Risk of recurrent acute lower urinary tract infections and prescription pattern of antibiotics in women with and without diabetes in primary care

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Background. Women with diabetes have an increased risk of urinary tract infections (UTIs), especially recurrences.

Aim. To investigate diabetes characteristics associated with the risk of recurrent lower UTIs and the antibiotic prescription pattern.

Methods. In an exploratory retrospective study involving 7063 women aged ≥30 years, we studied the incidence of recurrent UTI (relapses and reinfection) in women with (n = 340) and without diabetes (n = 6618). Multivariable logistic regression and multilevel multinomial logistic analyses were used to determine the adjusted associations between diabetes characteristics and recurrent UTI [odds ratio (OR); 95% confidence interval (CI)] and the influence of diabetes on the pattern of antibiotic prescriptions for UTI, respectively.

Results. Relapses and reinfections were reported in 7.1% and 15.9% of women with diabetes versus 2.0% and 4.1% of women without diabetes. There was an independent higher risk of recurrent UTI in women with diabetes compared with women without diabetes (OR 2.0; 95% CI 1.4–2.9). Women taking oral blood glucose-lowering medication (OR 2.1; 95% CI 1.2–3.5) or insulin (OR 3.0; 95% CI 1.7–5.1) or who had had diabetes for ≥5 years (OR 2.9; 95% CI 1.9–4.4) or who had retinopathy (OR 4.1; 95% CI 1.9–9.1) were at risk of recurrent UTI. The pattern of antibiotic prescriptions for UTI was not influenced by diabetes.

Conclusions. Women with diabetes ≥5 years or with glucose-lowering medication or with retinopathy have an increased risk of recurrent UTI. Diabetes itself does not seem to influence the antibiotic prescription pattern. Research focusing on effective antibiotic treatment of UTI in women at risk of recurrence is needed and may help limit the development of antibiotic resistance.

Keywords. Antibiotics, diabetes, general practice, urinary tract infection.

Introduction

In the Netherlands, >700 000 adult women visit a GP annually for acute symptomatic urinary tract infections (UTIs). Over 10% of these UTI occur in patients with diabetes and an even higher percentage occurs in postmenopausal women with diabetes. Most of these infections are treated in primary care. They may cause worsening of glycaemic control, necessitating increased monitoring of blood glucose, reduce quality of life and cause substantial costs due to treatment and sick leave. In general practice, adult women with diabetes are at increased risk of UTI, especially recurrences. However, the association between recurrent UTI and diabetes characteristics, such as glycaemic control and vascular complications, has not been studied. This means that it is not possible to tailor treatment in women with diabetes and recurrent UTI, which may in turn encourage the emergence of resistance.

Diabetes guidelines do not provide advice about the type and duration of antibiotic treatment of UTI in people with diabetes. Moreover, most guidelines on UTI consider women with diabetes and a UTI to have a complicated infection. Some guidelines do not give any specific recommendations. Available treatment recommendations are based on limited evidence.
since there have been no controlled clinical trials assessing preferred antimicrobial treatment. In a study that made use of a registration database that included pharmacy dispensing data, the recurrence of UTI was not reduced in women with diabetes given longer courses of antibiotics and treatment with second- and third-line drugs. However, it is not known whether GPs prescribe antibiotics differently for women with and without diabetes. The aim of this study was to investigate diabetes characteristics associated with the risk of recurrent UTI in subgroups of women of age ≥30 years with type 1 or type 2 diabetes and the pattern of antibiotics prescribed by GPs for these patients.

Methods

We conducted an exploratory retrospective study in two primary care health centres (22,007 patients and 10 GPs) in a large city in the Netherlands (2000–4). Patient contacts had been registered in computerized medical records and were anonymized. All women aged ≥30 years (n = 7063) with and without diabetes were eligible to participate (Fig. 1).

Inclusion criteria

Having diabetes was defined by at least one patient contact with an International Classification of Primary Care (ICPC) code of diabetes (T90). Women with a history of diabetes starting before 30 years of age and who used insulin within 1 year of diagnosis were classified as having type 1 diabetes (n = 50). Women who used oral antidiabetic medication [Anatomical Therapeutical Chemical (ATC) code A10B] with or without insulin (ATC code A10A) or who where referred to a dietician but were not on medication were classified as having type 2 diabetes (n = 290). All other women were classified as not having diabetes (n = 6618).

Exclusion criteria

Women (n = 76) with complicated UTI [defined as pyelonephritis (U70) or as infections with an invasive systemic presentation, i.e. a temperature >38.0°C or shivers] were excluded, as were pregnant women (n = 28), and women (n = 1) who had undergone kidney transplantation. These women required specific management for UTI.

Definition of recurrent UTI

One UTI episode could include one or more visits (within a 3-day period) to the general practice. A new episode was defined as a UTI occurring after a 6-week period free of symptoms. In accordance with the guideline of the Dutch College of General Practitioners in use during the study period, a primary care diagnosis of acute UTI was usually not confirmed by culture and sensitivity analyses. Relapse was defined as the need to re-prescribe antibiotics between 4 days and 6 weeks after the first prescription, and ‘reinfection’ was defined as the need for a new prescription after 6 weeks. The combined outcome was recurrent acute symptomatic UTI, including both relapses and reinfections.

Diabetes characteristics.

Based on literature, clinical knowledge information was collected on duration of diabetes, diabetes medication, presence of microvascular complications (retinopathy), macrovascular complications (stroke, transient ischaemic attack, myocardial infarction and amputation) and the most recent measurement of HbA1c within 180 days of the occurrence of the UTI, as indicator of the degree of glycaemic control. Reliable information on kidney function or albuminuria was not available.

Confounding variables.

Based on literature, we collected data routinely available in a primary care setting on variables that might confound the association between diabetes and UTI, such as age, socioeconomic status (SES), urinary tract stones and atrophic or candida vaginitis. In the Netherlands, during the
study period, all people with an annual gross income level <€30 000 (60% of the population) were insured through the Sick Fund, and this variable is an accepted proxy for SES. We collected information on the presence of urinary tract stones (ICPC code U95), atrophic vaginitis (ICPC X84 or X11, in combination with ATC code of local oestriol, commonly prescribed by GPs for local oestrogen deficiency) and candida vaginitis (ICPC X84 or X72 in combination with ATC code of oral or local antimycotics).

**Antibiotics.** During the study period, the guideline in use recommended nitrofurantoin or trimethoprim for all cases of acute symptomatic uncomplicated UTI, but some GPs continued to prescribe amoxicillin in these cases (first-line antibiotics). Furthermore, amoxicillin with betalactamase inhibitor or trimethoprim–sulfamethoxazole were recommended (as second-line drugs) for complicated UTI or in case of side effects with the first-line drugs, with quinolones being reserved as third-line treatment. All antibiotic prescriptions for an episode of acute UTI were categorized into first-, second- or third-line drugs.

**Analysis**
This study was performed in a primary care setting and the number of person-years could not be calculated. Since patients in the Netherlands usually stay on a GP’s list for a long time, we calculated the mean time the different groups stayed in the cohort. The clinical characteristics of the study population were calculated as proportions or means (±SD) using SPSS for Windows (version 12.0; SPSS inc., Chicago, IL). The cumulative incidence of first infection, reinfection (two and three or more episodes) and relapse of UTI was compared between women with type 1 diabetes, type 2 diabetes and no diabetes, using chi-square tests for categorical variables. A P-value <0.05 was considered to indicate statistical significance. Multivariable logistic regression analysis was used to investigate the associations between diabetes characteristics and recurrent UTI, adjusted for confounding factors (age, SES, urinary tract stones and treated atrophic or candida vaginitis). Adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) are given as approximation of the relative risks. We tested the various diabetes characteristics for collinearity with the method of Kleinbaum. The pattern of antibiotic prescription is presented as categorical variable for first or recurrent episodes of UTI. In order to correct for possible clustering effects (GPs might prefer to prescribe certain antibiotics), we used a multilevel multinomial logistic regression model (MLWin version 2.02; www.cmm.bristol.ac.uk). The GP was the highest level in the analysis. To determine whether antibiotic prescription patterns were different for first and recurrent episodes of UTI and for subgroups of women with type 1 or type 2 diabetes versus no diabetes. We corrected for antibiotics, diabetes, recurrences and the number of GPs.

**Results**
The mean time women with and without diabetes remained in the cohort was about the same. More than 97% of the women were Caucasian. Women with diabetes were older, were more often insured with the Sick Fund, more often received treatment for candida vaginitis and had a higher incidence of recurrent UTI compared with women without diabetes. Relapses and reinfections were reported in 7.1% and 15.9% of women with diabetes versus 2.0% and 4.1% of women without diabetes (Table 1). Women with type 1 diabetes compared with those with type 2 diabetes had a longer history of diabetes (19 ± 4 versus 6 ± 4 years), had a higher HbA1c level (8.1% ± 1.8% versus 7.3% ± 1.3%) and a higher prevalence of retinopathy (28% versus10%). Macrovascular complications were present in 17% of women in both groups. Treatment for type 2 diabetes consisted of insulin with or without oral medication (21%), only oral medication (53%) or diet only (26%). All women with type 1 diabetes were on insulin (not in table).

**Recurrent UTI**
Women with diabetes were at risk of recurrent UTI (crude OR 3.6; 95% CI 2.5–5.1) compared with women without diabetes (Table 2). Type of diabetes and metabolic control did not influence the association between diabetes and the risk of recurrent UTI. After adjustment for confounders, women with a duration of diabetes ≥5 years, women who used oral hypoglycaemic agents or insulin and especially women with retinopathy were at risk of recurrent UTI. Subgroup analyses for both types of diabetes showed similar results. There was insufficient collinearity to influence the results of the analysis (highest $R^2$ 0.143) (not in table).

**Pattern of antibiotic prescriptions**
Multinomial logistic regression analysis showed that, for the combined group of women with and without diabetes, the pattern of antibiotic prescription was significantly different between first and recurrent episodes of UTI (Table 3). However, there was no significant difference in the pattern of prescription of second- and third-line antibiotics between women with or without diabetes (Table 4).

**Discussion**
Women aged ≥30 years with type 1 or type 2 diabetes have a two times higher risk of recurrent symptomatic
UTI than women without diabetes. Clinical characteristics, such as duration of diabetes, treatment (especially insulin) and retinopathy, were found to be risk factors for recurrent UTI. Despite these differences, GPs seemed to prescribe the same antibiotics for UTI in women with and without type 1 and type 2 diabetes.

Comparison with the literature

The higher risk of recurrent UTI in women with diabetes might be due to the high incidence of persistent or recurrent asymptomatic bacteriuria, a risk factor for new episodes of UTI, seen in women with diabetes.\textsuperscript{2,23}

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**TABLE 1** Clinical characteristics of the study population divided in women with type 1 diabetes (DM1), type 2 diabetes (DM2) and without diabetes (no DM)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>All women (6958), n (%)</th>
<th>DM1 (50), n (%)</th>
<th>DM2 (290), n (%)</th>
<th>No DM (6618), n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time in cohort (months, SD)</td>
<td>43 (1.5)</td>
<td>43 (1.9)</td>
<td>43 (0.8)</td>
<td>43 (1.5)</td>
<td>n.s</td>
</tr>
<tr>
<td>Caucasian</td>
<td>6748 (97.5)</td>
<td>49 (98)</td>
<td>280 (96.5)</td>
<td>6419 (96.9)</td>
<td>n.s</td>
</tr>
<tr>
<td>Mean age (years, SD)</td>
<td>51 (17)</td>
<td>63 (17)</td>
<td>66 (14)</td>
<td>51 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sick Fund as a proxy for SES</td>
<td>4885 (70)</td>
<td>42 (84)</td>
<td>243 (84)</td>
<td>4600 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrophic vaginitis</td>
<td>116 (2)</td>
<td>1 (2)</td>
<td>12 (4)</td>
<td>104 (2)</td>
<td>0.022</td>
</tr>
<tr>
<td>Candida Vaginitis</td>
<td>252 (4)</td>
<td>7 (14)</td>
<td>33 (11)</td>
<td>212 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary tract calculi</td>
<td>54 (0.8)</td>
<td>0</td>
<td>2 (0.7)</td>
<td>52 (0.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Incidence ≥1 UTI</td>
<td>914 (13)</td>
<td>16 (32)</td>
<td>103 (36)</td>
<td>795 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 UTI</td>
<td>586 (8.3)</td>
<td>8 (16.0)</td>
<td>57 (19.7)</td>
<td>521 (7.9)</td>
<td>0.02a</td>
</tr>
<tr>
<td>Reinfecion 2 UTI</td>
<td>216 (3.7)</td>
<td>5 (10.0)</td>
<td>29 (10.0)</td>
<td>182 (2.8)</td>
<td>0.01a</td>
</tr>
<tr>
<td>Reinfecion ≥3 UTI</td>
<td>112 (2.5)</td>
<td>3 (6.0)</td>
<td>17 (5.8)</td>
<td>92 (1.4)</td>
<td>0.02a</td>
</tr>
<tr>
<td>Relapsed UTI (within the above episodes)</td>
<td>157 (2.9)</td>
<td>3 (6.0)</td>
<td>21 (7.2)</td>
<td>133 (2.0)</td>
<td>0.08a</td>
</tr>
</tbody>
</table>

Values are given as means with SD or numbers with percentages. NA, not applicable.

\textsuperscript{a}P DM1 versus no DM.

\textsuperscript{b}P DM2 versus no DM.

**TABLE 2** Associated risk of combined recurrent episodes of UTI in women with diabetes compared to those without diabetes (=reference), by characteristics (exposures) of interest

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes all types</td>
<td>3.6 (2.5–5.1)</td>
<td>2.0 (1.4–2.9)</td>
</tr>
<tr>
<td>Diabetes Type 1</td>
<td>3.5 (1.5–8.2)</td>
<td>1.9 (0.7–4.8)</td>
</tr>
<tr>
<td>Diabetes Type 2</td>
<td>3.6 (2.5–5.2)</td>
<td>2.0 (1.3–3.1)</td>
</tr>
<tr>
<td>Duration &lt;5 years</td>
<td>2.0 (1.0–4.3)</td>
<td>1.1 (0.5–2.5)</td>
</tr>
<tr>
<td>Duration ≥5 years</td>
<td>5.3 (3.6–7.9)</td>
<td>2.9 (1.9-4.4)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>1.0 (0.3–3.3)</td>
<td>0.6 (0.2–2.1)</td>
</tr>
<tr>
<td>Oral</td>
<td>3.8 (2.3–6.2)</td>
<td>2.1 (1.2–3.5)</td>
</tr>
<tr>
<td>Insulin</td>
<td>5.3 (3.2–8.8)</td>
<td>3.0 (1.7–5.2)</td>
</tr>
<tr>
<td>HbA1C &lt;7.0%</td>
<td>5.5 (3.0–10.2)</td>
<td>2.9 (1.7–5.0)</td>
</tr>
<tr>
<td>HbA1C &gt;7.0%</td>
<td>5.4 (3.4–8.5)</td>
<td>3.0 (1.6–5.4)</td>
</tr>
<tr>
<td>Macrovascular complications</td>
<td>3.9 (1.8–8.6)</td>
<td>1.8 (0.8–4.0)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>8.3 (4.2–16.8)</td>
<td>4.1 (1.9–9.1)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adjusted for age, SES, atrophic vaginitis and candida vaginitis.

Moreover, at the time the study was performed, GPs usually started antibiotic therapy empirically, without prior culture and sensitivity testing.\textsuperscript{11,19} This might have increased the risk of recurrent infections by favouring antibiotic resistance. A retrospective study performed when the same treatment guideline was in force as in our study showed no reduction in UTI recurrence when longer courses of antibiotics and more second- and third-line drugs were prescribed,\textsuperscript{15} which suggests that it is unlikely that resistance developed to antibiotics prescribed in accordance with the guidelines used.

The risk of recurrent UTI was higher in women who had had diabetes for ≥5 years. This finding is in contrast with a previous case–control study (117 women with 97% type 2 diabetes) in which the risk of acute UTI in postmenopausal women was not influenced by the duration of diabetes.\textsuperscript{3} However, a longer duration of diabetes as a risk factor for recurrent UTI is in line with the increased risk of women with longstanding complications of diabetes, such as retinopathy. An underlying mechanism may be the association between
First-line antibiotics and women without DM as reference categories.

<table>
<thead>
<tr>
<th>Guideline recommended antibiotics</th>
<th>DM1 (n = 50)</th>
<th></th>
<th>DM2 (n = 290)</th>
<th></th>
<th>No DM (n = 6618)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prescriptions</td>
<td></td>
<td>Prescriptions</td>
<td></td>
<td>Prescriptions</td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td>12</td>
<td>Reference</td>
<td>90</td>
<td>Reference</td>
<td>583</td>
<td>Reference</td>
</tr>
<tr>
<td>Second line</td>
<td>2</td>
<td>0.47</td>
<td>9</td>
<td>0.86</td>
<td>100</td>
<td>Reference</td>
</tr>
<tr>
<td>Third line</td>
<td>15</td>
<td>0.50</td>
<td>71</td>
<td>0.62</td>
<td>449</td>
<td>Reference</td>
</tr>
</tbody>
</table>

First-line antibiotics and women without DM as reference categories.

*P DM1 versus no diabetes.

**P DM2 versus no diabetes.

microvascular damage to the bladder innervation, resulting in incontinence and UTI. In the present study, we did not find the level of glycaemic control to be associated with acute UTI comparable to earlier findings. Therefore, the increased risk of UTI in women with diabetes may be associated with factors such as increased adherence of bacteria to the uroepithelial cells, asymptomatic bacteriuria and other host factors rather than with glycaemic control. Although the independent risks in the multivariable analysis for type 1 and type 2 diabetes were similar, findings were not significant for the type 1 diabetes group, possibly due to the smaller sample size. Further adjustment for confounders such as age, SES and history of both atrophic and candida vaginitis slightly reduced the various associations but otherwise did not influence the general results, indicating the results are robust.

In the present study, which lasted 3.5 years and involved an unselected primary care population, the prevalence of recurrent UTI in women with diabetes was comparable to that reported in a recent large retrospective study lasting 1 month. However, in the latter study, clinical characteristics of interest were not taken into account nor the difference between type 1 (mostly treated by specialists) and type 2 (mostly treated by GPs) diabetes. Moreover, drug-dispensing records were analysed without correction for clustering at a practice level.

GPs chose the same type of antibiotic treatment for first and recurrent episodes of lower UTI in women with and without diabetes. The recently updated guidelines of the Dutch College of General Practitioners on ‘Urinary Tract Infections’ recommend that culture and sensitivity tests be performed for all women with diabetes and an acute lower UTI and that prolonged empirical treatment (7 instead of 5 days) be given with the same antibiotics that are recommended for women without diabetes. Thus, the Dutch guidelines for the management of UTI in women with diabetes take a position between those that consider a lower UTI in all women with diabetes automatically as a complicated UTI and those that do not mention diabetes as a special group. However, there is limited evidence supporting culture and sensitivity testing for all women with diabetes and acute lower UTI since comparable species of microorganisms with comparable patterns of resistance to antibiotics cause UTI in women with and without diabetes. Moreover, the efficacy of prolonged first-line antimicrobial treatment has not been tested in randomized clinical trials. Until such trials have been performed and given the increased risk of recurrent UTI, we suggest a tailored approach to the choice of antibiotic treatment for women with diabetes in general practice. This may include first-line antimicrobials and should take the diabetes risk factors associated with recurrent UTI identified in this study and the presence of asymptomatic bacteriuria into consideration. Until randomized trials have been carried out, we propose that not all women with diabetes should get their urine tested (culture and sensitivity) at the end of the treatment as has been proposed by the current Dutch guideline but only those with one of the risk factors of recurrence. If indicated, either a prolonged course of antibiotics or an antibiotic that matches the sensitivity pattern should be considered. This approach may limit the number of prescriptions of antibiotics for women with diabetes and recurrent UTI and thereby contribute to limiting drug resistance in the community. To diminish the number of recurrent UTI in women with diabetes, studies of the effectiveness of treatment of asymptomatic bacteriuria, especially in women at higher risk, are warranted.

**Strengths and limitations of the study**
A strength of this cohort study is the unselected source of clinical data, including prescriptions of antibiotics and adjustment for the effects of collinearity and clustering in the analyses. There were some limitations. First, there may have been diagnostic misclassification. In general practice, the diagnosis of acute symptomatic UTI was made, according to the guidelines used, by positive dip slide, leukocyte esterase or nitrite tests, and in many instances, the diagnosis was not confirmed by culture and sensitivity testing. The problem of misclassification was taken into account by defining a UTI episode on the basis of an ICPC code or a history or laboratory findings consistent with a UTI in
combination with prescription of an antibiotic recorded in the patient’s record. Self-limiting episodes of UTI were excluded. We did not have access to specific data on anatomical abnormalities of the urinary tract or of compromised immune system of patients, but since we excluded women with pyelonephritis or infections with an invasive or systemic presentation, we think that few women were misclassified. It could also be argued that diabetes could have been misclassified by using ICPC and ATC codes, given that some cases may have been undiagnosed. Such misclassification would be non-selective and therefore might result in a bias towards the null value of any observed association. Secondly, selection bias could have been introduced by differences in the care-seeking behaviour of patients with and without diabetes. However, women would have recognized recurrent UTIs as such and started treatment.

Patients with a low SES visit the GP more often and this could have caused selection bias, a possibility that we cannot rule out. Thirdly, we did not have access to data on the duration of treatment. However, during the study period, there were no guidelines supporting longer duration of antibiotic treatment for women with diabetes. Therefore, we focused on the types of antibiotics. Fourthly, we did not have records on sexual activity, an important risk factor for recurrent UTIs in younger women; however, we did have records on candida vaginitis and atrophic vaginitis, which are important confounders of an increased risk of recurrent acute UTI, especially in older postmenopausal women. Therefore, we were able to control for these important confounders in the multivariable model. Lastly, the generalizability may be limited since we studied women from only one large city in the Netherlands and the number of women with type 1 diabetes was limited. However, the incidence of UTI in women >30 years without diabetes in the present exploratory retrospective study was similar to that reported in a large prospective multicentre cohort study in primary care.

In addition, the population of this study was mostly Caucasian, which would limit the generalizability of our findings to other ethnic groups.

**Conclusion and implications**

Our general practice study clearly showed that recurrent UTI are common in women with longstanding diabetes, especially those who are on insulin therapy or who have retinopathy. GPs could consider a more tailored approach in women with diabetes. However, they do not seem to take the risk of recurrent UTI due to diabetes into consideration when prescribing antibiotics to affected women. Therefore, randomized clinical trials focusing on effective antibiotic treatment of UTI in women with diabetes, especially those at high risk of recurrence, are needed. This could support the development of evidence-based guidelines and limit the development of resistance.

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**Declaration**

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Ethical approval: none.

Conflict of interest: none.

**References**


Women with diabetes risk recurrent UTIs