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Incidence and antibiotic prescription rates for common infections in patients with diabetes in primary care over the years 1995 to 2003


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KEYWORDS
Antibiotics; Diabetes; Infection; General practice; The Netherlands

Summary

Objective: To assess changes in incidence and in antibiotic prescription rates for infections of the lower respiratory tract (LRTI) and urinary tract (UTI) in patients with diabetes (DM) over the years 1995 to 2003.

Methods: This was a retrospective cohort study as part of the University Medical Center Utrecht General Practitioners Research Network. We included patients with DM aged ≥45 years. We assessed incidence and antibiotic prescription rates for LRTI and UTI. Incidence rates were calculated as episodes per 1000 person-years. Antibiotic prescription rates were calculated per 100 episodes of LRTI and UTI.

Results: The study population increased over the years 1995 to 2003. The male-to-female ratio and mean age of the study population remained constant over these years. The incidence rate for LRTI remained stable (13%; p = 0.442), and for UTI the incidence rate increased by 40% (p = 0.037). Antibiotic prescription rates increased in LRTI by 60% (p < 0.001) and in cystitis by 15% (p = 0.029).

Conclusions: Incidence rates for UTI and antibiotic prescription rates for LRTI in diabetes have increased over the years 1995 to 2003. In particular, attention should be paid to the increasing use of antibiotics in DM patients with LRTI.

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Introduction

Patients with diabetes (DM) have an increased risk of urinary tract infections (UTI) and lower respiratory tract infections (LRTI), in particular when they are treated with oral diabetes medication or insulin. Also, common infections may be more difficult to treat and often recur, and diabetes even
inpatient care has occurred,\textsuperscript{12} although in general, traditional antibiotic prescriptions have been the first choice treatment for UTI since 1989, and from 1989 to 1999 sulfamethizole was an additional alternative.\textsuperscript{10} Regarding exacerbations of chronic obstructive pulmonary disease (COPD), since 1997, antibiotics (amoxicillin, doxycycline, or other broad-spectrum antibiotics) have only been advised in high-risk cases.\textsuperscript{11} In 30\% of consultations for LRTI, an antibiotic is prescribed, and over the last 10 years a shift towards more costly, broad-spectrum antibiotic usage in outpatient care has occurred,\textsuperscript{12} although in general, traditional antibiotics provide similar outcomes compared to the newer ones.\textsuperscript{13,14}

Any benefit from antibiotics must be weighed against the possibility that excessive antibiotic use will increase patient morbidity and enhance antimicrobial resistance.\textsuperscript{15–17} In studying prescription rates, both the number of prescriptions and the incidence of the diseases under study have to be taken into account. Such data will help in making decisions about treatment and will allow health education programs to be tailored to diabetes care providers and patients. However, changes in the prescription of antibiotics for common infections in patients with DM over a period of several years are unknown. Therefore, we sought to assess the changes in incidence and in antibiotic prescription rates for LRTI and UTI in patients with DM over a number of years.

Methods

Patients

A retrospective cohort study was conducted using data from the computerized medical database of the University Medical Center Utrecht General Practitioners Research Network. This database consists of prospectively collected information on a cumulative primary care population of approximately 60,000 patients over the years 1989 to 2004. From 1995 onwards, medical data of all patients enlisted were recorded using a uniform, structured, contact registration in the general practitioner information system (GPIS) ELIAS\textsuperscript{18} (iSOFT). Approximately 35 participating general practitioners (GPs) received continued medical education from staff at the Julius Center of Health Sciences and Primary Care regarding the correct coding of diagnostic information according to the International Classification of Primary Care coding system (ICPC).\textsuperscript{19} GPs received feedback about the quality of registration (i.e., the proportion of contacts with an ICPC code). Ultimately, more than 90\% of contacts received an ICPC code, and accuracy appears high and was insured through financial arrangements. All prescriptions were recorded in the database, including drug name, Anatomical Therapeutic Chemical (ATC) classification code,\textsuperscript{19} dosage form, dose, and prescribed quantity. Decisions concerning diagnosis and treatment were left to the discretion of the GP. Patients and GP identifiers were recorded to ensure anonymity. The system complies with Dutch guidelines on the use of medical data for research purposes and has been shown to be valid in pharmaco-epidemiological studies.\textsuperscript{20,21}

Patients aged 45 years or older recorded in the GPIS with diabetes (ICPC code T90) were included. No patients were excluded.

Outcomes

The outcomes investigated were episodes of LRTI and UTI, rates of antibiotic prescription, and rates of type of antibiotic prescribed. LRTI was defined as pneumonia (R81), acute bronchitis (R78), and exacerbations of chronic bronchitis, COPD, or asthma. Exacerbations were recorded by GPs by the use of R78 in cases of chronic bronchitis, asthma, or COPD.\textsuperscript{22} UTI was defined as cystitis (U71), prostatitis (Y73), or acute pyelonephritis (U70). A new episode was recorded if a patient was free of complaints for a period of 28 days. We did not differentiate between a first episode, a relapse, or a recurrence of a registered infection. Since there was no direct link in the database between a disease episode and antibiotic prescription, we defined a time window beginning seven days before and ending seven days after the diagnosis.

Antibiotics prescribed for LRTI were classified into the following main categories: (1) broad-spectrum penicillins (J01CA/R): amoxicillin (J01CA04) and co-amoxiclav (J01CR02); (2) tetracyclines (J01AA): doxycycline (J01AA02); (3) macrolides (J01FA); (4) sulfonamides and trimethoprim (J01E); (5) other: quinolones (J01MA), fluoroquinolone (J01CF), and cephalosporins (J01D). The classification of antibiotics used for UTI was: (1) broad-spectrum penicillins (J01CA/R): amoxicillin (J01CA04) and co-amoxiclav (J01CR02); (2) quinolones (J01MA); (3) sulfonamides and trimethoprim (J01E); (4) nitrofurantoin (J01XE); (5) other: tetracyclines (J01AA), macrolides (J01FA), fluoroquinolone (J01CF), and cephalosporins (J01D).

Statistical analysis

Annual incidence rates of presented episodes of infections were calculated per 1000 person-years by dividing the number of UTI and LRTI episodes by the total number of person-years in a specific year. Average incidence rates were calculated for all years combined. Antibiotic prescription rates were calculated as the number and type of prescriptions per 100 episodes of UTI and LRTI registered in the database. Changes between 1995 and 2003 were studied by year beginning seven days before and ending seven days after the diagnosis. Subgroup analysis was done for patients with diabetes who did and did not use insulin, because previous studies have shown that the risk of infection is even more increased in insulin-using diabetes patients.\textsuperscript{14} We used SPSS version 12.0 (SPSS Inc., Chicago, USA) for all statistical analyses.

Results

The study population increased over the years 1995 to 2003. The male-to-female ratio and mean age of the study population remained constant over these years. The use of insulin and of oral diabetes medication increased over the years from 7\% to 14\% and from 45\% to 62\%, respectively (Table 1).
Table 1  Study population

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Mean age ± SD</th>
<th>Female</th>
<th>Use of insulin</th>
<th>Use of oral diabetes medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>721</td>
<td>68.6 ± 10.9</td>
<td>53.4</td>
<td>7.2</td>
<td>44.8</td>
</tr>
<tr>
<td>1996</td>
<td>906</td>
<td>68.8 ± 11.1</td>
<td>53.6</td>
<td>9.3</td>
<td>48.8</td>
</tr>
<tr>
<td>1997</td>
<td>1066</td>
<td>68.8 ± 11.1</td>
<td>53.1</td>
<td>10.6</td>
<td>52.6</td>
</tr>
<tr>
<td>1998</td>
<td>1221</td>
<td>69.1 ± 11.0</td>
<td>52.2</td>
<td>11.5</td>
<td>52.3</td>
</tr>
<tr>
<td>1999</td>
<td>1308</td>
<td>68.7 ± 11.1</td>
<td>52.5</td>
<td>11.9</td>
<td>54.7</td>
</tr>
<tr>
<td>2000</td>
<td>1393</td>
<td>68.7 ± 11.2</td>
<td>52.7</td>
<td>11.5</td>
<td>54.2</td>
</tr>
<tr>
<td>2001</td>
<td>1458</td>
<td>68.9 ± 11.2</td>
<td>53.5</td>
<td>13.2</td>
<td>58.0</td>
</tr>
<tr>
<td>2002</td>
<td>1544</td>
<td>69.0 ± 11.2</td>
<td>52.9</td>
<td>13.9</td>
<td>58.7</td>
</tr>
<tr>
<td>2003</td>
<td>1624</td>
<td>68.9 ± 11.1</td>
<td>52.3</td>
<td>13.8</td>
<td>61.9</td>
</tr>
</tbody>
</table>

Percentages unless otherwise specified.

Figure 1  Incidence of lower respiratory tract infection (LRTI) per 1000 person-years.
LRTI incidence and treatment

The overall LRTI incidence rate remained stable (13%; \( p = 0.442 \)), with 78 episodes per 1000 person-years (95% CI: 62–97%) in 1995 and 88 episodes per 1000 person-years in 2003 (95% CI: 71–108). The incidence rates for the different types of LRTI are shown in Figure 1. The relative risk of presenting to the GP with an infection in patients using insulin compared to those not using insulin varied across the years (range: 0.5 in 1995 to 1.9 in 1996; Figure 1).

Antibiotic prescription for LRTI increased significantly from 42 per 100 episodes (95% CI: 33–52%) in 1995 to 67 (95% CI: 57–75%) in 2003, an increase of 60% (\( p < 0.001 \)). The rate of doxycycline prescribed increased by 330% (\( p < 0.001 \)) over the years 1995 to 2003. The rate of amoxicillin prescription decreased (52%; \( p = 0.051 \)), whereas the rate of co-amoxiclav prescription increased (180%; \( p = 0.062 \)) and the rate of prescribed macrolides varied across the years, but overall increased by 186% (\( p = 0.127 \)) (Figure 2).

UTI incidence and treatment

UTI incidence rates increased significantly from 72 episodes per 1000 person-years (95% CI: 57–90%) in 1995 to 101 episodes per 1000 person-years in 2003 (95% CI: 83–122%), an increase of 40% (\( p = 0.037 \)). This increase was due to a more frequent presentation of episodes of cystitis; the incidence rates of prostatitis and acute pyelonephritis remained stable. The relative risks were greater in patients using insulin compared with those not using insulin (range: 1.2 in 2002 to 3.0 in 2001; Figure 3).

The antibiotic prescription rate for cystitis increased from 78 per 100 episodes (95% CI: 69–85%) in 1995 to 90 (95% CI: 83–94%) in 2003, an increase of 15% (\( p = 0.029 \)). Due to low

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Pneumonia</th>
<th>Acute bronchitis</th>
<th>Exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>42</td>
<td>57</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>1996</td>
<td>34</td>
<td>45</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>1997</td>
<td>48</td>
<td>52</td>
<td>55</td>
<td>13</td>
</tr>
<tr>
<td>1998</td>
<td>58</td>
<td>68</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>1999</td>
<td>60</td>
<td>52</td>
<td>69</td>
<td>35</td>
</tr>
<tr>
<td>2000</td>
<td>55</td>
<td>50</td>
<td>65</td>
<td>13</td>
</tr>
<tr>
<td>2001</td>
<td>56</td>
<td>47</td>
<td>69</td>
<td>30</td>
</tr>
<tr>
<td>2002</td>
<td>65</td>
<td>50</td>
<td>73</td>
<td>53</td>
</tr>
<tr>
<td>2003</td>
<td>67</td>
<td>70</td>
<td>74</td>
<td>44</td>
</tr>
</tbody>
</table>

Figure 2  Antibiotic prescription and first choice antibiotics prescribed per 100 episodes of lower respiratory tract infection (LRTI).
numbers we were not able to assess antibiotic prescription rates for prostatitis and acute pyelonephritis. The rate of broad-spectrum antibiotic use was about the same across the years, with a decrease in amoxicillin (71%; \( p = 0.036 \)) and an increase in co-amoxiclav (160%; \( p = 0.395 \)). The rate of prescribed sulfonamides and trimethoprim and also the rate of quinolones prescribed varied across the years, but overall decreased by 57% (\( p = 0.032 \)) and 29% (\( p = 0.313 \)), respectively. The rate of nitrofurantoin prescription increased by 480% (\( p < 0.001 \)) (Figure 4).

### Discussion

From 1995 to 2003, the incidence rate of UTI occurring in a Dutch primary care setting increased by 40%. Relative risks were greater in patients with UTI who used insulin compared with those who did not use insulin (range: 1.2 in 2002 to 3.0 in 2001). Antibiotic prescription rates increased in LRTI by 60%, which may enhance antibiotic resistance. The rate of doxycycline prescribed for LRTI increased by 330%, and for cystitis, the rate of prescribed nitrofurantoin increased by 480%.

---

**Figure 3** Incidence of urinary tract infection (UTI) per 1000 person-years.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Prostatitis</th>
<th>Cystitis</th>
<th>Acute pyelonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>72</td>
<td>6</td>
<td>65</td>
<td>1</td>
</tr>
<tr>
<td>1996</td>
<td>68</td>
<td>1</td>
<td>66</td>
<td>1</td>
</tr>
<tr>
<td>1997</td>
<td>72</td>
<td>1</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>1998</td>
<td>111</td>
<td>1</td>
<td>109</td>
<td>2</td>
</tr>
<tr>
<td>1999</td>
<td>89</td>
<td>5</td>
<td>82</td>
<td>2</td>
</tr>
<tr>
<td>2000</td>
<td>85</td>
<td>1</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>2001</td>
<td>75</td>
<td>1</td>
<td>72</td>
<td>3</td>
</tr>
<tr>
<td>2002</td>
<td>88</td>
<td>4</td>
<td>83</td>
<td>1</td>
</tr>
<tr>
<td>2003</td>
<td>101</td>
<td>2</td>
<td>95</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Insulin users</th>
<th>Non-insulin users</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>96</td>
<td>70</td>
<td>1.4 (1.1–1.7)</td>
</tr>
<tr>
<td>1996</td>
<td>110</td>
<td>63</td>
<td>1.7 (1.4–2.1)</td>
</tr>
<tr>
<td>1997</td>
<td>149</td>
<td>62</td>
<td>2.4 (2.0–2.8)</td>
</tr>
<tr>
<td>1998</td>
<td>194</td>
<td>100</td>
<td>1.9 (1.7–2.2)</td>
</tr>
<tr>
<td>1999</td>
<td>192</td>
<td>74</td>
<td>2.6 (2.2–3.0)</td>
</tr>
<tr>
<td>2000</td>
<td>166</td>
<td>73</td>
<td>2.3 (2.0–2.7)</td>
</tr>
<tr>
<td>2001</td>
<td>175</td>
<td>59</td>
<td>3.0 (2.6–3.4)</td>
</tr>
<tr>
<td>2002</td>
<td>100</td>
<td>85</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>2003</td>
<td>135</td>
<td>95</td>
<td>1.4 (1.2–1.7)</td>
</tr>
</tbody>
</table>
To our knowledge, this is the first study showing incidence rates for common infections and antibiotic prescription rates in an unselected population of patients with DM over a long period of time. When monitoring national figures of antibiotic prescription, it is sensible to use figures relating to periods of several years, because of yearly variations. Other strengths of our study were the use of multiple outcomes and the quality of the data registered by GPs. Most characteristics of the population remained unchanged over the study years, but glycemic control possibly improved as a result of higher numbers of prescriptions for insulin therapy. If anything, this change would have led to declines in our outcomes, hence the observed increases in UTI and LRTI episodes may even be underestimates.

Because of lacking data on the combination 'diabetes and infections', we are unable to compare our incidence and antibiotic prescribing rates with those of others. However, information is available on the incidence of UTI and LRTI and antibiotic prescription in general. In the UK, the incidence of LRTI fell between 1994 and 2000 and there were minimal reductions in the incidence of UTI. Since 2000, consultation rates for LRTI have shown evidence of stabilizing. Compared with our findings, an earlier study in the Netherlands found a lower GP consultation rate for LRTI in the general population during a 12-month period between May 2000 and April 2002: 44 per 1000 person-years. It is difficult to accurately compare UTI incidences because for example, in the USA, UTI are not reportable diseases. Our findings, an increase in the incidence of cystitis and a stabilization of the incidence of acute pyelonephritis, are comparable with findings in the general population, i.e., people with and without diabetes, from 1995 to 1999.

In the Netherlands, antibiotic prescribing rates are low compared with other European countries and the USA. However, Dutch GPs do not appear to be reluctant in prescribing antibiotics for LRTI, especially in acute bronchitis. In the general population, they are likely to prescribe at the same rates as their colleagues in the UK and the USA. In the Netherlands, antibiotic prescribing was not in accordance with the recommendations of the guidelines in 63% of the consultations for bronchitis. We found a strong increase in the rate of prescribed antibiotics for LRTI. This increase might be explained by a decrease in the 'wait and see' approach.

Figure 4 Antibiotic prescription and first choice antibiotics prescribed per 100 episodes of urinary tract infection (UTI).
attitude of the GP if patients with DM present themselves with a recurrent LRTI.

In 2003, doxycycline and co-amoxiclav were the two most prescribed antibiotics for LRTI. The rate of macrolide use for LRTI in diabetes varied across the years, but overall increased. This is noteworthy, because this type of antibiotic should not be a first choice treatment in Dutch general practice and is linked to a risk of growing resistance in relevant bacterial pathogens. Over the years we found a slight decrease in the rate of quinolone use for UTI in diabetes. This is important and reassuring because of the increasing resistance of Escherichia coli to these antibiotics.

Some limitations should be discussed. First, our study was based on patients visiting their GP, which may underestimate the true incidence rates in the general population. Second, misclassification due to missing data and differences in classification between years and GPs cannot be ruled out and this may have resulted in either an over- or under-estimation of the true incidence rates. It is, however, unlikely that this misclassification has affected the results substantially, since up to 90% of all patient contacts were coded. Third, we did not differentiate between patients with type 1 and type 2 diabetes. We think that most patients in our study had type 2 diabetes, because the mean age of the study population was 69 years. Fourth, we had inadequate power to analyze a large number of subgroups, for example, we were not able to study antibiotic prescription rates in prostatitis and acute pyelonephritis.

No evidence-based guidelines are available on the treatment of common infections in diabetes. Most recommendations for the treatment of UTI in diabetes are based on expert opinions. Some authors suggest that all UTI in patients with DM should be treated as complicated infections, while others think that the term ‘complicated’ should be reserved for (diabetic) patients with persistent or recurrent infections or for example abnormalities of the urinary tract or impaired renal function. Since evidence is lacking at the moment, we think that the term ‘complicated’ should be reserved for patients with DM at high risk for a complicated course of infection. For that reason, we have developed prediction models for a complicated course of UTI and LRTI. Randomized trials are needed to compare the optimal duration and the choice of treatment for common infections in diabetes. This may result in advice to use first-line antibiotics for UTI for certain patients, given over a longer period of time, and for others second-line antibiotics. At the same time a tailored recommendation for treatment of DM patients with LRTI should be given.

Acknowledgements

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Conflict of interest: No conflict of interest to declare.

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