Antibiotic resistance of urinary pathogens in female general practice patients

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Abstract

A cross-sectional study was performed to determine the prevalence of antibiotic resistance in women with uncomplicated and complicated lower urinary tract infection (UTI) in Germany. In 36 (of 118 invited) general practices, urine cultures and resistance testing were performed during 4 months on all women presenting with symptoms of UTI. Each patient's symptoms, risk factors and treatment were documented. A total of 445 women were included, and their median age was 53 y. Complicating factors were present in 27% of women. Urine cultures were available for 430 patients. They were sterile in 23%, 53% had 10^5 cfu/ml or more, and 24% had 10^2/C1/10^4 cfu/ml. E.coli was the most frequent pathogen (68%), followed by Enterococcus faecalis (10%) and Proteus spp. (10%). E.coli resistance levels were 25–40% for amoxicillin, co-amoxiclav, first generation oral cephalosporins, trimethoprim and co-trimoxazole. Nine percent were resistant to fluoroquinolones. E.coli resistance remained low for nitrofurantoin (2%) and third generation oral cephalosporins (3%). Odds for E.coli resistance to most antibiotics were 2–5 times higher in patients with complicating factors, and increased with age. Resistance levels to all common antibiotics were high even in unselected females with UTI in general practices. Older or complicated patients had a significantly higher risk for resistance.

Introduction

Appropriate targeting of antibiotic prescriptions in primary care is important to maintain clinical effectiveness and to contain antibiotic resistance. Lower urinary tract infection (UTI) is a common indication for antibiotics in primary care. Recently, there has been concern about rising resistance levels in urinary pathogens [1], and some discussion on appropriate diagnosis and targeting of antibiotic prescriptions [2–5]. Susceptibility is known to vary geographically, and within local populations [6]. Because of selection of high risk patients from laboratories or microbiology services [7], community or general practice based local surveys are needed to generalize results. Identifying predictors of antibiotic resistance in symptomatic patients can help general practitioners (GPs) to make appropriate decisions on the use of susceptibility testing and antibiotics.

Our aim was to determine the relative frequency of lower urinary tract infection in symptomatic female general practice patients in Germany, as well as the prevalence of resistance to relevant antibiotics in female patients with uncomplicated or complicated UTI, respectively.

Methods

This survey is part of a larger study on urinary tract infection in Germany, and methods have already been described elsewhere [8,9]. The local ethics review board had no objections to the study.

All 118 teaching general practices of the Department of General Practice, University of Göttingen, were invited to participate in this study, and 36 (31%) agreed (8 female GPs, 14 working in group practices with 2–4 partners). During the study period of 4 months (November 2000 to February 2001),
practices were telephoned regularly to ensure compliance with the study protocol.

All male and female patients in whom the GPs suspected UTI according to their history or symptoms, were to be included prospectively, including patients meeting the definition of complicated UTI [10,11], i.e. comorbidity or recent antibiotic treatment. This pragmatic approach was chosen to maximize generalizability and to reflect daily practice. However, patients with an obvious other cause for their symptoms (i.e. vaginitis) were not included. Only the subgroup of teenage (>12 y) and adult women is considered in this paper.

Patients were to be managed ‘as usual’, including use of dipstick tests and empirical treatment if considered appropriate. However, before beginning treatment, GPs were instructed to order a urine culture for all patients regardless of dipstick results, even if they would not have done so outside the study context. Urine samples were stored in sterile containers supplied by the laboratory and kept refrigerated until daily collection by laboratory staff. All costs were covered by the laboratory. Each patient’s age, gender, current symptoms and risk or complicating factors as well as diagnostic procedures and treatment were documented on a short, structured form identified by a patient code number. These forms were mailed to the department of general practice without disclosing patients’ identities.

All urine cultures were performed in the same laboratory (Medical partnership Wagner, Stibbe, Kast, Bispink & Partners). Internationally recommended standard procedures [12,13] were used for cultures and antibiotic susceptibility testing in the case of bacterial growth. Briefly, 10 µl specimen were plated on columbia blood-, CNA (colistin nalidixic acid)-, and McConkey-agar, respectively. After incubation at 37°C for 18–20 h the plates were analysed for growth. Growth colonies were counted semiquantitatively. Identification to species level and resistance testing of bacteria was carried out by the Vitrek identification and resistance testing system according to the manufacturer’s instructions (Api BioMerieux, Nürtingen, Germany) [14–18]. Minimal inhibitory concentration (MIC) values were determined, and the results were reported as sensitive, intermediate and resistant according to German standards [13]. Culture results were labelled with the patients’ code numbers and communicated to the department of general practice. Participating GPs were informed of culture results assigned to patients’ names.

All data were entered into SAS (Statistical Analysis System) software, Version 8 [19], patients’ documentation and laboratory results were linked by means of the patient code number. Our laboratory used the definition of 10^5 or more colony-forming units (cfu)/ml of a single species for a ‘microbiologically proven UTI’, cultures with 10^3 or 10^4 cfu/ml or several species of bacteria were labelled as ‘ambiguous’, and cultures with 10^2 cfu/ml as ‘negative’. Since 10^2 cfu/ml has been considered an appropriate cut-off value for female UTI by several authors [10,11,20], we did not restrict our analysis to traditionally defined ‘high count UTI’ (≥10^3 cfu/ml), but also included cultures yielding low count bacteriuria (≥10^2 cfu/ml) or mixed growth in our definition of UTI. However, the laboratory did not perform susceptibility testing in samples with only 10^2 cfu/ml, or growth of more than 2 species [12,13]. Patient age was stratified in 3 groups: pre- or peri-menopausal (<50 y), post-menopausal (between 50 and 74 y) and old age (>74 y). Intermediate susceptibility and resistance were grouped as ‘resistant’. All statistics were calculated in SAS. For bivariate analyses, odds ratios and 95% confidence intervals were determined based on 2 × 2 contingency tables. Age group, presence of any risk factor, recurrent UTI, and individual symptoms (urgency/frequency, dysuria, suprapubic pain, reported fever, kidney or flank pain) were used as independent variables in logistic regression models with backward selection, predicting resistance to individual antibiotics. Results of both bivariate and multivariate analyses are expressed as odds ratios (OR) with 95% confidence intervals (CI).

Results

The 36 participating practices had recruited 585 patients of both genders within 4 months. Only the subgroup of teenage (>12 y) and adult women (76%, n = 445) is considered in this paper. Results of male patients have been analysed and published separately [8], as well as the survey on general practitioners treatment decisions [9].

Women’s mean age was 53 y, 45% were aged under 50 y, 33% were 50–74 y and 22% over 75 y old. One-third had recurrent UTI; 27% had relevant comorbidity or risk factors, most commonly diabetes (9%), antibiotic treatment in the last 2 weeks (7%), an indwelling cathether (3%), history of urinary surgery (3%), neurological voiding dysfunction (3%) or chronic renal failure (3%). Symptoms were documented on the study sheet in 89% of the women.

Urine culture results were available for 430 women (96.6%): in 98 patients (22.8%) the urine was sterile. Bacteria counts of 10^3 cfu/ml were found in 50 patients (11.6%). In 52 patients (12.1%), 10^3 – 10^4 cfu/ml were found, and 230 patients (53.5%)
had $10^5$ cfu/ml; mixed growth was present in 56 of these cases (13%). In the 282 patients with $10^3$ cfu/ml or more, bacterial species were identified. Escherichia coli was isolated in 67.7% (191 patients), Enterococcus faecalis in 10.3% (29 patients), Proteus spp. in 8.9% (P. mirabilis and P. vulgaris in 25 and 2 patients, respectively), Streptococcus agalactiae in 7.4% (20 patients, 2 with high count UTI, 7 with low count UTI, 11 with multiple growth), and Klebsiella spp. and Staphylococcus saprophyticus in 1.4% (4 patients) each. Several other species were found in 1–3 urine samples, respectively. In the 186 patients with single organism growth of $\geq 10^5$ cfu/ml, the fraction of E. coli was higher (75.3%), and fewer patients had Enterococcus faecalis (5.2%) or S. agalactiae (1.1%). There were no significant differences in the frequency of low count or mixed growth culture results, and high count UTI in women with and without risk factors (OR 1.20, 95% CI 0.70–2.04), and E. coli, Enterococcus faecalis and Proteus spp. were equally prevalent in both groups.

With regard to age, infections with low counts or multiple growth were less common in women over 75 y of age compared to young women under 50 y (OR 0.49, 95% CI 0.25–0.75). There were no significant differences between the age group 50–75 y and either younger or older women. E. coli was found equally distributed in all age groups. Levels of resistance to common antibiotics are presented in Table I for the most frequent pathogens.

In multivariate logistic regression models, predictors for resistance were analysed in the 191 patients with UTI caused by E. coli (Table II). Additionally, odds for resistant E. coli were determined (bivariate analyses) comparing both women aged 50–74 y and over 74 y to young women under 50 y. There were no significant differences between young women and those aged 50–74 y. Odds for women over 74 y compared to young women under 50 y are presented in Table III. In women under 50 y, all E. coli were susceptible to nitrofurantoin; 4% and 2% resistance was found in patients aged 50–74 y and over 74 y, respectively.

Additional bivariate analyses found no significant associations between either age or presence of risk factors and resistance of Proteus spp., Enterococcus faecalis and S. agalactiae. Due to low sample size for these pathogens, confidence limits in monovariate statistics were very large and multivariate models not appropriate.

### Discussion

In our observational study on women consulting their GPs with symptoms of urinary tract infection, more than half of all patients were over 50 y old, and more than a quarter had complicating factors, such as diabetes, recent antibiotic treatment, or voiding dysfunction. Resistance levels were high: over 30% of E. coli was resistant to penicillins and older cephalosporins, almost 30% to trimethoprim and co-trimoxazole, and 9% to fluoroquinolones. Most E. coli remained highly susceptible to nitrofurantoin and newer oral cephalosporins. However, the relatively high prevalence of Enterococcus faecalis (naturally not susceptible to cephalosporins, trimethoprim and co-trimoxazole and – in our study – mostly (83%) resistant to fluoroquinolones), Proteus spp. (naturally not susceptible to nitrofurantoin) and S. agalactiae (not susceptible to trimethoprim and co-trimoxazole and highly resistant to fluoroquinolones) makes empirical choice of an antibiotic treatment difficult (see below). Our resistance rates are higher than those reported in most surveys from other countries, though rising levels of resistance are a recent concern everywhere [6,21–24].

One reason for the high prevalence of resistance may be the higher age and prevalence of complicating factors in our patients, which, however, corresponds to populations described in other German surveys on UTI [25,26].

### Table I. Resistance levels (%) in the most frequent pathogens.

<table>
<thead>
<tr>
<th></th>
<th>E. coli (n = 191)</th>
<th>Proteus spp. (n = 27)</th>
<th>Enterococcus faecalis (n = 29)</th>
<th>S. agalactiae (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>38.7</td>
<td>33.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>33.0</td>
<td>22.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>33.5</td>
<td>33.3</td>
<td>not susceptible</td>
<td>0</td>
</tr>
<tr>
<td>Cefixime</td>
<td>2.6</td>
<td>11.1</td>
<td>not susceptible</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8.9</td>
<td>11.1</td>
<td>82.8</td>
<td>95.0</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>28.8</td>
<td>40.7</td>
<td>not susceptible</td>
<td>not susceptible</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>29.3</td>
<td>48.1</td>
<td>not susceptible</td>
<td>not susceptible</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>2.1</td>
<td>not susceptible</td>
<td>3.4</td>
<td>0</td>
</tr>
</tbody>
</table>
Table II. Predictors of resistance to individual antibiotics in patients infected with E. coli, logistic regression models* (n = 191 patients).

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Risk factors + (compared to uncomplicated patients)</th>
<th>Risk factors + (compared to uncomplicated patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% confidence interval)</td>
<td>Odds ratio (95% confidence interval)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Amoxiclav</td>
<td>ns</td>
<td>2.20 (1.14–4.25)</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>ns</td>
<td>2.12 (1.10–4.09)</td>
</tr>
<tr>
<td>Cefixime</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3.21 (1.51–6.83)</td>
<td>ns</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>1.73 (1.10–2.71)</td>
<td>2.92 (1.44–5.89)</td>
</tr>
<tr>
<td>Cotrimoxazol</td>
<td>1.82 (1.15–2.86)</td>
<td>3.00 (1.48–6.09)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Presence of any risk or complicating factor [10].
*Recurrent UTI, reported fever and other individual symptoms did not significantly predict antibiotic resistance.

studies in countries without practice lists, we did not know the precise catchment rate of our study, but had to rely on participating GPs to include all their eligible patients [27,28]. In order to ensure a valid representation of GPs’ daily practice, we kept inclusion fairly open and purposely avoided restrictive exclusion criteria. We encouraged active participation through regular telephone monitoring. The number of included women corresponds to the practice prevalence reported in other German studies on UTI [25,26,29]. GPs participating in our survey practised in both rural and urban settings and were not routinely involved in research. Although there may be a selection bias concerning GPs, their patients are unlikely to differ from patients in non-participating practices.

In our study, E. coli resistance to several antibiotics was more likely in older women. Although no significant differences could be found between women under 50 y and aged 50–74 y, E. coli resistance to cefazolin, fluoroquinolones, trimethoprim and co-trimoxazole was more common in patients over 74 y than in young women (under 50 y). For fluoroquinolones, trimethoprim or co-
trimoxazole, E. coli resistance was significantly 2–3 times more likely in patients with complicated UTI or recent antibiotic exposure [30,31]. Due to sample size and low prevalence, we could not determine the predictive values of individual risk factors. In a large study on British patients in whom a urine sample had been cultured (samples were not collected systematically), exposure to trimethoprim and other antibiotics and having been in hospital were associated with trimethoprim-resistant pathogens [30]. Similar results have been found in other populations and for co-trimoxazole resistance [32–34]. Further research is needed to stratify risk for resistance, as well as implications of individual complicating factors for the outcome of UTI.

Another reason for high prevalence of resistance may be national patterns of antibiotic use, which have been shown to be closely associated with development of resistance [35–38]. In Germany, fluoroquinolones are commonly prescribed to patients with UTI, and it seems likely that rising levels of resistance (clearly indicated by the high rate of intermediate susceptibility) are a consequence of this practice [39–41]. In many countries, general practice guidelines recommend empirical treatment for uncomplicated UTI [11,42–45]. However, if resistance levels are high, this approach becomes problematic, as many patients are likely to receive ineffective antibiotics. Prescription of trimethoprim in uncomplicated patients is probably associated with at least 15% clinical treatment failures [36,46]. In our sample, nitrofurantoin was the antibiotic with lowest resistance rates. Although considered first choice in national and international recommendations, it is rarely prescribed in Germany, probably due to excessive warnings about possible risks and unwanted effects. As other countries’ experiences and current research do not provide evidence of an excessive risk [47], nitrofurantoin should probably be further advocated as drug of first choice in patients with uncomplicated UTI; however, there is only 1 recent controlled trial [48], and no recent comparative studies. Use of still relatively effective fluoroquinolones or third generation oral cephalosporins for common infections in daily practice is likely to enhance the problem of resistance rather than to provide solutions [39,49]. Ordering urine cultures for every patient with symptoms of UTI may be considered an option, but will result in increasing costs. Furthermore, it implies postponing antibiotic treatment until culture results are available, an approach which may not be well accepted by patients and GPs. However, the high prevalence of resistance in elderly women and patients with complicating factors highlights the

Table III. Older women’s risk of UTI with resistant E. coli compared to women under 50 y (n = 67).

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Age over 74 y (OR, 95% CI) n = 47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>ns</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>ns</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2.36 (1.06–5.29)</td>
</tr>
<tr>
<td>Cefixime</td>
<td>ns</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>6.52 (1.71–24.90)</td>
</tr>
<tr>
<td>Co-trimoxazol</td>
<td>4.48 (1.89–10.63)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>4.03 (1.73–9.41)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>ns</td>
</tr>
</tbody>
</table>
necessity of urine cultures and targeted antibiotic use in these patients [35,37].

Acknowledgements
We thank all participating GPs for their cooperation. The medical laboratory partnership Wagner, Stibbe, Kast, Bispink & Partners sponsored the urine cultures and susceptibility testing.

References
[30] Steinke DT, Seaton RA, Phillips G, MacDonald TM, Davey PG. Prior trimethoprim use and trimethoprim-resistant urinary tract infection: a nested case-control study with