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ORIGINAL RESEARCH

Psychoactive drug prescription and urine colonization with extended-spectrum β-lactamase-producing *Enterobacteriaceae*

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Background: The worldwide dissemination of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* has become a major health concern. Previous studies have shown that psychoactive drugs have intrinsic antimicrobial activity and may play a role in the dissemination of antibiotic resistance. The objective of this study was to assess the association between prescriptions for psychoactive drug and urine colonization with ESBL-producing *Enterobacteriaceae*.

Subjects: Ninety-five patients were included; 19 cases (urine colonization with an ESBL-producing *Enterobacteriaceae*) and 76 controls (urine colonization with non ESBL-producing *Enterobacteriaceae*); and were matched for age and gender.

Methods: A retrospective 1:4 matched case–control study design was used. All patients colonized with an *Enterobacteriaceae* isolate in Nantes University Hospital from March to November 2014, were screened before inclusion in the study. Prescriptions data for psychoactive drugs were collected from the electronic medical records. Univariate and multivariate conditional logistic regression analyses were performed.

Results: Thirty-seven patients (38.9%) were treated with psychoactive drugs, of whom 10 (52.6%) were in the ESBL-producing group and 27 (35.5%) were in the non-ESBL group. Mean (SD) age was 71.2 (23.1) years. In multivariate analyses, previous antimicrobial therapy within 6 months (OR=7.12, 95% CI 1.15–44.18; p=0.035) and previous colonization with an ESBL-producing organism (OR=44.87, 95% CI 1.26–1594.19; p=0.037) were associated with urine colonization with ESBL-producing *Enterobacteriaceae*.

Conclusions: Our findings revealed that a history of previous antimicrobial therapy and previous colonization with ESBL-producing organisms are important risk factors in an elderly population. Psychoactive drugs were not associated with urinary carriage of ESBL-producing *Enterobacteriaceae*. Further studies are required to explore the relationship between psychoactive drugs and colonization with ESBL-producing *Enterobacteriaceae*.

Keywords: ESBL, psychoactive drugs, antimicrobial resistance, elderly

Introduction

The increasing prevalence of infections caused by resistant bacteria, including extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, has become a major health concern worldwide, and is no longer limited to nosocomial infections.[1,2] Such infections are associated with increased morbidity, mortality, average length of hospital stay, and overall cost of treatment, leading to additional public health costs.[3] In Europe, data from the European Center for Disease Prevention and Control (ECDC) showed that the prevalence of resistance to third-generation cephalosporins among *Escherichia coli*

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and *Klebsiella pneumoniae* isolates, mainly mediated by an ESBL-producing enzyme, increased from 2.6% to 14.9% between 2001 and 2017.[4]

Urine colonization with ESBL-producing *Enterobacteriaceae* is a risk factor for infection with ESBL-producing *Enterobacteriaceae*.[5] The detection of bacteria in the urine (bacteriuria) does not necessarily mean that there is a urinary tract infection (UTI).[5] Urinary colonization, or asymptomatic bacteriuria (ABU), corresponds to asymptomatic carriage, ie, an absence of clinical symptoms associated with the presence of a microorganisms detected during a correctly performed urine sample collection. Among elderly patients, it is estimated that positive urine samples are found in 2.64 per 1,000 patients per day, of which 60% are ABU.[5] The ESBL phenotype is mainly mediated by the expression of plasmid-borne β-lactamases that cause acquired resistance against all β-lactam antibiotics, except for carbapenems and cephamycins.[2] Well-accepted risk factors for colonization with ESBL-producing *Enterobacteriaceae* have been reported, such as recent antibiotic use, residence in a long-term care facility (LTCF), hospitalization within the preceding 3 months, bladder catheterization, presence of comorbidity, male gender, age ≥65 years, and functional dependence.[6–12]

The gastrointestinal tract is a very large microbial community, housing trillions of microbial cells, facilitating contacts between bacteria and the emergence of resistant strains of Enterobacteriaceae by horizontal spread of plasmids.[13] It has been reported that 7.4–10.8% of patients admitted to hospital are fecal carriers of ESBL-producing *E. coli*.[14,15] Moreover, a fecal abundance of ESBL-producing *Enterobacteriaceae* has been linked to the occurrence of urinary colonization and UTIs caused by ESBL *Enterobacteriaceae*.[7] Rodríguez-Baño et al found that ESBL-producing *E. coli* causing community-acquired UTIs were derived from the host's intestinal flora in at least half of the patients, and that the prevalence of fecal carriage of ESBL-producing *E. coli* in the community was 67.9% in patients with UTIs.[14]

Prescriptions for psychoactive drugs have increased over the past two decades, especially in elderly patients.[16] Since the 1990s, it has been recognized that psychoactive drugs have intrinsic antimicrobial activity.[17–19] In a 2015 study, Bahr et al described that a 12-month intake of risperidone was associated with an increase in body mass index (BMI) and with an alteration of the microbiota (a lower *Bacteroidetes*/*Firmicutes* ratio compared to naïve antipsychotic controls).[20]

Our assumption was that psychoactive drugs, by causing an alteration in the composition of the intestinal microbiota, could promote both intestinal selection and urinary colonization with ESBL-producing Enterobacteriaceae. Our main objective was to determine whether there is an association between psychoactive drug prescriptions and urine colonization with ESBL-producing Enterobacteriaceae. We assume that such an association could have impacts on both clinical practice and public health.

Materials and methods

Study population

We performed a retrospective, monocenter, observational 1:4 matched case–control study in a tertiary, 2,600-bed, university-affiliated center in Nantes, France. This study was conducted from March to November 2014. We used a database that was previously created during a prospective cohort study.[21] In brief, the previous study consisted of the development of a rapid tool to diagnose UTIs caused by an amoxicillin-susceptible *E. coli*. All urine samples were screened daily from March to November 2014. Standard microbiological tests were performed as previously described.[21] Susceptibility tests were interpreted in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.[22] The exclusion criteria of the previous study were refusal or inability to give informed consent, pregnancy, and urine sampled more than 48 hours after hospital admission. Patients were included in the previous study if they had acute or recent-onset urinary symptoms suggestive of UTI. Patients with ABU were not included but their data were collected for further analysis.

The medical records of patients with ABU and one or more urine culture positive for *Enterobacteriaceae* were reviewed for this study. Only the first urine sample was considered. Each patient colonized with an ESBL-producing *Enterobacteriaceae* isolate was matched, through random sampling for age and gender, with four patients with a non ESBL-producing *Enterobacteriaceae*. The medical records of these patients were screened to collect the variable of interest, which was psychoactive drug prescriptions at the hospital admission. The different chemical classes of psychoactive drugs were detailed, including neuroleptic, antidepressant, benzodiazepine, or hypnotic drugs.

According to previous studies, the following well-accepted risk factors for colonization with ESBL-producing *Enterobacteriaceae* were also collected: demographic data, including residence in an LTCF; previous colonization with an ESBL-producing organism; history of antibiotic use in the previous 6 months; history of

hospitalization in the past 3 months; presence of an indwelling urinary catheter or a vascular catheter; presence of chronic wounds or pressure ulcer; history of travel abroad in the past few months; ability to walk; Charlson's Comorbidity Index score; history of dementia; cardiovascular disease; chronic renal failure; solid organ malignancy; repeated UTIs; and prostatic disease.

Statistical analysis

The participants' baseline characteristics were summarized using means and SDs or frequencies and percentages, as appropriate. The analyzed variable of interest was psychoactive drug prescriptions at the hospital admission. Between-group comparisons were performed using an independent sample *t*-test or the chi-squared test, as appropriate. Univariate and multivariate conditional logistic regressions were performed to examine the association between the presence of an ESBL-producing isolate and other variables. Variables with a significant association in univariate analysis and/or with a *p*-value <0.2 were entered into a logistic regressions model for multivariate analysis. The risks were expressed as ORs and 95% CIs. All reported *p*-values <0.05 were considered statistically significant. Analyses were performed using SPSS software version 15.0 (SPSS, Chicago, IL, USA).

Ethical considerations

The study was conducted in accordance with the ethical standards set forth in Helsinki Declaration (1983). This study was approved by the local ethics committee of Centre Hospitalier Universitaire of Nantes, the Groupe Nantais d'Ethique dans le Domaine de la Santé (GNEDS).

Results

Patient characteristics

In the previous study, 1,493 urine cultures were analyzed from March to November 2014, in the Bacteriology Department of Nantes University Hospital, France.[21] Of these, 526 isolates were non-*Enterobacteriaceae*-positive urine cultures, 200 patients had acute or recent-onset urinary symptoms suggestive of UTI, and 278 were excluded (Figure 1). Finally, 489 (33%) urine samples were positive for *Enterobacteriaceae* and were considered for this case–control study. Among these 489 isolates, 19 (3.9%) were ESBL-producing *Enterobacteriaceae* and 470 were non-ESBL-producing *Enterobacteriaceae*. Finally, a total of 95 patients were included, 19 cases and 76 controls matched for age and gender (Figure 1).

Patients' characteristics are shown in Table 1. Patients were mainly female (60 out of 96, 63.2%), the mean (SD) age was 71.2 (23.1) years, and 17 patients (17.9%) lived in an LTCF. No differences between groups were observed in terms of comorbidities. Thirty-seven patients (38.9%) were treated with at least one psychoactive drug, of whom 3.2% were treated with a neuroleptic, 16.8% with an antidepressant, 21.1% with a benzodiazepine, and 9.5% with a hypnotic. The comparison between groups revealed significant differences concerning the following factors: previous antimicrobial therapy within the past 6 months (p=0.001), previous hospitalization within the past 3 months (p=0.010), and previous colonization with an ESBL-producing organism (p=0.005).

Risk factors associated with urine colonization with ESBL-producing Enterobacteriaceae

In the ESBL-producing *Enterobacteriaceae* group, 10 of the 19 patients (52.6%) were treated with psychoactive drugs, while in the non-ESBL group, 27 out of 76 patients (35.5%) were treated with psychoactive drugs (Table 1). This difference was not significant in univariate analysis (OR=2.02, 95% CI 0.73–5.57; p=0.176) (Table 2). Although not significant, the prevalence of resistance to fluoroquinolones and to third-generation cephalosporins was higher among patients treated with psychoactive drugs compared with patients not treated (37.8% vs 22.4%, p=0.10 and 24.3% vs 13.8%, p=0.19, respectively).

In the univariate analysis, the following factors were significantly associated with urine colonization with ESBL-producing *Enterobacteriaceae* (Table 2): previous antimicrobial therapy within the past 6 months (OR=8.48, 95% CI 2.47–29.17; p=0.001), previous hospitalization within the past 3 months (OR=4.10, 95% CI 1.42–11.78; p=0.009), previous colonization with an ESBL-producing organism (OR=20.00, 95% CI 2.09–191.73; p=0.009), and presence of an indwelling urinary catheter (OR=2.73, 95% CI 0.86–8.70; p=0.009).

In multivariate analysis (Table 2), the two following factors were associated with colonization with ESBL-producing *Enterobacteriaceae*: previous antimicrobial therapy within the past 6 months (OR=7.12, 95% CI 1.15–44.18; p=0.035) and previous colonization with an ESBL-producing organism (OR=4.87, 95% CI 1.26–1594.19; p=0.037).

Discussion

The worldwide dissemination of Gram-negative bacteria that produce ESBLs has become a significant public health

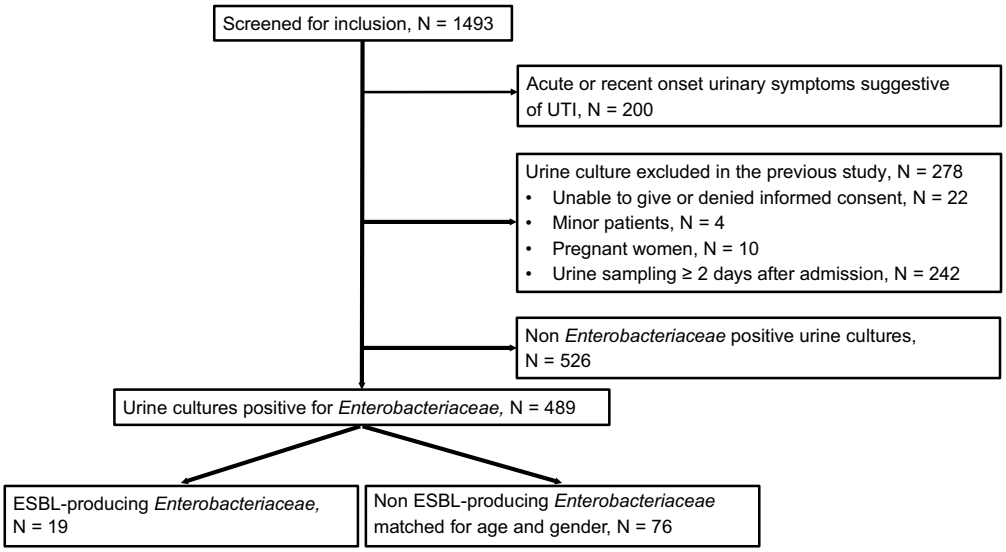

Figure 1 Screening, exclusion, and enrollment process of participants.
Abbreviations: ESBL, extended-spectrum β-lactamase; UTI, urinary tract infection.

Table 1 Demographic and clinical characteristics of the total population, ESBL group, and non-ESBL group

Variable	Total (N=95)	ESBL (N=19)	Non-ESBL (N=76)	*p*-Value[d]
Clinical characteristics				
Age (years), mean ± SD	71.2±23.1	71.2±23.1	71.2±23.7	1.000
Gender, female, n (%)	60 (63.2)	12 (63.2)	48 (63.2)	1.000
Residence in an LTCF, n (%)	17 (17.9)	4 (21.1)	13 (17.1)	0.740
Geriatric parameters				
Dementia, n (%)	28 (29.5)	6 (31.6)	22 (28.9)	0.786
Walking status,[a] n (%)	84 (88.4)	16 (84.2)	68 (89.5)	0.688
Charlson Comorbidity Index score ≥2, n (%)	79 (83)	17 (89.5)	62 (81.6)	1.000
Comorbidity and predisposing conditions				
Previous hospitalization,[b] n (%)	27 (28.4)	10 (52.6)	17 (22.4)	0.010*
Previous colonization with ESBL-producing organism, n (%)	5 (5.3)	4 (21.1)	1 (1.3)	0.005*
Previous antimicrobial therapy,[c] n (%)	14 (14.7)	8 (42.1)	6 (7.9)	<0.001*
Indwelling urinary catheter, n (%)	17 (17.9)	6 (31.6)	11 (14.5)	0.099
Repeated UTIs, n (%)	10 (10.5)	2 (10.5)	8 (10.5)	1.000
Active cancer, n (%)	15 (15.8)	3 (15.8)	12 (15.8)	1.000
Cardiovascular disease, n (%)	43 (45.3)	9 (47.4)	34 (44.8)	0.596
Chronic renal failure, n (%)	29 (30.5)	6 (31.6)	23 (30.3)	1.000
Chronic wounds or pressure ulcer, n (%)	9 (9.5)	4 (21.1)	5 (6.6)	0.075
Prostate disease, n (%)	10 (10.5)	2 (10.5)	8 (10.5)	1.000
Recent history of travel abroad, n (%)	1 (1.1)	0	1 (1.3)	1.000
Antipsychotic, n (%)	37 (38.9)	10 (52.6)	27 (35.5)	0.196
Neuroleptic, n (%)	3 (3.2)	0	3 (3.9)	1.000
Antidepressant, n (%)	16 (16.8)	4 (21.1)	12 (15.8)	0.732
Benzodiazepine, n (%)	20 (21.1)	5 (26.3)	15 (19.7)	0.538
Hypnotic, n (%)	9 (9.5)	3 (15.8)	6 (7.9)	0.377

Notes: [a]Able to walk; [b]within the past 3 months; [c]within the past 6 months. [d]Between-group comparisons (ESBLs vs non-ESBLs) were performed using an independent sample *t*-test or chi-squared test, as appropriate. *Significant difference ($p<0.05$).
Abbreviations: ESBL, extended-spectrum β-lactamase; LTCF, long-term care facility; UTI, urinary tract infection.

Table 2 Univariate and multivariate analysis of risk factors for urinary carriage of an ESBL-producing organism

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Clinical characteristics				
Age	1.00 (0.98–1.82)	1.000	0.98 (0.93–1.03)	0.360
Gender, female	1.00 (0.35–2.83)	1.000	1.34 (0.31–5.83)	0.692
Residence in an LTCF	1.29 (0.37–4.53)	0.689	0.34 (0.30–3.72)	0.374
Geriatric parameters				
Dementia	1.13 (0.38–3.36)	0.822	0.98 (0.93–1.03)	0.360
Walking status[a]	0.63 (0.15–2.63)	0.524	0.20 (0.20–2.10)	0.181
Charlson Comorbidity Index score ≥2	1.03 (0.89–1.20)	0.701	1.01 (0.63–1.60)	0.974
Comorbidity and predisposing conditions				
Previous hospitalization[c]	4.10 (1.42–11.78)	0.009*	4.57 (0.82–25.55)	0.84
Previous colonization with ESBL-producing organism	20.00 (2.09–191.73)	0.009*	44.87 (1.26–1594.19)	0.037*
Previous antimicrobial therapy[b]	8.48 (2.47–29.17)	0.001*	7.12 (1.15–44.18)	0.035*
Indwelling urinary catheter	2.73 (0.86–8.70)	0.009*	1.47 (0.26–8.47)	0.665
Repeated UTIs	1.00 (0.19–5.14)	1.000	0.19 (0.13–2.60)	0.211
Active cancer	1.00 (0.25–4.00)	1.000	0.26 (0.26–2.70)	0.262
Cardiovascular disease	0.71 (0.26–2.00)	0.522	0.70 (0.11–4.61)	0.713
Chronic renal failure	1.06 (0.36–3.14)	0.911		
Chronic wounds or pressure ulcer	3.79 (0.90–15.8)	0.068	1.47 (0.26–8.47)	0.665
Prostate disease	1.00 (0.19–5.14)	1.000	–	–
Recent history of travel abroad	–	–	–	–
Antipsychotics	2.02 (0.73–5.57)	0.176	1.31 (0.30–5.82)	0.726

Notes: [a]Able to walk; [b]within the past 6 months; [c]within the past 3 months. *Significant difference ($p<0.05$).
Abbreviations: ESBL, extended-spectrum β-lactamase; LTCF, long-term care facility; UTI, urinary tract infection.

threat.[1] Because colonization is associated with infection with ESBL-producing *Enterobacteriaceae*, the discovery of new factors associated with colonization has an important clinical impact and poses a challenge in limiting the dissemination of resistant bacteria.[23]

The main finding of our study is that the following variables were associated with urine colonization with ESBL-producing *Enterobacteriaceae*: previous antimicrobial therapy within the past 6 months, and previous colonization with an ESBL-producing organism. This expected finding has been documented in previous studies and confirms the validity of our study.[8,9,12,24] These two risk factors remain very important in identifying at-risk patients in daily clinical practice. Indeed, these variables have been taken into consideration by some authors, who tried to develop a clinical prediction rule to recognize patients who were at risk for carriage of ESBL-producing *Enterobacteriaceae*.[9]

To our knowledge, this study is the first to explore the association between psychoactive drug prescriptions and colonization with ESBL-producing *Enterobacteriaceae*. We did not observe significant associations between psychoactive drugs and urine colonization with ESBL-producing Enterobacteriaceae. Although the results of the conditional logistic regression analysis were not statistically significant, patients treated with psychoactive drugs seemed to be more often colonized with ESBL-producing *Enterobacteriaceae* compared with patients not treated with psychoactive drugs. Furthermore, the prevalence of resistance to fluoroquinolones and to third-generation cephalosporins was higher among patients treated with psychoactive drugs compared with patients not treated (37.8% vs 22.4%, $p=0.10$ and 24.3% vs 13.8%, $p=0.19$, respectively). These results suggest that patients treated with psychoactive drugs may have an increased risk of urine colonization with ESBL-producing *Enterobacteriaceae*. Our study has a lack of power to detect such an association but could serve to design further studies. Indeed, it is known that psychoactive drugs have antibacterial effects and previous studies highlighted the impact of psychoactive drugs, as well as other non-antibiotic drugs, on the gut microbiota.[25–29] A 2018 study analyzed the drug–microbiome species relationship and reported that psychoactive drugs inhibited gut bacteria more than the other medications tested.[30] As psychoactive drugs target dopamine and serotonin receptors, which are absent in bacteria, Maier et

al suggest that direct bacterial inhibition may not only manifest as a side effect of psychoactive drugs, but also be part of their mechanism of action, meaning that psychoactive drugs could be a marker to integrate into the risk of developing antimicrobial resistance.[30] Given that psychoactive drug prescriptions have increased among elderly patients, we hypothesized that such findings could have an impact on further studies and, later, on clinical practice.[16] Although their mechanisms of action remain unknown, the impact of psychoactive drugs on human gut bacteria has become a topic of intense study and warrants further exploration.

We did not observe an association between colonization with ESBL-producing *Enterobacteriaceae* and the following factors: dementia, a reduced ability to walk, age >65 years, or presence of an indwelling urinary catheter. However, other studies report controversial results concerning these well-accepted risk factors.[8,9,12] Flokas et al demonstrated that a previous history of repeated UTIs, a history of urinary catheter use, and an invasive procedure within 2 years were associated with colonization by ESBL-producing *Enterobacteriaceae* among LTCF residents.[8] Tumbarello et al identified the following variables as risk factors for urinary carriage of ESBL-producing bacteria: residence in an LTCF, Charlson's Comorbidity Index score ≥4, and age ≥70 years.[9] Another study highlighted several risk factors: the presence of cardiovascular disease, chronic renal failure, dementia, and solid organ malignancy.[12] Thus, we assume that our study may have been underpowered to detect these associations.

This study has several limitations that must be acknowledged. First, this study had an observational design and we report the results of a retrospective analysis, with a small sample size of cases and controls, which could explain large 95% CIs of the ORs. We chose this design because we wanted to begin with a small population to examine an outcome that had not been previously described and because of the low prevalence of ESBL-producing *Enterobacteriaceae*. Second, this was a monocentric study and the results may not be fully applicable to other settings. However, the prevalence of ESBL-producing isolates among urine cultures positive for Enterobacteriaceae was 3.9%, which is consistent with results reported in the USA and France, according to the MedQual network.[12,24] Nevertheless, the prevalence of ESBL-producing *Enterobacteriaceae* among LTCF residents is 18%.[8] Third, in multivariate analyses, we did not distinguish between the different classes of psychoactive drugs or the number of psychoactive drugs. Future studies are required to analyze these factors.

This study confirms that a history of previous antimicrobial therapy within 6 months and previous colonization with an ESBL-producing organism are two major risk factors associated with colonization with ESBL-producing *Enterobacteriaceae* in an elderly population. Although experimental evidence suggests an association between psychoactive drug prescriptions and the gut microbiota composition, we did not find an association between psychoactive drugs and urine colonization with ESBL-producing *Enterobacteriaceae*. Further research is needed to explore this intriguing relationship.

Key points

- Previous studies have shown that psychoactive drugs have intrinsic antimicrobial activity and may play a role in the dissemination of antibiotic resistance.
- Our objective was to assess the association between psychoactive drug prescriptions and urine colonization with ESBL-producing *Enterobacteriaceae*.
- Our findings confirm that a history of previous antimicrobial therapy and previous colonization with an ESBL-producing organism are important risk factors in an elderly population. Future studies are required to explore the relationship between psychoactive drugs and colonization with ESBL-producing *Enterobacteriaceae*.

Ethical approval

This study was approved by the local ethics committee of Centre Hospitalier Universitaire of Nantes, the Groupe Nantais d'Ethique dans le Domaine de la Santé (GNEDS).

Informed consent

According to French law, no consent was required from patients in this retrospective study.

Author contributions

All authors contributed towards data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no relevant financial interests, personal conflicts, or other potential conflicts in regard to this work.

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