Original Article

The Percentage of Antibiotic Resistance in Uncomplicated Community-Acquired Urinary Tract Infections

Findings of the RedAres Project

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Summary

Background: Uncomplicated bacterial urinary tract infections (uUTIs) are commonly seen in outpatient practice. They are usually treated empirically with antibiotics. The pertinent German Clinical Practice Guideline contains recommendations on antibiotic selection, with the additional advice that the local resistance situation should be considered as well. However, up-to-date information on local resistance is often unavailable, because microbiological testing is mainly recommended for complicated UTIs. Resistance rates are often higher in recurrent uUTIs than in single episodes. In this study, we aimed to determine the resistance rates of Escherichia coli (E. coli) in patients with community-acquired uUTIs and to make these data available to the treating physicians.

Methods: In a nationwide cross-sectional study in Germany (DRKS 00019059), we determined the percentages of resistance to antibiotics recommended for uUTIs (first choice: fosfomycin, nitroxoline, mecillinam, nitrofurantoin, trimethoprim; second choice: cefpodoxime, ciprofloxacin, cotrimoxazole, levofloxacin, norfloxacin, ofloxacin) over the period 2019–2021. The data were stratified by single episodes vs. recurrent UTIs (rUTIs).

Results: Data from 2390 subjects were analyzed. E. coli was found in 75.4% of the samples with positive urine cultures (1082 out of 1435). The resistance rate of E. coli in single episodes (n = 725) was less than 15% for all antibiotics tested. In rUTIs (n = 357), resistance rates were also less than 15% for the most part; the only exceptions were trimethoprim (21.4%) and cotrimoxazole (19.3%).

Conclusion: For single episodes of uUTI, all of the antibiotics studied can be recommended, at least as far as their resistance profiles are concerned. For recurrent UTI, all but trimethoprim and cotrimoxazole can be recommended. The second-choice antibiotics examined do not have a more favorable resistance profile than the first-choice antibiotics.

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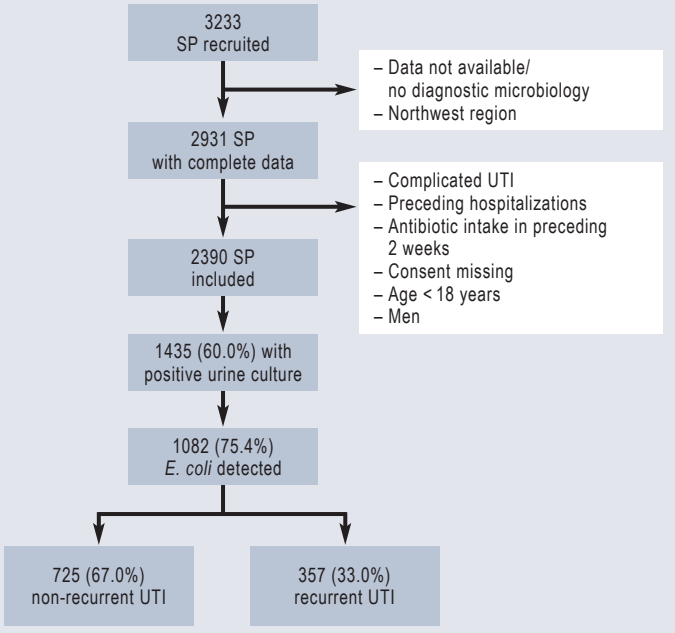
Urinary tract infections (UTIs) are among the most commonly occurring community-acquired bacterial infections. Antibiotics are the recommended treatment (1, 2). In 2013, UTIs (N39.0) were diagnosed in 7.3% of all females over 12 years of age with medical insurance provided by the German health insurance fund Barmer Gmünder Ersatzkasse (GEK), while acute cystitis (N30.0) was diagnosed in 1.7% (4). In uncomplicated cystitis, the most common lower urinary tract infection, the recommended treatment, the recommended treatment is empirical administration of antibiotics without prior microbiological testing (5). Although the use of fluoroquinolones has declined, there is continuing overprescription of broad-spectrum antibiotics for the empirical treatment of UTIs (2), despite the availability of five different narrow-spectrum antibiotics (fosfomycin, nitroxoline, mecillinam, nitrofurantoin, trimethoprim) that are recommended as first-line treatment in the relevant German Clinical Practice Guideline of 2017 (5). Among their other functions, guidelines are intended to support decision-making processes in the selection of the appropriate treatment, but they are often not heeded. Moreover, the selection of antibiotic is often not based on current resistance rates or spectrum of action, despite recommendations in the guidelines. (6). With regard to

Figure



Flow chart
E. coli, Escherichia coli; SP, study participants; UTI, urinary tract infection

Table 1

Numbers of participating laboratories and physicians' practices, number of study participants

	Number of labs	Number of practices	Number of study participants
Northeast	2	40	728
Northwest*	1	12	205
West	2	32	711
Southwest	2	25	799
Southeast	2	39	790
Total	9	148	3233

* Excluded from analysis owing to low number of study participants

resistance rates, an antibiotic is deemed appropriate for empirical use if the resistance rate of *Escherichia* (*E.) coli* to the substance concerned is below 20% (7).

For many women, the first UTI is followed by subsequent infections. In a representative population survey carried out in 2014 in the UK, 3% of women reported a history of recurrent infections (three or more infections in the previous 12 months) (8). The baseline survey of a clinical trial in women with UTIs in Germany found recurrent UTI (rUTI) rates of 17% and 23% in the two arms of the study (9). The proportion of women with rUTIs was shown to increase with age (10). Guidelines published to date make no recommendations on modified treatment options for rUTIs; however, there is evidence of different resistance rates in this group (11, 12).

Based on this knowledge, the RedAres study (REDuction of Antibiotic RESistance in the outpatient treatment of patients with uncomplicated urinary tract infections according to clinical practice guidelines) was undertaken.

The project was supported by healthcare research funding from the Innovation Fund of the German Federal Joint Committee (13, 14).

The survey presented here formed part of the RedAres project. In a Germany-wide cross-sectional study, the resistance rates of *E. coli* and other uropathogenic bacteria to the antibiotics recommended in the Clinical Practice Guideline were surveyed—stratified into single episodes and recurrent infections—for the period 2019–2021, in order to be able to provide the resistance data to primary care physicians.

Methods

The study was conducted in five regions of Germany: Northwest (the federal states of Lower Saxony, Bremen, Hamburg, and Schleswig-Holstein), North (Mecklenburg–West Pomerania, Saxony–Anhalt, Berlin, Brandenburg), Southeast (Thuringia, Saxony, Bavaria), Southwest (Baden–Württemberg, Hesse, Saarland, Rhineland–Palatinate), and West (North Rhine–Westphalia). Women were recruited to take part in the study by primary care physicians. A total of 148 practices (12–40 per region) took part in the study. The participating physicians were asked to recruit female patients with uncomplicated UTIs (uUTIs). The inclusion criteria were as follows:

- Female
- Age ≥ 18 years
- No functional or anatomical changes, urological/renal disease, kidney stones, immunosuppression, or urinary catheter (7)

Written consent was obtained from every participant. A urine sample (midstream urine) from each participant was analyzed. The following additional factors were recorded: pregnancy, diabetes mellitus, hospitalization in the preceding 2 weeks, antibiotic intake in the preceding 2 weeks, and frequency of occurrence of UTI in the preceding 6 months (7).

Patients with preceding hospitalization or preceding antibiotic intake were excluded. If the current UTI was at least the second episode within 6 months, the UTI was classified as recurrent (rUTI) (5).

The diagnostic microbiological testing of the urine samples was performed at nine different laboratories that were regularly used by the participating physicians' practices. Testing for pathogens and resistance was generally conducted by means of automated procedures. A positive urine culture was defined as detection of $\geq 10^3$ colony-forming units (CFU)/mL. The resistance of *E. coli* and other uropathogenic bacteria (*Klebsiella pneumoniae, Enterococcus* spp., *Proteus mirabilis*, group B streptococci/*S. agalactiae, Staphylococcus saprophyticus, Citrobacter* spp., *Staphylococcus aureus)* to all antibiotics recom-

Table 2

Distribution of pathogens

	Total	Northeast	Southeast	Southwest	West
Number of included samples with pathogen detection	1435	361	398	338	338
Escherichia coli	1082 (75.4%)	273 (75.6%)	311 (78.1%)	231 (68.3%)	267 (79.0%)
Klebsiella pneumoniae	96 (6.7%)	17 (4.7%)	23 (5.8%)	23 (6.8%)	16 (4.7%)
Enterococcus spp.*1	75 (5.2%)	19 (5.3%)	33 (8.3%)	18 (5.3%)	5 (1.5%)
Group B streptococci/*S. agalactiae*	69 (4.8%)	6 (1.7%)	22 (5.5%)	13 (3.8%)	28 (8.3%)
Proteus mirabilis	66 (4.6%)	20 (5.5%)	9 (2.3%)	17 (5.0%)	20 (5.9%)
Staphylococcus saprophyticus	35 (2.4%)	1 (0.3%)	11 (2.8%)	16 (4.7%)	7 (2.1%)
Citrobacter spp.*2	32 (2.2%)	9 (2.5%)	6 (1.5%)	7 (2.1%)	10 (3.0%)
Staphylococcus aureus	17 (1.2%)	4 (1.1%)	5 (1.3%)	2 (0.6%)	6 (1.8%)

The resistance rates refer to the total numbers of included samples with pathogen detection per region.
The resistance rates of the individual pathogens can add up to more than 100%, because in 11.7% of cases more than one pathogen was detected in the urine sample.
*1 *Enterococcus* spp. comprises *Enterococcus (E.)* spp., *E. faecalis, E. faecium*, and *E. gallinarum.*
*2 *Citrobacter* spp. comprises *Citrobacter (C.) amalonaticus, C. freundii, C. braakii*, and *C. koseri.*

mended for first- or second-line treatment of uUTIs in the Clinical Practice Guideline of 2017 was investigated. The results were interpreted according to the EUCAST standards. Antibiotics not included in the automated testing procedures were tested by means of agar diffusion. This was the case for nitroxoline, nitrofurantoin, and pivmecillinam in several laboratories, and for all other antibiotics in single cases.

The laboratories transmitted the resistance results via the German national Antimicrobial Resistance Surveillance (ARS) system, a laboratory-based surveillance system at the Robert Koch Institute (RKI) (15). The laboratories that took part in the study were already a part of ARS before the study began.

Statistical methods

Data analysis was carried out using R 4.2.1 (16). The 95% confidence intervals for rates were calculated by means of the Wilson method. Based on a sample size calculation designed to determine the resistance rate of *E. coli* to trimethoprim with uncertainty of ± 4%, at least 700 patients needed to be included per region in order to yield a high probability of being able to evaluate 385 samples per region in which *E. coli* was detected.

Before the study began, its data protection quality was assessed by the Data Protection Officer at the RKI. The RKI received exclusively pseudonymized data. The study is registered with the German Registry of Clinical Trials (DRKS00019059). (The following internal review board approvals had been obtained: ethics committee of Charité – Berlin University Medicine [EA2/127/19], Greifswald University Medicine [BB 126/19], North Rhine Medical Association [2019–353], Rhineland–Palatinate State Medical Association [2019–14585], Saxony State Medical Association [EK BR 77/19], Schleswig-Holstein Medical Association [011 20 m]).

Results

Altogether, 3233 females were recruited to take part in the study (205–799 per region) *(Table 1)*. The Northwest region was excluded from analysis due to the low number of participants. Further exclusion criteria were: absence of consent, failure to meet the inclusion criteria, and incomplete transmission of data *(Figure)*.

A total of 2390 participants were included for analysis. There was a positive urine culture in 1435 participants. The age distribution of the latter was 18–98 years (median 57, varying per region from 56 to 58.5 years).

In 11.7% of cases, two pathogens or more were detected in the urine culture. *E. coli* was confirmed in 75.4% (1082) of all positive urine cultures. In 67% of these cases (725 probands) it was a single episode, while 33% (3657 probands) had rUTIs. Pregnancy was reported by 0.3% of the study participants, diabetes mellitus by 13.8%.

Other commonly encountered pathogens were *Klebsiella pneumoniae* (5.5%), *Enterococcus* spp. (5.2%), *Proteus mirabilis* (4.6%), and group B streptococci/*S. agalactiae* (4.8%) *(Table 2)*.

Resistance rates of *E. coli*

Germany-wide

For single episodes, the rates of resistance of *E. coli* to fosfomycin, nitrofurantoin, and nitroxoline were 0.8%, 0.1%, and 0.6%, respectively *(Table 3)*. Higher resistance rates were seen to pivmecillinam (5.9%) and trimethoprim (14.1%). The resistance rates against the second-line antibiotics we investigated varied between 4.0% for cefpodoxime and 11.5% for cotrimoxazole.

There were minor differences between resistance rates to first-line antibiotics for rUTIs and single episodes; however, resistance tended to be slightly higher for rUTIs. These differences were more pronounced for the second-line antibiotics. The resistance rates against trimethoprim

Table 3

***Escherichia coli* resistance rates**

	Antibiotic	R rate	95% CI
Non-recurrent UTIs			
First line	Pivmecillinam	5.9%	[4.3; 8.1]
	Fosfomycin	0.8%	[0.3; 1.8]
	Nitrofurantoin	0.1%	[0.0; 0.8]
	Nitroxoline	0.6%	[0.2; 1.8]
	Trimethoprim	14.1%	[11.7; 16.8]
Second line	Cefpodoxime	4.0%	[2.6; 6.1]
	Norfloxacin	8.2%	[5.1; 12.9]
	Ofloxacin	9.5%	[5.3; 16.6]
	Levofloxacin	7.3%	[5.5; 9.6]
	Ciprofloxacin	6.7%	[5.1; 8.8]
	Cotrimoxazole	11.5%	[9.4; 14.1]
Recurrent UTIs			
First line	Pivmecillinam	5.1%	[3.2; 8.1]
	Fosfomycin	0.6%	[0.2; 2.2]
	Nitrofurantoin	1.1%	[0.4; 2.8]
	Nitroxoline	0.9%	[0.2; 3.1]
	Trimethoprim	21.4%	[17.5; 26.0]
Second line	Cefpodoxime	9.2%	[6.2; 13.4]
	Norfloxacin	9.5%	[4.7; 18.3]
	Ofloxacin	2.9%	[0.5; 14.9]
	Levofloxacin	11.5%	[8.3; 15.7]
	Ciprofloxacin	12.5%	[9.5; 16.4]
	Cotrimoxazole	19.3%	[15.5; 23.7]

First- and second-line antibiotics according to the recommendations of the interdisciplinary Clinical Practice Guideline (5).
CI, Confidence interval; *E. coli, Escherichia coli*; R rate, resistance rate; UTI, urinary tract infection

and cotrimoxazole were higher than for single episodes, at 21.4% and 19.3% respectively.

Regions

In the individual regions the differences in resistance rates between single episodes and rUTIs tended to be minor *(Table 4)*. Only in the Northeast region were the rates of resistance to trimethoprim and cotrimoxazole considerably higher for rUTIs than for non-recurrent uUTIs.

Resistance rates of uropathogenic bacteria

For single episodes nationwide, the lowest resistance rate of other uropathogenic bacteria was to nitrofurantoin at 4.5%.The highest resistance rates were to trimethoprim (14.5%), ofloxacin (13.8%), and cotrimoxazole (12.1%) *(eTable 1)*. For rUTIs, the lowest resistance rate was to nitrofurantoin (5.7%) and the highest rates were to trimethoprim (22.0%) and cotrimoxazole (20.1%). The resistance rates for all uropathogenic bacteria together tended to be higher than for *E. coli* alone.

Stratification by region showed higher resistance rates in the Southeast than elsewhere, particularly against the first-line antibiotics. Large differences were evident between the regions with regard to the rates of resistance to pivmecillinam.

Discussion

This study investigated the resistance rates of *E. coli* and other uropathogenic bacteria to first-line and second-line antibiotics recommended in the relevant Clinical Practice Guideline for use in community-acquired uUTIs, in four of five regions of Germany. Despite the exclusion of the fifth region (Northwest), this was the largest sample yet studied with regard to resistance rates among women with uUTIs in Germany. Regarding the empirical use of antibiotics for uUTIs, the Clinical Practice Guideline recommends that prescription should be guided by the current resistance rates in the region concerned; however, no valid large-scale data have previously been available.

For most antibiotics the resistance rates of *E. coli* were higher in rUTIs than in single episodes. The differences were minor for the antibiotics recommended as first-line agents, with the exception of trimethoprim. The resistance rates against the second-line antibiotics varied more widely. The marked differences in the resistance rates to trimethoprim and cotrimoxazole between single episodes and rUTIs had already been indicated in previous studies (11, 12). The resistance rates of *E. coli* to trimethoprim and cotrimoxazole in our study were similar to existing ARS data on routine diagnostic investigation of UTIs in the community *(eTable 2)*. The ARS data primarily reflect the state of resistance with regard to complicated UTIs. rUTIs tended to reflect the resistance rates of complicated UTIs more than uncomplicated UTIs (12, 17). Accordingly, trimethoprim and cotrimoxazole should not be used empirically as first-line antibiotics in the treatment of rUTIs.

Overall, the second-line antibiotics we investigated showed no advantage over the first-line agents with regard to resistance. This contradicts the frequently-used argument that one should primarily use second-line antibiotics due to their superior efficacy (18).

The resistance rates of nitroxoline, pivmecillinam, and fosfomycin were of particular interest. After being unlicensed for a long period of time, nitroxoline was again recommended for use in Germany in 2021. Yet it is one of the less frequently prescribed antibiotics for uUTIs (2, 19). *E. coli* showed hardly any resistance to nitroxoline. At the time of our study there were no recent data for comparison, especially with regard to uUTIs. In a study performed by Wagenlehner et al. in 2022, all *E. coli* isolates from women with the diagnosis of acute cystitis were sensitive to nitroxoline (20).

A low resistance rate of 4.5% *(E. coli)* was also found for pivmecillinam, which was first approved for use in Germany in 2016. Stratified by region, the resistance rates were consistently under 5% except in the West region, where the rate was 11.0%. In studies from other countries the reported rates are mostly under 5.0%, but in Poland

Table 4

Resistance rates of *Escherichia coli* stratified by region

	Antibiotic	Northeast		Southeast		Southwest		West	
		R rate	95% CI	R rate	95% CI	R rate	95% CI	R rate	95% CI
Non-recurrent UTI									
First line	Pivmecillinam	4.5%	[1.8; 11.0]	4.0%	[2.0; 7.7]	2.9%	[1.1; 7.3]	11.0%	[7.2; 16.4]
	Fosfomycin	0.0%	[0.0; 1.9]	2.2%	[0.8; 6.3]	0.7%	[0.1; 4.1]	0.5%	[0.1; 2.9]
	Nitrofurantoin	0.0%	[0.0; 1.9]	0.0%	[0.0; 1.9]	0.7%	[0.1; 4.0]	0.0%	[0.0; 2.0]
	Nitroxoline	1.9%	[0.5; 6.8]	0.5%	[0.1; 3.0]	0.0%	[0.0; 35.4]	0.0%	[0.0; 2.1]
	Trimethoprim	10.2%	[6.7; 15.2]	14.6%	[10.4; 20.2]	14.7%	[9.7; 21.6]	17.1%	[12.3; 23.3]
Second line	Cefpodoxime	3.3%	[1.5; 7.0]	4.5%	[2.0; 10.2]	0.0%	[0.0; 24.2]	4.7%	[2.5; 8.6]
	Norfloxacin	7.6%	[3.9; 14.3]	8.9%	[4.6; 16.6]	ND	ND	ND	ND
	Ofloxacin	9.5%	[5.3; 16.6]	ND	ND	ND	ND	ND	ND
	Levofloxacin	6.7%	[3.9; 11.1]	7.6%	[3.7; 14.9]	5.1%	[2.5; 10.2]	9.3%	[6.0; 14.3]
	Ciprofloxacin	7.1%	[4.3; 11.6]	5.0%	[2.7; 8.9]	5.1%	[2.5; 10.2]	9.3%	[6.0; 14.3]
	Cotrimoxazole	9.6%	[6.3; 14.6]	10.9%	[7.3; 16.0]	13.1%	[8.5; 19.8]	13.0%	[8.9; 18.4]
Recurrent UTI									
First line	Pivmecillinam	9.5%	[3.8; 22.1]	2.7%	[0.9; 7.6]	2.5%	[0.7; 8.7]	8.6%	[4.2; 16.8]
	Fosfomycin	1.3%	[0.2; 7.1]	0.0%	[0.0; 4.8]	1.3%	[0.2; 6.7]	0.0%	[0.0; 4.1]
	Nitrofurantoin	0.0%	[0.0; 4.8]	0.9%	[0.2; 4.9]	2.5%	[0.7; 8.7]	1.1%	[0.2; 6.0]
	Nitroxoline	0.0%	[0.0; 10.2]	0.9%	[0.2; 5.2]	0.0%	[0.0; 24.2]	1.2%	[0.2; 6.7]
	Trimethoprim	26.0%	[17.5; 36.7]	15.2%	[9.7; 23.0]	25.0%	[16.8; 35.5]	22.2%	[14.5; 32.4]
Second line	Cefpodoxime	13.3%	[7.4; 22.8]	4.2%	[1.4; 11.5]	15.4%	[4.3; 42.2]	8.9%	[4.6; 16.6]
	Norfloxacin	0.0%	[0.0; 10.2]	17.5%	[8.7; 31.9]	ND	ND	ND	ND
	Ofloxacin	2.9%	[0.5; 14.9]	ND	ND	ND	ND	ND	ND
	Levofloxacin	10.4%	[5.4; 19.2]	17.5%	[8.7; 31.9]	10.0%	[5.2; 18.5]	11.1%	[6.1; 19.3]
	Ciprofloxacin	10.4%	[5.4; 19.2]	15.2%	[9.7; 23.0]	12.5%	[6.9; 21.5]	11.1%	[6.1; 19.3]
	Cotrimoxazole	23.4%	[15.3; 34.0]	13.4%	[8.3; 20.9]	21.5%	[13.9; 31.8]	21.1%	[14.0; 30.6]

First- and second-line antibiotics as recommended in the interdisciplinary Clinical Practice Guideline (5).
CI, Confidence interval; ND, no data available; R rate, resistance rate; UTI, urinary tract infection

the rate is 10% (17). Assessment of pivmecillinam must consider the intrinsic resistance of *Staphylococcus saprophyticus*; this plays only a minor role, however, as the resistance rate is 2.4% nationwide *(Table 2)*.

In the case of fosfomycin the resistance rate of *E. coli* was below 2% both in single episodes and in rUTIs. The highest resistance rate in an individual region was 2.2%. Fosfomycin is among the most frequently administered antibiotics to treat community-acquired UTIs, yet is characterized by low resistance rates (2, 17, 19). A study published in 2019 revealed that the use of fosfomycin is unlikely to promote selection of a particular clone or the spread of transmissible resistance genes, because the fosfomycin-resistant isolates that were investigated did not display multiple resistance and carried no plasmidic fosfomycin resistance genes (21). To date, there is no sign of development of high resistance to fosfomycin, which might have been expected given its widespread use (22).

Nitrofurantoin was shown to have the lowest resistance rates out of all investigated antibiotics. This was evident primarily for *E. coli*, both in single episodes and in rUTIs, but also for the other uropathogenic bacteria. The low rates of resistance to fosfomycin, pivmecillinam, and nitrofurantoin support the recommendations of international guidelines (23).

The resistance rates for the individual pathogens are not shown due to the low numbers of samples. Considering that it is clinical practice in Germany to prescribe empirical antibiotic treatment without knowledge of the individual pathogen, the average resistance rates of all the typical uropathogenic bacteria together to each antibiotic have been presented. The patient's history and clinical signs do not suffice to predict the probability of specific pathogens. The representation of an overall resistance

rate of the typical pathogens is therefore convenient for prescribers, in order to determine the overall efficacy of a prescribed antibiotic, independent of the causative pathogen. Despite the occasionally higher resistance rates of all uropathogenic bacteria than of *E. coli*, all of the recommended antibiotics—except trimethoprim and cotrimoxazole—are suitable for use both in single episodes and in rUTIs.

In 2015 the resistance rates in uUTIs were investigated in the SARHA study (24). The RedAres project survey had a larger sample and additionally focused on rUTIs and on all uropathogenic bacteria. The antibiotics investigated differ to some extent because of the different recommendations in place at that time. For example, no data on mecillinam and nitroxoline were available in 2015. The resistance rates exhibited by *E. coli* in the SARHA study do not differ greatly from the survey presented here. An increase can be seen in the rates of resistance against ciprofloxacin (2015: 4.5% [2.5; 7.4]) (12).

Our study was carried out during the COVID-19 pandemic, which represented a challenge for all involved. Ultimately, 24% of the primary care practices that had originally agreed to take part were unable to do so. Recruitment of study participants also proved to be challenging. For this reason, the study in the Northwest region had to be discontinued. An intention-to-treat analysis of resistance rates for the 78 uUTIs with detection of *E. coli* that were received in this region revealed no essential deviations from the overall findings, except for a much higher rate of resistance of *E. coli* against ofloxacin *(eTable 3)*.

Limitations

The participating physicians were asked to include patients who met the predefined criteria. An incentive was paid to the participating physician for each recruited participant. The questionnaire was answered solely by treating physicians, and thus neither the responses nor correct implementation of the inclusion criteria could be independently verified within the scope of the study.

Conclusion

In terms of resistance, all of the antibiotics recommended in the German Clinical Practice Guideline are suitable for use in calculated treatment for single episodes of uUTI. Trimethoprim and cotrimoxazole are rendered unsuitable due to high resistance rates. Despite the favorable situation in regard to resistance, recurrence of UTI should always prompt microbiological testing.

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Conflict of interest statement

GS has received payments for acting as an instructor at training courses from various medical associations, from the German Federation of Primary Care Physicians (Hausärzteverband), and from the Institute for the Advanced Training of Primary Care Physicians (Institut für hausärztliche Fortbildung). He is a member of the German Society of General and Family Medicine (Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin, DEGAM) and of the Institute for the Advanced Training of Primary Care Physicians, Bremen.

IG leads the RedAres project consortium. She has received payments for acting as an instructor on the topic of the use of antibiotics in primary care at training courses for physicians (the "Tag der Allgemeinmedizin" in Göttingen and the "Fortbildungswoche der Praktischen Medizin" on Langeoog). She is a member of the Robert Koch Institute's Commission on Anti-Infectives, Resistance and Therapy.

TE has received payments for acting as an instructor at Antibiotic Stewardship Initiative training courses.

The remaining authors declare that no conflict of interest exists.

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Supplementary material
eTables:
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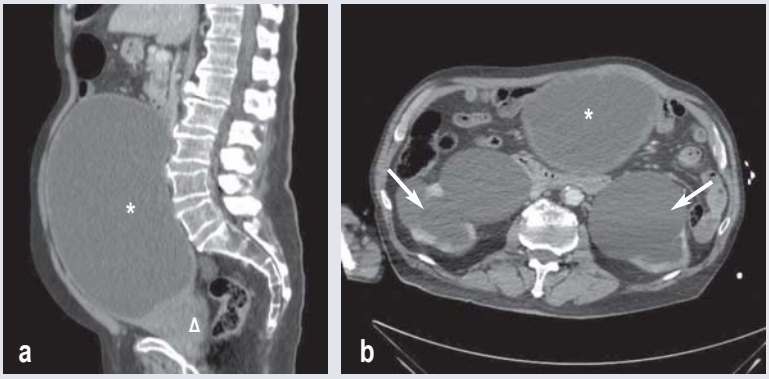
CLINICAL SNAPSHOT

Cardiovascular Arrest Due to Postrenal Kidney Injury

A 77-year-old man with increasing listlessness and unwanted weight loss visited a radiologist's office located on the premises of the hospital for elective cranial computed tomography (without contrast medium). Following the examination he suddenly collapsed in the foyer. The emergency team encountered a comatose patient (GCS 3) with an initially still palpable bradycardic pulse. Subsequent disappearance of the pulse was followed by cardiopulmonary resuscitation according to the guidelines, with the return of spontaneous circulation after 2 minutes. Electrocardiography showed a bradycardic ectopic atrial rhythm with grade I AV block and complete right bundle block. In the presence of severe metabolic acidosis and marked hyperkalemia (8.8 mmol/L), calcium gluconate and insulin/glucose were given. Physical examination revealed an abdominal swelling. Emergency sonography merely identified a cystic mass of unclear nature, but computed tomography *(Figures 1 and 2)* showed the cause of this hyperkalemia-induced cardiovascular arrest: postrenal kidney injury owing to massive prostatomegaly-related urinary retention with bilateral hydronephrosis. The patient survived the event, and after a long stay in intensive care he was transferred to a specialist center for weaning.



Computed tomography (CT) with contrast medium in the soft tissue window a) Sagittal CT with CM in the soft tissue window: pronounced enlargement of the prostate (triangle) with nodular protrusion of the massively distended urinary bladder (star). b) Axial CT with CM in the soft tissue window: massive distension of the urinary bladder (star) with resultant hydronephrosis grade III-IV (arrows).
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Supplementary material to the article

The Percentage of Antibiotic Resistance in Uncomplicated Community-Acquired Urinary Tract Infections

Findings of the RedAres Project

by Anja Klingeberg , Niklas Willrich, Marc Schneider, Guido Schmiemann, Ildikó Gágyor, Doreen Richter, Ines Noll, and Tim Eckmanns

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eTable 1

Resistance rates of uropathogenic bacteria

		Overall		Northeast		Southeast		Southwest		West	
	Antibiotic	R rate	95% CI	R rate	95% CI	R rate	95% CI	R rate	95% CI	R rate	95% CI
Non-recurrent UTI											
First line	Pivmecillinam	9.9%	[7.9; 12.4]	4.5%	[1.7; 11.0]	13.2%	[9.5; 18.1]	4.3%	[2.0; 9.0]	12.1%	[8.4; 17.3]
	Fosfomycin	7.3%	[5.7; 9.2]	4.7%	[2.6; 8.2]	14.5%	[10.1; 20.4]	6.6%	[3.7; 11.5]	4.7%	[2.7; 8.3]
	Nitrofurantoin	4.7%	[3.4; 6.3]	4.1%	[2.2; 7.6]	5.3%	[3.2; 8.8]	6.9%	[4.0; 11.7]	2.5%	[1.1; 5.6]
	Nitroxoline	7.6%	[5.6; 10.2]	6.3%	[3.1; 12.3]	14.4%	[10.3; 19.7]	0.0%	[0.0; 0.0]	1.1%	[0.3; 3.8]
	Trimethoprim	14.5%	[12.3; 17.0]	12.7%	[9.1; 17.6]	14.5%	[10.6; 19.5]	13.8%	[9.3; 19.9]	17.1%	[12.6; 22.6]
Second line	Cefpodoxime	6.1%	[4.5; 8.4]	3.2%	[1.6; 6.5]	12.1%	[7.7; 18.5]	0.0%	[0.0; 0.0]	5.7%	[3.3; 9.5]
	Norfloxacin	8.3%	[5.4; 12.6]	7.0%	[3.7; 12.8]	9.9%	[5.5; 17.3]	ND	ND	ND	ND
	Ofloxacin	13.8%	[8.9; 20.8]	13.8%	[8.9; 20.8]	ND	ND	ND	ND	ND	ND
	Levofloxacin	6.3%	[4.8; 8.2]	6.0%	[3.6; 9.8]	7.3%	[3.9; 13.3]	3.9%	[1.9; 7.9]	7.8%	[5.0; 11.8]
	Ciprofloxacin	7.9%	[6.3; 9.9]	8.0%	[5.2; 12.2]	9.4%	[6.4; 13.7]	5.0%	[2.6; 9.6]	8.3%	[5.4; 12.5]
	Cotrimoxazole	12.1%	[10.2; 14.4]	11.9%	[8.4; 16.6]	11.5%	[8.1; 15.9]	13.0%	[8.8; 18.7]	12.4%	[8.8; 17.1]
Recurrent UTI											
First line	Pivmecillinam	10.5%	[7.7; 14.1]	9.5%	[3.8; 22.1]	15.5%	[10.5; 22.3]	2.5%	[0.7; 8.7]	10.1%	[5.4; 18.1]
	Fosfomycin	10.5%	[7.9; 13.8]	8.6%	[4.4; 16.1]	14.5%	[9.2; 22.3]	9.4%	[5.2; 16.5]	9.1%	[5.0; 15.9]
	Nitrofurantoin	5.7%	[3.9; 8.2]	3.4%	[1.2; 9.4]	7.7%	[4.5; 13.0]	7.1%	[3.7; 13.5]	3.1%	[1.0; 8.6]
	Nitroxoline	9.2%	[6.2; 13.3]	2.8%	[0.9; 14.2]	16.7%	[11.2; 24.1]	0.0%	[0.0; 0.0]	2.3%	[0.6; 7.9]
	Trimethoprim	22.0%	[18.4; 26.1]	30.0%	[21.9; 39.6]	17.4%	[12.0; 24.4]	20.8%	[14.0; 29.7]	21.9%	[14.8; 31.1]
Second line	Cefpodoxime	10.4%	[7.5; 14.4]	12.5%	[7.1; 21.0]	10.9%	[6.0; 18.9]	15.4%	[4.3; 42.2]	7.7%	[3.9; 14.4]
	Norfloxacin	7.5%	[3.7; 14.7]	0.0%	[0.0; 0.0]	14.3%	[7.1; 26.7]	ND	ND	0.0%	[0.0; 0.0]
	Ofloxacin	8.7%	[3.4; 20.3]	6.8%	[2.3; 18.2]	ND	ND	ND	ND	50.0%	[9.5; 90.5]
	Levofloxacin	9.3%	[6.8; 12.6]	10.0%	[5.4; 17.9]	12.3%	[6.4; 22.5]	7.0%	[3.6; 13.1]	9.5%	[5.4; 16.2]
	Ciprofloxacin	12.6%	[9.9; 16.0]	9.6%	[5.1; 17.2]	16.6%	[11.5; 23.3]	10.8%	[6.1; 18.3]	11.4%	[6.7; 18.9]
	Cotrimoxazole	20.1%	[16.8; 23.9]	28.3%	[20.4; 37.8]	14.7%	[10.0; 21.2]	20.5%	[14.1; 28.9]	20.0%	[13.7; 28.2]

First- and second-line antibiotics as recommended in the interdisciplinary Clinical Practice Guideline (5).
The uropathogenic bacteria comprise *Escherichia coli, Klebsiella pneumoniae, Enterococcus* spp., *Proteus mirabilis*, group B streptococci/*Streptococcus agalactiae*, *Staphylococcus saprophyticus*, *Citrobacter* spp., and *Staphylococcus aureus*.
CI, Confidence interval; ND, no data available; R rate, resistance rate; UTI, urinary tract infection

eTable 2

Resistance rates of *E. coli* in ARS 2020

		Overall		Northeast		Southeast		Southwest		West	
	Antibiotic	R rate	95% CI	R rate	95% CI	R rate	95% CI	R rate	95% CI	R rate	95% CI
First line	Pivmecillinam	5.9%	[5.7; 6.0]	5.4%	[4.9; 5.8]	3.5%	[3.3; 3.7]	8.6%	[8.1; 9.1]	7.2%	[6.9; 7.6]
	Fosfomycin	1.0%	[1.0; 1.1]	1.1%	[1.0; 1.3]	1.1%	[1.0; 1.2]	0.9%	[0.7; 1.0]	0.9%	[0.8; 1.0]
	Nitrofurantoin	1.1%	[1.0; 1.1]	0.8%	[0.7; 0.9]	0.9%	[0.8; 1.0]	1.2%	[1.0; 1.4]	1.4%	[1.3; 1.5]
	Nitroxoline	0.7%	[0.6; 0.8]	0.5%	[0.0; 1.1]	0.8%	[0.6; 0.9]	0.3%	[0.1; 0.4]	0.3%	[0.0; 0.5]
	Trimethoprim	22.4%	[22.1; 22.6]	22.6%	[21.9; 23.3]	20.5%	[20.1; 21.0]	22.8%	[22.1; 23.4]	22.9%	[22.2; 23.6]
Second line	Cefpodoxime	8.2%	[8.1; 8.4]	7.7%	[7.2; 8.1]	7.5%	[7.2; 7.8]	9.7%	[9.3; 10.2]	8.8%	[8.4; 9.3]
	Norfloxacin	12.7%	[12.0; 13.4]	10.3%	[7.2; 13.4]	11.3%	[9.7; 12.9]	20.5%	[11.3; 29.8]	13.2%	[12.3; 14.0]
	Ofloxacin	12.4%	[11.5; 13.2]	ND	ND	12.1%	[11.2; 13.0]	11.8%	[7.1; 16.5]	17.7%	[13.9; 21.4]
	Levofloxacin	16.7%	[16.5; 16.9]	0.0%	[15.5; 16.8]	15.5%	[15.0; 16.0]	17.6%	[17.0; 18.1]	16.7%	[16.2; 17.2]
	Ciprofloxacin	13.4%	[13.2; 13.6]	12.2%	[11.7; 12.7]	12.1%	[11.8; 12.4]	14.6%	[14.1; 15.1]	14.4%	[14.0; 14.8]
	Cotrimoxazole	19.6%	[19.4; 19.8]	19.5%	[18.9; 20.1]	18.2%	[17.9; 18.6]	19.6%	[19.0; 20.2]	20.3%	[19.9; 20.8]

Resistance rates of *E. coli* in the year 2020 as demonstrated in urine cultures obtained for routine diagnostic purposes at physicians' offices in the field of general/internal medicine (from SAR data). Isolates from women aged 18 years or over were included (n = 120 566). Neither clinical data nor further detail is available. First- and second-line antibiotics as recommended in the interdisciplinary Clinical Practice Guideline (5).
CI, Confidence interval; *E. coli, Escherichia coli*; ND, no data available; R rate, resistance rate; ARS, Antibiotic Resistance Surveillance (12)

eTable 3

Resistance rates of *E. coli:* comparison between study and intention-to-treat analysis

		Overall		Overall including Northwest region	
	Antibiotic	R rate	95% CI	R rate	95% CI
Non-recurrent UTI					
First line	Pivmecillinam	5.9%	[4.3; 8.1]]	6.5%	[4.8; 8.7]
	Fosfomycin	0.8%	[0.3; 1.8]	0.7%	[0.3; 1.7]
	Nitrofurantoin	0.1%	[0.0; 0.8]	0.7%	[0.3; 1.5]
	Nitroxoline	0.6%	[0.2; 1.8]	0.6%	[0.2; 1.7]
	Trimethoprim	14.1%	[11.7; 16.8]	14.3%	[12.0; 17.0]
Second line	Cefpodoxime	4.0%	[2.6; 6.1]	4.0%	[2.6; 6.1]
	Norfloxacin	8.2%	[5.1; 12.9]	7.8%	[5.0; 11.9]
	Ofloxacin	9.5%	[5.3; 16.6]	8.5%	[4.9; 14.2]
	Levofloxacin	7.3%	[5.5; 9.6]	7.3%	[5.5; 9.6]
	Ciprofloxacin	6.7%	[5.1; 8.8]	6.7%	[5.1; 8.7]
	Cotrimoxazole	11.5%	[9.4; 14.1]	11.9%	[9.8; 14.4]
Recurrent UTI					
First line	Pivmecillinam	5.1%	[3.2; 8.1]	6.6%	[4.5; 9.8]
	Fosfomycin	0.6%	[0.2; 2.2]	0.6%	[0.2; 2.0]
	Nitrofurantoin	1.1%	[0.4; 2.8]	1.5%	[0.7; 3.3]
	Nitroxoline	0.9%	[0.2; 3.1]	0.8%	[0.2; 2.7]
	Trimethoprim	21.4%	[17.5; 26.0]	21.5%	[17.7; 25.9]
Second line	Cefpodoxime	9.2%	[6.2; 13.4]	9.2%	[6.2; 13.4]
	Norfloxacin	9.5%	[4.7; 18.3]	12.5%	[7.5; 20.2]
	Ofloxacin	2.9%	[0.5; 14.9]	10.9%	[5.4; 20.9]
	Levofloxacin	11.5%	[8.3; 15.7]	11.5%	[8.3; 15.7]
	Ciprofloxacin	12.5%	[9.5; 16.4]	12.6%	[9.6; 16.2]
	Cotrimoxazole	19.3%	[15.5; 23.7]	19.5%	[15.9; 23.8]

First- and second-line antibiotics as recommended in the interdisciplinary Clinical Practice Guideline (5).
CI, Confidence interval; *E. coli, Escherichia coli*; R rate, resistance rate; UTI, urinary tract infection