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**Antibiotic resistance in elderly patients: comparison of Enterobacterales causing urinary tract infections between community, nursing homes and hospital settings**

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## 1. Introduction

Antimicrobial resistance is a major public health concern that leads to increased morbidity, mortality, and hospitalization costs [1]. The elderly are particularly vulnerable to infections, and bacterial resistance increases with age [2,3]. Urinary tract infections (UTIs) are the second most common cause of antibiotic prescriptions after respiratory tract infections [4]. In the elderly, the frequent atypical clinical presentation of these infections makes diagnosis complicated [5,6]. Uncertainty in diagnosis leads to overuse of antibiotics, which contributes to increase antimicrobial resistance [7,8]. Because of the combination of risk factors for antibiotic resistance (elderly patients, overuse of antibiotics, and presence of medical devices) in nursing homes (NHs), they are considered reservoirs for multidrug-resistant pathogens [9,10].

Few studies have compared antibiotic resistance in patients of similar age, and none have done so across the three sectors of care (community setting, hospital settings [HSs], NHs) in a French region. The aim of this study was to compare, in the same area of France, the frequency of antibiotic resistance in urine cultures of the three major Enterobacterales responsible for UTIs (*Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* [11]) in the elderly between the HS, community, and NH sectors. The secondary objective was to compare antibiotic consumption in the elderly between the community, NH, and HS sectors.

## **2. Material and methods**

### **2.1 Data collection**

This study was a retrospective observational study conducted in Bourgogne-Franche-Comté (an eastern region of France) in the following sectors: community setting, NHs, and HSs. We collected 2016 antibiotic consumption and 2017 antibiotic resistance data from patients aged 75 years or older. Only health care establishments with high geriatric activity were included.

### **2.2 Antibiotic resistance data**

Data were obtained from urine cultures routinely performed in six private laboratories. These laboratories performed analyses in the three sectors of the health care system (except for one, which only has a community activity). Monomicrobial urine cultures for *E. coli*, *K. pneumoniae* and *P. mirabilis* in patients aged 75 years or older were collected. No clinical information about the suspected clinical diagnostic or the treatment was available. Urine culture positivity criteria were: 1)  $\geq 10^4$  leukocytes/mL and  $\geq 10^3$  CFU/mL for all Enterobacterales in males; 2)  $\geq 10^4$  leukocytes and  $\geq 10^3$  CFU/mL for *E. coli*, or  $\geq 10^4$  CFU/mL for other Enterobacterales in females [12]. Resistance data were deduplicated to keep only one resistance profile per bacterial species, per patient, per quarter, and per laboratory.

The antibiotics targeted were those of interest in the treatment of urinary tract infections: amoxicillin, amoxicillin-clavulanic acid, mecillinam, cefotaxime or ceftriaxone, ertapenem or imipenem or meropenem, nalidixic acid, ciprofloxacin, gentamicin, fosfomycin, nitrofurantoin, and sulfamethoxazole-trimethoprim. Antibiotic susceptibilities categorized as "intermediate" were classified as "resistant". Resistance to ceftriaxone or cefotaxime was interpreted as resistance to third-generation cephalosporins (3GC). Resistance mechanisms responsible for 3GC were not available. Resistance to ertapenem or imipenem or meropenem was

interpreted as resistance to carbapenems. Natural resistance patterns to amoxicillin for *K. pneumoniae* and to nitrofurantoin for *P. mirabilis* were excluded from the analysis. Multidrug-resistance rates were estimated considering co-resistance to 3GC, ciprofloxacin, and gentamicin. Antibiotic resistance was interpreted according to CA-SFM 2016 breakpoints [13].

### **2.3 Antibiotic consumption data**

Antibiotic consumption data in the community setting were obtained from the reimbursement data of the three main French health insurance funds. Data from patients over 75 years of age were collected (molecules and number of defined daily doses [DDD] according to the ATC/DDD Index 2022 [14]). The results were expressed in DDDs per 1,000 inhabitants over 75 years old per day. HSs and NHs data were provided by the facilities' in-house pharmacies and expressed in DDD/1,000 patients per days.

### **2.4 Data analysis**

Categorical variables were reported as proportions. Chi-square or Fisher's exact tests were used as appropriate. A p value <0.05 was considered significant.

### 3. Results

We collected 14,772 urine samples positive for *E. coli*, *K. pneumoniae*, or *P. mirabilis* in patients older than 75 years. After exclusion of incomplete susceptibility tests and duplicates, we included 13,932 isolates of which 81.5% were *E. coli*, 10.5% were *K. pneumoniae*, and 8.0% were *P. mirabilis* (Table 1). The distribution of species differed significantly between the three sectors ( $p < 0.001$ ).

#### 3.1 Antibiotic resistance results

Antibiotic resistance of *E. coli* in NHs did not differ significantly from other sectors, except for gentamicin (community setting [ $p = 0.004$ ] and HSs [ $p < 0.001$ ]) and mecillinam (HSs [ $p = 0.019$ ]). No significant difference was observed for 3GC resistance between NHs and the community setting ( $p = 0.213$ ) or between NHs and HSs ( $p = 0.238$ ). Antibiotic resistance of *K. pneumoniae* isolates from nursing homes was significantly higher than that of community strains for most antibiotics, with no significant differences from those from HSs (except for sulfamethoxazole-trimethoprim,  $p = 0.035$ ). Antibiotic resistance of *P. mirabilis* in NHs did not differ significantly from that observed in the community setting or HSs (except for gentamicin,  $p = 0.043$ ). All results are available in Table 2.

#### 3.2 Multidrug resistance rate

*E. coli* strains with multidrug resistance to 3GC, ciprofloxacin, and gentamicin accounted for 1.34%, 0.75%, and 2.73% of isolates in the community setting, NHs, and HSs, respectively. There was a significant difference between hospitals and NHs ( $p < 0.001$ ) but not between the community setting and NHs ( $p = 0.107$ ). *K. pneumoniae* with multidrug resistance to 3GC, ciprofloxacin, and gentamicin accounted for 6.1%, 11.6%, and 17.0% of strains in the

community setting, NHs, and HSs, respectively. There was a significant difference between the community setting and NHs ( $p < 0.01$ ) but not between HSs and NHs ( $p = 0.133$ ). No isolate of *P. mirabilis* was simultaneously resistant to 3GC, gentamicin, and ciprofloxacin.

### **3.3 Antibiotic consumption**

The hospital setting had the highest antibiotic use followed by nursing homes. Antibiotic use in nursing homes appears to be closer to the community setting than the hospital setting. Antibiotic consumption data for the community setting, NHs and HSs are available in Table 3.

## **4. Discussion**

This survey showed that in our region antibiotic resistance rates for *E. coli* and *P. mirabilis* are not significantly higher in NHs than in the community setting. The significant difference of multidrug resistance between NHs and HSs and the lack of difference between the community setting and NHs observed in this study suggest that antibiotic resistance rates in NHs are closer to community setting than to HSs. These results are consistent with a Norwegian study showing no significant difference between NHs and community setting for *E. coli* [15]. Conversely, in a French survey, Pulcini *et al.* found a significant difference in resistance between community setting and NHs for *E. coli* and *P. mirabilis* [16]. These differences can be explained by a difference in minimum age between the two populations studied (75 years in our study vs. 65 years in Pulcini's study), by epidemiological variations between the two regions concerned or by the study designs (multicentric in our study vs. monocentric in Pulcini's study). Interestingly, the 2018 French national monitoring (PRIMO) reports regional data very similar to ours in NHs and in the community setting which reinforces the representativeness of our results. [17,18].

Antimicrobial resistance rates of *K. pneumoniae* in NHs was significantly higher than in the community setting, with a significantly higher number of multidrug-resistant strains ( $p < 0.01$ ). The absence of a significant difference in resistance between NHs and HSs could be partly explained by the spread of multidrug-resistant clones from hospitals to NHs [19]. Indeed, a study conducted at the same time in the region revealed the spread of a CTX-M-15 producing ST663 *K. pneumoniae* clone (a single-locus variant of ST405) in NHs, firstly identified in the university hospital of our region [20,21].

Antibiotic consumption is considered the main driver of antibiotic resistance [22]. However, to our knowledge, this study is the first to compare antibiotic consumption in the elderly between NHs, the community setting, and HSs in a French region. We showed that antibiotic consumption in NHs is closer to that of the community setting and lesser than that of HSs. These differences are in line with differences of antibiotic resistance. However, for some antibiotic classes such as fluoroquinolones, we did not observe any difference in quinolone resistance for *E. coli* between the three sectors despite the variation in fluoroquinolone use.

Our study has several limitations. First, we do not have the indication for urine cultures, although according to French recommendations, urine cultures in the elderly should only be prescribed in case of suspected UTI [12]. Secondly, we did not collect some individual risk factors for antibiotic resistance (urinary catheter, dementia, autonomy, hospitalization within the year, antibiotics in the last 6 months, and history of extended spectrum beta-lactamase infection) which may be determinants explaining differences in resistance rates [9]. Thirdly,



we collected our data in 2016. Our ongoing surveillance as well as PRIMO reports however suggest some stability in rates of resistance in various sectors of our region.

In conclusion, this study compared data on antibiotic resistance and antibiotic consumption in the elderly between hospital, NH and community settings. Antibiotic resistance, as well as antibiotic consumption, in NHs appear to be closer to those in the community setting than those in HSs for *E. coli* and *P. mirabilis*. Patients living in NHs should not be considered at greater risk of multidrug-resistant *E. coli* infections than patients living in the community. Screening for multidrug-resistant *K. pneumoniae* in NHs may be useful to identify spread of these clones.

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**Table 1.** Characteristics of the positive urine samples included in the study

|            |               | <i>E. coli</i><br>(N=11,361)<br>n (%) | <i>K. pneumoniae</i><br>(N=1,461)<br>n (%) | <i>P. mirabilis</i><br>(N=1,110)<br>n (%) |
|------------|---------------|---------------------------------------|--|---|
| Age        | 75 – 85       | 6,242 (54.7)                          | 748 (51.2)                                 | 516 (46.5)                                |
|            | >85           | 5,149 (45.3)                          | 713 (48.8)                                 | 594 (53.5)                                |
| Gender     | Female        | 9,609 (84.6)                          | 1,141 (78.1)                               | 698 (62.9)                                |
|            | Male          | 1,752 (15.4)                          | 320 (21.9)                                 | 412 (37.1)                                |
| Sector     | Community     | 8,547 (75.2)                          | 961 (65.8)                                 | 702 (63.2)                                |
|            | Hospital      | 1,755 (15.4)                          | 311 (21.3)                                 | 248 (22.3)                                |
|            | Nursing homes | 1,059 (9.3)                           | 189 (12.9)                                 | 160 (14.4)                                |
| Laboratory | Lab1          | 1,564 (13.8)                          | 253 (17.3)                                 | 158 (14.2)                                |
|            | Lab2          | 1,772 (15.6)                          | 216 (14.8)                                 | 198 (17.8)                                |
|            | Lab3          | 1,704 (15.0)                          | 207 (14.2)                                 | 177 (16.0)                                |
|            | Lab4          | 1,982 (17.5)                          | 228 (15.6)                                 | 203 (18.3)                                |
|            | Lab5          | 1,629 (14.3)                          | 208 (14.2)                                 | 150 (13.5)                                |
|            | Lab6          | 2,710 (23.8)                          | 349 (23.9)                                 | 224 (20.2)                                |

**Table 2.** Prevalence of antibiotic resistance by bacterium between community, nursing homes, and hospital settings

| Antibiotics                   | Overall % | Community samples % | NH samples % | HS samples % | Community vs NHs <i>p</i> | NHs vs HSs <i>p</i> | HSs vs Community <i>p</i> |
|-------------------------------|-----------|---------------------|--------------|--------------|---------------------------|---------------------|---------------------------|
| <i>E. coli</i>                | N=1,1361  | N=8,547             | N=1,059      | N=1,755      |                           |                     |                           |
| amoxicillin                   | 48.2      | 47.5                | 50.0         | 50.4         | 0.137                     | 0.807               | <b>0.027</b>              |
| amoxicillin-clavulanic acid   | 22.3      | 21.6                | 23.0         | 24.9         | 0.299                     | 0.264               | <b>0.002</b>              |
| mecillinam                    | 9.7       | 9.4                 | 9.0          | 11.8         | 0.672                     | <b>0.019</b>        | <b>0.001</b>              |
| nalidixic acid                | 19.9      | 19.7                | 21.4         | 20.4         | 0.170                     | 0.511               | 0.476                     |
| ciprofloxacin                 | 13.5      | 13.3                | 14.7         | 13.4         | 0.214                     | 0.319               | 0.963                     |
| gentamicin                    | 5.6       | 5.4                 | 3.4          | 7.5          | <b>0.004</b>              | <b>&lt; 0.001</b>   | <b>&lt; 0.001</b>         |
| fosfomicin                    | 1.4       | 1.4                 | 1.4          | 1.4          | 0.925                     | 0.914               | 0.968                     |
| nitrofurantoin                | 2.1       | 2.0                 | 2.5          | 2.2          | 0.270                     | 0.510               | 0.727                     |
| sulfamethoxazole-trimethoprim | 24.3      | 24.7                | 22.6         | 23.2         | 0.126                     | 0.703               | 0.177                     |
| 3GC                           | 6.0       | 5.6                 | 6.6          | 7.8          | 0.213                     | 0.238               | <b>&lt; 0.001</b>         |
| carbapenem                    | 0.1       | 0.1                 | 0.2          | 0.3          | 0.717                     | 0.218               | <b>0.027</b>              |
| <i>K. pneumoniae</i>          | N=1,461   | N=961               | N=189        | N=311        |                           |                     |                           |
| amoxicillin-clavulanic acid   | 19.6      | 16.5                | 23.8         | 26.7         | <b>0.016</b>              | 0.474               | <b>&lt; 0.001</b>         |
| nalidixic acid <sup>a</sup>   | 21.1      | 17.4                | 24.2         | 30.4         | <b>0.034</b>              | 0.150               | <b>&lt; 0.001</b>         |
| ciprofloxacin                 | 15.6      | 12.1                | 18.5         | 24.8         | <b>0.016</b>              | 0.104               | <b>&lt; 0.001</b>         |
| gentamicin                    | 12.4      | 9.8                 | 14.8         | 19.0         | <b>0.039</b>              | 0.234               | <b>&lt; 0.001</b>         |
| nitrofurantoin                | 32.9      | 32.3                | 39.1         | 31.2         | 0.068                     | 0.725               | 0.066                     |
| sulfamethoxazole-trimethoprim | 15.9      | 14.0                | 14.8         | 22.5         | 0.782                     | <b>0.035</b>        | <b>&lt; 0.001</b>         |
| 3GC                           | 14.7      | 10.9                | 18.5         | 24.1         | <b>0.003</b>              | 0.142               | <b>&lt; 0.001</b>         |
| carbapenem                    | 0.1       | 0.0                 | 0.0          | 0.6          | 1                         | 0.529               | 0.060                     |
| <i>P. mirabilis</i>           | N=1,110   | N=702               | N=160        | N=248        |                           |                     |                           |
| amoxicillin                   | 46.7      | 47.3                | 50.6         | 42.3         | 0.500                     | 0.100               | 0.203                     |
| amoxicillin-clavulanic acid   | 14.9      | 14.5                | 16.9         | 14.5         | 0.530                     | 0.519               | 1                         |
| nalidixic acid                | 24.8      | 24.6                | 30.0         | 21.8         | 0.193                     | 0.061               | 0.409                     |
| ciprofloxacin                 | 22.5      | 22.9                | 25.6         | 19.3         | 0.534                     | 0.134               | 0.279                     |
| gentamicin                    | 18.6      | 18.5                | 23.7         | 15.7         | 0.162                     | <b>0.043</b>        | 0.372                     |
| sulfamethoxazole-trimethoprim | 35.9      | 35.9                | 34.4         | 27.4         | 0.786                     | 0.134               | <b>0.018</b>              |
| 3GC                           | 0.8       | 0.8                 | 0.6          | 0.0          | 1                         | 0.392               | 0.349                     |
| carbapenem                    | 0.0       | 0.0                 | 0.0          | 0.0          | 1                         | 1                   | 1                         |

NHs: nursing homes; HSs: hospital settings; 3GC: third-generation cephalosporins, p<0.05 highlighted in bold.

<sup>a</sup> N=1,233. One laboratory did not report nalidixic acid susceptibility for *K. pneumoniae* strains.

**Table 3.** Antibiotic consumption in the elderly (>75 years) by sector

| Antibiotic                                 | Community                           | Nursing homes                    | Hospital settings                |
|--|-------------------------------------|----------------------------------|----------------------------------|
|  | In DDD/1,000<br>inhabitants/day (%) | In DDD/1,000<br>patients/day (%) | In DDD/1,000<br>patients/day (%) |
| <b>Penicillin</b>                          | <b>22.6 (60.0)</b>                  | <b>35.9 (67.8)</b>               | <b>87.0 (63.7)</b>               |
| amoxicillin                                | 12.8 (56.5)                         | 17.9 (49.9)                      | 30.1 (34.6)                      |
| pivmecillinam                              | 0.2 (0.8)                           | 0.1 (0.3)                        | 0.6 (0.7)                        |
| amoxicillin +<br>clavulanic acid           | 8.9 (39.5)                          | 17.2 (47.9)                      | 49.6 (57.0)                      |
| piperacillin-<br>tazobactam                | <0.01 (0.0)                         | <0.01 (0.0)                      | 4.5 (5.2)                        |
| <b>Cephalosporins</b>                      | <b>3.1 (8.3)</b>                    | <b>4.8 (9.1)</b>                 | <b>14.1 (10.3)</b>               |
| ceftriaxone                                | 0.4 (13.3)                          | 2 (41.7)                         | 9.4 (66.7)                       |
| cefixime                                   | 1.4 (44.3)                          | 2.2 (45.8)                       | 1.0 (7.1)                        |
| cefpodoxime                                | 0.7 (23.8)                          | 0.4 (8.3)                        | 0.1 (0.7)                        |
| <b>Carbapenems</b>                         | <b>&lt; 0.01 (0.01)</b>             | <b>&lt; 0.01 (0.02)</b>          | <b>0.4 (0.3)</b>                 |
| <b>Sulfamethoxazole +<br/>trimethoprim</b> | <b>1.00 (2.6)</b>                   | <b>1.7 (3.2)</b>                 | <b>4.2 (3.1)</b>                 |
| <b>Macrolides</b>                          | <b>4.7 (12.5)</b>                   | <b>3.9 (7.4)</b>                 | <b>12.7 (9.3)</b>                |
| <b>Aminoglycosides</b>                     | <b>0.06 (0.2)</b>                   | <b>0.1 (0.2)</b>                 | <b>0.4 (0.3)</b>                 |
| amikacin                                   | < 0.01 (0.0)                        | < 0.01 (8.1)                     | 0.1 (25.0)                       |
| gentamicin                                 | 0.02 (35.2)                         | 0.1 (91.9)                       | 0.1 (25.0)                       |
| <b>Fluoroquinolones</b>                    | <b>3.0 (8.0)</b>                    | <b>3.2 (6.0)</b>                 | <b>12.6 (9.2)</b>                |
| ofloxacin                                  | 1.0 (32.0)                          | 1.3 (40.6)                       | 5.2 (41.3)                       |
| ciprofloxacin                              | 1.1 (35.3)                          | 1.2 (37.5)                       | 4.6 (36.5)                       |
| norfloxacin                                | 0.5 (16.9)                          | 0.5 (15.6)                       | 0.4 (3.2)                        |
| levofloxacin                               | 0.4 (13.1)                          | 0.3 (0.6)                        | 2.2 (17.5)                       |
| <b>Tetracyclines</b>                       | <b>1.35 (3.6)</b>                   | <b>1 (1.9)</b>                   | <b>0.4 (0.3)</b>                 |
| <b>Nitrofurantoin</b>                      | <b>0.9 (2.4)</b>                    | <b>1.5 (2.8)</b>                 | <b>1.8 (1.3)</b>                 |
| <b>Fosfomycin</b>                          | <b>0.5 (1.2)</b>                    | <b>0.6 (1.1)</b>                 | <b>0.8 (0.6)</b>                 |
| <b>Other</b>                               | <b>0.4 (1.0)</b>                    | <b>0.26 (0.5)</b>                | <b>2.1 (1.5)</b>                 |
| <b>Total</b>                               | <b>37.7</b>                         | <b>53.0</b>                      | <b>136.5</b>                     |