ORIGINAL ARTICLE

A Survey of Outpatient Antibiotic Prescribing for Cystitis

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SUMMARY

Background: In view of the currently increasing rates of antibiotic resistance, we studied the factors that affect the prescribing of specific antibiotics for uncomplicated cystitis in outpatient care.

Methods: A nationwide cross-sectional survey of physicians in private practice in various specialties (internal medicine, general medicine, surgery, obstetrics/gynecology, child and adolescent medicine, otorhinolaryngology, dermatology, urology) was carried out in 2008. The sample was derived from the German state directories of medical specialists.

Results: 1810 (60%) of the physicians surveyed reported that they made decisions about antibiotic treatment every day, with uncomplicated urinary tract infection as the most common diagnosis (715 physicians). The antibiotics that they prescribed most commonly for it were cotrimoxazole (61%) and fluoroquinolones (21%). The following factors were significantly associated with a preference for fluoroquinolones: being a gynecologist (odds ratio [OR] 0.47, 95% confidence interval [CI] 0.27–0.80), location of practice in the former East Germany (OR 2.01, CI 1.16–3.46), a treatment strategy incorporating a switch from empirical to targeted treatment (OR 1.72, CI 1.02–2.90), and the stated intention of avoiding inconvenience to the patient (OR 2.14, CI 1.25–3.68).

Discussion: Fluoroquinolones are no longer recommended as the drug of first choice for uncomplicated urinary tract infections because of the development of resistance, but are still commonly prescribed for it. ARS (Antibiotic Resistance Surveillance in Germany) publishes current regional and patient-group-specific resistance rates to promote good clinical practice and improve prescribing behavior.

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There has been a steady increase in resistance to the antibiotics that are commonly prescribed to treat uncomplicated urinary tract infections (UTIs), particularly fluoroquinolones. Clinical practice guidelines nearly unanimously recommend (with only a few special exceptions) that broad-spectrum antibiotics should not be given as the drug of first choice for uncomplicated UTI, for a number of reasons including the development of resistance, high cost, and side effects. There is evidence, however, that broad-spectrum antibiotics such as fluoroquinolones are still being prescribed in Europe as the drug of first choice for certain diagnoses (1, 2). Their use as the drug of first choice for uncomplicated UTI can be considered a marker for possibly inappropriate prescribing behavior.

Until recently, bacteriostatic folic-acid antagonists such as cotrimoxazole were generally held to be a more appropriate choice than fluoroquinolones. These agents account for 8–10% of antibiotic prescriptions in Germany; in the last decade, rates of resistance to them have risen as well (3, 4). In 2010, the S3 guideline of the Association of Scientific Medical Societies in Germany (AWMF) for uncomplicated UTI no longer recommended cotrimoxazole as a drug of first choice for this indication, because of increasing resistance (5). Rather, the new recommendation is for fosfomycin-trometamol and nitrofurantoin as drugs of first choice for this indication in Germany (and also pivmecillinam outside Germany), with fluoroquinolones as second-line agents. Cotrimoxazole and trimethoprim are now only recommended in regions where the local resistance rate is known to be under 20% (6). Most guidelines from other countries recommend empirical treatment for uncomplicated UTI while stating that antimicrobial treatment should be appropriately modified in areas known to have high resistance rates (7). In its guideline, the Infectious Diseases Society of America recommends that cotrimoxazole should not be given to treat uncomplicated UTI if the local resistance rate exceeds 20% (8, 9). The guideline of the European Association of Urology (EAU) does not give a uniform recommendation on this matter, citing the wide variation in cotrimoxazole resistance rates from one European country to another (10) *(Table 1)*.

The prescribing of antibiotics for uncomplicated UTI in outpatient care is a problematic matter in a number of ways. What factors affect the physician's decision to give a particular antibiotic to treat an uncomplicated UTI? Potentially, these factors might include the diagnosis, the patient's signs and symptoms, the patient's expectations as perceived by the physician, or whether the physician feels well-informed or has access to clinical practice guidelines.

A representative national survey recently carried out by the Robert Koch Institute (RKI) revealed associations of sociodemographic factors such as hospital-based versus private practice, regional location of practice and the physician's sex with attitudes towards antibiotic prescribing, (11, 12). 60% of the private practitioners surveyed said that they decided every day whether to prescribe antibiotics, and that the commonest diagnosis was uncomplicated urinary tract infection. The drugs of first choice for this were cotrimoxazole followed by fluoroquinolones. In view of the recent change of the AWMF guideline recommendations, we analyzed the data of the RKI survey to determine what factors affect the prescribing of cotrimoxazole or fluoroquinolones as drugs of first choice for the diagnosis of uncomplicated UTI.

Methods

The data analyzed in this study were derived from a survey, by questionnaire, that was carried out in 2008 in a representative sample of German physicians. Their addresses had been chosen at random from the statewide directories of medical specialists in 15 of the 16 German federal states (only Saxony supplied no addresses) and then forwarded to the RKI for the performance of the survey.

The physicians to be surveyed were randomly selected within each specialty group. In order to detect potential regional differences in the factors affecting antibiotic prescribing, the federal states were grouped together, for purposes of analysis, in four regions: north, south, east, and west. In each region, physicians providing outpatient care and hospital-based physicians were considered separately.

The appropriate sample size for each specialty group was determined from data supplied by the regional medical associations about the number of physicians in their respective areas, with the aid of STATA software (Version 10, 2007). 544 outpatient-care physicians and 544 hospital-based physicians per region were found to be necessary to detect differences of 10% or more between fields (outpatient vs. inpatient) and regions. With an expected survey response rate of 40%, 1360 questionnaires would have to be sent per field (outpatient vs inpatient) and region.

When the size of the individual regions and the distribution of physicians across specialties was taken into account, it was found that an overall total of 10 998 questionnaires would have to be sent. The number to be sent in each participating federal state was communicated to the state medical associations. A detailed description of the procedure and its results was recently published elsewhere (11, 13).

Questionnaires were sent to both hospital-based physicians and physicians in private practice. Specialists in the following areas with high antibiotic prescription volumes were selected: internal medicine, general medicine, surgery, obstetrics/gynecology, child and adolescent medicine, otorhinolaryngology, dermatology, and urology.

The physicians were asked to supply some basic information about themselves and their medical practice activities as well as their knowledge, experience, and attitudes with respect to diagnostic evaluation, antibiotics, and antibiotic prescribing. They were asked, among other things, how often they had made decisions about antibiotic treatment in the past year and what experience they had with antibiotics and antibiotic resistance in their practice. They were also asked what the most common diagnosis was for which they had prescribed antibiotics in the past year, what antibiotics they had generally prescribed for it, whether they had decided for or against empirical treatment, whether they had performed a diagnostic test, and how frequently they had switched to targeted antibiotic treatment.

The data were evaluated with STATA software. For the particular questions addressed in the present study, we considered only the data from physicians providing outpatient care who gave uncomplicated UTI/cystitis as their most common diagnosis. We considered the free-text entries "UTI," "cystitis," and "uncomplicated urinary tract infection" to correspond to this diagnosis; other designations, such as "adnexitis," "cervicitis," or "pyelonephritis," were excluded. The physicians' responses regarding the antibiotic treatment that they prescribed for this diagnosis were categorized by substance class. The analysis was based on a comparison of two groups: physicians who indicated that they normally prescribed cotrimoxazole and those who said they normally prescribed fluoroquinolones.

Potential differences in the demographic features of these two groups were tested for statistical significance at the 5% level with Pearson's chi-square test. Differences with respect to the ordering of diagnostic tests before the initiation of antibiotic treatment, decisions regarding empirical treatment, and switching from empirical to targeted treatment were assessed with the Wilcoxon rank-sum test (Mann–Whitney test) at the 5% level. Finally, a stepwise multivariate logistic regression with forward-backward elimination (95% confidence interval [CI]: $p \leq 0.05$) was performed to identify factors associated with the choice of fluoroquinolones as the normally prescribed antibiotic treatment for uncomplicated UTI. For this purpose, an *a priori* model was defined that incorporated the following variables: the physician's sex, age, specialty (with urologists as the reference group), and site of practice,

TABLE 1

Overview of guidelines for the treatment of uncomplicated cystitis: the AWMF S3 guideline on urinary tract infections (reg. n. 043/044) and the guidelines of the European Association of Urology (EAU) und the Infectious Diseases Society of America (ISDA)

Recommendation	Antibiotics	Alternatives	Other	Remarks
AWMF as of 2011 (6)	fosfomycin/trometamol 3000 mg qd for 1 day nitrofurantoin 50 mg q6h for 5 days nitrofurantoin SR 100 mg bid for 5 days pivmecillinam* 200 mg bid for 7 days pivmecillinam* 400 mg bid for 3 days	ciprofloxacin 250 mg bid for 3 days ciprofloxacin SR 500 mg qd for 3 days levofloxacin 250 mg qd for 3 days norfloxacin 400 mg bid for 3 days ofloxacin 200 mg bid for 3 days cefpodoxime proxetil 100 mg bid for 3 days	depending on the local resistance situation: (*E. coli* resistance <20%) cotrimoxazole 160/180 mg bid for 3 days trimethroprim 200 mg bid for 5 days	The guidelines contain a clear recommendation to prescribe on the basis of the local resistance situation.
European Association of Urology (EAU) as of 2012 (10)	fosfomycin/trometamol 3000 mg qd for 1 day nitrofurantoin 50 mg q6h for 7 days nitrofurantoin macrocrystal 100 mg bid for 5–7 days pivmecillinam* 200 mg bid for 7 days pivmecillinam* 400 mg bid for 3 days	ciprofloxacin 250 mg bid for 3 days levofloxacin 250 mg qd for 3 days norfloxacin 400 mg bid for 3 days ofloxacin 200 mg bid for 3 days cefpodoxime proxetil 100 mg bid for 3 days	depending on the local resistance situation: (*E. coli* resistance <20%) trimethoprim-sulphamethoxazole 160/800 mg bid for 3 days trimethroprim 200 mg bid for 5 days	The resistance pattern of *E. coli* strains causing uncomplicated urinary tract infections varies widely across regions and countries in Europe. Thus, no generally valid recommendation can be made for all of Europe.
Infectious Diseases Society of America (ISDA) as of 2011 (9)	nitrofurantoin 100 mg bid for 5 days (to be avoided if pyelonephritis is suspected) cotrimoxazole 160/800 mg qd for 3 days (to be avoided if the prevalence of resistance is known to exceed 20% or if the agent has already been used to treat UTI in the past three months) fosfomycin/trometamol in a single dose (lower efficacy than other drugs; to be avoided if pyelonephritis is suspected) pivmecillinam* 400 mg qd for 5 days (lower efficacy than other drugs; to be avoided if pyelonephritis is suspected)	fluoroquinolones (high resistance in some areas) β-lactams (avoid use of ampicillins or amoxicillin alone; low efficacy compared to other antibiotics; close follow-up needed)		The prevalence of in vitro resistance and the ecological side effects of antibiotic treatment (collateral damage) are mentioned as important considerations for practice and treatment decisions The guidelines devote specific attention to women with acute, uncomplicated cystitis and pyelonephritis.

*pivmecillinam only outside Germany

the frequency with which the physician ordered diagnostic tests, prescribed empirical treatment, or switched to targeted treatment, and all other major prescribing factors.

Results

3492 physicians returned the questionnaire (response rate, 33%). A total of 1810 physicians in private practice participated, of whom 715 said that uncomplicated UTI had been their most common diagnosis in the past year. Among these 715 physicians, 468 (65%) were general practitioners and 150 (21%) were gynecologists. 433 (61%) said they prescribed antimicrobial drugs at least once per day, and 649 (91%) said they did so at least once a week. 580 (81%) stated which antibiotic they usually prescribed for uncomplicated UTI: Among them, 354 (61%) named cotrimoxazole, and 170 (21%) fluoroquinolones. Fewer physicians stated they usually prescribed β-lactam antibiotics (aminobenzylpenicillin: 22 [4%]), cephalosporins (18 [3%]), benzylpenicillin (1 [<1%]), tetracyclines (10 [2%]), or macrolides (5 [1%]). None of these is recommended as a drug of first choice.

Among the physicians who said they usually prescribed cotrimoxazole for uncomplicated UTI, 91% practiced in the former West Germany and 9% in the former East Germany. On the other hand, in the comparison group (fluoroquinolone prescribers), 84% practiced in the former West Germany and 16% in the former East Germany. 31% of the fluoroquinolone prescribers and 25% of the cotrimoxazole prescribers said they very often took a urine sample before initiating treatment. Correspondingly, 66% of the cotrimoxazole prescribers and 55 % fluoroquinolone prescribers said they very often gave empirical treatment. Very frequent switching from apparently effective empirical treatment to more specific treatment on the basis of culture and resistance findings was reported by 18% of the fluoroquinolone prescribers and 13% of the cotrimoxazole prescribers. All of these differences were significant in univariate analysis, but only the last-named remained significant in a multivariate analysis, that is, the strategy of switching from empirical to targeted treatment on the basis of test results is correlated with a preference for fluoroquinolones as the drug of first choice for uncomplicated UTI (odds ratio [OR] 1.72, 95% CI 1.02–2.90). The multivariate analysis also revealed that gynecologists were much less likely than other specialists to say they prescribed fluoroquinolones for uncomplicated UTI (OR 0.47, KI 0.27–0.80). Moreover, having one's practice in the former East Germany was associated with a preference for fluoroquinolones as the usually prescribed antibiotic treatment (OR 2.01, CI 1.16–3.46). A further significant factor, as revealed by multivariate analysis, was the stated tendency to prescribe antibiotics if the patient would have difficulty returning to the doctor's office for follow-up (OR 2.14, CI 1.25–3.68) *(Table 2)*.

Discussion

For a number of reasons, fluoroquinolones should not be used as a drug of first choice for uncomplicated UTI. Fluoroquinolone-resistant *E. coli*, a frequent cause of uncomplicated UTI, has become more widespread in recent years. The empirical use of fluoroquinolones as a drug of first choice has become markedly more popular in Germany, even though most guidelines recommend them only as second-line treatment (1, 14–16). There was a 34% rise in quinolone prescriptions from 2003 to 2008 (17).

In the sample of physicians who participated in the present study, there was a statistically significant association between practice location in the former East Germany and a preference for fluoroquinolone treatment of uncomplicated UTI. The frequent use of fluoroquinolones to treat uncomplicated UTI has been linked to a marked rise in antibiotic resistance, particularly in the USA (18). An association of fluoroquinolone use with resistance in *E. coli* has also been found in many European countries (2), whereas this particular association was not found in *E. coli*

isolates from urine samples of patients in the former East Germany. A comparison of data from the German Antibiotic Resistance Surveillance System (ARS, *Box*) in the former East Germany versus the former West Germany reveals differences in sensitivity to both cotrimoxazole and fluoroquinolones: Sensitivity to both is higher in the East.

We cannot explain why there is less resistance in the eastern part of Germany, as the situation is highly complex. The difference may be accounted for in some measure by more sophisticated strategies as can be concluded from the responses pertaining to switching from empirical to targeted treatment.

Even though attitudes toward the prescribing of cotrimoxazole have been transformed in recent years, most of the gynecologists in the study sample said they gave cotrimoxazole for uncomplicated UTI, and this indeed seems to be justified by the current resistance situation. In Europe, resistance of *E. coli* from urine samples to cotrimoxazole has been found to be less common in gynecological practice than in any other medical specialty (almost 12% lower than in general medical practice and 16% lower than in urological practice) (2). Resistance rates may well be higher in surveillance data than in the real world, because most of the samples tracked by the surveillance data are derived from previously treated patients. Thus, cotrimoxazole might be an appropriate treatment for this group of patients in Germany.

The surveyed physicians who said they gave fluoroquinolones as a drug of first choice also more commonly manifested attitudes that gave priority to patients' personal needs, e.g., they favored prescribing antibiotics to patients who would have trouble returning to the doctor's office for a follow-up visit. This may reflect a typical management strategy for uncomplicated UTI in outpatient care, with the goal of minimizing inconvenience to the patient, independently of conformity to the guidelines (19, 20). Most of the

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BOX

Antibiotic Resistance Surveillance in Germany (ARS)

The purpose of ARS (Antibiotic Resistance Surveillance in Germany) is to establish representative surveillance of antibiotic resistance covering both inpatient and outpatient care in all regions of the country. It is expected to produce robust data on the epidemiology of antibiotic resistance in Germany and to enable a detailed analysis of structural traits of health care, including regional differences. The interactive database offers comprehensive opportunities to generate resistance reports for the most important bacterial pathogens. For more information, see https://ars.rki.de (in German).

TABLE 2

Physicians in private practice who reported in a survey taken in 2008 that they made decisions about antibiotic treatment every day, and that the most common diagnosis for which they did so was uncomplicated urinary tract infection (total, 524 physicians)

Factor	Cotrimoxazole (354 physicians)		Fluoroquinolones (170 physicians)		Univariate analysis	Multivariate analysis
	Yes/all	(% yes)	Yes/all	(% yes)	p	OR (95% CI)
Sex						
Male	219/346	(63)	110/168	(65)	0.63	–
Female	127/346	(37)	58/168	(35)	0.63	–
Age						
30–39	27/352	(8)	12/170	(< 1)	0.8	–
40–49	138/352	(39)	31/170	(18)	0.13	–
50–59	128/352	(36)	67/170	(39)	0.5	–
>60	59/352	(17)	36/170	(21)	0.22	–
Specialty						
General practice / internal medicine	250/350	(71)	121/168	(72)	0.89	–
Surgery	6/350	(2)	2/168	(1)	0.65	–
Otorhinolaryngology	0	(0)	0	(0)	–	–
Pediatrics	5/350	(1)	0/168	(0)	–	–
Urology	18/350	(5)	22/168	(13)	0.185	(Reference)
Gynecology	70/350	(20)	21/168	(13)	0.036	0.47 (0.27–0.80)
Dermatology	0	(0)	2/168	(1)	0.57	–
None	1/350	(< 1)	0	(0)	0.19	–
Practice location						
Former East Germany	33/354	(9)	28/170	(16)	0.017	2.01(1.16–3.46)
Former West Germany	321/354	(91)	142/170	(84)	0.017	(Reference)
Diagnostic testing and empirical treatment						
Taking a urine sample to identify the pathogen before starting treatment (very often)	87/350	(25)	53/170	(31)	< 0.01	–
Initiating empirical treatment (very often)	232/350	(66)	93/169	(55)	< 0.01	–
Switching apparently effective empirical treatment to targeted treatment based on the identified pathogen(s) and resistance pattern (very often)	42/342	(13)	31/168	(18)	0.02	1.72 (1.02 – 2.90)
Attitudes about prescribing antibiotics						
Yes, I tend to prescribe an antibiotic . . .						
. . . when the patient demands one	30/352	(9)	13/170	(8)	0.73	–
. . . when the patient is determined to keep working	59/354	(17)	36/170	(21)	0.21	–
. . . when I need to save time and prevent additional work for myself and my staff	6/353	(2)	2/170	(1)	0.29	–
. . . when I do without laboratory testing because of the cost	19/353	(5)	15/168	(9)	0.13	–
. . . when my impression as a physician is that the patient is determined to keep working	36/352	(10)	31/169	(18)	< 0.01	–
. . . to "keep on the safe side"	74/351	(21)	46/109	(27)	< 0.01	–
. . . to shorten the consultation	10/353	(3)	11/167	(7)	0.04	–
. . . when the patient would have trouble returning for a follow-up consultation because of the distance	34/353	(10)	29/170	(17)	0.01	2.14 (1.24–3.68)
Knowledge of, and experience with, antibiotic treatment						
Yes, I consider myself well-informed about antibiotics and the issues to be considered when I prescribe them	278/318	(87)	130/150	(87)	0.82	--
Yes, in my daily work I orient myself to the currently valid recommendations or guidelines on antibiotic therapy	269/318	(85)	113/150	(75)	0.02	--
Yes, I consider the problem of antibiotic resistance to be relevant to my daily work	256/340	(75)	123/161	(76)	0.79	--

Reults of uni- and multivariate analyses of the comparison between cotrimoxazole and fluoroquinolone prescribers for uncomplicated UTI with respect to demographic features, statements about typical practice, attitudes about diagnostic testing and prescribing antibiotics, and knowledge of and experience with antibiotic treatment.
All factors listed were included in the multivariate regression analysis

physicians who indicated that they treated uncompli-cated UTI were general practitioners, and it has been found that general practitioners commonly base the choice of treatment on the patient's personal needs. Wood et al. have expressed the opinion that the deci-sion to prescribe fluoroquinolones reflects a complex compromise between the actual findings and the patients' perceived interests and is not merely an irrational practice (21). Other studies have indicated that antibiotics tend to be prescribed when the patient expects it; yet what probably happens even more com-monly is that physicians prescribe antibiotics because they think the patient expects it, even though the pa-tient's real expectations are unknown (15, 22, 23). These findings indicate patient-friendly prescribing practices that do not necessarily accord with the current recommendations.

Conclusion

In the sample of physicians surveyed, cotrimoxazole and fluoroquinolones were found to be the most commonly prescribed antibiotics for uncomplicated UTI in the year 2008. Because fluoroquinolone resis-tance in *E. coli* has become more common in Ger-many (as in many other countries around the world), fluoroquinolones are no longer recommended as a drug of first choice for this indication. Similar con-siderations apply to cotrimoxazole; for this drug, however, attention should be paid to the local resis-tance situation—cotrimoxazole should only be given if the local resistance rate is under 20%. Some of the findings of the present study suggest that decisions regarding antibiotic treatment are often fraught with uncertainty. Guidelines on antibiotic treatment in which the choice is partly determined by regional re-sistance rates can promote good clinical practice and improve prescribing behavior. This presupposes, however, that up-to-date regional and patient-group-specific resistance data are available. Data of this type are regularly reported by the ARS.

Limitations

This study is based on a survey in which physicians answered questions on their attitudes toward pre-scribing antibiotics and their prescribing behavior. Such information is subject to the usual sources of bias in surveys, e.g., the perceived social desirability of particular answers. Any conclusions about actual prescribing practices are, therefore, tentative.

The findings suggest that quinolones are often prescribed for UTI in the former East Germany, where resistance rates are reportedly low. This result may partly reflect bias, as the data from the eastern regions may be incomplete. The data analyzed here were derived exclusively from physicians who said that UTI was their most common diagnosis; perhaps eastern German physicians who treated other diseases even more commonly than UTI (and were therefore not included in this study) prescribed differently for UTI than those who were included.

KEY MESSAGES

- Because of the increasing resistance of *E. coli* to fluoro-quinolones in Germany and around the world, fluoroquinolones are no longer recommended as first-line treatment in uncomplicated urinary tract infection.

- Decisions about antibiotic treatment are often fraught with uncertainty..

- Guidelines on antibiotic treatment in which the choice is partly determined by regional resistance rates can promote good clinical practice and improve prescribing behavior.

- Up-to-date regional and patient-group-specific resis-tance data must be available.

- ARS (Antibiotic Resistance Surveillance in Germany) provides such data in an interactive database that offers comprehensive opportunities to generate resistance reports for the most important bacterial pathogens.

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Survey questionnaire:
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