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Brief Report

Impact of an Antimicrobial Stewardship Program on Resistance to Fluoroquinolones of Urinary *Enterobacteriaceae* Isolated From Nursing Home Residents: A Retrospective Cohort Study

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A B S T R A C T

Objectives: This study investigated the impact of an antimicrobial stewardship program on fluoroquinolone (FLQ) resistance in urinary *Enterobacteriaceae* isolated from residents of 3 French nursing homes.
Design: A multicentric retrospective before-and-after study was conducted.
Setting and Participants: All the first urinary *Enterobacteriaceae* isolates obtained from nursing home residents were included. Two time frames were analyzed: 2013-2015 and 2016-2017.
Methods: The antimicrobial stewardship program started in 2015 and was based on (1) 1-day training for use of an "antimicrobial stewardship kit for nursing homes;" and (2) daily support and training of the coordinating physician by an antibiotic mobile team (AMT) in 2 of 3 nursing homes.
Results: Overall, 338 urinary isolates were analyzed. *Escherichia coli* was the most frequent species (212/338, 63%). A significant reduction of resistance to ofloxacin was observed between 2013-2015 and 2016-2017 in general ($\Delta = -16\%$, $P = .004$) and among isolates obtained from patients hospitalized in the county nursing home with AMT support ($\Delta = -28\%$, $P < .01$). A nonstatistically significant reduction in ofloxacin resistance was also observed in the hospital nursing home with AMT support ($\Delta = -18\%$, $P = .06$).
Conclusions and Implications: Our antimicrobial stewardship program resulted in a decrease in resistance to FLQ among urinary *Enterobacteriaceae* isolated from nursing home residents. The support of an AMT along with continuous training of the coordinating physician seems to be an important component to ensure efficacy of the intervention.

It is estimated that 50% to 80% of nursing home residents receive at least 1 antibiotic treatment each year, and 6.3% receive more than 10 antibiotic treatments per year.[1,2] Urinary infection is the main reason of antibiotic prescriptions in this setting (32%-66%).[3] However, 75% of antibiotic prescriptions in nursing homes are not appropriate.[4] Because of this, antibiotic resistance is common in isolates from nursing home residents, affecting in particular *Enterobacteriaceae* and urinary isolates.[5,6]

Fluoroquinolones (FLQs) reach high fecal concentrations, and they facilitate selection of resistant *Enterobacteriacae*.[7] Indeed, they affect variability of human gut microbiota and disturb the growth competition balance in favor of minority species, including *Enterobacteriaceae* and *Clostridium difficile*.[8,9] Moreover, FLQs facilitate the selection of multidrug-resistant bacteria, namely, extended spectrum beta

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lactamase and carbapenemase producers.[10] Because the risk of selection of multidrug-resistant bacteria is high, FLQ restriction is advisable both in hospital and community.[11,12] FLQ restriction, whenever possible, resulted in restoration of FLQ sensitivity among urinary *Enterobacteriaceae* and reduction of hospitalization rates.[13−15]

In France, there is an excessive prescription of antibiotics.[16−18] For this reason, 3 national campaigns for the preservation of antibiotic efficacy were conducted from 2002 to 2016, resulting in a reduction of >25% of antibiotic prescription in 2016.[19] In the context of this struggle against excessive antibiotic prescription, an antimicrobial stewardship program targeting nursing homes was developed in the Ile de France region in 2015 with the specific purpose of reducing prescription of large-spectrum antibiotics, namely FLQs.

The aim of this study was to investigate the effectiveness of an antimicrobial stewardship program in decreasing FLQ resistance in urinary *Enterobacteriaceae* isolated from residents of a network of 3 nursing homes in France.

Methods

The study focused on 3 nursing homes in the Ile de France region in France from January 1, 2013, to December 31, 2017. Only the first urinary *Enterobacteriaceae* isolates of each patient were analyzed, according to European Recommendations for Antimicrobial Resistance Surveillance.[20]

Approval by the local ethics committee was not required because of the retrospective design of the study. No study consent was required from any of the patients because inclusion in the study did not cause any modification in daily clinical practice.

Two time frames were analyzed: 2013-2015 and 2016-2017. The choice of these time frames was motivated by the introduction of an antimicrobial stewardship program in 2015. The main objective of this program was to reduce resistance to FLQs in urinary *Enterobacteriaceae*.

The antimicrobial stewardship program started at the end of 2015 and included 2 steps. The first step was a single training day for the use of an "antimicrobial stewardship kit for nursing homes" carried out by the Drugs, Medical Device, and Therapeutic Innovation Observatory (*Observatoire des Médicaments, des Dispositifs Médicaux et de l'Innovation Thérapeutique*) from October to December 2015.[21] This training day targeted all medical professionals of each nursing home. The kit included the following:

1. A tool for medical professionals (physicians, biologists, and nurses) to determine situations where urinary culture was needed, along with instructions on adequate sample collection. This tool included an interactive Power Point file focused on situations of "non-recommended bacterial culture" and a paper file that summarized all information included in the interactive file.
2. A physician's therapeutic guide to alternative molecules for FLQ and the shortest treatment duration (either as empiric or targeted therapy).
3. A patient's guide for a nursing home resident with a summary of situations of "non-recommended bacterial culture."

The second step consisted of daily support, training, and revision of all antibiotic prescriptions by an antibiotic management team (AMT). The AMT consisted of an infectious disease specialist, a clinical microbiologist, and a pharmacist from the local public hospital. The main objective of this AMT was to reduce consumption of broad-spectrum antibiotics, mainly FLQs. This support was offered only to the coordinating physician of 2 of 3 nursing homes from January 1, 2016. Of these nursing homes, one was independent from the public hospital (county nursing home with AMT support), whereas the other was located within the public hospital (hospital nursing home with AMT support). The third nursing home was not supported by the AMT (county nursing home without AMT support).

Cultures from the 3 nursing homes were obtained from 3 different laboratories. All laboratories used the same automated technique for detecting antibiotic susceptibility (VITEK®) throughout the study period.[22] No difference in culture techniques and conditions of transport occurred during the study period. Cultures were prescribed only when a urinary infection was suspected, and they were obtained before the start of antibiotic treatment or when an antibiotic treatment failure was suspected. No urinary samples were collected at the end of treatment, as recommended by international guidelines.[20]

Ofloxacin was chosen as the reference molecule to evaluate susceptibility to FLQs because its breakpoints for *Enterobacteriaceae* are equal or lower than the breakpoints of other FLQs (ciprofloxacin and levofloxacin). Moreover, mechanisms of resistance are the same for all FLQs, and resistance to a single molecule confers resistance to all other FLQs.[23] Ofloxacin was the reference molecule for detecting FLQ resistance in all 3 laboratories involved in this study.

Susceptibility to other antibiotics was analyzed to evaluate a potential negative impact of the antimicrobial stewardship program as a result of increased prescription of molecules other than FLQ. Susceptibility to the following molecules was analyzed: ampicillin, amoxicillin/clavulanic acid, ceftriaxone, gentamicin, fosfomycin, nitrofurantoin, and trimethoprim/sulfamethoxazole. All susceptibility tests were performed according to recommendations from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) applied to the instrument VITEK®.[22,24] We used the EUCAST breakpoints and considered as resistant all isolates with minimal inhibitory concentration interpreted as intermediate or resistant. EUCAST clinical breakpoints changed in 2015 for aminopenicillins (amoxicillin/clavulanic acid and ampicillin). Indeed, breakpoints were raised from 4 mg/mL to 8 mg/mL for both amoxicillin/clavulanic acid and ampicillin. No other clinical breakpoints changed during the study period.[24]

The following between-group comparisons were made: (1) overall antibiotic susceptibility in 2013-2015 vs 2016-2017; (2) antibiotic susceptibility per nursing home in 2013-2015 vs 2016-2017; (3) ofloxacin susceptibility in 2013-2015 in nursing homes with AMT vs nursing home without AMT; (4) ofloxacin susceptibility in 2016-2017 in nursing homes with AMT vs nursing home without AMT; and (5) antibiotic susceptibility according to bacterial species in 2013-2015 vs 2016-2017.

Fisher's exact test was performed using Epi Info. Nominative significance was set at $P < .05$.

Results

During the study period, a total of 427 *Enterobacteriaceae* were isolated from urinary samples; of these, 338/427 (79.2%) were included in the study after exclusion of all subsequent isolates obtained from the same patients.

Overall, *Escherichia coli* was the most frequent species (212/338, 63%), followed by *Proteus* spp (55/338, 16%), *Klebsiella* spp (41/338, 12%), *Citrobacter* spp (15/338, 4.4%), *Enterobacter* spp (10/338, 3%), and *Morganella* spp (5/338, 1.4%).

In all isolates, a significant decrease in resistance to ofloxacin ($\Delta = -16\%$, $P = .004$) and amoxicillin/clavulanic acid ($\Delta = -26\%$, $P < .001$) was observed between 2013-2015 and 2016-2017. A significant decrease in resistance to ofloxacin occurred among isolates obtained from patients hospitalized in the county nursing home with an AMT support ($\Delta = -28\%$, $P < .01$). A significant increase of resistance to amikacin was observed in all isolates ($\Delta = 5\%$, $P = .04$) and in the nursing home with AMT support ($\Delta = 11\%$, $P = .01$) as shown in Table 1. No significant differences were observed for ofloxacin resistance when the 2 nursing homes

Table 1
Antibiotic Resistance of Urinary *Enterobacteriaceae*

A. Overall

Antibiotic	2013-2015, n (%) (n = 225)	2016-2017, n (%) (n = 113)	Δ%	*P* value
Ampicillin	176 (78)	76 (67)	−11	.01*
Amoxicillin/clavulanic acid	116 (52)	29 (26)	−26	<.001*
Ceftriaxone	24 (11)	9 (8)	−3	.5
Amikacin	7 (3)	9 (8)	5	.04
Gentamicin	22 (10)	9 (8)	−2	.6
Fosfomycin	17 (8)	5 (4)	−4	.2
Ofloxacin	102 (45)	33 (29)	−16	.004
Nitrofurantoin	46 (20)	18 (16)	−4	.4
TMP-SMX	52 (23)	19 (17)	−6	.3

B. County Nursing Home Without Antibiotic Management Team Support

Antibiotic	2013-2015, n (%) (n = 30)	2016-2017, n (%) (n = 33)	Δ%	*P* value
Ampicillin	25 (83)	18 (55)	−28	.01*
Amoxicillin/clavulanic acid	17 (57)	3 (9)	−48	<.001*
Ceftriaxone	1 (3)	1 (3)	0	.7
Amikacin	4 (13)	5 (15)	2	.5
Gentamicin	3 (10)	1 (3)	−7	.2
Fosfomycin	1 (3)	0 (0)	−3	.5
Ofloxacin	13 (43)	13 (39)	−4	.4
Nitrofurantoin	0 (0)	0 (0)	0	>.99
TMP-SMX	0 (0)	0 (0)	0	>.99

C. Hospital Nursing Home With Antibiotic Management Team Support

Antibiotic	2013-2015 (n = 147)	2016-2017 (n = 27)	Δ%	*P* value
Ampicillin	117 (80)	19 (70)	−10	.2*
Amoxicillin/clavulanic acid	76 (52)	7 (26)	−26	.01*
Ceftriaxone	21 (14)	3 (11)	−3	.4
Amikacin	1 (0)	3 (11)	11	.01
Gentamicin	10 (10)	4 (14)	4	.1
Fosfomycin	12 (7)	0	−7	.2
Ofloxacin	64 (44)	7 (26)	−18	.06
Nitrofurantoin	38 (26)	5 (18)	−8	.2
TMP-SMX	41 (28)	8 (29)	1	.5

D. County Nursing Home With Antibiotic Management Team Support

Antibiotic	2013-2015 (n = 48)	2016-2017 (n = 53)	Δ%	*P* value
Ampicillin	35 (73)	39 (75)	2	.5*
Amoxicillin/clavulanic acid	24 (53)	19 (35)	−18	.1*
Ceftriaxone	2 (4)	5 (10)	6	.2
Amikacin	2 (4)	1 (2)	−2	.4
Gentamicin	9 (19)	4 (7)	−12	.08
Fosfomycin	4 (8)	5 (9)	1	.5
Ofloxacin	25 (53)	13 (25)	−28	<.01
Nitrofurantoin	8 (17)	13 (25)	8	.2
TMP-SMX	11 (23)	11 (21)	−2	.4

TMP-SMX, trimethoprim-sulfamethoxazole.
*For these molecules, statistical analysis was biased by a change in clinical breakpoints.

with AMT were compared to the nursing home without AMT both in 2013-2015 (45% vs 43%; $P = .8457$) and 2016-2017 (25% vs 39%, $P = .1732$).

When the 4 groups of species (*E coli*, *Proteus* spp, *Klebsiella* spp, and other *Enterobacteriaceae*) were analyzed separately, a statistically significant decrease in resistance to amoxicillin/clavulanic acid between 2013-2015 and 2016-2017 was observed for *E coli* ($\Delta = -24\%$, $P = .001$), *Proteus* spp ($\Delta = -55\%$, $P = .005$), and *Klebsiella* spp ($\Delta = -42\%$, $P < .001$). Only for *Proteus* spp, a significant decrease in resistance to ampicillin ($\Delta = -33\%$, $P = .02$) and trimethoprim-sulfamethoxazole ($\Delta = -28\%$, $P < .001$) was registered. On the other hand, an increase in resistance to amikacin was observed for *E coli* ($\Delta = 11\%$, $P = .001$). No other significant changes were observed (Table 2).

Discussion

This study reports the results of a successful antibiotic stewardship program that achieved lower FLQ resistance in urinary *Enterobacteriaceae* isolated from residents of 3 nursing homes in France. Indeed, ofloxacin resistance significantly decreased, and it almost reached the national mean value (29% vs 24%) by the end of the study period. This is a notable result if we consider that in French nursing homes the risk of FLQ resistance in *Enterobacteriaceae* is 30% higher than community.[25]

Even though antimicrobial stewardship programs typically need longer periods of intervention to produce a change in patterns of antibiotic resistance, our results are in line with the results of other antimicrobial stewardship programs performed in hospital settings, which quickly achieved a restoration of FLQ susceptibility among urinary *Enterobacteriaceae* and a decrease in hospitalization rates through FLQ-sparing policies.[13–15,26] Moreover, our results confirm that antimicrobial stewardship programs can also be effective in nursing homes, and they are therefore strongly encouraged.[5,27–29]

Antimicrobial stewardship programs in nursing homes based only on training of local health care professionals are not effective in reducing antibiotic resistance.[30] In our study, no significant decrease in ofloxacin resistance was observed when the single training day was not associated with the continuous support of an AMT to the coordinating physician of the nursing home. On the contrary, a significant decrease in ofloxacin resistance was observed in isolates obtained from hospital nursing home residents with AMT support. A decrease (even though not statistically significant) was also observed in isolates obtained from residents of county nursing homes with AMT support. The absence of a statistically significant difference in ofloxacin resistance between the 2 nursing homes with AMT support and the nursing home without AMT support in 2016-2017 was probably due to the short period of observation after the start of the antibiotic stewardship program. These results suggest that the direct and constant intervention of an infectious disease specialist and a clinical microbiologist helped to overcome the limitations of a single day of training. The main benefit of the constant support of an AMT is due to a decrease in antimicrobial consumption in nursing homes, as demonstrated by other authors.[31]

The success of our antibiotic stewardship program when the coordinator physician was continuously guided by an AMT highlighted the importance of leadership in influencing the clinical practice of existing groups.[32] The current acceptance of an “authority role” of the reference hospital and its specialists (namely, infectious diseases specialists, clinical microbiologists, and pharmacists) most likely encouraged nursing home care professionals to respect the instructions of the antimicrobial stewardship program.[33] Indeed, in our study, the goal of the antimicrobial stewardship program was achieved principally because the continuous training allowed the coordinating physicians to acquire the necessary skills and the “authority” to enforce the antimicrobial stewardship instructions. Thus, we suggest that antimicrobial stewardship programs should primarily focus on training potential “opinion leaders” in medical facilities, such as coordinating physicians in our study, rather than being dispersed on the contemporary training of different healthcare workers.

Table 2
Antibiotic Resistance of Urinary *Enterobacteriaceae* per Species

A. *Escherichia coli*					B. *Klebsiella* spp				
Antibiotic	2013-2015, n (%) (n = 143)	2016-2017, n (%) (n = 69)	Δ%	*P* value	Antibiotic	2013-2015, n (%) (n = 24)	2016-2017, n (%) (n = 17)	Δ%	*P* value
Ampicillin	104 (73)	41 (59)	−14	.05*	Ampicillin	24 (100)	17 (100)	0	>.99*
Amoxicillin/clavulanic acid	71 (50)	18 (26)	−24	.001*	Amoxicillin/clavulanic acid	13 (54)	2 (12)	−42	.005*
Ceftriaxone	11 (8)	5 (7)	−1	.9	Ceftriaxone	6 (25)	2 (12)	−13	.3
Amikacin	3 (2)	9 (13)	11	.001	Amikacin	2 (8)	0 (0)	−8	.2
Gentamicin	17 (12)	6 (9)	−3	.5	Gentamicin	1 (4)	1 (6)	2	.8
Fosfomycin	1 (1)	0 (0)	−1	.5	Fosfomycin	6 (25)	2 (12)	−13	.3
Ofloxacin	63 (44)	22 (33)	−11	.1	Ofloxacin	8 (33)	3 (18)	−15	.3
Nitrofurantoin	0 (0)	0 (0)	0	>.99	Nitrofurantoin	4 (17)	5 (29)	12	.3
TMP-SMX	31 (22)	14 (20)	−2	.8	TMP-SMX	4 (17)	3 (18)	1	.9
C. *Proteus* spp					D. Other *Enterobacteriaceae*†				
Antibiotic	2013-2015, n (%) (n = 42)	2016-2017, n (%) (n = 13)	Δ%	*P* value	Antibiotic	2013-2015, n (%) (n = 16)	2016-2017, n (%) (n = 14)	Δ%	*P* value
Ampicillin	33 (79)	6 (46)	−33	.02*	Ampicillin	15 (94)	12 (86)	−8	.5*
Amoxicillin/clavulanic acid	23 (55)	0 (0)	−55	<.001*	Amoxicillin/clavulanic acid	9 (56)	9 (64)	8	.7*
Ceftriaxone	5 (12)	0 (0)	−12	.2	Ceftriaxone	2 (13)	2 (14)	1	.9
Amikacin	1 (2)	0 (0)	−2	.6	Amikacin	0 (0)	0 (0)	0	>.99
Gentamicin	3 (7)	1 (8)	1	.9	Gentamicin	1 (6)	0 (0)	−6	.3
Fosfomycin	7 (17)	0 (0)	−17	.1	Fosfomycin	3 (19)	3 (21)	2	.9
Ofloxacin	26 (62)	5 (38)	−24	.1	Ofloxacin	5 (31)	2 (14)	−17	.3
Nitrofurantoin	39 (93)	10 (77)	−16	.1	Nitrofurantoin	3 (19)	3 (21)	2	.9
TMP-SMX	15 (36)	1 (8)	−28	.04	TMP-SMX	2 (13)	1 (7)	−6	.6

TMP-SMX, trimethoprim-sulfamethoxazole.
*For these molecules, statistical analysis was biased by a change in clinical breakpoints.
†Including *Citrobacter* spp, *Enterobacter* spp and *Morganella* spp.

A statistically significant increase of resistance to aminoglycosides (amikacin) was observed during the study period in all isolates. The fact that an increased prescription of aminoglycosides as part of the FLQ sparing strategy could have contributed to this result cannot be ruled out. However, the analysis of antimicrobial resistance per species showed that our data were in line with the data of the European Centre for Disease Prevention and Control (ECDC). Indeed, 7.8% of aminoglycoside resistance among *E coli* in 2016-2017 is comparable to the 7.4% reported in France by the ECDC during the same period.[34] Moreover, in 2016-2017, no isolates of *Klebsiella* spp, *Proteus* spp, and other *Enterobacteriaceae* were resistant to aminoglycosides in our study. Therefore, the overall reduction of susceptibility to aminoglycoside reported in this study is more likely to be related to a tendency toward the national average rather than a consequence of changes in antibiotic prescriptions.

Our study presents several limitations: (1) a certain amount of missing data was expected (retrospective cohort study); (2) no sample size calculation was estimated; (3) the relatively small sample size may have limited the power of statistical analysis; (4) it is not possible to exclude that other factors could be associated with changes in antibiotic susceptibility; and (5) antimicrobial resistance was used as a marker of success of the antimicrobial stewardship program because it is more specific than antibiotic consumption, and it can reduce even in the presence of global antibiotic consumption increase.[15] Nevertheless, our results justify a new strategy for antibiotic stewardship in nursing homes, based principally on 4 points: (1) healthcare professional training is not sufficient; (2) it is necessary to involve other specialists (namely infectious diseases specialists, clinical microbiologists, and pharmacists); (3) a continuous and prolonged support of coordinating physicians by the AMT is required; and (4) the main goal should be the training of "opinion leaders" within each health care worker category.

Conclusions and Implications

In conclusion, our antimicrobial stewardship program allowed a decrease of FLQ resistance in urinary *Enterobacteriaceae* obtained from nursing home residents but failed when the coordinating physician was not supported by an AMT. These results should encourage us to develop new antibiotic stewardship programs involving infectious disease specialists and clinical microbiologists and to focus on training potential opinion leaders within each health care professional category.

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