

Effectiveness of extended- versus normal-release nitrofurantoin for cystitis: an instrumental variable analysis

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Background: It is unknown whether nitrofurantoin 50 mg normal-release every 6 h (NF50) and nitrofurantoin 100 mg extended-release every 12 h (NF100) are equally effective for treating cystitis in primary care. In the Netherlands, GP prescription of either option largely depends on pharmacy procurement, rather than on patient-related factors.

Methods: GP data between January 2013 and July 2018 were retrospectively collected. Inclusion criteria were the use of nitrofurantoin for uncomplicated cystitis, complicated cystitis or cystitis in pregnancy. Criteria for early and late failure were a second antibiotic prescription for cystitis or pyelonephritis within 14 and 28 days post-prescription, respectively. Crude and confounder-adjusted (CA) risk differences (RDs) were estimated using linear regression. Instrumental variable analysis and CA instrumental variable analysis used GP practice proportion of NF50 versus NF100 use as the instrumental variable.

Results: For uncomplicated cystitis ($n=46855$), treatment with NF50 and NF100 resulted in late failure in 9.7% and 9.6%, respectively. The CA RD, instrumental variable RD and CA instrumental variable RD were 0.2% (95% CI = -0.5 to 0.8), -0.7% (95% CI = -1.7 to 0.3) and 0.0% (95% CI = -0.9 to 1.0), respectively. In complicated cystitis ($n=10767$), late failure occurred in 10.9% and 11.1% after using NF50 and NF100, respectively [CA RD = 0.5% (95% CI = -1.2 to 1.8), instrumental variable RD = -0.8% (95% CI = -3.4 to 1.8) and CA instrumental variable RD = -0.3% (95% CI = -3.0 to 2.4)]. For cystitis in pregnancy ($n=1087$), NF50 and NF100 resulted in late failure in 13.4% and 7.8%, respectively [CA RD = -5.4% (95% CI = -10.0 to -1.4), instrumental variable RD = -8.9% (95% CI = -16.0 to -1.8) and CA instrumental variable RD = -8.9% (95% CI = -16.0 to -1.7)]. No differences were observed in early failure.

Conclusions: In patients with cystitis in pregnancy, NF100 was associated with a lower incidence of late clinical failure compared with NF50. We found no differences in clinical failure between NF50 and NF100 for uncomplicated and complicated cystitis.

Introduction

Nitrofurantoin is the first-choice treatment for cystitis in the Netherlands and in most countries.^{1,2} The antimicrobial activity derives from metabolites that are formed by reduction of nitrofurantoin, but the exact structure and antimicrobial activity of each metabolite is still unclear.³ Despite the widespread use of nitrofurantoin, reported resistance rates to nitrofurantoin among Enterobacterales are low.^{2,4,5} Nitrofurantoin reaches high concentrations in urine, with very low concentrations in plasma, and nitrofurantoin is therefore exclusively used to treat or prevent cystitis.

The Dutch guideline for GPs recommends treatment of uncomplicated cystitis with a 5 day nitrofurantoin regimen in patients of 12 years and older, and treatment for 7 days in patients with complicated cystitis or cystitis in pregnancy.¹ Cystitis is defined as complicated in the presence of risk factors for worse outcome, such as being male, having diabetes mellitus, using immunosuppressive drugs or having urogenital abnormalities. The guideline does not distinguish between the use of the normal-release macrocrystal formulation of 50 mg of nitrofurantoin, available as Furadantine[®] (NF50), and the extended-release formulation of 100 mg of nitrofurantoin, available as Furabid[®] (NF100). The extended-release

formulation consists of 25 mg of nitrofurantoin in the form of macrocrystals and 80.7 mg in the form of monohydrate, corresponding to 75 mg of anhydrous nitrofurantoin. The NF50 formulation has been available since 1969 and needs to be taken every 6 h, while the NF100 formulation was registered in 1994 and can be taken every 12 h.⁶ Pharmacokinetic studies suggest that the NF100 extended-release formulation could be superior to NF50.³ Moreover, compliance with a twice-daily regimen may be higher compared with a four-times-daily regimen. However, the comparative effectiveness of these two regimens for the treatment of cystitis has not been assessed in clinical studies.¹

In the Netherlands, GP prescription of either NF50 or NF100 depends on the pharmacy's procurement, which is based on economic or logistic reasons. We made an inventory of this procurement and found that 4/10 pharmacies only procured NF100, 2/10 only procured NF50 and 4/10 procured both NF100 and NF50. Consequently, GP practice prescription of either option does not primarily depend on patient-related factors, creating a natural experiment. Next to multivariable regression analysis this study used instrumental variable analysis with GP practice as the instrumental variable to compare the effectiveness of NF50 with NF100 for the treatment of cystitis.

Methods

Population

Data were collected from the Julius General Practitioners' Network (JGPN) consisting of 806105 patients from 64 GP practices in the province of Utrecht, The Netherlands, between January 2013 and July 2018.⁷ Diagnoses were coded according to the International Classification of Primary Care (ICPC) and medication prescriptions were coded according to the Anatomical Therapeutic Chemical (ATC) classification system (see the [Supplementary data](#) available at JAC Online).

Episodes were included if nitrofurantoin was prescribed according to the Dutch treatment guideline for patients ≥ 12 years of age. An episode was defined as uncomplicated if nitrofurantoin was prescribed for 5 days in the absence of pregnancy or the following risk factors: male gender, diabetes mellitus, anatomical/functional deficits in the urinary tract or kidney, having used immunosuppressive drugs within 6 months before the prescription, or solid organ transplantation. For complicated cystitis, patients who received a 7 day nitrofurantoin regimen in the absence of pregnancy were included. Since prescription of nitrofurantoin for 7 days is not common practice for GPs, we assumed that this duration reflected the presence of complicating factors. Therefore, patients without documented risk factors and receiving the extended course were included in the complicated cystitis group. In accordance with the Dutch guideline, cystitis during pregnancy was interpreted and analysed as a separate population, and was defined as prescriptions of nitrofurantoin for 7 days with a pregnancy-related consultation within the 9 months prior to the episode. Cystitis episodes were not included if they occurred within 28 days of a previous therapeutic antibiotic prescription for cystitis, i.e. short-course nitrofurantoin, trimethoprim or fosfomycin/trometamol, as these are assumed to represent treatment failures of a prior cystitis episode. Inclusion and exclusion criteria, as structured on ATC and ICPC codes, are provided in the [Supplementary data](#). Socioeconomic status was estimated on aggregated level of the patient's postal code and based on education, income and labour market position of that neighbourhood.⁸

Endpoints

The endpoints in this study were clinical failure within 14 days post-prescription (early failure) and clinical failure within 28 days post-

prescription (late failure). Clinical failure was defined as a new antibiotic prescription for cystitis (nitrofurantoin, trimethoprim or fosfomycin/trometamol, with exclusion of prophylactic prescriptions based on the number of prescription days) or pyelonephritis, i.e. ciprofloxacin, amoxicillin/clavulanic acid or trimethoprim/sulfamethoxazole, combined with an ICPC code for urinary tract infections (see the [Supplementary data](#)).

Statistical analysis

Crude and multivariable linear regression (adjusted) models were used to estimate the risk difference (RD) of clinical failure between NF50 and NF100. A sandwich estimator was used to obtain robust standard errors and 95% CIs. Prior to data analysis, the following set of confounding variables was selected to be included in the multivariable model: age, renal insufficiency, previous antibiotic use for cystitis (nitrofurantoin, trimethoprim or fosfomycin/trometamol), dementia, other forms of cognitive impairment, depression, sexually transmitted disease, oral contraceptive use and socioeconomic status. For complicated cystitis, we additionally corrected for sex, diabetes mellitus, anatomical/functional defects in the urinary tract or the kidney, using immunosuppressive drugs and solid organ transplantation. For cystitis during pregnancy, we corrected for the same factors as for complicated cystitis, except for sex and the use of oral contraceptives. The potential confounding variables were defined by ATC and ICPC codes (see the [Supplementary data](#)). Renal insufficiency was categorized with three levels, based on the estimated glomerular filtration rate [≥ 60 mL/min or < 60 mL/min, as calculated by the Chronic Kidney Disease epidemiology collaboration (CKD-epi) formula using serum creatinine, gender and age] or as 'unknown' in the case of serum creatinine not being measured. Two sensitivity analyses were performed to check the robustness of the results, using multivariable linear regression analyses as above. The first looked at severe late clinical failure, defined as: 'a new prescription for pyelonephritis within 28 days'. In the second model only unique patients were analysed, with one random episode included per patient.

Next, instrumental variable analysis was performed, which has the potential to control for unobserved confounding.⁹ We used GP practice preference as the instrumental variable, where GP practice preference was defined as the proportion of NF50 prescriptions for cystitis compared with all (NF50 and NF100) prescriptions for cystitis per GP practice. With instrumental variable analysis, treatment failure rates per GP practice are regressed on GP practice preference. The observed relationship is then extrapolated to provide an estimate of treatment failure rates if only NF50 was prescribed versus if only NF100 was prescribed among those patients in whom there is an option to choose for either of the two.

The three assumptions of instrumental variable analysis are explained in Figure 1. Whether GP practices differ in their preference for either NF100 or NF50 (instrumental variable assumption 1) was tested using the F-statistic of a linear regression of actual NF50/NF100 prescription on GP practice. In our study, the prescription of NF50 or NF100 per GP practice largely depended on the pharmacy procurement, which is assumed to be independent of the effect of GP practice itself on the outcome clinical failure (instrumental variable assumption 2), e.g. through differences in advice or tendency to prescribe antibiotics. Next, we assumed this prescription per GP practice to be independent of patient characteristics (instrumental variable assumption 3), which was checked for measurable confounders by calculating F-statistics with multivariable linear regression analysis. Additionally, we performed instrumental variable analysis with adjustment for the same measured confounders as in the multivariable linear regression model (adjusted instrumental variable analysis).

As treatment failure rates were expected to be low with either option, and as both options yield an identical cumulative nitrofurantoin dose, we defined equivalence as a difference in clinical failure of less than 2%, which was tested using the 95% CI of the RD. R software version 3.4.1 was used for data analysis, with R package 'ivpack' version 1.2 to perform instrumental variable analysis and applying the sandwich method.

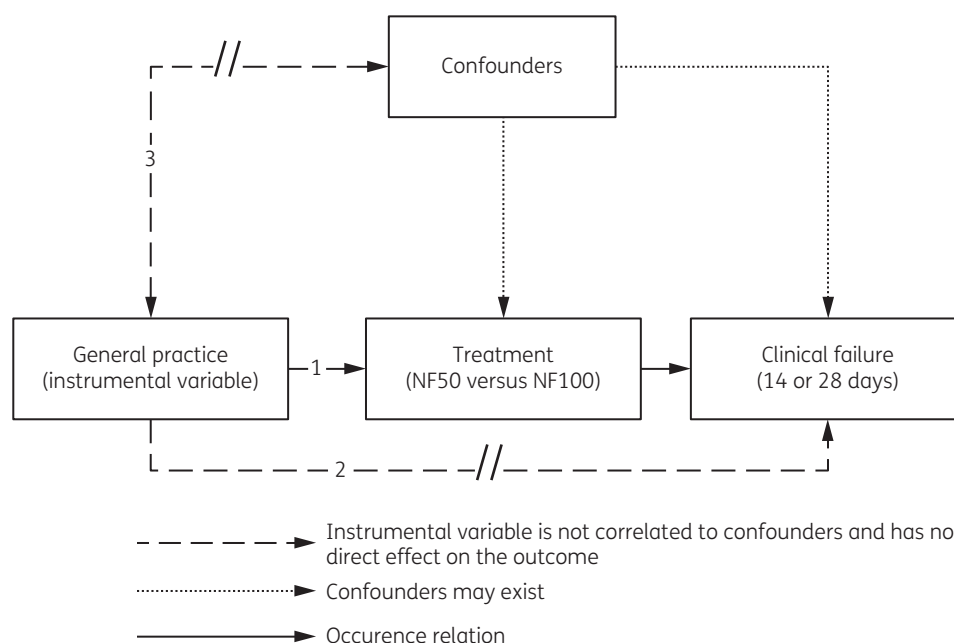


Figure 1. Graphical representation of the model and the assumptions for instrumental variable analysis. GP practice preference is assumed to affect clinical failure only through prescription of NF50 or NF100. This instrumental variable analysis is unbiased if: (i) GP practices differ in their preference for either NF100 or NF50; (ii) GP practice itself has no direct effect on the outcome clinical failure; and (iii) GP practices do not differ in the type of patients for whom they prescribe NF50 or NF100. Figure adapted from Chen and Briesacher.¹⁸ The diagonal lines (//) indicate absence of an association. NF50, 50 mg of nitrofurantoin every 6 h; NF100, 100 mg of nitrofurantoin every 12 h.

Ethics

Ethical approval was obtained from the ethical board of directors of the University Medical Center Utrecht, The Netherlands, with a waiver for informed consent, with reference WAG/mb/18/022909, on 26 June 2018. Individuals are not traceable as all data were provided coded.

Results

Data collection

A total of 119342 cystitis episodes were identified during the study period. Of these, nitrofurantoin was prescribed 93250 times (78% of all cystitis prescriptions). After exclusion of 34541 episodes, we analysed 58709 episodes in 36439 patients, of which 46855 episodes (80%) were of uncomplicated cystitis, 10767 (18%) of complicated cystitis and 1087 (2%) of cystitis during pregnancy (Figure 2). Of the included cystitis episodes, 46155 (79%) were treated with NF100 and the remainder with NF50. The number of patients under care per GP practice in 2017 ranged from 1936 to 44079. Nitrofurantoin was prescribed in 64 GP practices in a range of 256 to 3059 times per GP practice in the study period and for a median of 18 times per 1000 person years with an IQR of 14 to 34 between GP practices.

Assumption instrumental variable analysis

For uncomplicated cystitis, complicated cystitis and cystitis during pregnancy, GP practices used NF50 in a median of 10% (IQR=5%–43%, range=1%–95%), 6% (IQR=3%–23%, range=0%–96%) and 8% (IQR=0%–58%, range=0%–100%) of the episodes, respectively (Figure S1, available as [Supplementary data](#) at JAC Online). The

F-statistics of the linear models predicting prescribed nitrofurantoin dosage based on GP practice preference were 656.5, 96.8 and 11.4 for uncomplicated cystitis, complicated cystitis and cystitis during pregnancy, respectively. The F-statistics of the linear models predicting GP practice preference based on measured confounders were 79.4, 8.9 and 1.5 for uncomplicated cystitis, complicated cystitis and cystitis during pregnancy, respectively. The approximately 8- to 10-fold higher F-statistic of the first model compared with the second demonstrates that the prescription of NF100 or NF50 is much better explained by the GP practice than by measured confounders, confirming the appropriateness of GP practice as the instrumental variable.

Uncomplicated cystitis

Patients who received NF100 were younger and had a higher socioeconomic status compared with those receiving NF50 (Table 1). Clinical failure within 14 days post-prescription was observed in 606/10476 (5.8%) and 2150/36379 (5.9%) patients receiving NF50 and NF100, respectively. Clinical failure within 28 days post-prescription was observed in 1014/10476 (9.7%) in the NF50 group and 3487/36379 (9.6%) in the NF100 group. Crude, adjusted, instrumental variable and adjusted instrumental variable analysis revealed no differences in clinical failure rate between NF50 and NF100 (Table 2). In the sensitivity analyses no differences were found between NF50 and NF100 when analysing unique patients [RD=−0.3% (95% CI=−1.1 to 0.5)] or when looking at severe failure [RD=0.1% (95% CI=−0.2 to 0.4)].

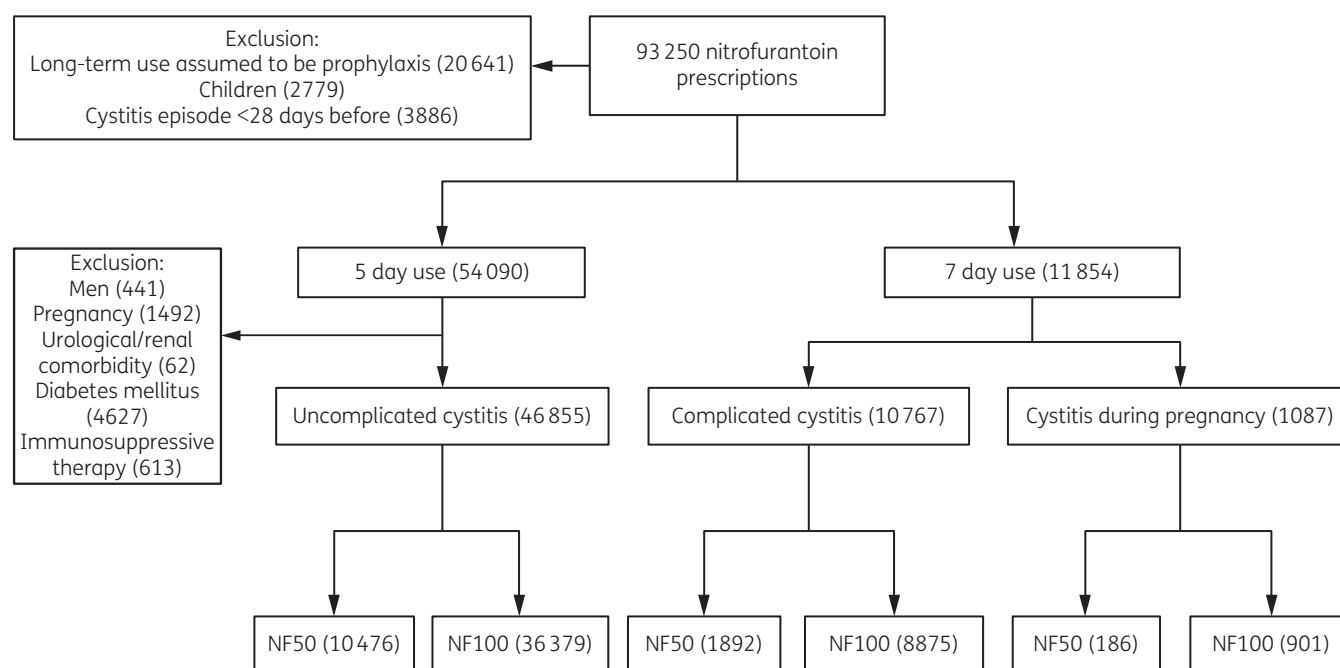


Figure 2. Flowchart for inclusion of uncomplicated cystitis, complicated cystitis and cystitis during pregnancy collected from the JGPN consisting of 806 105 patients from 64 GP practices in the province of Utrecht, The Netherlands, between January 2013 and July 2018. NF50, 50 mg of nitrofurantoin every 6 h; NF100, 100 mg of nitrofurantoin every 12 h.

Table 1. Baseline characteristics of patients receiving NF50 and NF100 for cystitis in primary care in the Netherlands

Variable	Uncomplicated cystitis		Complicated cystitis		Cystitis during pregnancy	
	NF50 (N=10 476)	NF100 (N=36 379)	NF50 (N=1 892)	NF100 (N=8 875)	NF50 (N=186)	NF100 (N=901)
Age (years), median (IQR)	46 (28–64)	40 (26–60)	67 (49–78)	66 (46–78)	30 (27–34)	31 (28–34)
SES ^a , median (IQR)	0.50 (0.27–1.50)	0.96 (0.19–1.63)	0.39 (0.39–1.36)	0.78 (0.44–1.59)	0.68 (0.27–1.35)	0.78 (0.13–1.54)
Glomerular filtration rate (mL/min), mean (SD)	97.3 (17.9)	98.4 (18.1)	85.8 (23.2)	86.0 (24.0)	128 (12.2)	125 (13.1)
Men, n (%)	NA	NA	737 (39.0)	2940 (33.1)	NA	NA
Diabetes mellitus, n (%)	NA	NA	866 (45.8)	3789 (42.7)	13 (7.0)	26 (2.9)
Urological/renal comorbidity, n (%)	NA	NA	3 (0.2)	40 (0.5)	0	0
Immunosuppressive drugs, n (%)	NA	NA	89 (4.7)	230 (2.6)	0 (0)	1 (0.1)
Cognitive impairment, n (%)	12 (0.1)	44 (0.1)	4 (0.2)	10 (0.1)	0	0
Dementia, n (%)	70 (0.7)	300 (0.8)	56 (3.0)	206 (2.3)	0	0
Depression (ICPC) <6 months, n (%)	851 (8.1)	2878 (7.9)	234 (12.4)	1094 (12.3)	7 (3.8)	25 (2.8)
Oral contraceptive use <6 months, n (%)	1978 (18.9)	6107 (16.8)	139 (7.3)	577 (6.5)	NA	NA
Number of prescriptions for cystitis or pyelonephritis in the past 365 days before the episode, median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)
Sexually transmitted disease <6 months, n (%)	293 (2.8)	1223 (3.4)	75 (4.0)	420 (4.7)	4 (2.2)	25 (2.8)

NA, not applicable; NF50, 50 mg of nitrofurantoin every 6 h; NF100, 100 mg of nitrofurantoin every 12 h.

^aSocioeconomic status ranges from –7 to +7 and is estimated on the neighbourhood in which the patient lives (postal code).

Table 2. RD of clinical failure between NF50 and NF100 in cystitis patients in primary care

Entity	Time horizon	NF50, number of failures/total episodes (%)	NF100, number of failures/total episodes (%)	Crude RD (95% CI)	Multivariable ^a RD (95% CI)	Instrumental variable analysis RD (95% CI)	Adjusted instrumental variable analysis ^a RD (95% CI)
Uncomplicated cystitis	day 14	606/10476 (5.8)	2150/36379 (5.9)	0.1% (-0.4 to 0.6)	0.3% (-0.2 to 0.9)	-0.5% (-1.2 to 0.3)	0.0% (-0.7 to 0.8)
	day 28	1014/10476 (9.7)	3487/36379 (9.6)	-0.1% (-0.8 to 0.5)	0.2% (-0.5 to 0.8)	-0.7% (-1.7 to 0.3)	0.0% (-0.9 to 1.0)
Complicated cystitis	day 14	127/1892 (6.7)	579/8875 (6.5)	-0.2% (-1.4 to 1.1)	0.0% (-1.4 to 1.1)	-0.3% (-2.3 to 1.8)	0.3% (-1.8 to 2.4)
	day 28	207/1892 (10.9)	986/8875 (11.1)	0.3% (-1.3 to 1.8)	0.5% (-1.2 to 1.8)	-0.8% (-3.4 to 1.8)	-0.3% (-3.0 to 2.4)
Cystitis during pregnancy	day 14	15/186 (8.1)	48/901 (5.3)	-2.7% (-6.4 to 1.0)	-2.4% (-6.2 to 1.2)	-3.7% (-9.6 to 2.1)	-3.3% (-9.3 to 2.6)
	day 28	25/186 (13.4)	70/901 (7.8)	-5.6% (-10.1 to -1.2)	-5.4% (-10.0 to -1.4)	-8.9% (-16.0 to -1.8)	-8.9% (-16.0 to -1.7)

NA, not applicable; NF50, 50 mg of nitrofurantoin every 6 h; NF100, 100 mg of nitrofurantoin every 12 h.

A positive RD is in favour of NF50 and a negative RD is in favour of NF100.

^aFor uncomplicated cystitis, adjusted for age, renal insufficiency, previous antibiotic use for cystitis (nitrofurantoin, trimethoprim or fosfomycin/trometamol), dementia, other forms of cognitive impairment, depression, sexually transmitted disease, oral contraceptive use and socioeconomic status. For complicated cystitis, additionally for sex, diabetes mellitus, anatomical/functional defects in the urinary tract or the kidney, using immunosuppressive drugs and solid organ transplantation. For cystitis during pregnancy, adjusted for the same factors as for complicated cystitis, except for sex and oral contraceptive use.

Complicated cystitis

Of complicated cystitis episodes, in 7276 of 10767 episodes (68%) we found at least one risk factor for a complicated course. Patients that used NF100 instead of NF50 had a higher mean socioeconomic status. The use of NF50 and NF100 was associated with clinical failure rates of 127/1892 (6.7%) and 579/8875 (6.5%) within 14 days and of 207/1892 (10.9%) and 986/8875 (11.1%) within 28 days, respectively. No differences were found in clinical failure rate between NF50 and NF100 in crude, adjusted, instrumental variable and adjusted instrumental variable analysis (Table 2). The sensitivity analyses on unique patients [RD=-0.5% (95% CI=-1.2 to 0.7)] and on severe failure [RD=-0.2% (95% CI=-2.0 to 1.9)] revealed no differences between NF50 and NF100.

Cystitis during pregnancy

No large differences existed between women who received either NF50 or NF100 (Table 1). Using NF50 and NF100 led to clinical failure within 14 days in 15/186 (8.1%) and 48/901 (5.3%), respectively. Clinical failure within 28 days post-therapy was found in 25/186 (13.4%) and 70/901 (7.8%) in the NF50 and NF100 users, respectively, which was statistically significant in crude, adjusted, instrumental variable and adjusted instrumental variable analysis (Table 2). The sensitivity analyses on unique patients [RD=-5.0% (95% CI=-9.6 to -0.3)] and severe failure [RD=-4.2% (95% CI -7.9 to -1.1)] resulted in significant differences in favour of NF100. In a *post hoc* analysis we looked at whether the enhanced renal function that is observed in this population could explain this effect. For this, a multivariable linear regression model was performed in 1973 patients with an enhanced renal function (estimated glomerular filtration rate >120 mL/min) with any form of cystitis, i.e. uncomplicated cystitis, complicated cystitis or cystitis during pregnancy. There was a non-significant trend towards fewer late failures in patients using NF100 compared with NF50 [RD=-5.4% (95% CI=-14.1 to 3.2)].

Discussion

In the treatment of cystitis during pregnancy, the use of NF50 was associated with a significantly higher incidence of late clinical

failure than when using NF100, as estimated by crude, multivariable, instrumental variable and adjusted instrumental variable analysis, and in the multivariable sensitivity analyses on unique patients and severe clinical failure. The 95% CIs for the RD between NF50 and NF100 for uncomplicated cystitis were within the predefined 2%, demonstrating clinical equivalence. For complicated cystitis, the upper and lower margin of the 95% CIs exceeded this margin in some analyses, which means no statement can be made about clinical equivalence. Previous studies comparing different antibiotic classes for cystitis used a higher margin for equivalence of 5%-10%.^{10,11}

To the best of our knowledge, the clinical effectiveness of NF50 and NF100 for treating cystitis has not been compared before. Our findings suggest that NF50 is suboptimal for cystitis in pregnancy, whereas especially in pregnancy, effective antimicrobial treatment for cystitis is important to prevent pyelonephritis, which may affect pregnancy outcome.¹²

Nitrofurantoin should be administered with food, is absorbed in the upper part of the small intestine and is bound to plasma-albumin, after which it is excreted mainly in urine, where it has its highest activity.¹¹ The extended-release formulation (NF100) is 1.3 to 1.45 times better absorbed as a consequence of prolonged residence in the gastrointestinal (GI) tract and therefore yields higher total urinary excretion rates compared with the normal-release formulation (NF50).³ This higher bioavailability of NF100 could result in better efficacy. It is unclear why this was only observed in pregnancy. Potentially the physiological changes that occur in pregnancy, with the combination of an increased glomerular filtration rate and an increased total body volume, necessitate this higher GI uptake, which may not be clinically relevant in non-pregnant patients.¹³ According to our *post hoc* analysis results, enhanced renal function might explain the difference observed in pregnancy. Although less likely, an alternative explanation could be that the difference in compliance with the 'every 6 h' instead of the 'every 12 h' regimen is more pronounced in pregnant women compared with the other patient groups.

Even in the non-pregnant patient, a four-times-daily regimen is considered not very patient-friendly. One of the reasons why not all pharmacies or patients choose the 100 mg extended-release

regimen is the limited availability of extended-release formulations and the extra costs of this regimen. In the Netherlands, the NF100 formulation costs 0.76€ per day and the NF50 formulation costs 0.51–0.61€ per day, and the difference of around 2.50€ per regimen has to be paid directly by the patient. Patients are free to choose their own pharmacy and some pharmacies have both the NF50 and the NF100 formulation available. This could possibly explain why, on an individual level, patients with a lower socioeconomic status more often used the NF50 formulation. However, on GP practice level, the ratio between NF50 and NF100 was not associated with socioeconomic status and therefore we may assume it did not confound the instrumental variable analysis.

Some potential limitations of this study need to be mentioned. First, retrospective data collection may suffer from inaccurate data. However, the JGPN database that was used provides reliable demographic data, drug prescriptions (ATC codes), symptoms (ICPC codes) and laboratory values.⁷ The cystitis diagnosis in our database is based on a GP's decision to prescribe a 5 or 7 day nitrofurantoin regimen as no other indications exist for these regimens. Yet, we were unable to confirm that both the actual existence of cystitis and episodes that resemble cystitis, for which nitrofurantoin was prescribed, could have been included. However, there is no reason to expect imbalances of cystitis-like episodes between the NF50 and NF100 groups. In addition, it is known that Dutch GPs frequently use a dipstick test to confirm the presence of cystitis and prescribe antibiotics once they are convinced of the diagnosis, as compared with other European countries, meaning that the entity of cystitis in the Netherlands is considered concordant to its definition.¹⁴ In the Netherlands, urine screening during pregnancy is not routine thus we expect that the majority of cystitis episodes in pregnancy are symptomatic. Second, there may exist misclassification between episodes of uncomplicated cystitis, complicated cystitis and cystitis during pregnancy. We excluded a substantial number of episodes for which a 5 day nitrofurantoin regimen was started while, based on registered comorbidity and the Dutch guideline, they should have received a 7 day course for complicated cystitis. Episodes could have been misclassified as complicated cystitis if a GP wrongly prescribed an extended 7 day regimen for uncomplicated cystitis, although we expect this to occur rarely. We decided to not exclude episodes that were treated for 7 days in which no risk factors were found for a complicated course. First, because not all risk factors are available in the JGPN database. Next, GPs are not used to prescribing a 7 day nitrofurantoin prescription, as this deviates from their normal prescription behaviour. This implies that, if they do, they must have considered a risk factor for a complicated course. Of included complicated cystitis episodes, we found that 68% had at least one risk factor for a complicated course. The existence of cystitis in pregnancy was based on two arguments: a consultation for pregnancy within the prior 9 months; and the use of an extended 7 day nitrofurantoin regimen. We excluded patients with a pregnancy-related consultation within the prior 9 months who were treated with nitrofurantoin for 5 days, as these were either treated wrongly or they were not pregnant at the moment of cystitis. Consequently, we would not have been able to interpret these results. According to the literature, in more than 50% of pregnancies the GP is not consulted; however, this fraction is probably lower if the patient has to consult the GP for cystitis anyway.¹⁵ Cystitis episodes during pregnancy, in which no pregnancy-related consultation was registered, are

probably misclassified as uncomplicated or complicated cystitis, depending on the duration of therapy. As the number of these episodes is probably small in comparison with the population of uncomplicated or complicated cystitis, the effect of these misclassified episodes is probably negligible. Colloquially, women with a recent pregnancy may have been included as cystitis during pregnancy if treated for 7 days. The majority of these will have been treated for 5 instead of 7 days and will have been excluded from the analysis based on this treatment duration. However, those with complicated cystitis and recent pregnancy may have biased the estimate for the cystitis-during-pregnancy group towards zero, given the absence of an effect in the complicated cystitis group.

Third, the endpoint clinical failure is based on a new prescription for cystitis or pyelonephritis by the GP. Therefore, clinical failures were missed if prescriptions were made out of office hours due to the severity of the disease, either by the GP urgent care centre or in the hospital. Yet, the occurrence of pyelonephritis after using nitrofurantoin for uncomplicated cystitis was 0.4% in a recent study.¹¹ Additionally, only 6% of total antibiotic prescriptions occur out of office hours in primary care in the Netherlands.¹⁶ We consequently expect to have missed only a few outcomes. In a recent trial investigating uncomplicated cystitis, the late clinical failure rate for 100 mg of nitrofurantoin thrice daily was around 30%,¹¹ which is much higher than the around 10% in the current study. This may have resulted from the strict definition for clinical response in that trial, taking into account residual symptoms and not only antibiotic use. The clinical failure rate in our study corresponds to other trials investigating nitrofurantoin for this indication.¹⁷

Fourth, we have no information about the reason for clinical failure. Theoretically, a patient could require a new antibiotic prescription as a consequence of relapse or recurrence of infection or due to adverse events. The latter is less likely as nitrofurantoin is tolerated well as a short course.¹¹ Theoretically, it is not expected that the tolerability structurally differs between the NF50 and NF100 regimens, as they contain an identical cumulative dose. Perhaps, differences in tolerability could arise from the better absorption of NF100 than NF50.

Fifth, the validity of the instrumental variable analysis is based on the assumption that the GP practice ratio to prescribe NF50 or NF100 is not correlated to the average prognosis of cystitis patients of that GP practice. These assumptions are based on the underlying theory and were strengthened by the fact that differences in baseline characteristics between those receiving NF50 and NF100 that were found on an individual level were not seen at the GP practice level and results of the adjusted instrumental variable analysis did not differ from the unadjusted instrumental variable analysis. However, it is not possible to demonstrate that this also holds for non-observed confounders. The multivariable regression analysis, on the other hand, has the assumption that there are no unobserved confounders. Therefore, the combined analyses should be considered as complementary as both have assumptions that cannot be tested.

Sixth, we evaluated the clinical failure rate for three cystitis entities. To not increase the type II error rate, we decided to not correct for multiple testing. However, this increases the risk of type I errors. Therefore, as with any research finding, independent confirmation of our results is mandated.

Based on the results of this study, it would be interesting to study the pharmacokinetic profile of both regimens in pregnant women with cystitis. A randomized controlled trial would provide an unbiased estimate of the efficacy of both regimens for all cystitis entities. Until that time, we would recommend prescribing NF100 instead of NF50 for pregnant women with cystitis and we argue for reimbursement of the full price for this patient group. Unfortunately the extended-release formulation is not available in all countries and some national guidelines (e.g. France and Belgium) recommend the normal-release formulation of 100 mg of nitrofurantoin thrice daily while the European and American guidelines recommend the NF100 extended-release formulation twice daily for cystitis.^{2,11} Investigating the pharmacokinetic profile and the efficacy between twice-daily, extended-release NF100 and the thrice-daily original formulation of 100 mg of nitrofurantoin would be interesting especially in pregnancy.

In conclusion, we found no differences between NF50 and NF100 in the treatment of patients with uncomplicated and complicated cystitis for early and late treatment failure. NF100 was superior in patients with cystitis during pregnancy, yielding a lower rate of late treatment failures.

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Transparency declarations

None to declare.

Supplementary data

Supplementary data, including Figure S1, are available at JAC Online.

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