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**Impact of a long-term antibiotic stewardship program targeting fluoroquinolones in a
French local hospital**

**Impact à long terme d'une politique d'épargne des fluoroquinolones dans un hôpital local
français**

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ABSTRACT

Introduction. Fluoroquinolones (FQs) are major antibiotics but their wide use in hospital and community settings has led to an increased bacterial resistance against this antibiotic class. We aimed to assess the efficiency of an antibiotic stewardship program targeting FQs in a local hospital, and its impact on bacterial resistance.

Methods. This observational study was conducted in the local hospital of Morteau (Franche-Comté region, East of France). The hospital has 166 beds with health and medico-social sectors and a medical home affiliated with the facility. Local guidelines on empirical treatment regimens was released in 2007 aiming to reduce the use of FQs, especially for urinary tract infections. The following monitoring indicators were assessed: total consumption of antibiotics and of FQs (DDD/1,000 hospital patient-days), and resistance to nalidixic acid among *Escherichia coli* strains. Changes in the number of FQ packs sold in a community pharmacy were also recorded.

Results. The FQ consumption decreased by 85.6% between 2006 and 2015 (from 41.1 to 5.9 DDD/1,000 patient-days). The resistance to nalidixic acid among *E. coli* strains substantially decreased after remaining steady until 2011 (-57.2% between 2007 and 2015). The number of norfloxacin packs sold in the assessed community pharmacy decreased by 88%.

Conclusion. Setting up an antibiotic stewardship program in a local hospital can lead to a substantial reduction in FQ use and in *E. coli* resistance to FQs. It may also have a positive impact on community prescriptions.

RÉSUMÉ

Introduction. Les fluoroquinolones (FQ) sont des antibiotiques majeurs dont la large utilisation, à l'hôpital comme en ville, a entraîné une augmentation de la résistance bactérienne contre cette classe. Notre objectif était d'évaluer l'efficacité d'une politique de bon usage des antibiotiques ciblant les FQ et d'évaluer son impact sur la résistance bactérienne.

Méthodes. Étude observationnelle au centre hospitalier de Morteau (Franche-Comté), comportant des lits en secteurs sanitaire et médico-social (166 lits au total) et une maison médicale attachée à la structure. Un guide local de prescription probabiliste des antibiotiques, axé sur l'épargne des FQ (notamment dans le traitement des infections urinaires) a été diffusé en 2007. Le suivi des consommations et de la résistance était fondé sur des indicateurs (DDJ/1 000 journées d'hospitalisation et pourcentage de résistance à l'acide nalidixique chez *Escherichia coli*). L'évolution du nombre de boîtes de FQ vendues dans une pharmacie de la ville a été recueillie.

Résultats. La consommation de FQ entre 2006 et 2015 a diminué de 85,6 % (de 41,1 à 5,9 DDJ/1 000 JH). La résistance à l'acide nalidixique chez *E. coli* a également fortement diminué, après être restée stable jusqu'en 2011 (-57,2 % entre 2007 et 2015). Le nombre de boîtes de norfloxacine vendues dans une des pharmacies de Morteau a diminué de 88 %.

Conclusion. Une politique de bon usage des antibiotiques mise en place dans un hôpital local peut permettre de réduire considérablement la consommation des FQ et la résistance. Elle peut également avoir un impact positif sur les prescriptions communautaires.

Introduction

Fluoroquinolones (FQs) are a major antibiotic class in human health. They are recommended in the treatment of severe infections such as bone and joint infections, prostatitis, or pulmonary infections (e.g., legionellosis). Their wide spectrum of activity, rapid bactericidal effect, excellent oral absorption, and tolerability make them easy-to-prescribe antibiotics and has resulted in their extensive use. However, at equal consumption, the ecological impact of FQs seems to be more important than that of other antibiotic classes; notably, the worldwide expansion of the major clones *Escherichia coli* ST131 H30-Rx, methicillin-resistant *Staphylococcus aureus* EMRSA-15, and *Clostridium difficile* 027 are caused by the clinical use of FQs [1–5]. Alternatives to FQ prescription are available in numerous clinical situations and antibiotics with a lesser ecological impact may be substituted to FQs to preserve their activity for complicated hospital-acquired infections. An audit was conducted in our region in 2006 to evaluate the adequacy and relevance of FQ prescriptions. Results highlighted an important misuse of this antibiotic class [6]. The local hospital of Morteau participated in the regional audit and decided to take part in an antibiotic stewardship program targeting FQs. We aimed to assess the efficiency of the antibiotic stewardship program on FQ consumption and its impact on resistance rates. The secondary objective was to determine whether the antibiotic stewardship program had an impact on FQ consumption in the community setting. Physicians who prescribed in the hospital were family physicians (FPs) and also practiced in the community.

Methods

We conducted this observational study in the local hospital of Morteau, a 166-bed facility with a health sector (70 beds: 20 acute care, 20 post-acute care and rehabilitation, and 30

long-term care beds) and a medico-social sector (96 nursing home beds). A medical home is also affiliated with the hospital. Seventeen family physicians, who all have outpatient and inpatient consultations, work in the facility and a pharmacist works full-time in the hospital pharmacy. The Morteau hospital is located in the Franche-Comté region, in the Val de Morteau (eastern France; 19,550 inhabitants in 2012) [7]. There are three community pharmacies in the city of Morteau.

Design and setting

Regional guidelines drafted by a multidisciplinary group of specialists were developed to improve the prescription of FQs. A regional audit evaluating the prescribers' compliance with guidelines in hospital and community settings was then conducted in the Franche-Comté region in 2006 [6]. Professional practices were evaluated before the beginning of the prescriber training program. Results of the audit highlighted a misuse of FQs in the hospital of Morteau as none of the evaluated prescriptions complied with regional guidelines. Local guidelines on empirical treatment regimens were released in 2007. The aim of the antibiotic stewardship program was to reduce the rate of unnecessary prescriptions of FQs. Two main messages were for instance included in the guidelines for UTIs: *(i)* a reminder on the proper prescription of the cytobacteriological examination of urine; *(ii)* FQs should not be used for uncomplicated acute cystitis; fosfomycin-trometamol (single dose of 3 g) or nitrofurantoin (300 mg/day for 5 days) should be the preferred first-line treatment. The working group (including the president of the medical committee, the medico-social sector coordinating physician, the regional infectious diseases specialist, the pharmacist, and the biologist) defines the policy for an appropriate use of antibiotics, meets several times a year, organizes an annual professional practices assessment, and suggests updates to the local guidelines.

The following monitoring indicators were set up in the hospital setting: total consumption of antibiotics (ATC code J01) and of FQs expressed in defined daily doses (DDD) per 1,000 patient-days, and surveillance of the nalidixic acid resistance among *Escherichia coli* strains. Bacteriological data was supplied by the laboratory biologist who analyzes the samples of the patients of Morteau hospital, and the resistance of *E. coli* strains was evaluated by antimicrobial susceptibility testing. The use of FQs in the community was assessed by the number of packs sold in one community pharmacy which provided its sales data.

Results

Hospital setting

An almost 10-fold decrease in hospital FQ consumption was observed between 2006 and 2015 (from 41.1 to 5.9 DDD/1,000 patient-day). The most important reduction was observed during the first year of the antibiotic stewardship program (-66.9%). We observed a delayed effect on the resistance to nalidixic acid among *E. coli* strains, which started decreasing in 2011 (716 strains were analyzed during the study period) (Figure 1).

The fosfomycin consumption increased but remained very low, and the nitrofurantoin consumption decreased after initially increasing until 2008 (data not shown). The resistance of *E. coli* strains to these antibiotics remained low (<15%) and even decreased for nitrofurantoin. The consumption of most antibiotic classes was stable during the study period, especially that of third-generation cephalosporins (3GC) which has even decreased. The consumption of broad-spectrum antibiotics remained close to zero (piperacillin-tazobactam, carbapenems, aminoglycosides, glycopeptides). An increased consumption of

amoxicillin and amoxicillin-clavulanic acid was observed in 2010, followed by a decrease in the following years (data not shown). The global consumption of antibiotics decreased, except in 2010 which was marked by a peak in consumption (Figure 2).

Data concerning the health sector and the medico-social sector was analyzed separately for the years 2008 to 2015 (data not available for 2006 and 2007): a 14.7% decrease in FQ consumption and a 20.3% increase in the global antibiotic consumption were observed for the health sector, whereas in the medico-social sector the FQ consumption remained stable and the global antibiotic consumption decreased by 18.2% (data not shown for FQ consumption) (Figure 2).

Community setting

The consumption of norfloxacin in the community setting decreased by 88% during the study period. A marked reduction was also observed in the consumption of lomefloxacin (-54%).

The consumption of ofloxacin remained low and steady over the study period (Figure 3).

The consumption of fosfomycin and nitrofurantoin concomitantly increased (respectively +68% and +45.7% from 2007 to 2013) (Figure 3).

Discussion

The cautious use of antibiotics in hospital and community settings has become a public health priority. Numerous studies assessing antimicrobial prescription in hospitals all around the world highlighted inappropriate practices and high levels of use, which led to a worrying

increase in bacterial resistance. The implementation of antibiotic stewardship programs such as the diffusion of guidelines or surveys on antibiotic consumptions, are not systematically associated with an improved use of antibiotics. Antibiotic consumptions are still high, despite improvement measures, in particular in France which is one of the biggest antibiotic consumers in Europe [8]. This issue is particularly concerning for FQs as their misuse has an important ecological impact.

This study showed that the implementation of an antibiotic stewardship program focused on FQs in a local hospital can be effective in reducing the use of FQs in the long-term. We observed a sharp decrease (-85%) in FQ consumption between 2006 and 2015 at the Morteau hospital; the hospital used to be a high FQ consumer and is now a small consumer [9]. Compared with the 2015 national results from the French national network [10], the FQ consumption in the health sector of the Morteau hospital was lower than the median FQ consumption for comparable health care facilities (hospitals with $\leq 33\%$ of short stay beds) (12.8 vs 23.9 DDD per 1,000 patient-days, respectively).

The main target of the antibiotic stewardship program was FQs prescribed for UTIs. Our results suggest that the decreased FQ prescription was mainly associated with a decrease in the use of cytobacteriological examinations of urine (-62% between 2008 and 2016). Indeed, we did not observe any compensatory increase in nitrofurantoin and fosfomycin consumptions. Moreover, the antibiotic prescription policy for UTI treatment had to be updated in 2011 because of the concern of family physicians about the adverse events of nitrofurantoin. These concerns prompted family physicians to come back to prescribing FQs instead of nitrofurantoin, which presumably accounts for the FQ consumption peak observed that year [11].

During the study period the overall antibiotic consumption in the whole hospital decreased, unlike national results [10]. The decrease in FQ use was not balanced by an increased use of other antibiotic classes. We therefore did not observe the so-called “squeezing the antibiotic balloon” effect, i.e. when the decreased use of an antibiotic class leads to the increased use of another one, by way of compensation [12].

A sharp decrease in nalidixic acid resistance among *E. coli* strains was observed after the decrease in FQ consumption (-57.2% between 2006 and 2015), although after a long period of time. The absence of immediate decrease in FQ resistance among *E. coli* strains after such a decrease in FQ use was also observed by Langford in a Canadian hospital [13]. Several studies showed that the carriage of multidrug-resistant *E. coli* may be prolonged even in the absence of antimicrobial selection pressure [14], particularly in nursing homes [15]. We may thus assume that the time lag observed between the reduction in FQ use and the effect on FQ resistance is associated with this prolonged carriage of multidrug-resistant *E. coli* strains in patients hospitalized in long-term care facilities. It will take several years to achieve a sufficient patient turnover and to observe the effect of FQ use reduction. Although this hypothesis has to be confirmed, it suggests that in specific situations the effect of an antibiotic stewardship program may be observed years after its implementation.

All physicians of this study who work in the local hospital are family physicians who also have outpatient consultations in the medical home affiliated with the hospital. The positive impact of the guidelines could also impact the prescriptions for these ambulatory patients as a sharp decrease was observed in the number of FQ packs sold in a community pharmacy of Morteau, especially for the norfloxacin sales, whereas an increase was observed in fosfomycin and nitrofurantoin prescriptions. However, no evidence proves the causal

relation between the antibiotic stewardship program implemented in the Morteau hospital and the decrease in FQ sales in the community pharmacy.

A key component of this improvement in practices is the deep involvement of the physicians, who regularly take part in the anti-infective agent committee meetings, but also of the hospital pharmacist who monitors and validates antibiotic prescriptions on a daily basis: when non-compliance is observed, a notice is sent to the prescriber *via* the computerized medical record, and every non-compliant prescription is collected by the pharmacist to be presented in the next anti-infective agent committee meeting. The involvement of an infectious disease specialist also impacted antibiotic prescription practices, in particular in local facilities where only family physicians who are not always aware of the latest recommendations work. Another key component of this measure is the continuous learning opportunity for the prescribers during the meetings with the pharmacist and the infectious disease specialist. Subjects discussed are chosen according to non-compliance behaviors targeted by the professional practice evaluation.

This study has several limitations: first, community data is scarce as data about FQ sales in community pharmacies is available for only one of the three pharmacies in the city, and the non-availability of data on bacterial resistance in the community prevents the evaluation of the effect of FQ prescription decrease in the community. Another limitation is that data on bacterial resistance at the hospital is based on a small number of strains isolated from hospitalized patients (716 strains between 2007 and 2015); the resistance rate should therefore be interpreted with caution. This data also included patients of the whole facility and was not stratified between patients of the health sector and of the medico-social sector.

Conclusion

Our study demonstrated that an antimicrobial stewardship program in a local hospital can greatly reduce the use of FQs, decrease FQ resistance, and may have a positive impact on the surrounding community.

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None

Declaration of interests

The authors declare no competing interests.

Contribution of authors

AM and XB: writing of the article

AM: data exploitation

KR, DS, and JL: writing of the local guide

KR: data collection for antibiotic consumption

JFN: data collection for bacterial resistance

KR and JL: reviewing of the article

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Figure 1. Trends of fluoroquinolone consumption (DDD/1,000 patients-days) and resistance to nalidixic acid among *E. coli* strains (% of resistant strains) for the whole facility between 2006 and 2015

Figure 1. Évolution des consommations de fluoroquinolones (DDJ/1 000 JH) et de la résistance à l'acide nalidixique chez *E. coli* (% de souches résistantes) pour l'ensemble de l'établissement entre 2006 et 2015

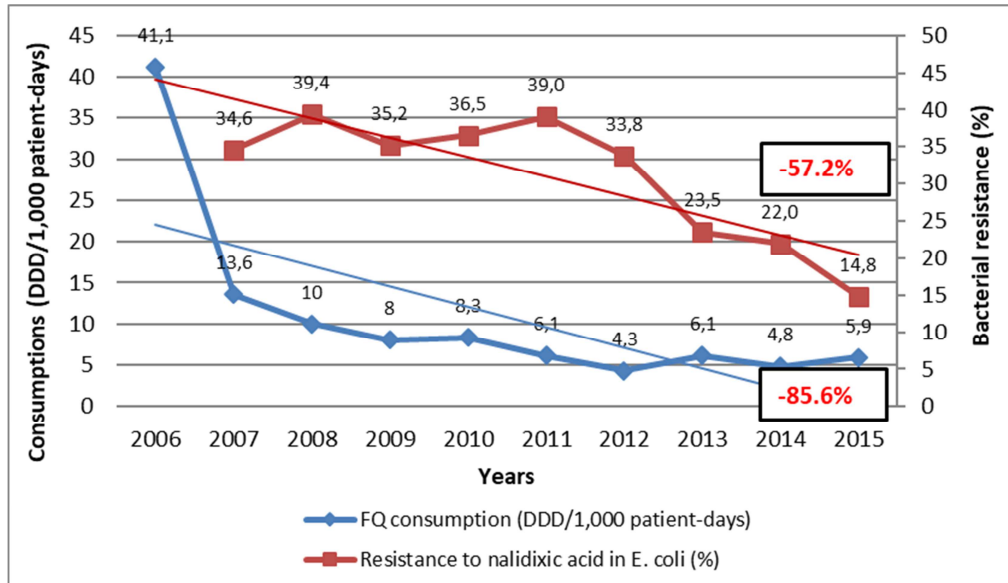


Figure 2. Changes in the global antibiotic consumption (DDD/1,000 patient-days) for the whole facility and for the health and medico-social sectors (data missing for 2006 and 2007) between 2006 and 2015

Figure 2. Évolution des consommations d'antibiotiques globales (DDJ/1 000 JH) pour l'ensemble de l'établissement et pour les secteurs sanitaire et médico-social (données manquantes pour 2006 et 2007) entre 2006 et 2015

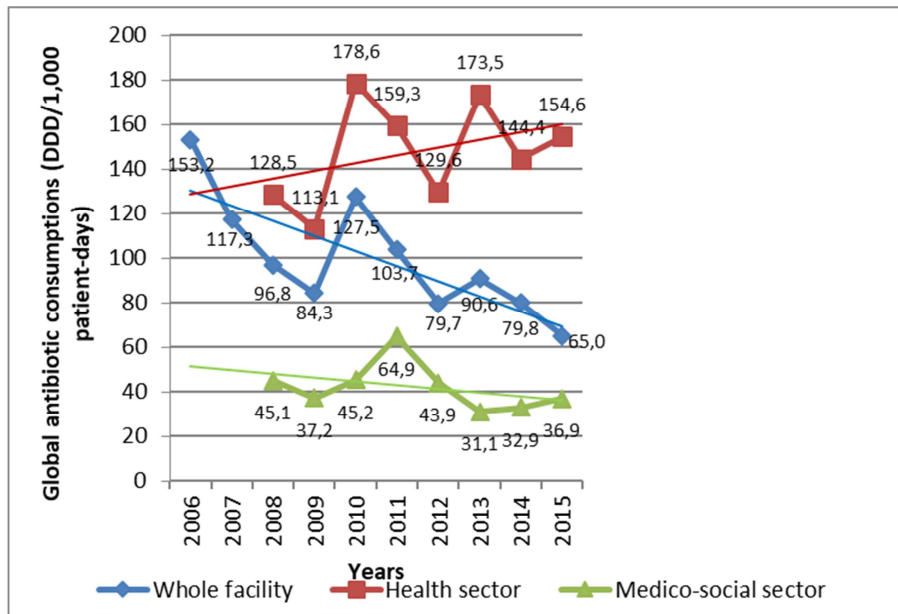


Figure 3. Changes in fluoroquinolone, fosfomycin, and nitrofurantoin consumptions by number of packs sold in a community pharmacy of Morteau from 2007 to 2013

Figure 3. Évolution des consommations de fluoroquinolones, fosfomycine et nitrofurantoïne par nombre de boîtes vendues dans une officine de Morteau entre 2007 et 2013

