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Bacterial resistance in urinary tract infections in patients with diabetes matched with patients without diabetes

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ABSTRACT

Background: With bacterial resistances having increased, patients with diabetes who are at higher risk of urinary tract infection (UTI) need to be studied. The study aim was to compare bacterial resistances to ofloxacin, cefixim, co-trimoxazole, nitrofurantoin and fosfomycin in UTI between patients with and without diabetes.
Methods: A cross-sectional study was conducted in ambulatory laboratories, including patients over 18 coming for urinalyses. Patients with diabetes were matched with two patients without diabetes based on risk factors for UTI using a propensity score.
Results: Among 1119 patients with UTI, 124 patients with diabetes were matched with 246 patients without diabetes. In patients with diabetes, the bacteria identified were: *Escherichia coli* (71%), *Klebsiella* (6%), *Staphylococcus* (5%), *Enterococcus* (4%), *Proteus* (2%) and *Pseudomonas* (1%); these findings were similar to those found in patients without diabetes. Resistances to ofloxacin and cefixim regardless of the bacteria were increased in patients with diabetes after matching on age, sex and history of UTI (respectively: OR = 2.09; p = 0.04 and OR = 3.67; p = 0.05).
Regarding *E. coli* resistance, there was no difference whatever the antibiotic.
Conclusion: The increased ofloxacin and cefixim resistance in patients with diabetes should be considered when prescribing probabilistic antibiotics, and could lead to changes in first-line treatments in UTI.

1. Background

The prevalence of diabetes mellitus has nearly doubled between 2000 and 2013, and it affects 5% of the French population (Boris & Giral, 2013; Fagot-Campagna, Romon, Fosse, & Roudier, 2010). However, data on the epidemiology of bacterial resistance in urinary tract infections (UTI) are limited in patients with diabetes. The risk of UTI in these patients compared to patients without diabetes has increased from 1.24 in 2007 to 1.53 in 2012 (Geerlings, 2008; Hirji, Guo, Andersson, Hammar, & Gomez-Caminero, 2012). The evolution of UTI shows that patients with diabetes are at higher risk of complications than patients without diabetes (Stapleton, 2002) and that choosing suitable treatment may decrease and/or prevent bacterial resistance (Nicolle, 2014).

Recent European studies have not been able to find any difference between patients with and without diabetes in terms of bacteria found in their urinalyses. The main bacteria identified usually are *Escherichia coli* (*E. coli*), then *Enterococcus* spp. *E. coli* resistance to quinolones is not significantly increased in patients with diabetes (Bonadio, Costarelli, Morelli, & Tartaglia, 2006; Papazafiropoulou et al., 2009), but the results are sometimes controversial (Meiland, Geerlings, De Neeling, & Hoepelman, 2004).

Risk factors for bacterial resistance in hospitalised patients are the age, female gender, recurrent or complicated UTI, urinary catheter, use of antibiotics in the last 3 months (Alós, Serrano, Gómez-Garcés, & Perianes, 2005; Société de Pathologie Infectieuse de Langue Française, 2014), hospitalisation in the last 6 months, and diabetes mellitus (Rodríguez-Baño, 2008; van der Starre et al., 2011), which increases by 2.4 the risk of infection by a multidrug-resistant pathogen (Wright, Wrenn, Haynes, & Haas, 2000).

We hypothesised that diabetes could be related to a change in bacterial epidemiology in UTI and lead to an increase in bacterial resistance. The French Language Infectious Pathology Society (SPILF) in 2014 (Société de Pathologie Infectieuse de Langue Française, 2014) has recommended the use of fosfomycin, nitrofurantoin or quinolones as probabilistic treatments for acute cystitis and the use of quinolones or third generation cephalosporins (3GC) for acute pyelonephritis. The aim of the study was to compare bacteria responsible for UTI and their resistances to antibiotics, especially to ofloxacin which may be used in all UTI as a probabilistic treatment, in patients with *versus* without diabetes.

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2. Methods

2.1. Study design and population

This cross-sectional study included patients from 12 ambulatory medical laboratories in urban and semi-rural places of the Parisian area. Patients aged over 18 years coming in one of the participating laboratories for urinalysis were consecutively included between April and July 2014. They received an information sheet and a consent form before their inclusion by qualified medical secretaries. Those who refused to give their consent, who did not meet criteria for UTI or who had non-bacterial infections such as *Candida*, were excluded.

2.2. Endpoints and covariates

The main endpoint was to compare species and bacterial resistance to ofloxacin regardless of the bacteria in UTI patients with versus without diabetes.

The secondary endpoints were to study bacterial species causing UTI in these populations, bacterial resistance to the main antibiotics used in primary care and to compare *E. coli* resistance to these antibiotics as it is the main bacteria studied in previous trials.

The last endpoint was to study bacterial resistance in patients with diabetes depending on the haemoglobin A1C (HbA1C) level.

Urine samples were collected at home or in the laboratory after genital cleaning. Mid-stream urines were collected and brought to the laboratories for analyses within 2 h according to the laboratory protocol. UTI was defined by a urinalysis with a pyuria $>10^4$ white cells/ml with bacteria $>10^3$ CFU/ml for infections by *Enterobacteria* spp and *Staphylococcus saprophyticus*, $>10^4$ CFU/ml for infection with another bacteria in women and $>10^3$ CFU/ml in men, according to guidelines (Société de Pathologie Infectieuse de Langue Française, 2014).

The main bacteria known to cause an UTI were studied: *E. coli*, *Enterococcus* spp, *Pseudomonas* spp, *Klebsiella* spp, *Proteus mirabilis* and *Staphylococcus* spp. Urinalyses were kept 24 h for culture and sensitivity tests. Identification of multidrug resistant bacteria such as extended spectrum beta-lactamases (ESBL), could take up to 48 h. The results of the sensitivity test and culture were given by an automated urinalysis device (Vitek II). The main reference strains were *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* ssp ATCC 35657, *Proteus mirabilis* ATCC 35659 and *Staphylococcus aureus* ATCC 29213.

The antibiotics tested were those commonly used in family practice as probabilistic treatments: ofloxacin, cefixim, co-trimoxazole, nitrofurantoin and fosfomycin.

The diabetic status was identified if the laboratory files had the information regarding diabetes mellitus or if any blood test in the file contained an HbA1C level >6.5% (48 mmol/mol) or two fasting plasma glucose (FPG) tests >7 mmol/L or one FPG test >11 mmol/L (American Diabetes Association, 2011).

The last HbA1C value was investigated in all patients with diabetes. Diabetes was considered as uncontrolled if the HbA1C level was >8% (64 mmol/mol) whatever the patient comorbidities (Fagot Campagna et al., 2009).

The laboratory files of each patient were used to collect risk factors for UTI such as age, sex and history of UTI in the last 6 months. These files were completed by the medical secretaries with patient reports and information on medical prescriptions.

The result of each urinalysis was recorded by the investigator, a senior resident in family medicine.

2.3. Sample size and statistical analysis

As resistances to quinolones have rarely been studied regardless of the bacteria in patients with diabetes, data on *E. coli* were used for the sample size calculation before starting inclusion. A difference of 10% in *E. coli* resistances to quinolones between patients with and without diabetes was expected, as it was increasing for years (5% in 2006 (8) and 6.5% in 2008 (Papazafiropoulou et al., 2009)). To obtain a power of 80% with α equal to 5%, at least 250 patients per group were needed.

Patients with and without diabetes were matched. A propensity score including age, sex and history of UTI was used in order to take into account confounders and allowed matching patients with the closest score with a width calliper equal to 0.1. Each patient with diabetes was matched with two patients without diabetes. For each antibiotic studied, the final model was analysed using a conditional logistic regression on matched samples. Statistical tests were two-sided and results were significant when $p < 0.05$. Data were analysed with "R" (http://www.R-project.org) and "SAS version 9.4" software by the investigator.

2.4. Ethics

The protocol was approved by an ethics committee (CPP Ile de France II).

3. Results

3.1. Patients

During the 3 months of the study, 6133 urinalyses were analysed: 1410 were excluded because they involved children, 3602 because they did not meet criteria for UTI and 2 because they were positive for fungal infections (0.18% in adults). Finally, 1119 patients were included (Fig. 1). Patients with and without diabetes were different regarding some characteristics: patients with diabetes were older (73.9 ± 11.9 years *versus* 57.3 ± 20.0 years) and they were more numerous to have a history of UTI (Table 1). All patients with diabetes were matched with two patients without diabetes based on these factors, except two who were matched with only one patient without diabetes, in order to have an optimal matching. In patients without diabetes, the mean age was 72.4 years (±12.5). Both groups showed similar findings for the following risk factors for UTI: history of UTI in the last 6 months, sex and age (Table 1).

3.2. Bacterial species

In patients with diabetes, the main bacteria identified were *E. coli* (71%), *Klebsiella* spp (6%), *Staphylococcus* spp (5%) and *Enterococcus* spp (4%). In patients without diabetes, *Enterococcus* spp were more commonly found then *Klebsiella* spp and *Staphylococcus* spp. However, no significant difference was found between both groups. Rates of *Proteus* spp, *Pseudomonas* spp and other bacteria such as *Streptococcus B* were close in both groups (Table 2).

3.3. Overall resistances

The overall resistance to ofloxacin in patients with diabetes reached 23% (95% CI = [16%; 30%]) *versus* 17% (95% CI = [12%; 22%]) in patients without diabetes. In patients with diabetes, the risk of ofloxacin resistance was doubled regardless of the bacteria (OR = 2.09; 95% CI = [1.02; 4.29]). The overall resistance to cefixim was also increased in patients with diabetes (9% *vs* 5%; OR = 3.67; 95% CI = [1.02; 13.14]). There was no difference for the other antibiotics (Table 3).

3.4. Resistances of E. coli

In patients with diabetes, 24% (95% CI = [15%; 33%]; 21 cases) of UTI caused by *E. coli* showed a resistance to ofloxacin *versus* 20% (95% CI = [15%; 25%]; 49 cases) in patients without diabetes but the difference was not significant (OR = 1.75; 95% CI = [0.73; 4.17],