Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

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

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ARTICLE INFO

Article history:
Received 16 December 2019
Received in revised form
24 February 2020
Accepted 1 March 2020
Available online xxx

Editor: L. Scudeller

Keywords:
Cystitis
Fosfomycin
Nitrofurantoin
Renal impairment
Trimethoprim

ABSTRACT

Objectives: We evaluated the effect of renal function on clinical failure rates of nitrofurantoin, fosfomycin and trimethoprim for the treatment of cystitis in primary care.
Methods: Data were retrospectively obtained from 78 Dutch general practitioner (GP) practices between 2013 and 2019. Eligible episodes in patients (>11 years) were those requiring 5 days of nitrofurantoin (NF5), single-dose fosfomycin–trometamol (FT1), 3 days of trimethoprim (TMP3) for uncomplicated cystitis, or 7 days of nitrofurantoin (NF7) or trimethoprim (TMP7) for complicated cystitis. Clinical failure was defined as second antibiotic prescription for cystitis or pyelonephritis within 28 days post-prescription. Mixed effects regression analysis was used, with patient and GP practice as random effects and demography, comorbidity, and cystitis history as fixed effects.
Results: Adjusted odds ratios (aORs) for clinical failure per 10mL/min decrease in estimated glomerular filtration rate (eGFR) were 1.05 (95% CI: 1.01–1.09) for NF5 (n = 24,591), 0.96 (95% CI: 0.92–1.01) for FT1 (n = 5359), 0.98 (95% CI: 0.89–1.08) for TMP3 (n = 1064), 1.05 (95% CI: 1.02–1.09) for NF7 (n = 10,628) and 1.02 (95% CI: 0.93–1.14) for TMP7 (n = 831). In uncomplicated cystitis and eGFR ≥60 mL/min, clinical failures occurred in 14.6% (1895/12 980) of NF5-treated, 20.7% (266/1283) of FT1-treated (aOR versus NF5 1.37, 95% CI 1.18–1.59) and 20.8% (66/318) of TMP3-treated patients (aOR 1.42, 95% CI 1.07–1.87 versus NF5). In uncomplicated cystitis and eGFR <60 mL/min, FT1 resulted in 16.0% (39/244) and NF5 in 23.3% clinical failures (110/472), aOR: 0.61, 95% CI: 0.39–0.95).
Conclusions: In eGFR ≥60 mL/min treatment with fosfomycin or trimethoprim for uncomplicated cystitis was associated with more clinical failure than treatment with nitrofurantoin, while in eGFR <60 mL/min nitrofurantoin was associated with more clinical failure than fosfomycin–trometamol. Renal function, if known, should be considered in the clinical decision-making for cystitis treatment. **T. ten Doesschate, Clin Microbiol Infect 2020;▪:1**

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]. In primary care in The Netherlands, nitrofurantoin is recommended as first-choice oral treatment for acute uncomplicated cystitis, with fosfomycin–trometamol (fosfomycin) as second choice and trimethoprim as third choice [1]. Extended regimens of nitrofurantoin and trimethoprim are first and second choice respectively in patients with complicated cystitis, defined as having risk factors for a complicated course (male gender, diabetes mellitus (DM), urological abnormalities and immunosuppression) [1].

The efficacy of antimicrobial treatment for cystitis depends largely on its antimicrobial activity against the pathogen and the concentration achieved in the urine [2,3]. Nitrofurantoin,

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https://doi.org/10.1016/j.cmi.2020.03.001

fosfomycin and trimethoprim are active against most uropathogens and are eliminated by renal excretion, resulting in high concentrations in the 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 the drug concentrations achieved in the urine are insufficient; however, strong pharmacokinetic-based evidence for this concern is lacking [6,7]. Retrospective cohort studies failed to demonstrate clear effects of impaired renal function on the clinical effectiveness of nitrofurantoin or trimethoprim for the treatment of cystitis [8,9]. To the best of our knowledge, no such studies have been conducted for fosfomycin. Consequently, little evidence exists to guide the choice of antibiotic treatment of cystitis for patients with impaired renal function.

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 of 444 782 patients receiving care from 78 general practitioner (GP) practices in the province of Utrecht, The Netherlands, in 2018 [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. Episodes were selected between January 2013 and June 2019 (see Supplementary Material S1 for definitions).

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 recommends a regimen consisting of 5 days of nitrofurantoin 100 mg extended release (Furabid®) every 12 h or 50 mg normal release (Furadantin®) every 6 h (NF5), a single-dose of fosfomycin 3000 mg (FT1) or a 3-day treatment with trimethoprim 300 mg every 24 h (TMP3). We excluded cystitis episodes that were treated as uncomplicated cystitis despite the presence of one of the following risk factors which define it as complicated cystitis: male gender, pregnancy, DM, urological abnormalities and immunosuppression. For complicated cystitis, the guideline recommends nitrofurantoin and trimethoprim in an extended duration of 7 days (NF7 and TMP7). Patients without documented risk factors but receiving an extended course were considered as cases of complicated cystitis. Prescriptions occurring within 28 days of a UTI episode were considered to represent treatment failures and were therefore not included as a new cystitis episode.

Renal function was based on the most recent estimated glomerular filtration rate (eGFR) value measured within 6 months before or after the prescription date. Episodes were excluded from the main analysis if no eGFR was measured in this period. The eGFR was calculated with the chronic kidney disease epidemiology (CKD-Epi) 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 or 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, cotrimoxazole or amoxicillin–clavulanic acid. The secondary outcome, pyelonephritis, was defined as a prescription of ciprofloxacin, cotrimoxazole or amoxicillin–clavulanic acid with an ICPC code for pyelonephritis within 28 days of the initial prescription.

Statistical analysis

Effect of renal function on clinical failure per treatment regimen

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 treatment regimens. Renal function was analysed in the model as a continuous variable. The linearity assumption was tested by visual inspection of residuals plots. eGFR values $\geq$ 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, incorporating the correlation among repeated episodes within one patient and within one GP practice using a random intercept. The adjusted model was corrected for fixed variables in the population of uncomplicated cystitis: age, socioeconomic status, number of cystitis prescriptions in the previous year, year of prescription, history of dementia, cognitive impairment other than dementia, depression, a consultation because of a (presumed) sexually transmitted disease (STD) within the prior 6 months, and oral contraceptive use. In the population of complicated cystitis, we added gender, pregnancy, solid-organ transplantation, diabetes mellitus, anatomical/functional deficits in the urinary tract or kidney, and immunosuppressive medicine use as confounders. For nitrofurantoin, the dosing regimen (50 mg normal release every 6 h versus 100 mg slow release every 12 h) was included as a confounding variable. Fixed variables were predefined as (potential) risk factors for clinical failure. Depression and dementia seemed to be associated with a higher risk of clinical failure in our own data. Oral contraceptive use and STD presume active sexual behaviour, which is associated with the occurrence of urinary tract infections. Moreover, STD could mimic and be misclassified as cystitis and vice versa. Year of prescription as a confounder was included because the use of fosfomycin has increased since 2013, as a consequence of a guideline change (Supplementary Material S2) with a possible effect on the risk of clinical failure. Linearity to the log odds was observed for the continuous values socioeconomic status and age. Missing data were imputed using multiple imputation. Two sensitivity analyses were performed for the primary endpoint in which we applied the same multivariable model as for the first model. In sensitivity analysis A we additionally included patients with unknown serum creatinine, for which we set the eGFR at 90 mL/min. In sensitivity analysis B, we selected episodes in which the eGFR was measured before or at the day of prescription.

Effect of treatment regimen 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

Please cite this article as: ten Doesschate T et al., The effectiveness of nitrofurantoin, fosfomycin and trimethoprim for the treatment of cystitis in relation to renal function, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2020.03.001

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 without patient as random effect. We compared the short regimens for uncomplicated cystitis (NF5, FT1, TMP3) and extended regimens for complicated cystitis (NF7, TMP7) in patients with normal to mild decreased renal function (eGFR ≥60 mL/min; Kdigo stage G1 or G2) and in patients with moderately decreased renal function to kidney failure (eGFR <60 mL/min; Kdigo stage G3–G5) [13]. We performed the sensitivity analysis A for the population with eGFR ≥60 mL/min in which we included a factor indicating whether eGFR had been measured or not. Sensitivity analysis B was performed on both renal function populations (eGFR <60 mL/min and eGFR ≥60 mL/min).

The models were fit to maximum likelihood using the Laplace approximation. In all cases, p values < 0.05 were considered statistically significant. 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 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 164 589 episodes of nitrofurantoin, fosfomycin and trimethoprim prescriptions. After applying the exclusion criteria, 42 473 episodes in 21 891 patients remained for analysis, of which 31 014 (73%) consisted of a short regimen for uncomplicated cystitis and 11 459 (27%) an extended regimen for complicated cystitis (Fig. 1). Table 1 gives the patient characteristics at baseline in the five treatment regimens. Supplementary Material S2 indicates the frequency of antibiotic use over the past years in this period, with the patient characteristics at baseline of the population without known renal function (sensitivity analysis A).

Effect of renal function on clinical failure per antibiotic regimen

After adjusting for confounders, every 10 mL/min decrease in eGFR resulted in significantly more clinical failures when using NF5 and NF7, but not when using FT1, TMP3 or TMP7 (Table 2 and Supplementary Material S3, graphical display). Results were similar for sensitivity analyses A and B. Decreasing renal function also tends to higher rates of pyelonephritis for NF5, although there is wide uncertainty around the estimate (Table 2).

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

In first episodes per patient, clinical failure occurred in 16.3% of all episodes (3578/21 891): 14.9% after using NF5, 20.0% after using FT1, 21.4% after using TMP3, 18.1% after using NF7, and 19.7% after using TMP7 (Supplementary Material S4). Pyelonephritis as a manifestation of clinical failure occurred in 4.0% of all episodes (886/21 891): 2.8% after using NF7, 4.1% after using FT1, 3.6% after using TMP3, 6.6% after using NF7, and 6.4% after using TMP7. In first episodes in patients in whom no renal function was measured, the clinical failure rate was 11.0% (3286/29 768) overall and 2.2% (660/29 768) for pyelonephritis.

The probability of clinical failure in patients with eGFR <60 mL/min was significantly higher when treated with NF5 in comparison to FT1 for uncomplicated cystitis (Table 3). In patients with eGFR ≥60 mL/min significantly more clinical failures occurred when using FT1 or TMP3 instead of NF5. Results were similar in sensitivity analyses A and B, and with pyelonephritis as outcome, although the latter had larger confidence intervals.

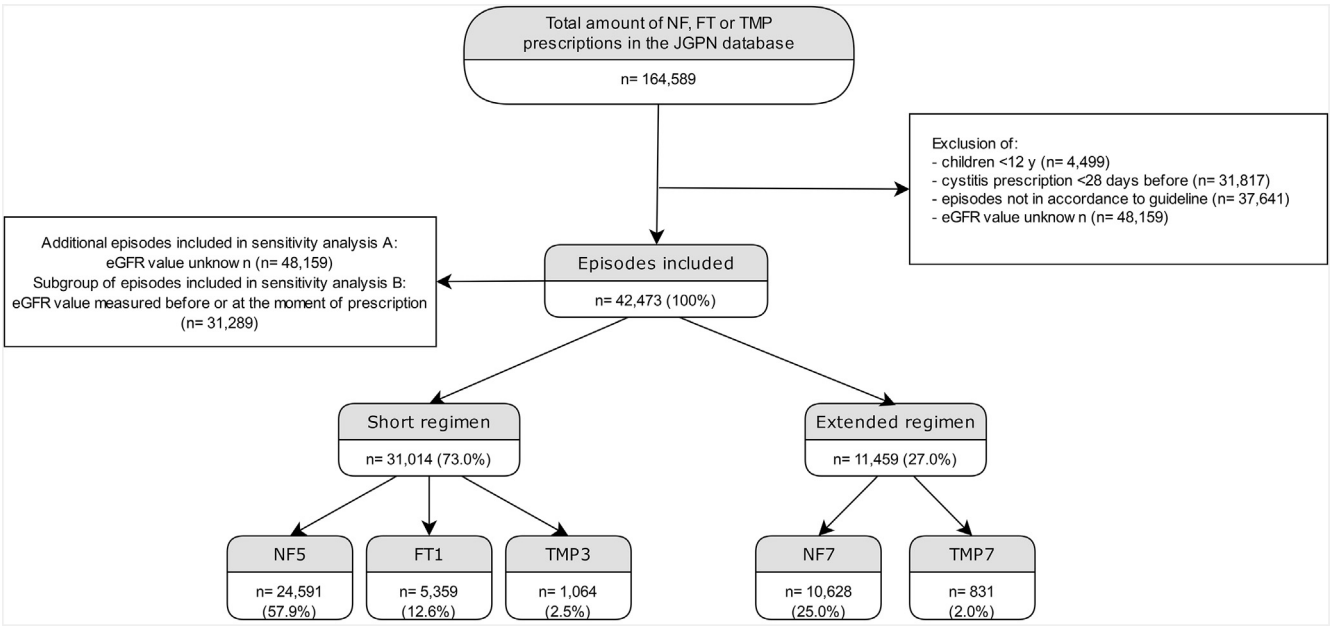

Fig. 1. Flowchart for inclusion of episodes from the Julius General Practitioners' Network (JGPN) consisting of data from 78 general practitioner practices (GP practices) in the province of Utrecht, The Netherlands, between January 2013 and June 2019. NF, nitrofurantoin; FT, fosfomycin–trometamol; TMP, trimethoprim; eGFR, estimated glomerular filtration rate.

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Table 1
Baseline characteristics of cystitis episodes for each antimicrobial regimen

Patient characteristics	Treatment (n = 42 473)				
	Short regimen			Extended regimen	
	NF5 (n = 24,591)	FT1 (n = 5359)	TMP3 (n = 1064)	NF7 (n = 10 628)	TMP7 (n = 831)
Age (years)					
Median	61	72	73	71	77
Interquartile range	43–75	58–83	55–84	59–81	67–85
Gender					
Male (%)	NA	NA	NA	3367 (31.7%)	209 (25.2%)
eGFR (mL/min)					
Mean ± SD	85.5 ± 10.1	80.0 ± 17.0	79.4 ± 17.8	78.6 ± 16.1	73.2 ± 19.5
eGFR levels					
≥90	17 686 (71.9%)	3009 (56.1%)	625 (58.7%)	5434 (51.1%)	333 (40.1%)
60–90	5840 (23.7%)	1630 (30.4%)	278 (26.1%)	3586 (33.7%)	295 (35.5%)
30–60	1026 (4.2%)	580 (10.8%)	128 (12.0%)	1501 (14.1%)	172 (20.7%)
0–30	39 (0.2%)	140 (2.6%)	33 (3.1%)	107 (1.0%)	31 (3.7%)
Pregnancy (%)	NA	NA	NA	413 (3.9%)	13 (1.6%)
STD (%)	1176 (4.8%)	348 (6.5%)	56 (5.3%)	612 (5.8%)	66 (7.9%)
Cognitive impairment[a] **(%)**	29 (0.12%)	3 (0.06%)	5 (0.47%)	23 (0.22%)	1 (0.12%)
Dementia (%)	435 (1.8%)	181 (3.4%)	20 (1.9%)	326 (3.1%)	45 (5.4%)
Use of OAC (%)	2637 (10.7%)	420 (7.8%)	93 (8.7%)	379 (3.6%)	19 (2.3%)
Depression (%)	1868 (7.6%)	410 (7.7%)	94 (8.8%)	691 (6.5%)	53 (6.4%)
Diabetes mellitus (%)	NA	NA	NA	5089 (47.9%)	448 (53.9%)
Urological abnormalities (%)	NA	NA	NA	418 (3.9%)	20 (2.4%)
Use of immunosuppressants (%)	NA	NA	NA	372 (3.5%)	36 (4.3%)
Socioeconomic status score[b]					
Median	0.19	0.19	0.32	0.19	0.19
Interquartile range	−0.19–1.24	−0.12–1.10	−0.48–1.31	−1.16–0.97	−1.16–0.97
N episodes of cystitis previous year[c]					
Median	0	1	1	0	1
Interquartile range	0–1	0–2	0–2	0–1	0–2

eGFR, estimated glomerular filtration rate; STD, sexually transmitted disease, OAC, oral anticonception; NF5, nitrofurantoin 5-day treatment; FT1, fosfomycin–trometamol 1-day treatment; TMP3, trimethoprim 3-day treatment; NF7, nitrofurantoin 7-day treatment; TMP7, trimethoprim 7-day treatment.
[a] Other than dementia.
[b] Socioeconomic state ranges from −7 to +7 and is estimated on the neighbourhood the patient lives (postal code) (271 missing).
[c] Number of prescriptions for cystitis or pyelonephritis in the past 365 days before the episode (four missing).

Discussion

In patients with uncomplicated and complicated cystitis treated with nitrofurantoin, an association was seen between decreased renal function and clinical failure, which was not seen in those treated with fosfomycin or trimethoprim. Treatment with a single dose of fosfomycin for uncomplicated cystitis resulted in less clinical failures in patients with eGFR <60 mL/min compared to 5 days of nitrofurantoin. In contrast, in patients with eGFR ≥60 mL/min nitrofurantoin appeared more effective than fosfomycin or trimethoprim for uncomplicated cystitis. The latter is in line with the results of a trial in which nitrofurantoin for 5 days was more efficacious than a single dose of fosfomycin for uncomplicated cystitis, although a

Table 2
The effect of every 10 mL/min decrease in estimated glomerular filtration rate (eGFR) on the odds ratio of clinical failure within 28 days post-prescription

Therapy	Patients	Clinical failure	Crude analysis	Multivariable analysis[a]	Sensitivity analysis A[a]	Sensitivity analysis B[a]	Secondary outcome pyelonephritis[a]
	Number	Number (%)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
NF5	24 591	4245 (17.3)	1.02 (1.02–1.03)[b]	1.05 (1.01–1.09) [c]	1.05 (1.01–1.09)[c]	1.04 (1.00–1.09)[d]	1.34 (0.96–1.87)
FT1	5359	1235 (23.0)	1.00 (0.99–1.00)	0.96 (0.92–1.01)	0.97 (0.93–1.02)	0.93 (0.88–0.98)[d]	0.83 (0.58–1.20)
TMP3	1064	248 (23.3)	1.00 (0.98–1.01)	0.98 (0.89–1.08)	0.96 (0.88–1.05)	0.97 (0.87–1.08)	1.12 (0.89–1.41)
NF7	10 628	2113 (19.9)	1.01 (1.01–1.02)[b]	1.05 (1.02–1.09)[c]	1.01 (0.98–1.04)	1.05 (1.01–1.10)[d]	1.00 (0.93–1.06)[e]
TMP7	831	201 (24.2)	0.99 (0.98–1.01)	1.02 (0.93–1.14)	0.99 (0.93–1.05)	0.99 (0.88–1.12)	0.86 (0.73–1.02)

NF5, nitrofurantoin 5-day treatment; FT1, fosfomycin–trometamol 1-day treatment; TMP3, trimethoprim 3-day treatment; NF7, nitrofurantoin 7-day treatment; TMP7, trimethoprim 7-day treatment.
[a] Adjusted for the following confounding variables: age, year of prescription, a consultation because of sexual transmitted disease in the prior half year, cognitive impairment other than dementia, oral contraceptive use, depression, dementia, socioeconomic status, number of episodes of cystitis in the previous year, 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 gender, pregnancy, diabetes mellitus, urological abnormalities, use of immunosuppressants, solid-organ transplantation. Sensitivity analysis A, multivariable analysis using the same confounders as above with addition of patients with unknown serum creatinine, for whom we set the eGFR to 90 mL/min; sensitivity analysis B, multivariable analysis using the same confounders as above with selection of patients in whom the eGFR was measured before or at the moment of prescription; patients with unknown eGFR were not included; outcome pyelonephritis, multivariable analysis using the same confounders as above with the outcome pyelonephritis as manifestation of clinical failure.
[b] $p < 0.001$.
[c] $p < 0.01$.
[d] $p < 0.05$.
[e] Due to convergence problems when adjusting for both patient and the general practitioners' practice as random effects, only first episodes were analysed with only general practitioners' practice as random effect.

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Table 3
The odds ratio on clinical failure at 28 days within strata of renal function

eGFR (mL/min)	Cystitis population	Therapy	Crude analysis	Multivariable analysis	Sensitivity analysis A[a]	Sensitivity analysis B[a]	Outcome pyelonephritis[a]
			Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
<60	Uncomplicated	FT1 vs NF5	0.63 (0.42–0.94)[b]	0.61 (0.39–0.95)[b]	NA	0.73 (0.46–1.12)	0.67 (0.25–1.76)
		TMP3 vs NF5	1.05 (0.58–1.92)	0.96 (0.51–1.82)	NA	0.53 (0.25 –1.16)	0.28 (0.04–2.23)
		TMP3 vs FT1	1.68 (0.87–3.25)	1.59 (0.79–3.21)	NA	0.73 (0.32–1.68)	0.42 (0.05–3.62)
	Complicated	TMP7 vs NF7	0.89 (0.49–1.59)	0.89 (0.48–1.65)	NA	0.62 (0.32–1.22)	1.50 (0.66– 3.42)
≥60	Uncomplicated	FT1 vs NF5	1.53 (1.33–1.77)[c]	1.37 (1.18–1.59)[c]	1.29 (1.14–1.46)[c]	1.35 (1.16–1.58)[c]	1.52 (1.13–2.06)[b]
		TMP3 vs NF5	1.53 (1.16–2.02)[d]	1.42 (1.07–1.87)[b]	1.55 (1.26–1.92)[c]	1.48 (1.08–2.02)[c]	1.32 (0.74–2.36)
		TMP3 vs FT1	1.00 (0.74–1.36)	1.03 (0.76–1.40)	1.20 (0.95–1.53)	1.09 (0.78–1.53)	0.87 (0.47–1.63)
	Complicated	TMP7 vs NF7	1.15 (0.82–1.62)	0.99 (0.69–1.41)	0.99 (0.72–1.35)	1.06 (0.74–1.51)	0.83 (0.44–1.56)

NF5, nitrofurantoin 5-day treatment; FT1, fosfomycin–trometamol 1-day treatment; TMP3, trimethoprim 3-day treatment; NF7, nitrofurantoin 7-day treatment; TMP7, trimethoprim 7-day treatment.

[a] Adjusted for the following confounding variables: age, year of prescription, a consultation because of sexual transmitted disease in the prior half year, cognitive impairment other than dementia, oral contraceptive use, depression, dementia, socioeconomic status, number of episodes of cystitis in the previous year, the use of normal or slow-release nitrofurantoin formulation, with as random effects general practitioners practice. For complicated cystitis additionally for gender, pregnancy, diabetes mellitus, urological abnormalities, use of immunosuppressants, solid-organ transplantation. Sensitivity analysis A, multivariable analysis using the same confounders as above with addition of patients with unknown serum creatinine, for whom we set the eGFR to 90 mL/min; sensitivity analysis B, multivariable analysis using the same confounders as above with selection of patients in whom the eGFR was measured before or at the moment of prescription; outcome pyelonephritis, multivariable analysis using the same confounders as above with the outcome pyelonephritis as manifestation of clinical failure.

[b] $p < 0.05$.

[c] $p < 0.001$.

[d] $p < 0.01$.

nitrofurantoin schedule of 100 mg three times daily with normal release was used in this trial [14].

Based on the pharmacokinetic profile, it could have been expected that renal function impacted the efficacy of nitrofurantoin more than that of fosfomycin or trimethoprim. All three antibiotics are eliminated by glomerular filtration [15–18]; however, in contrast to nitrofurantoin, high urinary concentrations of trimethoprim and fosfomycin are reached after administration of the registered dose [19–23]. The effect of decreased renal function on the efficacy of cystitis treatment has not been thoroughly investigated as prior randomized controlled trials excluded patients with decreased renal function [14,24–28]. A retrospective cohort study investigated the effect of eGFR on the effectiveness of nitrofurantoin compared to trimethoprim; eGFR <80 mL/min/1.73m^2 was not associated with decreased effectiveness of nitrofurantoin or trimethoprim, although confidence intervals were wide [9]. In the same study, a significant association between decreased renal function (eGFR <50 mL/min/1.73m^2) and the occurrence of pulmonary reactions leading to hospitalization was found for nitrofurantoin. In another retrospective cohort study on the effectiveness of nitrofurantoin for cystitis in males the odds ratio of clinical failure was 1.13 (95% CI: 1.04–1.23) for every 10 mL/min decrease in eGFR, which is in line with the odds ratio of 1.05 (95% CI: 1.01–1.09) derived in this study [8]. We are not aware of clinical studies that have evaluated the effect of renal function on the effectiveness of fosfomycin for cystitis.

The population in the current study is relatively old, with substantial comorbidities, and therefore serum creatinine levels were available. The overall clinical failure rate was high (16.3%), as compared to episodes in generally younger patients with unknown renal function (11.0%). We do not suggest routine testing of renal function in all patients with cystitis, but only in those cases where renal impairment is suspected. In patients with uncomplicated cystitis, if renal impairment is not suspected, the renal function may be assumed adequate; in fact, our results did not change when patients with unknown eGFR were included in the normal renal function group.

Our study has limitations, the most important being its retrospective design. Although the JGPN database provides reliable quantitative estimates of demographic data, drug prescriptions (ATC codes), symptoms (ICPC codes) and laboratory values, detailed information on dipstick results, treatment compliance, microbiological cultures, and considerations for clinical decision-making are missing [10]. However, Dutch GPs usually confirm the presence of cystitis with dipstick before prescribing antibiotics, which increases the likelihood that true cystitis episodes were treated [29]. In particular, severe clinical failure rates may have been underestimated as prescription data from hospitals and out-of-office GP services were lacking. However, in The Netherlands only 6% of total antibiotic prescriptions in primary care occur in out-of-office hours [30,31].

A second limitation is that confounding by indication could not be excluded when comparing the different treatment options, as nitrofurantoin is the first choice 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.

Third, the treatment regimens and definitions of cystitis as used in this study comply with Dutch primary care guidelines. Generalizability of the results may therefore be limited for countries or healthcare settings where different definitions apply. Nevertheless, we expect that the effect of renal function on clinical effectiveness is to some extent generalizable to the therapeutic use of nitrofurantoin, fosfomycin and trimethoprim for urinary tract infections.

Fourth, in some patients the renal function was estimated on eGFR values that were measured after the prescription date, which is inconsistent with the aetiological nature of the study and does not represent the clinical decision-making. Therefore, sensitivity analysis B was performed that only included eGFR measured within 6 months prior to the episode, which resulted in similar findings.

Fifth, the results of our study were not corrected for multiple testing, because distinct hypotheses were tested for separate antibiotic regimens, and the comparisons between the effectiveness of cystitis regimens were a derivative of these results. However, there might be a risk of type I errors, and independent confirmation of our results is required.

In conclusion, the results of this study indicate that impaired renal function reduces the effectiveness of nitrofurantoin for treatment of cystitis, which could have clinically relevant

Please cite this article as: ten Doesschate T et al., The effectiveness of nitrofurantoin, fosfomycin and trimethoprim for the treatment of cystitis in relation to renal function, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2020.03.001

implications for the patient. Consequently, fosfomycin might be more effective than nitrofurantoin in patients with eGFR <60 mL/min. These findings should be considered in the clinical decision-making for treatment of cystitis. New trials, including patients with impaired renal function, are needed to confirm these findings. Next, more studies are warranted investigating the pharmacokinetic/pharmacodynamic profile of nitrofurantoin, fosfomycin and trimethoprim for the treatment of cystitis in patients with impaired renal function.

Author contributions

T.t.D. and E.v.H. contributed equally to this work. We describe contributions to the paper using the CRediT taxonomy [32]. Writing – original draft: T.D. and E.H.; writing – review & editing:C.W., R.W., B.K., and M.B; conceptualization: T.D., E.H., and C.W.; methodology: T.D., E.H., and C.W.; investigation: T.D., E.H., C.W., and R.W.; data curation: T.D., and C.W. Formal analysis: T.D., E.H., and C.W. Project administration: T.D.; supervision: R.W., M.B., and B.K.

Transparency declaration

All authors have no conflicts of interest to disclose. No external funding was received for this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.03.001.

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