bacterial resistance.[4,8]

Antibiotic susceptibility test methods were chosen locally and included liquid media automated systems (n= 35 for Vitek-2, BioMérieux; n=4 for BD Phoenix system, BD Biosciences; n=4 for Microscan WalkAway, Siemens Healthcare diagnostics) and the disk diffusion method (n=6). ESBL-production was determined according to national recommendations as described elsewhere. [9]

Isolates were considered susceptible to tested antibiotics by using the following breakpoints: ≤4/2 mg/L for amocicilline/clavulanate, ≤1 mg/L for cefixime, ≤0.5 mg/L for ciprofloxacin, ≤32 mg/L for fosfomycin, ≤64 mg/L for nitrofurantoin, and ≤2/38 mg/L for cotrimoxazole.

Database

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Data were retrospectively collected for each *E. coli* or *K. pneumoniae* strain isolated from urines routinely collected for diagnosis of community-onset urinary tract infections in outpatients or those in nursing home during September to November 2013. Data included patient's age, gender, and susceptibility tests results including ESBL production. In case of duplicates, only the first isolate was retained for the study. Whenever possible and for comparison purpose, similar data were collected for 2010.

Data analysis

Data have been analysed by using STATA 11 (StataCorp, College Station, TX, USA). Fisher's exact test was used to compare proportions. The Chi2 test for trend has been used to assess the impact of age on the proportion of ESBL-producing isolates. A p-value < 0.05 was considered as statistically significant.

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Results

E. coli isolated from outpatients in 2013

Data on 51,463 *E. coli* isolates were collected from urine samples of outpatients during the 3-month study period. The median age of the patients was 60 years and 86.4% were females. Among all isolates, 1,694 (3.3%) were ESBL-positive. Patients with ESBL-producing isolates were older (median, 70 years) than those with ESBL-negative isolates (median, 60 years; p<0.001). The proportion of ESBL-producing *E. coli* was higher in males (4.8%) than in females (3.0%, p<0.001). The proportion of patients harbouring ESBL-producing isolates increased with age (Table 1): from 2.0% among patients under 20 years, to 5.4% among those over 80 years (p<0.001, chi-square test for trend). This significant trend was observed after stratified analysis by gender (Table 1).

As expected, ESBL-producing isolates were significantly less frequently susceptible to antibiotics than ESBL-negative isolates: 22.7% against 67.6% for co-amoxiclav, 47.5% *versus* 80.8% for cotrimoxazole, 44.0% against 91.0% for ciprofloxacin, 4.0% against 98.0% for cefixime, 93.7% against 98.9% for fosfomycin, 95.4% against 98.9% for nitrofurantoin (Table 2). Overall, 6.0% of the isolates were resistant to at least 3 of the 6 drugs.

E. coli isolated in nursing homes in 2013

A subset of 17 technical centres analysing samples for 237 laboratories provided data on 908 *E. coli* isolates from patients located in nursing homes during the study period. The median age of patients in nursing homes (88 years) was higher than for outpatients (60 years; p<0.001). The proportion of ESBL-producing isolates was higher in nursing homes in 2013 (12.1%) than in outpatients (3.3%; p<0.001). Of interest, the proportion of ESBL-producing isolates in nursing homes, did not differ significantly according to gender (14.0% in males *versus* 11.7% in females; p=0.5). The percentage of susceptibility to ciprofloxacin was lower for *E. coli* isolated in nursing homes than for those from outpatients for isolates taken as a

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whole (73.8% *versus* 89.5%, respectively; p<0.001) or when considering only ESBL-producing isolates (17.4% *versus* 44.0%, respectively; p<0.001).

K. pneumoniae isolated from outpatients in 2013

A subset of 41 technical centres analysing samples for 493 laboratories provided data on 3,495 *K. pneumoniae* isolates from outpatients. Patients harbouring *K. pneumoniae* were older than those harbouring *E. coli* (median, 67 *versus* 60 years; p<0.001), and were more frequently male (17.8% *versus* 13.6%; p<0.001). The proportion of ESBL-producing *K. pneumoniae* was 6.6% as compared to 3.3% for *E. coli* (p<0.001). As for *E. coli,* the proportion of ESBL-producing *K. pneumoniae* was higher among males than females (11.6% *versus* 5.6%; p<0.001), and increased with age (Table 1). Regarding antibiotic susceptibility (Table 2), *K. pneumoniae* isolates were significantly less frequently susceptible than *E. coli* isolates to cefixime (93.2% *versus* 95.0%), fosfomycin (74.4% *versus* 98.7%), and nitrofurantoin (71.0% *versus* 98.8%). On the contrary, *K. pneumoniae* isolates were significantly more susceptible than *E. coli* isolates to ciprofloxacin (91.2% *versus* 89.5%), and cotrimoxazole (88.4% *versus* 79.6%). Overall, 5.9% of the isolates were resistant to at least 3 of the 5 drugs.

E. coli isolated from outpatients in 2010

A subset of 27 centres analysing samples for 222 laboratories provided data on 15,658 *E. coli* isolates from outpatients from September to November 2010. The proportion of ESBL-producing isolates was 2.0% in 2010 as compared to 3.3% in 2013 (p<0.001). The proportion of ESBL-producing isolates increased with patients' age in 2010, 1.5% before 60 years old to 2.6% in patients over 60 years (p<0.001). Overall, isolates were significantly more susceptible to cefixime and cotrimoxazole in 2010 (96.5% and 82.9%, respectively) than in 2013 (95.0% and 79.6%, respectively; p<0.001 for both comparisons). Isolates were slightly less susceptible to fosfomycin in 2010 compared to 2013 (97.7% and 98.7%, respectively;

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$p<0.001$). The susceptibility to ciprofloxacin and nitrofurantoin was similar in 2010 and 2013. The susceptibility of ESBL-producing isolates to these antibiotics didn't change between 2010 and 2013.

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Discussion

We conducted a retrospective survey on the proportion of ESBL-producing *E. coli* and *K. pneumoniae* isolated from urines of ambulatory or nursing home patients in 2010 and 2013. We showed that the proportion of ESBL-producing isolates was rather high and increased with age, was higher for males as compared to females and increased since 2010. Nevertheless, the proportions of susceptible isolates remain elevated for most antibiotics used in the treatment of uncomplicated *E. coli* UTI.

The 3.3% proportion of ESBL-producing *E. coli* in urine samples in France in 2013 is lower than what was reported in numerous European countries such as Spain (7,6%) Italy, United-Kingdom and Germany (all circa 6%) between 2008 and 2011.[10–13] On the opposite, a lower proportion (1.7%) of ESBL-producing *E. coli* was reported from outpatients in Switzerland in 2009-2010.[14] These differences may be explained by variations in populations surveyed, use of systematic urinalysis for UTI diagnosis, or by levels of antibiotic use in the community.[14,15]

We report a significant increase in the proportion of ESBL-producing *E. coli* from 2010 to 2013. This is in accordance with previous findings in France showing that the proportion of ESBL-producing *E. coli* was 0.3% in 1999 and 1.1% in 2006.[5,16] In addition, during the same period of time, there was a 10-fold increase in the prevalence asymptomatic carriers of ESBL-producing *E. coli* in the community.[6] However, these studies have been conducted with different methodologies, and comparisons should be interpreted with caution. The significant upward trend in ESBL-producing isolates with age as been previously reported.[17,18] In addition, we confirmed that men have a higher risk of ESBL-positive infections than women.[18,19] These findings underline the importance of age and gender stratification for correct interpretation of resistant data and for comparisons between populations in different settings. It suggests also that guidelines for the treatment of UTI should be adapted to age and gender.

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Antibiotic susceptibility

Despite the rise of ESBL-producing isolates, *E. coli* and *K. pneumoniae* isolates remain highly susceptible to fosfomycin, and nitrofurantoin, two drugs for which susceptibility rates were not affected by ESBL production. These data reinforce the 2014 French guidelines for empirical treatment of uncomplicated UTI, which recommend fosfomycin as first line drug and nitrofurantoin as an alternative.[20,21] Desperately, we could not gather data regarding pivmecillinam, which is recommended in the French guidelines. However, a high rate of clinical failure has been reported recently for the treatment of ESBL-producing isolates with this drug.[22] We report that 95.0% of all *E. coli* isolates were susceptible to cefixime. However, this third generation cephalosporin is currently not recommended for the empiric treatment of simple UTI mainly because of its ecological impact. In addition, the activity of cefixime is highly susceptible to the production of ESBL, which is now more frequent.

Limitations

Our study has some limitations. First, we collected routine data on urinary samples without information regarding clinical symptoms and risk factors. This is of importance in the context of UTI in the community where urinalysis for uncomplicated cystitis is not recommended. Therefore it is likely that urinalysis was partly performed for the most complicated UTI, and the observed proportions of ESBL-producing isolates or of antibiotic resistance are likely to overestimates “true” proportions. However, the observed trend, which is in accordance with other studies, is likely to be real and calls for actions. The fact that we did not collect risk factors of antibiotic resistance limits the interpretation of the results. Second, no specific quality control was organized for the study. However, all French laboratories are now in the process of national accreditation, which makes mandatory internal and external quality controls such as the one annually organised by the French Medical Agency.

Conclusion

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The retrospective study allowed assessing the magnitude of ESBL-producing isolates in the outpatients settings. The observed proportion, which is ten times higher than the one observed 15 years ago is worrisome. Such study with a large network has to be repeated to assess trends over time of antibiotic resistance and the impact of national plans against antibiotic resistance.

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Competing interest

All authors declare no conflict of interest regarding the results of the study

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Table 1. Proportion of extended-spectrum beta-lactamase producing strains isolated from urines according to age in ambulatory patients in 2013

Variable	Age group					*P*
	0-20	21-40	41-60	61-80	> 80	value*
Escherichia coli						
- Total (n=51463)	2.0	1.9	2.5	3.9	5.4	0.001
- Female (42839)	2.0	1.9	2.3	3.6	5.1	0.001
- Male (6733)	2.9	1.7	3.6	5.5	6.8	0.001
Klebsiella pneumoniae						
- Total (n=3495)	3.4	4.1	4.8	6.5	10.3	0.001
- Female (n=2753)	2.4	3.8	3.3	4.3	10.7	0.001
- Male (n=594)	NA	9.1	11.7	13.7	7.6	0.001

NA: the number of isolates was <30;

* *P*-value: chi-square for trend

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Table 2. Susceptibility (%) to the main antibiotics of strains isolated from urines in ambulatory patients in 2013

Variable	Co-amox	Cefixime	Ciprofloxacin	Fosfomycin	Nitrofurantoin	Cotrimoxazole
***Escherichia coli* (n=51463)**						
Total	66.1	95.0	89.5	98.7	98.8	79.6
Gender						
- Female	66.9	95.4	90.3	98.7	98.9	80.0
- Male	61.6	92.8	84.4	98.6*	98.1	77.5
ESBL production						
- ESBL-negative isolates	67.6	98.0	91.0	98.9	98.9	80.8
- ESBL-positive isolates	22.7	4.0	44.0	93.7	95.4	47.5
***Klebsiella pneumoniae* (n=3495)**						
- Total	-	93.2	91.2	74.4	71.0	88.4

Co-amox: co-amoxiclav.

All differences between ESBL-positive and ESBL-negative isolates, between female and male patients, and between total *E. coli* and *K. pneumoniae* isolates are statistically significant ($p<0.001$) but for *

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The production of extended-spectrum beta-lactamase in Enterobacteriaceae has been associated with increased treatment failure and higher management costs.

The prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in urinary samples from outpatients has increased significantly in France to reach 3.3%.

The prevalence of extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* in the outpatient setting is circa twice than for *Escherichia coli*

The prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in nursing homes is circa 4 times higher than in the outpatient setting.

The prevalence of extended-spectrum beta-lactamase producing *Escherichia coli* in urinary samples increases significantly with patient's age.

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