The effectiveness of nitrofurantoin, fosfomycin and trimethoprim for cystitis in relation to renal function

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ABSTRACT

Objective

We evaluated the effect of renal function on the effectiveness of nitrofurantoin, fosfomycin and trimethoprim for cystitis in primary care patients.

Methods

Data was retrospectively obtained from 75 Dutch primary care practices between 2013 and 2019. Episodes were classified as uncomplicated or complicated cystitis based on the medical records and prescription according to the guidelines. Renal function was categorized as normal to mildly decreased (eGFR ≥60 mL/min), or moderately decreased to kidney failure (eGFR <60 mL/min). Clinical failure was defined as a second antibiotic prescription for cystitis or pyelonephritis within 28 days post-prescription. We used mixed effects regression analysis, with patient and GP practice as random effects.

Results

In total, 40,916 episodes were included, of which 29,873 for uncomplicated cystitis (NF5: 23,793, FT1: 5,048, TMP3: 1,032) and 11,043 for complicated cystitis (NF7: 10,236, TMP7: 807). An eGFR below 60 mL/min was observed in 8.8% (3612/40,916) of episodes and clinical failure occurred in 7.0% (2867/40,916). After adjustment, renal function was not significantly associated with clinical failure in any regime, with odds ratios of 0.96 for NF5 (95%CI: 0.90-1.01), 0.93 for FT1 (95%CI: 0.76-1.08), 0.93 for TMP3 (95%CI: 0.80-1.07), 0.95 for NF7 (95%CI: 0.65-1.26), 1.03 for TMP7 (95%CI: 0.90-1.16). In the treatment of uncomplicated and complicated cystitis no differences were observed between regimens in normal or decreased renal function after adjustment for confounders.

Conclusion

Renal function was not independently associated with increased clinical failure in patients with cystitis.

Key words Renal impairment, Cystitis, Nitrofurantoin, Trimethoprim, Fosfomycin

INTRODUCTION

Cystitis is a common bacterial infection with an annual incidence of approximately 70 per 1000 in adult women and 10 per 1000 in adult men (1). The most common causative pathogen for community-acquired cystitis is *Escherichia coli* (75-90%) (2). The aim of antimicrobial treatment is to eradicate the pathogen from the urogenital tract, to reduce symptom duration and to prevent aggravation and re-infections (3).

In primary care in the Netherlands, nitrofurantoin for five days (NF5) is recommended as first-choice oral treatment for acute uncomplicated cystitis, with a single dose of fosfomycin-trometamol (fosfomycin, FT1) as second choice and trimethoprim for three days (TMP3) as third choice (1). An extended seven-day regimen of nitrofurantoin (NF7) is the first choice and seven days of trimethoprim (TMP7) the second choice in patients with complicated cystitis, defined as having risk factors for a complicated course such as male gender, diabetes mellitus (DM), urologic abnormalities and immunosuppression (1). The efficacy of antimicrobial treatment for cystitis largely depends on its antimicrobial activity against the pathogen and the achieved concentration in urine (4). Nitrofurantoin, fosfomycin and trimethoprim are active against most uropathogens and are eliminated by renal excretion resulting in high concentrations in urine (4–6).

Lower urinary concentrations have been reported for all three antibiotics in patients with impaired renal function (4–7). The concern is that efficacy declines if insufficient drug concentrations are achieved in urine, although strong, pharmacokinetic-based, evidence for this is lacking (6, 7). Retrospective cohort studies do not show a clear answer about the effect of impaired renal function on the clinical effectiveness of nitrofurantoin for the treatment of cystitis (8, 9). To the best of our knowledge, no such studies have been conducted for fosfomycin and trimethoprim. Consequently, little evidence exists to guide the choice of antibiotic treatment of cystitis for patients with decreased renal function in primary care.

The aim of this study was to evaluate the effect of renal function on the occurrence of clinical failure when using nitrofurantoin, fosfomycin or trimethoprim for the treatment of cystitis. Furthermore, the effectiveness of nitrofurantoin, fosfomycin and trimethoprim for cystitis was compared for normal and decreased renal function.

METHODS

Design and data collection

Data were retrospectively obtained from the Julius General Practitioners' Network (JGPN) consisting data from 75 general practices (GPs) in the province of Utrecht, the Netherlands, between January 2013 and June 2019 (10). The database consists

of all antibiotic prescriptions to treat cystitis and includes information on patient characteristics, comorbidities and co-medication. Diagnoses were coded according to the International Classification of Primary Care (ICPC). Medication prescriptions were coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

Study population

Episodes were eligible for analysis if antibiotic therapy was prescribed by the GP for the treatment of cystitis according to the Dutch guideline in patients of at least 12 years of age. Diagnoses were classified as uncomplicated or complicated according to the duration of treatment. For uncomplicated cystitis, the guideline advices a regimen consisting of five days nitrofurantoin 100 mg extended release (Furabid®) every 12 hours or 50 mg normal release (Furadantin®) every 6 hours (NF5), a single gift of fosfomycin 3000 mg (FT1) or a three-day treatment with trimethoprim 300 mg every 24 hours (TMP3). Cystitis episodes that were treated as being uncomplicated in which one of the following risk factors were present for a complicated course were excluded: male gender, pregnancy, DM, urologic abnormalities and immunosuppression. For complicated cystitis, the guideline recommends nitrofurantoin and trimethoprim in an extended treatment duration for seven days (NF7 and TMP7). Patients without documented risk factors and receiving the extended course were included in the complicated cystitis group. Episodes that are assumed to represent treatment failures of a prior cystitis episode were excluded, that are episodes within 28 days of a prior antibiotic prescription for cystitis, i.e. short-course nitrofurantoin, trimethoprim or fosfomycin.

Renal function was based on the most recent estimated Glomerular Filtration Rate (eGFR) value measured within six months before or after the prescription date. Episodes were excluded from analysis if no eGFR was measured in this period. The eGFR was calculated with the Chronic Kidney Disease Epidemiology (CKDepi) formula using plasma creatinine values, age and gender (11).

Outcome

Clinical failure was defined as the prescription of one of the following antibacterial agents within 28 days of the initial prescription: nitrofurantoin, fosfomycin and trimethoprim, with exclusion of prophylactic use of trimethoprim or nitrofurantoin (>7-day use), or one of the following antimicrobials in combination with an ICPC code for cystitis or pyelonephritis: ciprofloxacin, co-trimoxazole or amoxicillin-clavulanic acid.

Statistical analysis

Effect of renal function on clinical failure per antibiotic class

Odds ratios were calculated to determine the association between the patients' renal function and the risk of clinical failure (crude analysis) within each of the antibiotic classes. Renal function was analysed in the model as a continuous variable. Odds ratios for clinical failure were calculated per 10 mL/min increase of eGFR. eGFR values ≥90 mL/min were truncated, as no effect is expected across the range of normal glomerular filtration rates on the effectiveness of these antibiotics (12).

For the multivariable analysis, a logistic model with mixed effects was used, that incorporated the correlation among repeated episodes within one patient and within one GP practice using a random intercept. The adjusted model was corrected for the following fixed variables: in the population of uncomplicated cystitis: age, gender, socio-economic status, number of cystitis prescriptions in the previous year, year of prescription, a history of dementia, cognitive impairment other than dementia, depression, a (presumed) sexually transmitted disease, and oral contraceptives use. In the population of complicated cystitis, the analysis was additionally corrected for the following variables: solid organ transplantation, diabetes mellitus, anatomic/functional deficits in the urinary tract or kidney, and immunosuppressive medicine use. For nitrofurantoin, the dosing regimen (50 mg normal release every 6 hours vs. 100 mg slow release every 12 hours) was included as confounding variable. For the crude and the multivariable model, the assumption of linearity was tested by visually inspecting the residuals. Missing data of socio-economic status (n=172) and number of cystitis prescriptions (n=1) were imputed using multiple imputation. As a sensitivity analysis, a logistic model was performed in which we included patients with unknown serum creatinine as having an eGFR of 90 mL/min. In this analysis the same fixed and random effects were used as above for all regimen including a binomial determinant that indicates whether eGFR had been measured or not.

Effect of antibiotic class on clinical failure rate within strata of renal function

To compare the effect of antibiotic classes on clinical failure within strata of renal function, a crude and multivariable mixed effects logistic regression model was used with only first cystitis episodes per patient included for analysis. The same fixed effects as described above were used with additionally eGFR as a continuous variable and GP practice as random effect. We compared the short regimens for uncomplicated cystitis (NF5, FT1, TMP3) and extended regimens for complicated cystitis (NF7, TMP7). These comparisons were performed for episodes in patients with normal to mild decreased renal function (eGFR ≥60 mL/min; Kdigo stage G1 or G2) and in moderately decreased renal function to kidney failure (eGFR <60 mL/min; Kdigo stage G3-G5) (13). In all

cases, P-values less than 0.05 were considered statistically significant. The same sensitivity analysis as above was performed for episodes in patients with normal to mild decreased renal function (eGFR ≥60 mL/min) including patients with unknown serum creatinine as having an eGFR of 90 mL/min.

The models were fit to maximum likelihood using the Laplace approximation. All analyses were performed using R software (version 3.4.1), using the lme4 package (version 1.1-21).

Ethics

Approval for the study was obtained with a waiver for informed consent from the ethical board of the University Medical Centre Utrecht, the Netherlands, with reference WAG/mb/18/022909.

RESULTS

Study population

The complete dataset consisted of 160,399 episodes of nitrofurantoin, fosfomycin and trimethoprim prescriptions. After exclusion of children younger than 12 years (n=4,416), episodes that were not in accordance with the guideline (n= 35,821), episodes with a cystitis prescription in the prior 28 days (31,034), and episodes in which the eGFR value was not measured (n= 48,212) 40,916 episodes remained for analysis. Of these, 29,873 consisted of a short regimen for uncomplicated cystitis and 11,043 consisted of an extended regimen for complicated cystitis (Figure 1).

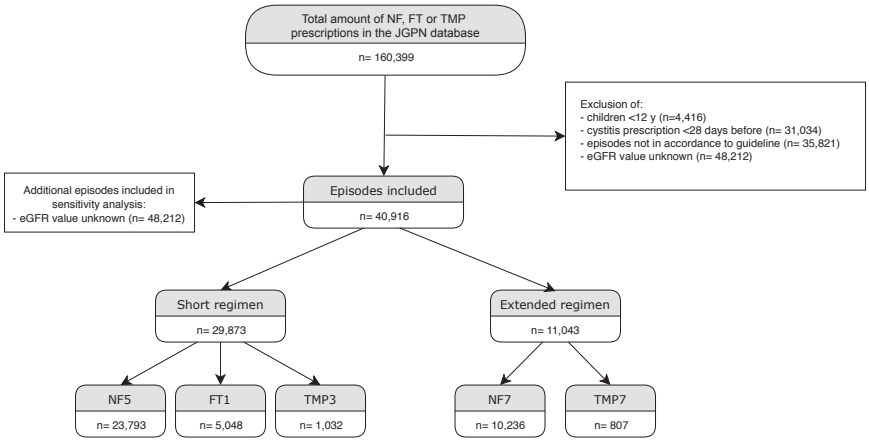

Figure 1: Flowchart for inclusion of episodes from the Julius General Practitioners' Network (JGPN) consisting of data from 75 general practitioner practices (GP practices') in the province of Utrecht, the Netherlands, between January 2013 and July 2019.

Table 1 shows the patient characteristics at baseline in the five treatment arms. In the past six years the amount of FT1 prescriptions for cystitis increased yearly whereas the amount of NF5, NF7, TMP3 and TMP7 prescriptions each year were stable. Of all episodes, 8.8% (3,612/40,916) had an eGFR below 60 mL/min. The mean eGFR was higher (85.5 mL/min) in the NF5 arm in comparison to FT1 (80.0 mL/min) and TMP3 (79.1 mL/min). In patients that were prescribed NF5, the median age was lower (61 years vs. resp. 72 and 73 years), and the amount of cystitis episodes in the previous year was lower (median 1 vs. resp. 0 and 0) compared to patients that were prescribed FT1 or TMP3. Among those treated with extended regimens, the median age was lower (71 vs. 77 years), the eGFR was higher (78.9 vs. 73.3 mL/min), and the number of cystitis episodes in the previous year was lower (median 0 vs. median 1) when being treated with NF7 compared to TMP7.

The population with cystitis that is included for the sensitivity analysis in which no renal function was measured had a median age of 33 years in the NF5 population up to 55 in the TMP7 population, with 31% (1,891/6,057) of patients being male and 9.0% (547/6,057) having DM in the NF7 population.

Effect of renal function on clinical failure per antibiotic class

Clinical failure occurred in 7.0% (2,867/40,916) of all episodes: 7.1% after using NF5, 6.0% after using FT1, 7.7% after using TMP3, 7.3% after using NF7, and 6.8% after using TMP7.

No significant associations were found in any of the treatment arms after adjusting for confounders (table 2). In the sensitivity analysis a higher eGFR was associated with a lower risk of clinical failure for NF5 and TMP3, but not for FT1, NF7 or TMP7.

Effect of antibiotic class on clinical failure rate within strata of renal function

Table 3 shows the odds ratios of the antibiotic regimens for clinical failure within categories of renal function. The probability of treatment failure among patients with moderate to severely decreased renal function (eGFR <60 mL/min) was not significantly different between the treatment regimens for uncomplicated cystitis, nor between the treatment regimens used for complicated cystitis. Similar non-significant results were observed in the sensitivity analysis.

Table 1: The baseline characteristics of cystitis episodes classified on the prescribed antimicrobial therapy.

Patient characteristics	Treatment (n=49,115)				
	Short regimen			Extended regimen	
	NF5 (n=23,793)	**FT1 (n=5,048)**	**TMP3 (n=1,032)**	**NF7 (n=10,236)**	**TMP7 (n=807)**
Age (years)					
Median	61	72	73	71	77
Interquartile range	43 – 75	57 - 83	56 - 84	59 – 81	66 - 85
Gender					
Male (%)	NA	NA	NA	3,238 (31.6%)	210 (26.0%)
eGFR (mL/min)					
Mean ± SD	85.5± 10.1	80.0 ± 17.1	79.1 ± 18.2	78.9 ± 16.0	73.3 ± 19.4
eGFR levels					
≥90	17,125 (72.0%)	2,850 (56.4%)	606 (58.7%)	5,256 (51.3%)	327 (40.5%)
60-90	5,618 (23.6%)	1,527 (30.2%)	262 (25.3%)	3,458 (33.8%)	275 (34.1%)
30-60	1,014 (4.3%)	541 (10.7%)	129 (12.5%)	1,415 (13.8%)	176 (21.8%)
0-30	36 (0.15%)	130 (2.6%)	35 (3.4%)	107 (1.0%)	29 (3.6%)
Prescription year					
2013	3,189 (13.4%)	364 (7.2%)	193 (18.7%)	1,183 (11.6%)	81 (10.0%)
2014	3,995 (16.8%)	622 (12.3%)	157 (15.2%)	1,555 (15.2%)	102 (12.6%)
2015	4,190 (17.6%)	832 (16.5%)	200 (19.4%)	1,717 (16.8%)	131 (16.2%)
2016	4,178 (17.6%)	954 (18.9%)	167 (16.2%)	1,824 (17.8%)	149 (18.5%)
2017	4,061 (17.1%)	1,163 (23.0%)	161 (15.6%)	1,874 (18.3%)	166 (20.6%)
2018	3,523 (14.8%)	919 (18.2%)	130 (12.6%)	1,729 (16.9%)	144 (17.8%)
2019-June	657 (2.8%)	194 (3.8%)	24 (2.3%)	354 (3.5%)	34 (4.2%)
Pregnancy	NA	NA	NA	396 (3.9%)	13 (1.6%)
STD	1,144 (4.8%)	337 (6.7%)	55 (5.3%)	586 (5.7%)	62 (7.7%)
Cognitive impairment*	29 (0.12%)	3 (0.06%)	5 (0.48%)	17 (0.17%)	0 (0.0%)
Dementia	428 (1.8%)	176 (3.5%)	20 (1.9%)	317 (3.1%)	45 (5.6%)
Use of OAC	2,556 (10.7%)	394 (7.8%)	90 (8.7%)	363 (3.5%)	16 (2.0%)
Depression	1,815 (7.6%)	395 (7.8%)	91 (8.8%)	675 (6.6%)	53 (6.6%)
Diabetes Mellitus	NA	NA	NA	4,894 (47.8%)	433 (53.7%)
Urologic abnormalities	NA	NA	NA	394 (3.8%)	19 (2.4%)
Use of immunosuppressant's	NA	NA	NA	360 (3.5%)	37 (4.6%)

Table 1: The baseline characteristics of cystitis episodes classified on the prescribed antimicrobial therapy. (*continued*)

Patient characteristics	Treatment (n=49,115)				
	Short regimen			Extended regimen	
	NF5 (n=23,793)	**FT1 (n=5,048)**	**TMP3 (n=1,032)**	**NF7 (n=10,236)**	**TMP7 (n=807)**
Socio-economic status score					
Median	0.19	0.19	0.32	0.19	0.19
Interquartile range	-0.19 – 1.24	-0.12 – 1.81	-0.48 – 1.31	-0.94 – 0.97	-1.16 – 0.97
N episodes of cystitis previous year					
Median	0	1	1	0	1
Interquartile range	0 - 1	0 - 3	0 - 2	0 - 1	0 - 2

eGFR = estimated glomerular filtration rate
STD = sexually transmitted diseases
OAC = oral anticonception
NF5 = NF five-day treatment
NF7 = NF seven-day treatment
FT1 = FT one day treatment
TMP3 = TMP three-day treatment
TMP7 = TMP seven-day treatment
*other than dementia

Table 2: The effect of every 10 mL/min increase in eGFR on the odds ratio of clinical failure within 28 days post-prescription.

	Crude analysis	Multivariable analysis	Multivariable sensitivity analysis
Therapy	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
NF5	0.87 (0.78-0.97) **	0.96 (0.90-1.01)	0.65 (0.54-0.80) ***
FT1	1.02 (0.96-1.08)	0.93 (0.76-1.08)	0.97 (0.89-1.06)
TMP3	0.96 (0.87-1.05)	0.93 (0.80-1.07)	0.81 (0.70-0.94) **
NF7	0.94 (0.91-0.98) *	0.95 (0.65-1.26)	0.84 (0.68-1.04)
TMP7	1.04 (0.93-1.14)	1.03 (0.90-1.16)	0.56 (0.20-1.56)

Adjusted for the following confounding variables: gender, age, year of prescription, pregnancy, sexual transmitted diseases, cognitive impairment other than dementia, oral contraceptive use, depression, dementia, use of immunosuppressant's, socio-economic status, number of episodes of cystitis in the previous year and in the previous 28 days, the use of normal or slow release nitrofurantoin formulation, with as random effects the patient and the general practitioners practice. For complicated cystitis additionally for fixed variables diabetes mellitus, urologic abnormalities, solid organ transplantation
Significance levels: * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$
TMP3 = trimethoprim three-day treatment
NF5 = nitrofurantoin five-day treatment
NF7 = nitrofurantoin seven-day treatment
FT1 = fosfomycin single dose treatment
TMP7 = trimethoprim seven-day treatment

Table 3: The incidence of clinical failure at 28 days compared between the treatment arms within renal function groups.

			Crude analysis	Multivariable analysis	Multivariable sensitivity analysis
eGFR (mL/min)	**UTI group**	**Therapy**	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
<60	Uncomplicated	FT1 vs. NF5†	0.53 (0.28-1.00)	0.54 (0.27-1.09)	NA
		TMP3 vs. NF5†	1.04 (0.45-2.40)	1.21 (0.49-2.98)	NA
		TMP3 vs. FT1	1.95 (0.75-5.10)	2.24 (0.79-6.33)	NA
	Complicated	TMP7 vs. NF7†	0.55 (0.29-1.07)	0.62 (0.31-1.24)	NA
≥60	Uncomplicated	FT1 vs. NF5	0.94 (0.75-1.18)	0.91 (0.73-1.15)	1.01 (0.85-1.19)
		TMP3 vs. NF5	1.03 (0.68-1.56)	1.05 (0.69-1.60)	1.19 (0.88-1.61)
		TMP3 vs. FT1	1.10 (0.69-1.74)	1.15 (0.72-1.84)	1.18 (0.84-1.65)
	Complicated	TMP7 vs. NF7	1.05 (0.77-1.44)	2.39 (0.86-6.63)	0.79 (0.50-1.26)

Adjusted for the following confounding variables: gender, age, year of prescription, pregnancy, sexual transmitted diseases, cognitive impairment other than dementia, oral contraceptive use, depression, dementia, use of immunosuppressant's, socio-economic status, number of episodes of cystitis in the previous year and in the previous 28 days, the use of normal or slow release nitrofurantoin formulation, with as random effects the general practitioners practice. For complicated cystitis additionally for fixed variables diabetes mellitus, urologic abnormalities, solid organ transplantation.

NF5 = NF five-day treatment
NF7 = NF seven-day treatment
FT1 = FT single dose treatment
TMP7 = TMP seven-day treatment
TMP3 = TMP three-day treatment
† Nitrofurantoin is contraindicated in patients with eGFR <30 mL/min (1)

DISCUSSION

The results of this study suggest that no large effect exists of (decreased) renal function on the effectiveness of nitrofurantoin, fosfomycin or trimethoprim for cystitis. This is surprising given the fact that all three antibiotics are being eliminated by glomerular excretion (14–17). Especially for nitrofurantoin, it was expected that a decreased renal function could have led to low, sub-therapeutic urinary concentrations of nitrofurantoin as urinary concentrations of nitrofurantoin are relatively low compared to those for fosfomycin and trimethoprim (18–20). The crude results suggest that in patients with moderately decreased renal function to kidney failure, treatment with FT1 for uncomplicated and TMP7 for complicated are associated with lower clinical failure rates than respectively treatment with NF5 and NF7. However, this difference was not observed after adjustment for confounders.

The population of analysis is relatively old and has much comorbidities. As these are both reasons to measure serum creatinine, a sensitivity analysis was performed to evaluate the effect of renal function on clinical failure when also including the population with unknown serum creatinine. This population consisted of younger patients with less comorbidities, in which we assumed the renal function to be normal (eGFR =90ml/min). This sensitivity analysis indicate that a higher clinical failure rate is observed in patients with decreasing renal function after using NF5 or TMP3 for cystitis. This was not observed for FT1. These results point to the hypothesis that the effectiveness of fosfomycin is less affected by renal function compared to nitrofurantoin or trimethoprim in the primary care population. This is likely to be related to the relatively high urinary concentrations of fosfomycin.

Little is known about the effect of decreased renal function on clinical efficacy of cystitis treatment as previous randomized controlled trials excluded patients with decreased renal function (21–26). A retrospective cohort study investigated the effect of renal function on the effectiveness of nitrofurantoin and used trimethoprim as a control arm. A decreased renal function (eGFR <50 mL/min/1.73m^2) was not associated with a decreased effectiveness of nitrofurantoin or trimethoprim, although confidence intervals were wide (9). In the same study, a significant association between a decreased renal function and the occurrence of pulmonary reactions leading to hospitalization was found for nitrofurantoin. Another retrospective cohort study evaluated the effectiveness of nitrofurantoin in the treatment of cystitis in outpatient males with varying renal functions. It was found that for every 10 mL/min decrease in eGFR, the odds of clinical failure increased by 13% (8). No clinical studies have been performed that evaluated the effect of decreased renal function on the efficacy or effectiveness of oral fosfomycin for the treatment of cystitis.

Little pharmacokinetic data is available to support our findings. In a small study with 28 kidney failure patients, it was found that urinary concentrations of nitrofurantoin were lower in patients with severely reduced renal function (4-11 mL/min) compared to patients with normal renal function (27). Taken into account the ECOFF of *E.coli* for nitrofurantoin of 64 mg/L as reported by the EUCAST, urinary drug concentrations in these patients did not exceed the ECOFF so urinary concentrations in these patients were sub therapeutic (28). We therefore expected to find a relationship between renal function and clinical treatment failure for nitrofurantoin, but this was not found. However, an effect of kidney failure on the effectiveness of nitrofurantoin could not be excluded with this study because our database contains only few patients with kidney failure that were treated with nitrofurantoin for cystitis. This is likely to be a consequence of the Dutch guideline that advices against using nitrofurantoin in eGFR below 30 mL/min. In contrast to nitrofurantoin, high urinary concentrations of trimethoprim and fosfomycin are reached after administration of the registered dose, making it less likely that a decrease in renal function will result in sub therapeutic concentrations in urine (19, 20). This hypothesis was supported for fosfomycin by the findings of a small study in seven patients with different levels of renal function (eGFR ranged from 21-72 mL/min). Urinary concentrations of fosfomycin were found to be lower and excretion was delayed with progressive renal failure compared to those in healthy subjects (29). Despite these concentrations were lower, they remained higher than the breakpoint of 128 mg/L for susceptible *E. coli* for as long as 48 hours in all seven patients. No data is available on the urinary concentrations of trimethoprim in patients with decreased renal function (30). More research is needed into the effect of the renal function on the treatment outcome of fosfomycin and trimethoprim.

Our study has some limitations. The most important limitation was the retrospective nature of the data. It is known that the JGPN database provides reliable quantitative estimates of demographic data, drug prescriptions (ATC codes), symptoms (ICPC codes) and laboratory values, but detailed information is lacking. For example, details about dipstick results, drug concentrations, microbiological cultures, and decision to treat are missing (10). However, it is known that Dutch GPs usually confirm the presence of cystitis using dipstick before prescribing antibiotics, making it more likely that a true cystitis was treated (31). Second, clinical failure rates may have been underestimated as prescription data from hospitals and out of office GP services were lacking so the follow-up was limited. However, only 6% of total antibiotic prescriptions in primary care occurs out of office hours in the Netherlands and the occurrence of pyelonephritis after treatment for uncomplicated cystitis was found to be low (around 1%) in patients with uncomplicated cystitis, diminishing the effect of underestimation (32, 33).

Second, confounding by indication could not be excluded when comparing the treatment with nitrofurantoin, fosfomycin and trimethoprim because nitrofurantoin is

the first choice option for cystitis according to the treatment guideline and nitrofurantoin is contraindicated in patients with a severely decreased renal function (GFR <30 mL/min) (1). Although we only included first episodes of cystitis and we adjusted for the number of cystitis prescriptions in the previous year, residual confounding is possible. If so, we expect bias in favour of NF5 and NF7.

In conclusion, we found no important effect of (decreased) renal function on the effectiveness of nitrofurantoin, fosfomycin or trimethoprim. New studies, including patients with kidney failure as well as young healthy patients are needed to confirm our findings. Next, more studies are warranted investigating the PK/PD profile of nitrofurantoin, fosfomycin and trimethoprim for cystitis in patients with decreased renal function. Our findings suggest that the impact of renal function on the treatment outcome with one of the three drugs for cystitis might be overestimated during clinical practice nowadays.

Conflict of interest

The authors declare that there are no conflicts of interest.

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