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Comparison of antibiotic treatment guidelines for urinary tract infections in 15 European countries: Results of an online survey

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ABSTRACT

Appropriate antibiotic use for urinary tract infections (UTIs) is important in order to provide effective and safe treatment while minimising the risk of antimicrobial resistance development. This survey was carried out to compare existing national guidelines for UTIs in Europe. Experts in 37 European countries were asked to participate. An electronic questionnaire was used to obtain information on treatment recommendations, factors considered important when setting guidelines, acceptable resistance rates for empirical therapy, evidence grading, and existing resistance surveillance for uropathogens. Treatment guidelines and antimicrobial susceptibility data were collected. In total, 22 experts (59%) responded to the survey. National guidelines were missing in four countries and data were incomplete in three cases. Fifteen national guidelines published between 2004 and 2017 were included in the analysis. Great variability was found between guidelines in the selection of antibiotics, dosing regimens and treatment duration. For example, 10 different antibiotics were recommended as first-line therapy for uncomplicated cystitis. National surveillance data on antimicrobial susceptibility of uropathogens were available in 13 of 15 countries. Resistance epidemiology could not explain the observed differences between guidelines, and comparison of resistance rates was hampered by variations in methods. This study revealed major differences in treatment guidelines for UTIs within Europe, indicating that there are opportunities for improvement. More clinical research and a more systematic and stratified approach to resistance surveillance, including also antibiotics that are currently not available in all countries, is needed.

1. Introduction

Urinary tract infections (UTIs) are common and are one of the leading indications for antibiotic treatment worldwide [1,2]. Adequate management of these infections is important in order to provide effective and safe treatment for individual patients and to reduce healthcare-associated costs [3,4]. UTIs are also a high priority of antimicrobial stewardship interventions to reduce inappropriate use of antibiotics. Improving treatment practices for UTIs can have a large impact on overall antibiotic consumption and, consequently, on the selection and spread of antimicrobial-resistant bacteria [5] as well as on other antibiotic-induced collateral damage such as *Clostridioides difficile* infection [6]. Whilst broad-spectrum parenteral antibiotics might be needed for severely ill patients, narrow-spectrum oral antibiotics and a short duration of treatment are sufficient in most cases [7,8].

Access to evidence-based treatment recommendations is essential to promote appropriate antibiotic use for UTIs. International guidelines have been published jointly by the European Society of

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Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) in 2010 [7] and by the European Association of Urology (EAU) in 2015 [8]. Nevertheless, national or local adaptation in the selection of antibiotics may be necessary considering the reported variations in resistance rates in *Escherichia coli* and other uropathogens [9]. The availability and marketing of old antibiotics differs significantly between countries [10,11], which is probably also an important factor when setting national guidelines. Furthermore, the level of evidence supporting treatment recommendations for UTIs is sometimes low [7,8], as is the case for many guidelines in the field of infectious diseases [12], which could result in variable conclusions on optimal therapy between guideline-setting committees.

Mapping existing national guidelines for UTIs is a first step to systematically review the management of these infections in different countries and to explore opportunities for improvement. In this study, we approached participants of national guideline-setting committees for UTIs in Europe to assess the recommendations for antibiotic treatment, factors considered important when setting the guidelines, procedures for evidence grading (if provided) and the availability of resistance surveillance data.

2. Methods

2.1. Study design

This study was initiated by researchers at ReAct, Uppsala University (Uppsala, Sweden), in collaboration with the ESCMID Study Group for Antimicrobial Stewardship (ESGAP). The study was designed according to published reporting guidelines for surveys [13]. An electronic questionnaire was developed to obtain details on existing recommendations for empirical antibiotic therapy of UTIs with regard to selection of antibiotic, dosing and treatment duration. Only antibiotics listed as first-line options were considered in the analysis. Information was requested regarding the following issues: categorisation of UTI (e.g. uncomplicated versus complicated); specific recommendations for bacteria resistant to third-generation cephalosporins or carbapenems; factors considered most important when setting the guidelines; acceptable resistance rates for empirical treatment options; evidence grading; and available resistance surveillance data. Furthermore, the guidelines and surveillance reports were collected. Pilot testing of the survey was conducted by co-authors and members of ESGAP in March 2017, which resulted in minor adjustments of the questionnaire (the final version is provided in the Supplementary material).

2.2. Data collection and analysis

The study was conducted from April–August 2017. The electronic questionnaire was distributed using SurveyMonkey® (SurveyMonkey, San Mateo, CA). Invitations to participate in the survey were sent to experts in 37 European countries who were identified by the researchers and through the ESGAP network. Only respondents who had been actively involved in the development of national UTI guidelines (if existing) were included, and only one response per country was allowed. If separate treatment guidelines were provided for primary care and the hospital setting, the latter was used in the analysis because they included more information on parenteral therapy. Up to three reminders were sent to the invited experts. No incentives were provided for participation, except being listed as an investigator of the study. Data were checked for completeness and were compared with the published guidelines and surveillance reports on antimicrobial susceptibility. Extracted information and the draft manuscript were sent to respondents for review to ensure that data were accurate.

3. Results

3.1. Respondents and guidelines

In total, experts from 22 of the 37 countries (response rate 59%) responded to the questionnaire. Four respondents indicated that national recommendations for UTIs were lacking (Estonia, Latvia, Luxembourg and the Republic of Macedonia), and in three cases the provided data were incomplete. Fifteen national guidelines published between 2004 and 2017 (Supplementary Table S1) were included in the analysis. The recommendations were intended for use in the hospital setting (the Netherlands, Norway and Sweden), primary care setting (Belgium, England and Serbia) or both (Austria, Denmark, Finland, France, Germany, Russia, Slovenia, Spain and Switzerland). Therapy for multidrug-resistant bacteria was discussed in seven guidelines but the recommendations were generally unspecific and did not allow further analysis. Only guidelines for adult patients are presented, as specific recommendations for children were lacking in most cases.

3.2. Recommendations for acute cystitis/lower urinary tract infection

Treatment recommendations for acute cystitis/lower UTI showed great variability between countries (Table 1). Heterogeneity was also found in the classification of patient subgroups. For example, no male UTIs were classified as acute cystitis/lower UTI in France, and in the Dutch guidelines some of the recommendations were restricted by patient age, presence of complicating factors and local resistance levels.

As many as 10 and 12 different antibiotics were listed as first-line empirical treatment options for women without complicating factors (e.g. immunosuppression, urinary tract catheter or urogenital abnormalities) and pregnant women, respectively (Table 1). Nine guidelines did not provide specific recommendations for women with complicating factors. Nitrofurantoin was the most frequently recommended antibiotic for female patients with this indication and was listed as a first-line option for uncomplicated cystitis in 12 of the 15 guidelines, followed by pivmecillinam ($n=7$) and fosfomycin ($n=7$). Recommendations for male patients with lower UTI were provided in 12 countries. For this indication, 15 different antibiotics were recommended, most often ciprofloxacin ($n=6$), nitrofurantoin ($n=6$) and pivmecillinam ($n=5$).

Substantial variations were also noted in the recommended dose, dose interval and treatment duration (Table 1). For example, nitrofurantoin was recommended at doses ranging from 50 mg every 8 h to 100 mg every 6 h, and for treatment durations of 3–7 days in women with uncomplicated cystitis. A longer duration of antibiotic therapy, typically 7–14 days, was recommended for male patients. For ciprofloxacin, the recommended treatment duration for lower UTI in male patients ranged from 3–14 days.

3.3. Recommendations for pyelonephritis and urosepsis

Comparison of guidelines for pyelonephritis and urosepsis was complicated by differences in the categorisation of UTI and the lack of specific recommendations in some cases (Table 2). For example, the severity of infection (mild-to-moderate diseases versus severe sepsis/septic shock) had implications for treatment in six countries, whereas the other guidelines presented similar recommendations for both patient groups or provided specific recommendations for only one or none of these groups.

Up to nine different oral empirical antibiotic regimens were recommended for pyelonephritis or urosepsis in the same patient subgroup (Table 2). Ciprofloxacin was the most frequent first-line antibiotic for oral therapy and was listed in 10 of the

Table 1
Recommended first-line antibiotics for empirical treatment of acute cystitis/lower urinary tract infection (UTI).

Country	Females			Males
	Without complicating factors	With complicating factors	Pregnant	
Austria[a]	CIP 500 mg × 1 or 250 mg × 2, 3 days FOS 3 g × 1, 1 day LVX 500 mg × 1, 3 days PIV 400 mg × 2–3, 3 days PRU 600 mg × 1, 1 day	–	PIV 400 mg × 2–3, 3 days	CIP 500 mg × 1 or 250 mg × 2, 3 days FOS 3 g × 1, 1 day LVX 500 mg × 1, 3 days PIV 400 mg × 2–3, 3 days PRU 600 mg × 1, 1 day
Belgium	NIT 100 mg × 3, 3–5 days	–	–	–
Denmark	PIV 400 mg × 3, 3 days	PIV 400 mg × 3, 7 days	PIV 400 mg × 3, 7 days	PIV 400 mg × 3, 7 days
England	NIT 100 mg × 2, 3 days TMP 200 mg × 2 (if low risk of resistance), 3 days	–	NIT 100 mg × 2, 7 days	NIT 100 mg × 2, 7 days TMP 200 mg × 2 (if low risk of resistance), 7 days
Finland	PIV 200 mg × 3 or 400 mg × 2, 3 days	As for women without complicating factors, but longer treatment duration	NIT 75 mg × 2, 5 days	CIP 500 mg × 2, ≥7 days
	NIT 75 mg × 2, 3 days TMP 160 mg × 2 or 300 mg × 1, 3 days		LEX 500 mg × 3, 5 days PIV 200 mg × 3, 5 days	OFX 200 mg × 2, ≥7 days LVX 250–500 mg × 1, ≥7 days TMP 160 mg × 2, ≥7 days
France	FOS 3 g × 1, 1 day PIV 400 mg × 2, 5 days	NIT 100 mg × 3, 7 days[b] FOS 3 g × 1, Days 1, 3 and 5	FOS 3 g × 1, 1 day PIV 400 mg × 2, 5 days	–[c]
Germany	FOS 3 g × 1, 1 day	–	As for non-pregnant women, but the duration is often 7 days	PIV 400 mg × 2–3, 3 days[d]
	NIT 50 mg × 4, 7 days NIT RT 100 mg × 2, 5 days NTR 250 mg × 3, 5 days PIV 400 mg × 2–3, 3 days			NIT 50 mg × 4, 7 days[d] NIT RT 100 mg × 2, 5 days[d]
Netherlands	NIT 50 mg × 4 or 100 mg × 2, 5 days[e]	CIP 500 mg × 2, 10–14 days[f]	NIT 100 mg × 2 (not the last 30 days of pregnancy), ≥5 days	NIT 50 mg × 4 or 100 mg × 2, 7 days[e] If complicating factors: CIP, 14 days[f] AMX + AG, 14 days 2GC + AG, 14 days 3GC, 14 days
Norway	PIV 200 mg × 3, 3 days NIT 50 mg × 3, 3–5 days TMP 300 mg × 1 or 160 mg × 2, 3 days	–	PIV 200 mg × 3, 5–7 days	SXT 160/800 mg × 2, 7–10 days PIV 200 mg × 3, 7–10 days CIP 500 mg × 2, 7–10 days
Russia	FOS 3 g × 1, 1 day FUZ 50–100 mg × 3, 5–7 days NIT 100 mg × 3–4, 5 days	–	FOS 3 g × 1, 1 day CFM 400 mg × 1, 7 days CTB 400 mg × 1, 7 days NIT 100 mg × 2, 7 days CXM 250–500 mg × 2, 7 days AMC 625 mg × 3, 7 days	LVX 500 mg × 1, 7 days OFX 400 mg × 2, 7 days CIP 500 mg × 2, 7 days
Serbia	NIT 100 mg × 2, 5–7 days SXT 160/800 mg × 2, 3 days	NIT 100 mg × 3, 3–7 days	NIT 100 mg × 2, 5 days AMX 250 mg × 3, 5–7 days LEX 250–500 mg × 3, 5–7 days	SXT 160/800 mg × 2, 3 days NIT 100 mg × 4 (if complicating factors), 3–7 days
Slovenia	NIT 100 mg × 2, 5–7 days	As for women without complicating factors, but treatment duration 7 days	NIT 100 mg × 2, 7 days	CIP 500 mg × 2, 7–14 days
	SXT 160/800 mg × 2, 3 days FOS 3 g × 1, 1 day			DOX 100 mg × 2, 7–14 days
Spain	FOS 3 g × 1, 1 day NIT RT 50–100 mg × 4, 5–7 days	–	–	FOS 3 g × 1, Days 1 and 4 NIT 50–100 mg × 4, ≥7 days
Sweden	NIT 50 mg × 3, 5 days PIV 200 mg × 3, 5 days (or 400 mg × 3, 3 days if <50 years)	–	NIT 50 mg × 3, 5 days PIV 200 mg × 3, 5 days CFR 500 mg × 2 or 1 g × 1, 5 days	NIT 50 mg × 3, 7 days PIV 200 mg × 3, 7 days
Switzerland	FOS 3 g × 1, 1 day NIT 100 mg × 2, 5 days SXT 160/800 mg × 2, 3 days	–	FOS 3 g × 1, 1 day NIT 100 mg × 2, 5 days SXT 160/800 mg × 2, 3 days	–[g]

2GC, second-generation cephalosporin; 3GC, third-generation cephalosporin; AG, aminoglycoside; AMC, amoxicillin/clavulanic acid; AMX, amoxicillin; CFM, cefixime; CFR, cefadroxil; CIP, ciprofloxacin; CTB, ceftibuten; CXM, cefuroxime; DOX, doxycycline; FOS, fosfomycin; FUZ, furazidin; LEX, cefalexin; LVX, levofloxacin; NIT, nitrofurantoin; NIT RT, macrocrystalline nitrofurantoin, retard-form; NTR, nitroxoline; OFX, ofloxacin; PIV, pivmecillinam; PRU, prulifloxacin; SXT, trimethoprim/sulfamethoxazole; TMP, trimethoprim.

[a] National guidelines consist of a consensus paper, listing antibiotic treatment regimens for physicians to evaluate and choose from.

[b] Empirical treatment is discouraged but, if requested, NIT is the first-line option.

[c] No male UTIs are classified as acute cystitis/lower UTI in France.

[d] These are recommendations for uncomplicated infections in young men only. NIT should only be administered to men whose infection does not involve the prostate.

[e] Recommendations from the guidelines for UTIs of the Dutch College of General Practitioners, which is referred to in the national guidelines for complicated UTIs. Treatment recommendations for men are only applicable for uncomplicated infections in patients aged <40 years.

[f] CIP should only be administered if the whole treatment is given orally, when hospitalisation is not required and if local levels of resistance are <10%. Use in patients in the urology department and in patients who have received quinolones in the past 6 months is contraindicated.

[g] UTIs in men are only described in general terms.

Table 2
Recommended first-line antibiotics for empirical treatment of pyelonephritis and urosepsis. Treatment duration refers to the total duration of therapy, including both empirical and targeted therapy when relevant.

Country	Females						Males		
	Without complicating factors			With complicating factors					
	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock
Austria[a]	–	3GC, 10–14 days APN + BLI	–	–	–	–	–	3GC 10–14 days APN + BLI	–
Belgium[b]	CIP 250–500 mg × 2, 7–14 days OFX 400–800 mg/day in 1–2 doses, 7–14 days LVX 500 mg × 1, 7–14 days	–	–	–	–	–	CIP 250–500 mg × 2, 7–14 day OFX 400–800 mg/day in 1–2 doses, 7–14 days LVX 500 mg × 1, 7–14 days	–	–
Denmark	–[c]	MEC 1 g × 3, 7 days + GEN 5 mg/kg × 1, ≤3 days	TZP 4/0.5 g × 4, 7 days AMP 2 g × 4, 7 days + GEN 5 mg/kg × 1, ≤3 days	–[c]	MEC 1 g × 3, 7 days + GEN 5 mg/kg × 1, ≤3 days	TZP 4/0.5 g × 4, 7 days AMP 2 g × 4, 7 days + GEN 5 mg/kg × 1, ≤3 days	–[c]	MEC 1 g × 3, 7 days + GEN 5 mg/kg × 1, ≤3 days	TZP 4/0.5 g × 4, 7 days AMP 2 g × 4, 7 days + GEN 5 mg/kg × 1, ≤3 days
England[b]	AMC 500/125 mg × 3, 7 days CIP 500 mg × 2, 7 days	–	–	–	–	–	AMC 500/125 mg × 3, 7 days CIP 500 mg × 2, 7 days	–	–
Finland	CIP 500 mg × 2, 7 days OFX 200 mg × 2, 7 days LVX 250–500 mg × 1, 7 days	CXM 750–1500 mg × 3, 10–14 days	–	–	–	–	CIP 500 mg × 2, 14 days LVX 250–500 mg × 1, 14 days OFX 200 mg × 2, 14 days	CXM 750–1000 mg × 3	–
France	CIP 500 mg × 2, 7 days	CTX 1–2 g × 3, 7 days	CTX 1–2 g × 3, 10–14 days + AMK 15 mg/kg × 1, 1–3 days	CIP 500 mg × 2, 10–14 days	CTX 1–2 g × 3, 10–14 days	CTX 2 g × 3, 10–14 days + AMK 30 mg/kg × 1, 1–3 days	CIP 500 mg × 2, 14–21 days	CTX 1–2 g × 3, 21 days	CTX 1–2 g × 3, 21 days + AMK 30 mg/kg × 1, 1–3 days
	LVX 500 mg × 1, 7 days[d]	CRO 1–2 g × 1, 7 days[d]	CRO 1–2 g × 1, 10–14 days + AMK 15 mg/kg × 1, 1–3 days	LVX 500 mg × 1, 10–14 days[e]	CRO 1–2 g × 1, 10–14 days[e]	CRO 2 g × 1, 10–14 days + AMK 30 mg/kg × 1, 1–3 days	LVX 500 mg × 1, 14–21 days[e]	CRO 1–2 g × 1, 21 days[e]	CRO 1–2 g × 1, 21 days + AMK 15 mg/kg × 1, 1–3 days

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Table 2 (*continued*)

Country	Females						Males		
	Without complicating factors			With complicating factors					
	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock
Germany	CIP 500–750 mg × 2, 7–10 days LVX 750 mg × 1, 5 days CPD 200 mg × 2, 10 days CTB 400 mg × 1, 10 days	CIP 400 mg × (2)–3, 7–14 days LVX 750 mg × 1, 7–14 days CRO (1)–2 g × 1, 7–14 days CTX 2 g × 3, 7–14 days	–	–	–	–	FLQ 5–10 days[f]	–	–
Netherlands	CIP 500 mg × 2, 7 days	AMX + AG, 10–14 days 2GC + AG, 10–14 days 3GC, 10–14 days	AMX + AG, 10–14 days 2GC + AG, 10–14 days 3GC, 10–14 days	CIP 500 mg × 2, 10–14 days	AMX + AG, 10–14 days 2GC + AG, 10–14 days 3GC, 10–14 days	AMX + AG, 10–14 days 2GC + AG, 10–14 days 3GC, 10–14 days	CIP 500 mg × 2, 14 days	AMX + AG, 14 days 2GC + AG, 14 days 3GC, 14 days	AMX + AG, 14 days 2GC + AG, 14 days 3GC, 14 days
Norway	SXT 160/800 mg × 2, 7–10 days + GEN 5 mg/kg × 1, ≥1 day	AMP 1–2 g × 4 or SXT 160/800 mg × 2, 7–10 days + GEN 5 mg/kg × 1, ≥1 day	AMP 2 g × 4, 10–14 days + GEN 5–7 mg/kg × 1, 3–5 days CXM 1.5 g × 3, 10–14 days CTX 1 g × 3, 10–14 days	–	AMP 1–2 g × 4, 10–14 days + GEN 5 mg/kg × 1, 3–5 days CXM 1.5 g × 3, 10–14 days CTX 1 g × 3, 10–14 days	AMP 2 g × 4, 10–14 days + GEN 5–7 mg/kg × 1, 3–5 days CXM 1.5 g × 3, 10–14 days CTX 1 g × 3, 10–14 days	As for women	As for women	As for women
Russia	LVX 500 mg × 1, 7–10 days or 750 mg × 1, 5 days CIP 500–750 mg × 2, 7–10 days or 1 g × 1, 5 days	–	ETP 1 g × 1, 7–10 days IPM 500 mg × 4, 7–10 days MEM 1 g × 3, 7–10 days TZP 2.25 g × 4, 7–10 days TCC 3.2 g × 3, 7–10 days ± AMK 15 mg/kg × 1, ≤7 days	–	LVX 500 mg × 1, 7–14 days CIP 400 mg × 2, 7–14 days OFX 400 mg × 2, 7–14 days TCC 3.2 g × 4, 7–14 days CTX 1–2 g × 2–3, 7–14 days CAZ 1–2 g × 3, 7–14 days CRO 2 g × 1, 7–14 days CXM 0.75–1.5 g × 3, 7–14 days ETP 1 g × 1, 7–14 days ± AMK 15 mg/kg × 1 or GEN 240 mg × 1, ≤7 days	ETP 1 g × 1, 10–14 days or TCC 3.2 g × 4 10–14 days ± AMK 15 mg/kg × 1, 5–7 days or NET 4–6 mg/kg × 1, 10–14 days	LVX 500 mg × 1, 7 days OFX 400 mg × 2, 7 days CIP 500 mg × 2, 7 days	–	ETP 1 g × 1, 7–10 days IPM 500 mg × 4, 7–10 days MEM 1 g × 3, 7–10 days TZP 2.25 g × 4, 7–10 days TCC 3.2 g × 3, 7–10 days ± AMK 15 mg/kg, ≤7 days

(*continued on next page*)

Table 2 (*continued*)

Country	Females						Males		
	Without complicating factors			With complicating factors					
	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock	Oral, mild disease	IV, mild-to-moderate disease	IV, severe sepsis/septic shock
Serbia[b]	CIP 500 mg × 2, 7–14 days	CRO 2 g × 1, 14 days	CRO 2 g × 1, 10–14 days + AMK 30 mg/kg × 1, 1–3 days	–	–	–	CIP 250–500 mg × 2, 14 days	CRO 2 g × 1, 10 days	CRO 2 g × 1, 10–14 days + AMK 30 mg/kg × 1, 1–3 days
Slovenia	–[g]	GEN 5–7 mg/kg × 1, 14 days	–	–	–	–	–[g]	GEN 5–7 mg/kg × 1, 14 days	–
Spain	CXM (axetil) 500 mg × 2–3, 7–10 days	CXM (sodium) 0.75–1.5 g × 3, 7–10 days	MEM 0.5–2 g × 3, 10–14 days	–	–	–	CXM (axetil) 500 mg × 2–3, 7–10 days	CXM (sodium) 0.75–1.5 g × 3, 7–10 days	MEM 0.5–2 g × 3, 10–14 days
	CTB 400 mg × 1–2, 7–10 days	CRO 1–2 g × 1, 7–10 days					CTB 400 mg × 1–2, 7–10 days	CRO 1–2 g × 1, 7–10 days	
	CFM 0.4 g × 1–2, 7–10 days[h]	CTX 1–2 g × 3, 7–10 days					CFM 400 mg × 1–2, 7–10 days[h]	CTX 1–2 g × 3, 7–10 days	
		ETP 1 g × 1, 7–10 days[i]						ETP 1 g × 1, 7–10 days[i]	
Sweden	CIP 500 mg × 2, 7 days	CTX 1 g × 3, 7–10 days	CTX 1–2 g × 3[j]	CIP 500 mg × 2, 7 days	CTX 1 g × 3, 7–10 days	CTX 1–2 g × 3[j]	CIP 500 mg × 2, 14 days	CTX 1 g × 3, 14 days	CTX 1–2 g × 3
			CAZ 1–2 g × 3[j]		CAZ 1 g × 3, 7–10 days	CAZ 1–2 g × 3[j]			CAZ 1–2 g × 3[j]
			TZP 4 g × 3–4[j]		TZP 4 g × 3, 7–10 days	TZP 4 g × 3–4[j]			TZP 4 g × 3–4[j]
			MEM or IPM 0.5–1 g × 3[j], 7–10 days ± GEN or TOB 5–7 mg/kg or AMK 25–30 mg/kg × 1		CIP 400 mg × 2, 7–10 days	MEM or IPM 0.5–1 g × 3[j], 7–10 days ± GEN or TOB 5–7 mg/kg or AMK 25–30 mg/kg × 1			MEM or IPM 0.5–1 g × 3[j], 7–10 days ± GEN or TOB 5–7 mg/kg or AMK 25–30 mg/kg × 1
Switzerland	CIP 500 mg × 2, 7 days	CRO 1 g × 1 GEN 5 mg/kg × 1	CRO 1 g × 1 GEN 5 mg/kg × 1	–	–	–	–[k]	–[k]	–[k]

2GC, second-generation cephalosporin; 3GC, third-generation cephalosporin; AG, aminoglycoside; AMC, amoxicillin/clavulanic acid; AMK, amikacin; AMP, ampicillin; AMX, amoxicillin; APN, aminopenicillin; BLI, β-lactamase inhibitor; CAZ, ceftazidime; CFM, cefixime; CIP, ciprofloxacin; CPD, cefpodoxime; CRO, ceftriaxone; CTB; ceftibuten, CTX, cefotaxime, CXM, cefuroxime; ESBL, extended-spectrum β-lactamase ETP, ertapenem; FLQ, fluoroquinolone; GEN, gentamicin; IPM, imipenem; IV, intravenous; LVX, levofloxacin; MEC, mecillinam; MEM, meropenem; NET, netilmicin; OFX, ofloxacin; SXT, trimethoprim/sulfamethoxazole; TCC, ticarcillin/clavulanic acid; TOB, tobramycin; TZP, piperacillin/tazobactam.

[a] The national guidelines consist of a national consensus paper, listing antibiotic treatment regimens for physicians to evaluate and choose from. The general recommendation is to initiate IV treatment and to have a total treatment duration of 14 days. The recommendation is to use a high dose of a 3GC or an APN with a BLI, but LVX and CIP are also mentioned.

[b] Recommendations of national treatment guidelines for primary care.

[c] For hospitalised patients, oral alternatives are only recommended after initial parenteral treatment.

[d] Oral quinolones and parenteral 3GCs are both first-choice options for treatment of mild pyelonephritis in women without complicating factors, but treatment with quinolones is advocated if the patient has not been exposed to this antibiotic class in the last 6 months.

[e] Oral quinolones and parenteral 3GCs are both first-choice options for treatment of mild pyelonephritis in women with complicating factors and in men, although initial treatment with parenteral 3GCs is recommended. Quinolones are not indicated in patients who have been treated with this class of antibiotics in the past 6 months.

[f] The national guidelines only specify oral treatment recommendations for uncomplicated pyelonephritis in young men. The recommendations apply if the local level of resistance in *Escherichia coli* is <10%.

[g] Only second-line options are specified for oral treatment in the guidelines. These should be used after adjustment of the initial parenteral treatment with GEN.

[h] Parenteral antibiotic treatment is recommended for patients requiring hospital admission. The listed therapies are recommended for use in patients with uncomplicated community-acquired acute pyelonephritis who do not require hospital admission and have no specific risk factors for ESBL-producing Enterobacteriaceae.

[i] In patients with specific risk factors for ESBL-producing Enterobacteriaceae.

[j] An extra dose should be given at mid-interval between the first two doses.

[k] Urinary tract infections in men are only described in general terms.

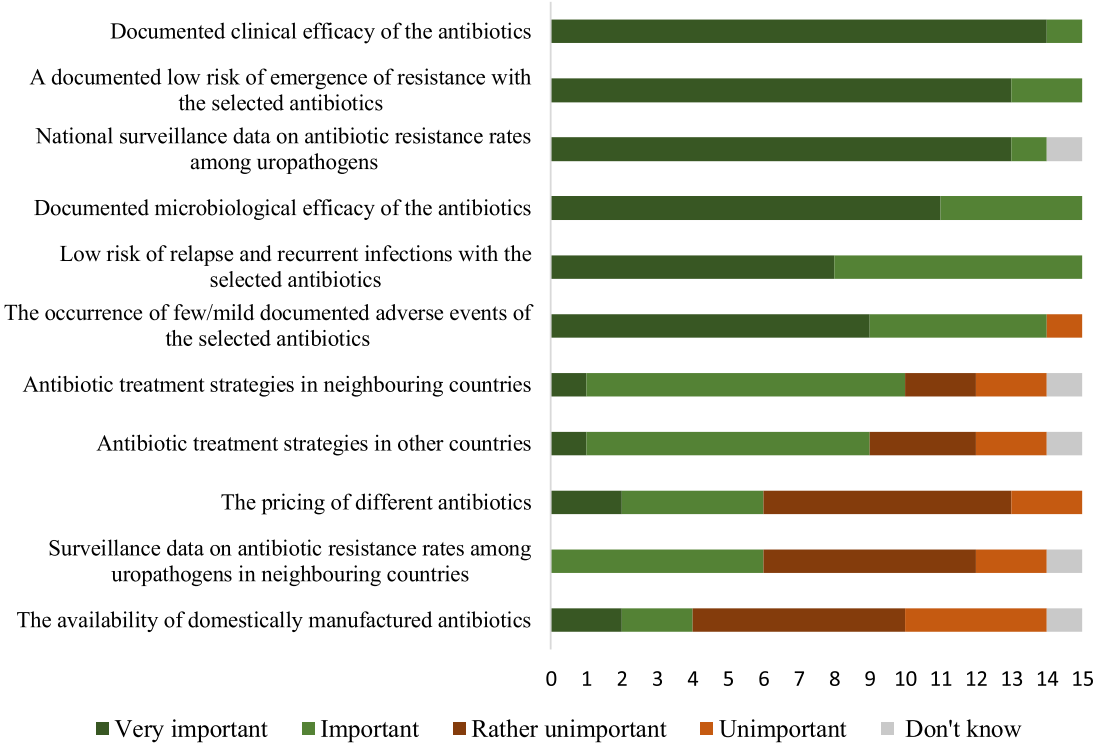

Fig. 1. Relative importance of factors that could have influenced the recommendations of antibiotic regimens in the national treatment guidelines for urinary tract infections in 15 European countries.

12 guidelines that provided specific recommendations. Trimethoprim/sulfamethoxazole was recommended for empirical treatment only in one country (Norway) and, when used, should always be combined with gentamicin.

For parenteral treatment of patients with mild-to-moderate disease, second- and third-generation cephalosporins were most frequently recommended (9 of 12 countries) (Table 2). Aminoglycosides, usually in combination with a β-lactam, were listed as first-line therapy for patients with severe sepsis/septic shock in eight of nine guidelines where specific recommendations were provided, and carbapenems were only recommended in three countries (Russia, Spain and Sweden). For pregnant women, recommendations for oral treatment were not provided in 11 countries. Parenteral third-generation cephalosporins were the most frequently recommended antibiotics also in this patient group (9 of 10 countries; data not shown).

3.4. Important factors, evidence grading and surveillance data

Clinical efficacy and a low risk for emergence of resistance were identified as the most important factors in the selection of antibiotics when setting the guidelines (Fig. 1). Resistance rates according to national surveillance data, microbiological efficacy, low risk of relapse and recurrent infections, and adverse events were considered important or very important by at least 14 of the 15 respondents. Treatment strategies of other countries were considered less important, and the resistance rates of neighbouring countries, pricing and domestic manufacturing of drugs were perceived as rather unimportant or unimportant by most respondents. The underlying evidence for the recommendations of antibiotics, dosing and treatment duration was specified in all guidelines except one, which referred to the IDSA/ESCMID background information on which the guideline is based (Switzerland). Systematic grading of evidence was presented for the selection of antibiotic and treatment duration in 11 of 15 guidelines, and less frequently for dosing (7 of 15).

For an antibiotic to be recommended for empirical therapy, a resistance rate of <20% in *E. coli* was considered acceptable for cystitis according to most respondents who answered this question (8 of 10), whilst a lower resistance rate of <10% or <5% was selected in two cases. For pyelonephritis, a resistance rate of <10% was usually considered acceptable (6 of 10), followed by <5% (2) and <20% (2). National surveillance data on antimicrobial susceptibility in uropathogens were available in most countries (13 of 15) (Supplementary Table S2). In Serbia data are analysed on a regional rather than national level, and in Spain resistance data are derived from national and regional studies. In Slovenia, aggregated data on pathogens exist but are not stratified by sampling site. The reported resistance data for the most commonly recommended antibiotics are presented in Table 3. However, due to great variability in sample size, selection of antibiotics and presentation of data (e.g. blood, urine or aggregated data) between the existing surveillance reports, a comparative analysis was not possible.

4. Discussion

In this study, substantial variation in recommendations for empirical antibiotic treatment of UTIs between 15 European countries was observed. Differences with regard to selection of antibiotics were notable for lower UTI, where fosfomycin and pivmecillinam were first-line options in less than one-half of the countries (Table 1). For pyelonephritis and urosepsis, quinolones and second- or third-generation cephalosporins were recommended as first-line empirical treatment in most guidelines (Table 2). However, there was great variability in the selection of specific substances within these antibiotic classes, and multiple other antibiotics were also recommended. Furthermore, differences in dosing regimens and treatment durations of specific antibiotics were often noted between guidelines also when used for the same indication and patient group.

Adaptation to national resistance epidemiology is probably an important reason behind the observed differences. As expected,

Table 3
National susceptibility data for *Escherichia coli* according to reports available at the time of the study. Note that the numbers should be interpreted with great caution as important differences exist in the collection of samples (e.g. primary care versus hospital setting, blood versus urine samples), methods for susceptibility testing and antibiotic class representatives. For Russia, data are based on very few isolates (<100). For Belgium and England, non-susceptibility is reported rather than resistance. Where multiple rates were reported, a range is presented in the table. Data for invasive *E. coli* isolates as reported in EARS-Net 2016 are presented within parenthesis for comparison.

Country	Year	Resistance/non-susceptibility rate in *E. coli* (%)						
		FLQ	3GC	AG	CARB	NIT	FOS	MEC
Austria	2016	15.2–19.8 (19.8)	6.9–10 (10.0)	5.1–7.8 (7.8)	0.0 (0.0)	1.4–1.8	–	6.4–6.7
Belgium	2015	– (24.5)	8.6 (10.5)	– (8.4)	0.1–0.2 (0.1)	–	–	–
Denmark	2016	10–11 (11.0)	4–7 (6.6)	4–6 (6.1)	<1 (0.0)	–	–	6–13
England (UK)[a]	2017	18.2 (16.3)	12.2 (9.2)	10.1 (9.9)	– (0.0)	2.9	–	–
Finland	2016	6.3–14.9 (11.5)	4.8–6.7 (6.9)	5 (4.9)	0 (0.0)	0.7–1.1	–	3.5–4.8
France	2015	10.1–14.1 (16.7)	4.3–12.9 (11.2)	1.7 (7.9)	0.1 (0.0)	1	1.2	7.2
Germany	2013/2014	16–22.6 (19.7)	5.9–16.4 (11.5)	5.1–6.8 (7.1)	0 (0.0)	1	0.8	–
Netherlands	2016	9–23 (12.8)	2–8 (6.4)	4–8 (6.2)	0 (0.0)	2–4	1–2	–
Norway	2016	8.8–12.6 (10.9)	2.4–6.0 (5.6)	4.4–6.3 (5.5)	0 (0.1)	1.5	–	5.9
Russia	2016	75–76.7 (–)	56.7–84.6 (–)	5–53.8 (–)	0–13.5 (–)	–	6.7–7.7	–
Serbia[b]	2014/2015	27 (–)	28 (–)	35 (–)	1 (–)	–	–	–
Slovenia	2016	20.1 (25.6)	6.8–8.6 (12.5)	0.4–8.3 (10.6)	0.0 (0.0)	0.9	–	–
Spain[c]	2016	10–30 (32.8)	6.7 (15.0)	3.4–11 (14.5)	0.0 – (0.1)	5	3	–
Sweden	2016	9.5–13.7 (13.7)	8.3 (8.3)	7.2 (7.2)	0.1 (0.1)	1.1	–	4.2
Switzerland	2015/2016	18.6–20 (–)	ca. 7.5	6.1–8.9 (–)	0–0.1 (–)	1.2–2.6	0.9–1.4	–

3GC, third-generation cephalosporins; AG, aminoglycosides; CARB, carbapenems; FLQ, fluoroquinolones; FOS, fosfomycin; MEC, mecillinam; NIT, nitrofurantoin; EARS-Net, European Antimicrobial Resistance Surveillance Network.
[a] National data for England; EARS-Net data for UK.
[b] Results from the CAESAR project including data obtained at 14 microbiological laboratories.
[c] Resistance data are reported from different national and regional studies.

this aspect was perceived very important by most respondents, with resistance levels up to 20% and 10% typically considered acceptable for acute lower UTI and pyelonephritis, respectively, although it is clear that these cut-offs were not always applied in practice (Tables 1–3). Also, the current approach to resistance surveillance may not provide sufficient data to determine the most appropriate substance for empirical therapy. This is illustrated by the lack of data on fosfomycin and mecillinam susceptibility in *E. coli* in countries where these antibiotics are not used (Table 3). Similarly, only susceptibilities for the specific quinolones and cephalosporins tested in the microbiology laboratories are known to the national guideline-setting committees. Thus, the potential of all antibiotics available worldwide is partly neglected when the antibiotic panels are restricted to the locally available and recommended drugs.

Comparison of national surveillance data is hampered by variations in methodologies across European countries [14]. Also, important differences may exist also within countries between different settings and patient groups. For example, Finland reported 6.3% and 14.9% quinolone resistance in *E. coli* obtained from female and male patients, respectively (Table 3). This information is important in the clinical situation especially in cases where the resistance levels are close to what is considered acceptable for empirical therapy. Surveillance data typically overestimate resistance rates in urinary isolates as they are based on cultures predominantly from patients with complicated UTI, whilst urine cultures are usually not recommended for uncomplicated cystitis in women [15].

A better harmonisation in methods and reporting of antimicrobial resistance data, testing also antibiotics that are not currently used in all countries, as well as stratification by patient groups would be very valuable in the development of national treatment guidelines. International collaborative resistance surveillance projects, e.g. the ECO•SENS study assessing *E. coli* susceptibility in women with uncomplicated community-acquired UTI [16], EARS-Net presenting comparative data on susceptibility of invasive isolates in Europe [9], and the SENTRY programme reporting susceptibility profiles of bloodstream infection organisms in more than 40 countries [17], can provide complementary information.

In addition to national resistance epidemiology, there are probably several other factors underlying the differences between treatment guidelines. Pivmecillinam is available in less than one-third of European countries [10] despite that it has excellent activity against the primary pathogen *E. coli* [16] as well as against isolates producing extended-spectrum β-lactamases (ESBLs), and has been extensively used for cystitis in some countries [18]. In this study, there was a large number of cephalosporins with similar antibacterial activities listed in the recommendations. Such variations cannot be explained by differences in resistance rates between countries but are probably caused by strategic decisions on marketing and pricing made by pharmaceutical companies that consequently determine the availability of specific antibiotics.

The observed variations in dosage and treatment duration for the same antibiotics and indications probably reflect the limited evidence behind many of the recommendations, implying that some decisions must be made based on consensus or expert opinion. According to this survey, the guidelines of other countries are generally not considered important when setting the recommendations. However, there is no medical reason to adapt dosing or treatment duration to local conditions. Therefore, a comparison with other guidelines could be of value to detect differences and to serve as a basis for discussion and reconsideration. Furthermore, a systematic assessment of existing evidence aiming for an agreement on suitable dosing and treatment durations could be initiated for example by ESCMID, IDSA and EAU.

This study has several limitations. We consider the response rate of 59% acceptable for a survey and sufficient for the study objectives. Nevertheless, data for many European countries were not assessed, meaning that the variability across guidelines was probably underestimated. Qualitative research with guidance developers via interviews, or detailed evaluation of guidance rationales is required to determine the underlying reasons for the differences between countries. Re-evaluation of empirical treatment is important in the management of patients with UTI but as precise recommendations for targeted therapy were unavailable in most guidelines, only recommendations for empirical treatment are presented. Comparison of guidelines was hampered by variations in the categorisation of UTI subgroups. Harmonising the classification

of uncomplicated versus complicated UTI and other disease entities of importance for antibiotic treatment would be very valuable and could be carried out in collaboration between expert organisations and guideline-setting committees.

Whilst most guidelines included in this study are applied in the hospital setting, some were intended for primary care only. We did not assess regional or local guidelines or the adherence to national guidelines. It should be emphasised that the presented resistance data must be interpreted with caution and are not directly comparable between countries owing to major differences in the laboratory methods and collection of data. Furthermore, the results on factors considered important when setting the national guidelines reflect the opinions of the respondents of the study and may to some extent differ from those of other members of the national guideline-setting committees. Still, we believe that our study provides valuable new insights on current approaches to resistance surveillance and treatment of UTIs in a relatively large number of European countries.

The present comparison of existing national guidelines could be a starting point to identify knowledge gaps and opportunities for improvement in the management of UTIs. We conclude that a systematic and stratified approach to resistance surveillance, including testing for antibiotics that are not currently available in all countries, is required to determine which substances are most appropriate. National guidelines should promote the use of antibiotics that provide effective therapy and are ecologically favourable with a low risk of resistance development. To this end, more research evaluating the collateral damage of commonly used antibiotics on the microbiome is needed to support treatment decisions, and stewardship interventions aiming to reduce unnecessary antibiotic prescriptions for suspected UTI should be reinforced. Importantly, the availability of antibiotics in each country should be based on clinical evidence and medical needs rather than financial considerations. In an era of rapidly increasing antimicrobial resistance in uropathogens and few new antibiotics, this should be a high priority.

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Ethical approval

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Supplementary materials

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