

Differences in the pattern of antibiotic prescription profile and recurrence rate for possible urinary tract infections (UTI) in women with and without diabetes

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ABSTRACT

Background. Women with diabetes mellitus (DM) have a high incidence and complication rate of urinary tract infections (UTI's). Our aims were to compare current treatment strategies with respect to recurrence rates in women with DM compared to those without DM.

Methods. We used a Dutch registration database containing pharmacy dispensing data. A total of 10,366 women with DM (17.5% pre-menopausal ≤ 55 years) and 200,258 women without DM (68% pre-menopausal) who received a first course of trimethoprim, nitrofurantoin, fosfomycin or norfloxacin between January 1999-January 2006 were included. We compared short (≤ 5 days) with long (> 5 days) prescriptions and norfloxacin with trimethoprim, nitrofurantoin, fosfomycin. A recurrence was defined as a second prescription for one of the above mentioned agents or a first with amoxicillin (clavulanic-acid), fluoroquinolones, or trimethoprim/sulfamethoxazole (TMP/SMX) between 6 and 30 days after inclusion.

Results. Pre-menopausal women with DM more often received a long (26.5% versus 19.2% $P < 0.001$) treatment with norfloxacin (10.7% versus 6.2% $P < 0.001$), but still had a higher recurrence rate (16.1% versus 12.2% $P = 0.003$) compared to those without DM. Similarly, postmenopausal women with DM more often received a longer (32.8% versus 28.8% $P < 0.001$) treatment with norfloxacin (15.2% versus 12.7% $P < 0.001$), but had a higher recurrence rate (19.1% versus 16.4% $P < 0.001$) compared to those without DM.

Conclusions. Despite the fact that patients with DM more often received initial longer and more potent treatment than patients without DM, pre- and postmenopausal women with DM more often had recurrences of their UTI's.

Diabetes Mellitus (DM) is an increasingly important endocrine disease. Incidence of infections is increased in diabetes (type 1 and type 2) patients compared to controls (1), (2) and the urinary tract is the most prevalent site of these infections (3). Furthermore, diabetes patients with a UTI develop more often severe and rare complications such as emphysematous cystitis and papillary necrosis (4), (5). Studies addressing differences in UTI recurrence rates between diabetic patients and controls show contradictory results for uncomplicated lower (2), (6) and upper UTI (7), (8). At this moment there are no controlled clinical trials investigating the optimal antimicrobial treatment strategy in diabetes patients with UTI. Current recommendations rely on the opinion of experts (5), (9). It is generally recommended to treat UTI's in diabetic patients with antibiotics with high tissue penetration during 7-14 days. Importantly, we lack data on the clinical practice how diabetes patients with a UTI are actually treated, to assess recurrence rates.

The aims of this study are to describe the treatments (duration and agents) for uncomplicated UTI's in women with and without diabetes in the Netherlands and to analyze recurrence rates of these UTI's within 30 days after the last treatment.

MATERIALS AND METHODS

Database- Data were obtained from the PHARMO Record Linkage System. The PHARMO Institute is an independent scientific research organisation dedicated to study drug use and outcomes in daily practice in the Netherlands. This PHARMO Record Linkage System includes, among other databases, the drug-dispensing records from community pharmacies linked to hospital discharge records of more than two million community-dwelling inhabitants of 40 demographically well defined Dutch regions. For all residents, the computerized drug-dispensing histories contain data concerning the dispensed drug, prescriber

specialty, dispensing date, dispensed amount, prescribed dose regimens, and the legend duration of use (prescription length). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification. The hospital records include detailed information concerning the primary and secondary diagnoses, procedures, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (<http://www.pharmo.nl/>). Data between the first of January 1999 and 31 December 2005 were used.

Study population

Inclusion criteria

- Data of all women older than 12 years old, receiving at least one prescription of trimethoprim, norfloxacin, nitrofurantoin or fosfomycin (6) in the period after the first of January 1999 and first of January 2006 with follow-up data of at least 30 days were extracted.

Following the Dutch guidelines, trimethoprim/sulfamethoxazole (TMP/SMX), amoxicillin and fluorquinolones other than norfloxacin are rarely prescribed for an uncomplicated UTI because of the high resistance rates (<http://www.swab.nl>) in the Netherlands or due to the advice to preserve these antibiotics for complicated UTIs.

Exclusion criteria

To limit the study population to women with uncomplicated UTI's we wanted to exclude all women with possible recurrent UTI's because of secondary diseases or underlying abnormalities. Therefore all factors that belong to the definition of complicated UTI's (10) were considered exclusion criteria:

- Pregnancy (delivery during the follow-up period or folic acid prescription in the preceding year and during the follow-up)
- Patients with known anatomical abnormalities, for example

- indwelling urinary catheter or hospitalization for a urethral stricture in the follow-up period
- The use of the following medication in the preceding year and during the follow-up:
 - Antiretroviral treatment for human immunodeficiency virus infection (HIV)
 - Immune suppressive drugs
 - Chemotherapy
 - Medication for renal insufficiency, such as calcium binding agents
 - Patients receiving a first prescription with duration of more than 30 days
 - Patients with a second prescription within 5 days after their first prescription, indicating acute side effects or loss of recipe or medication, were excluded.
 - Patients receiving in the preceding year: trimethoprim, norfloxacin, nitrofurantoin or fosfomycin, indicating prophylaxis for recurrent UTI

Outcome parameters - The primary outcome was the prescription for a second antibiotic course or a hospitalisation admission for a UTI during the follow-up period.

Definitions - The cohort-entry date was defined as the day that the patient received her first prescription trimethoprim, norfloxacin, nitrofurantoin or fosfomycin. The history period was defined as one year before study inclusion. The follow-up period was defined as the duration of the first prescription plus 30 days after the cohort entry date.

Patients with DM were defined by prescription of one or more glucose-lowering medication (tablets or insulin) in the history or in the follow up period.

Pre-menopausal women were defined as 55 years or younger at the dispensing date of their first prescription. Postmenopausal women were women older than 55 years at the moment of the dispensing date of their first prescription. This is a conservative

definition of postmenopausal women, since the worldwide mean age of menopause is 49.2 years .

A 'new' diagnosis of UTI (inclusion criteria for this study) was defined as a patient with no prescription for trimethoprim, norfloxacin, nitrofurantoin or fosfomycin in the history (one year) and a first prescription for trimethoprim, norfloxacin, nitrofurantoin or fosfomycin in the period from the first of January 1999 to 31 December 2005. The first prescription is always one of the following antibiotics trimethoprim, norfloxacin, nitrofurantoin or fosfomycin. A recurrent UTI was defined as a prescription for trimethoprim, norfloxacin, nitrofurantoin or fosfomycin, or amoxicillin, fluoroquinolones, amoxicillin/clavulanic-acid or trimethoprim/sulfamethoxazole (TMP/SMX) in the follow up period (5 days after the first prescription till 30 days after the end of the first prescription) or hospitalization admission with the diagnosis of a UTI. These recurrences could be relapses (second infection with the same organism) or reinfections (second infection with a different organism)., Hospital admissions were included as cases diagnosed according to ICD-9 system with either an infection of the kidneys (590), or cystitis (595), or urethritis (not sexually transmitted)(597), or urethral syndrome(597) or other disorders of urethra and urinary tract (599).

Some of the above mentioned antibiotics for a recurrent UTI could also be used for other diseases than UTI's. To exclude antibiotics prescriptions for other infections than a UTI all analyses were repeated with the use of co-medication, defined as medication given at the same moment as the antibiotic for a recurrent UTI from one of the following ATC groups: A (gastrointestinal), D (skin), R (respiratory) and S (ear, eye). Similarly, analyses were repeated with prescriptions from other specialties than GP's excluded.

Aggressive treatment for a UTI was defined as a treatment with an antibiotic that has high tissue penetration (in kidney and

prostate). For the first prescription agents only norfloxacin has this potency.

Statistical analyses and ethics - Data were analyzed using SPSS software for Windows, version 14.0. Medication use and recurrence rate were compared between women with and without diabetes. Analyses were done with a Chi square test. We corrected for age by comparing different age strata. A p-value < 0.05 was considered to be statistically significant.

Ethical approval was not necessary because all data were anonymized before entering the PHARMO database. Researchers only have information on gender and age of the patient. All other identifying information is deleted after the linkage with the hospital records from the national registry. This approach has been approved by the Dutch Data Protection Authority (6).

RESULTS

Study population

Inclusion criteria - Initially, the database consisted of 246,306 women who were 12 year or older and received a prescription for trimethoprim, norfloxacin, nitrofurantoin or fosfomycin in the study period (See Figure 1).

Exclusion criteria - A total number of 21,808 women were excluded with different reasons (see Figure 1) and another 15,539 women were excluded because they had a UTI in the year before the cohort-entry date. Finally the study included 210,624 women: 10,366 women with DM (17.5% premenopausal <=55 years) and 200,258 women without DM (68% premenopausal) were included.

Premenopausal women - Baseline characteristics of the premenopausal women are shown in Table 1. Percentage prescriptions with norfloxacin were significantly higher and the treatment duration was significant longer in premenopausal women with DM compared to those without. The recurrence rate (Table 2) was significantly higher in premenopausal women with diabetes: 16.1% in women with DM and 12.2% in women without DM ($P =$

0.002). There was no significant difference between hospitalisation of women with and without diabetes (0.1% versus 0.1%, $P = 0.790$). In both analyses the results were similar in age strata.

Postmenopausal women - Baseline characteristics of the postmenopausal women are shown in Table 1. Percentage prescriptions with norfloxacin were significantly higher and the treatment duration was significantly longer in postmenopausal patients with DM compared to those without. The recurrence rate (Table 2) was significantly higher in postmenopausal women with diabetes: 19.1% in women with and 16.4% in women without DM ($P < 0.001$). There was a significant difference in hospitalisation frequency between postmenopausal women with and without DM (0,3% versus 0,2%, $P = 0.003$). A total number of 23 of the postmenopausal women with diabetes and 83 without DM were hospitalized because they had an infection at the kidneys or other disorder of the urinary tract. In both analyses the results were similar in age strata.

Secondary analyses - Therapeutic courses given to diabetic (DM+) or non-diabetic (DM-) pre- or postmenopausal women were consistent with the Dutch guidelines (see Discussion) in respectively 71% (premenopausal DM+), 79,8% (premenopausal DM-), 51,8% (postmenopausal DM+), and 55,4% (postmenopausal DM-) of the cases.

General practitioners (GPs) prescribed 92.0-96.1% of the antimicrobials in all patient groups. When all analyses were repeated with only the prescriptions by the GPs similar results were found. The same was true when all analyses were repeated after exclusion patients who were using co-medication at the time of the antibiotic prescription.

DISCUSSION

In this study, we found that both pre- and postmenopausal women with diabetes receive longer and more potent antimicrobial treatment for uncomplicated UTI's

compared to pre- and postmenopausal women without diabetes. However, despite this more aggressive treatment, both pre- and postmenopausal women with diabetes had more recurrences of their UTI's than women without diabetes. Besides that, hospitalisation for complications of the UTI was significantly more often seen in postmenopausal women with diabetes.

The choice for a more potent antibiotic was not to treat a recurrent UTI, since all patients with a UTI in the previous 12 month were excluded. The percentages of women with a recurrent UTI were comparable to the results found by Lawrenson et al. (7), who demonstrated that overall 14% of 75,045 newly treated patients with a UTI (0,7% of all patients had diabetes) received a second antibiotic within 28 days.

The longer prescription period for diabetes patients with an uncomplicated UTI with norfloxacin is not in accordance with the national Dutch guideline in use in the study period. The recommendation in the national Dutch guideline 1999 in use during the study period for an uncomplicated UTI was a 3-day oral antimicrobial regimen with either nitrofurantoin 100mg tid or trimethoprim 300mg once daily for patients with and without DM (11). There were no differences in antimicrobial resistance percentages of causative uropathogens, isolated in the period as the present study between women with and without DM (12). Treating physicians may have been chosen for longer treatment duration and a more aggressive antibiotic due to the higher risk of complications of UTI's .

Postmenopausal women with diabetes were significantly more often admitted to the hospital than women without diabetes. These results are comparable to those from a Canadian study which demonstrated that patients with diabetes more often had a hospitalization or physician claims for an infectious disease than patients without diabetes (1). However, in contrast to the mortality rate outside the hospital, the mortality rate inside the hospital is not higher in patients with diabetes (1), (3). So it

seems possible that physicians refer patients with DM faster and treat them more aggressively in the hospital compared to patients without DM.

To our knowledge this is the first study of its kind with this amount of (more than 200.000) patients. In addition, in contrast to most earlier studies in which the recurrence rate of UTI's were described (2), (6), (7), we also compared the different treatment strategies between women with and without DM and analyzed pre- and postmenopausal women separately. The risk factors for UTI's are partly different in pre- and postmenopausal women (13), (14) and therefore they should not be regarded as identical entities. Furthermore, it is only possible to interpret the recurrence rates when the initial treatment strategies of the two groups are known.

This study has several limitations. In the first place it is retrospective and we do not have records on the reasons of the treating physician were when prescribing a specific antimicrobial agent or a longer duration. It can be possible that diabetes patients more often had symptoms of a UTI with tissue invasion (pyelonephritis or urosepsis)(15),(16). We have shown before that only 0.5% of the diabetes patients with a UTI had clinical symptoms of a pyelonephritis (17) compared to 0,2% in controls. Although, others have demonstrated that the risk ratio for pyelonephritis in patients with compared to those without diabetes ranges from 1.86 to 4.4 (18), (19). These numbers make clear that even when more women with DM had clinical symptoms of a pyelonephritis and therefore were treated with norfloxacin during a longer period, this can not totally explain the demonstrated differences. It therefore seems likely that the physician took the diabetes status into account when prescribing antibiotic therapy. Based on drugs dispensing data we may have missed diabetic women treated with diet and exercise only. On the other hand, we know that many patients with DM are not diagnosed (20) so any definition of diabetes

in this type of database research has imperfections. Furthermore it is not possible to distinguish between diabetes type 1 and type 2 because patients in both groups could receive a treatment with insulin. This division is for this study not that important, because in an earlier study we showed a comparable incidence of UTI in patients with diabetes type 1 and type 2 (21). Unfortunately, because we did not have urine cultures results we were not able to distinguish between a relapse and a reinfection, which could have influenced the subsequent treatment decision.

Furthermore, because follow up was only 30 days, it is possible that pregnant women might have been misclassified (delivery after > 30 days). Another limitation is that the level of sexual activity was unknown despite the fact that this is an important risk factor for UTI in premenopausal women. However, we do not expect that a higher percentage of pregnant women (and therefore women with a complicated UTI) were included in the diabetic women group or that diabetic women had a higher frequency of sexual intercourse. Moreover, pregnant women with a UTI are mostly treated with

amoxicillin/clavulanic-acid or a cephalosporin in the Netherlands and therefore would not have been included in this study at all. Therefore it is unlikely that this possible misclassification or lack of information on risk factors would have influenced our results.

Furthermore, no differences were found after analyzing only the prescriptions of the GPs. Another limitation is that women with a recurrence could have underlying anatomical abnormalities like bladder neuropathy. Therefore, we excluded all women who had a UTI in the previous year to minimize this group.

In conclusion, we showed that both pre- and postmenopausal women with diabetes and a UTI receive a more aggressive and longer treatment, but still have more recurrences of their UTI's than women without diabetes. Whether therapy with a longer duration or an antibiotic with high tissue penetration contributes to lower recurrence rates needs further investigation. Therefore, a prospective randomized control trial with different treatments strategies must answer the question which treatment strategy is optimal in diabetic women with a UTI.

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TABLE 1_ Treatment of urinary tract infections (UTI's) in pre- and postmenopausal women with and without Diabetes Mellitus (DM).

| | Premenopausal women | | | Postmenopausal women | | |
|--|---------------------|-----------------|---------|----------------------|----------------|---------|
| | With DM | Without DM | P-value | With DM | Without DM | P-value |
| Total Number(N) | 1,817 | 136,195 | | 8,549 | 64,063 | |
| Age (median (25 ^e ;75 ^e)) | 47 (38;52) | 34 (23;44) | | 75 (67;81) | 70 (62;79) | |
| % Use of insulin | 892 (49.1%) | 0 (0.0%) | | 2,830 (33.1%) | 0 (0.0%) | |
| % Use of oral antidiabetics | 1,163 (64.0%) | 0 (0.0%) | | 6,841 (80.0%) | 0 (0.0%) | |
| % trimethoprim | 773 (42.5%) | 63,094 (46.3%) | 0.001 | 3,499 (40.9%) | 27,573 (43.0%) | <0.001 |
| % nitrofurantoin | 847 (46.6%) | 64,357 (47.3%) | 0.588 | 3,737 (43.7%) | 28,239 (44.1%) | 0.520 |
| % fosfomicin | 2 (0.1%) | 245 (0.2%) | 0.484 | 15 (0.2%) | 136 (0.2%) | 0.483 |
| % norfloxacin | 195 (10.7%) | 8,499 (6.2%) | <0.001 | 1,298 (15.2%) | 8,115 (12.7%) | <0.001 |
| Treatment duration<= 5 | 1,336 (73.5%) | 110,024 (80.8%) | <0.001 | 5,748 (67.2%) | 45,617 (71.2%) | <0.001 |
| Treatment duration > 5 | 481 (26.5%) | 26,171 (19.2%) | <0.001 | 2,801 (32.8%) | 18,446 (28.8%) | <0.001 |

TABLE 2 - Recurrence rates and treatment of a recurrent UTI in pre- and postmenopausal women with and without DM.

| | Premenopausal women | | | Postmenopausal women | | |
|--|---------------------|----------------|---------|----------------------|----------------|---------|
| | With DM | Without DM | P-value | With DM | Without DM | P-value |
| Total Number(N) | 1,817 | 136,195 | | 8,549 | 64,063 | |
| % Second prescription | 292 (16.1%) | 16,586 (12.2%) | 0.002 | 1,636 (19.1%) | 10,498 (16.4%) | <0.001 |
| % Hospitalization | 2 (0.1%) | 124 (0.1%) | 0.790 | 25 (0.3%) | 97 (0.2%) | 0.003 |
| % trimethoprim ¹ | 53 (18.2%) | 3,176 (19.1%) | 0.667 | 306 (18.7%) | 1,871 (17.8%) | 0.387 |
| % nitrofurantoin ¹ | 82 (28.1%) | 5,848 (35.3%) | 0.011 | 476 (29.1%) | 3,153 (30.0%) | 0.440 |
| % fosfomicin ¹ | 0 (0.0%) | 37 (0.2%) | 0.419 | 1 (0.1%) | 24 (0.2%) | 0.165 |
| % norfloxacin ¹ | 54 (18.5%) | 2,449 (14.8%) | 0.076 | 351 (21.5%) | 2,252 (21.5%) | 0.998 |
| % amoxicillin ¹ | 28 (9.6%) | 1,603 (9.7%) | 0.965 | 112 (6.8%) | 664 (6.3%) | 0.423 |
| % amoxicillin/clavulanic acid ¹ | 26 (8.9%) | 1,192 (7.2%) | 0.261 | 129 (7.9%) | 716 (6.8%) | 0.116 |
| % TMP/SMX ¹ | 22 (7.5%) | 1,183 (7.1%) | 0.792 | 97 (5.9%) | 784 (7.5%) | 0.026 |
| % ciprofloxacin ¹ | 17 (5.8%) | 783 (4.7%) | 0.380 | 120 (7.3%) | 774 (7.4%) | 0.957 |
| % fluoroquinolones ^{1,2} | 10 (3.4%) | 315 (1.9%) | 0.060 | 44 (2.7%) | 260 (2.5%) | 0.608 |

FIGURE 1 - Numbers of included and excluded women in the total study group.

