Kidney function and the use of nitrofurantoin to treat urinary tract infections in older women

Namisha Singh BSc, Sonja Gandhi BSc, Eric McArthur MSc, Louise Moist MD MSc, Arsh K. Jain MD MSc, Aiden R. Liu BSc, Manish M. Sood MD, Amit X. Garg MD PhD

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Abstract

Background: The antibiotic nitrofurantoin is commonly used to treat uncomplicated urinary tract infections. However, when this drug is used by patients with reduced kidney function, its urine concentration may be subtherapeutic.

Methods: We conducted a population-based study of older women (mean age 79 years) in Ontario, Canada, whose estimated glomerular filtration rate was relatively low (median 38 mL/min per 1.73 m^2) and for whom 1 of 4 antibiotics had been prescribed for urinary tract infection: nitrofurantoin, ciprofloxacin, norfloxacin or trimethoprim–sulfamethoxazole. We assessed 2 measures of treatment failure in the subsequent 14 days: receipt of a second antibiotic indicated for urinary tract infection and hospital encounter (emergency department visit or hospital admission) with a urinary tract infection. We repeated the analysis for older women with relatively high estimated glomerular filtration rate (median 69 mL/min per 1.73 m^2).

Results: The baseline characteristics of the 4 antibiotic groups were similar. Relative to nitrofurantoin, the other antibiotics (including ciprofloxacin) were associated with a lower rate of treatment failure among women with relatively low estimated glomerular filtration rate (for ciprofloxacin v. nitrofurantoin: second antibiotic prescription, 130/1989 [6.5%] v. 516/3739 [13.8%], odds ratio [OR] 0.44, 95% confidence interval [CI] 0.36–0.53; hospital encounter, 21/1989 [1.1%] v. 95/3739 [2.5%], OR 0.41, 95% CI 0.25–0.66). However, a similar risk of treatment failure with nitrofurantoin was also observed among women with relatively high estimated glomerular filtration rate. The results were consistent in multiple additional analyses.

Interpretation: In this study, the presence of mild or moderate reductions in estimated glomerular filtration rate did not justify avoidance of nitrofurantoin.

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Correspondence to: Amit Garg, amit.garg@lhsc.on.ca

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Nitrofurantoin is a first-line antibiotic commonly used to treat uncomplicated urinary tract infection, and an estimated 25 million prescriptions are filled worldwide each year.[1,2] Therapeutic concentrations of nitrofurantoin are achieved only in the urine, and the drug is eliminated primarily by glomerular filtration, with some secretion through the renal tubules.[3] Reduction in the estimated glomerular filtration rate is common among older adults, and over 25% of those 65 years of age or older have an estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2.[4] The renal elimination of nitrofurantoin is reduced in patients with low estimated glomerular filtration rate, which can increase the risk of treatment failure for urinary tract infection and possibly also the risk of adverse events caused by elevated blood concentrations of the drug.[5,6] Therefore, nitrofurantoin is not recommended for patients with estimated glomerular filtration rate below 60 mL/min per 1.73 m.[7] However, this recommendation remains controversial, as the supporting evidence originates from studies with small sample sizes (< 20 patients with reduced creatinine clearance) and outcomes of drug concentration in the urine, rather than treatment success.[5,6]

A recent review suggested that the drug be avoided only for those with estimated glomerular filtration rate below 40 mL/min per 1.73 m^2.[8] Two recent retrospective studies suggested that the effectiveness of nitrofurantoin is no different between those with and those without reduced kidney function;[9,10] however, both studies included a limited number of patients with estimated glomerular filtration rate below 40 mL/min per 1.73 m^2. In routine care, nitrofurantoin is frequently prescribed for patients with low estimated glomerular filtration rate, but the safety and effectiveness of this practice remain uncertain.[11]

We studied older women (age 65 years or older) with relatively low and relatively high estimated glomerular filtration rates to assess and compare the risk of treatment failure for urinary tract infection between patients treated with nitrofurantoin and those treated with other antibiotics indicated for this type of infection.

Methods

Study design and setting

We conducted a population-based, retrospective cohort study for the period June 2002 to March 2013 using linked health care databases in the province of Ontario, Canada. Ontario has more than 13 million residents, 15% of whom are 65 years of age or older.[12] All residents have universal access to hospital care and physician services, and those 65 years of age or older have universal prescription drug coverage. We conducted this study at the Institute for Clinical Evaluative Sciences according to a prespecified protocol that had been approved by the institute's research ethics board. We used datasets that were held securely in linkable files without any direct patient identifiers. The reporting of this study follows guidelines for observational studies (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150067/-/DC1).

Data sources

We ascertained patient characteristics, drug use, covariate information and outcome data from records in 6 databases. We obtained vital statistics from the Ontario Registered Persons Database, which contains demographic information for all Ontario residents who have ever been issued a health card. We used the Ontario Drug Benefit Program database to identify prescription drug use. This database contains highly accurate records of all outpatient prescriptions dispensed to patients aged 65 or older, with an error rate of less than 1%.[13] We identified diagnostic and procedural information on all hospital admissions from the Discharge Abstract Database and information on emergency department visits from the National Ambulatory Care Reporting System, both maintained by the Canadian Institute for Health Information. We obtained covariate information from the Ontario Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. Finally, we used the Institute for Clinical Evaluative Sciences Physician Database for information about antibiotic prescribers. Previously, we have used these databases for research concerning adverse drug events and health outcomes, including estimates of effect in patients with reduced estimated glomerular filtration rate.[14–18]

To assess baseline comorbidities in the 5 years before receipt of the index prescription, we used codes from the International Classification of Diseases (9th revision [pre-2002] and 10th revision [ICD-10; post-2002]). All outcomes occurred after 2002, so only ICD-10 codes were used to identify outcome information. For a small proportion of the cohort, outpatient serum creatinine values were provided by a large commercial laboratory in the year before cohort entry, and we determined kidney function in this subpopulation using these data to estimate glomerular filtration rate. Codes used to ascertain comorbidities and outcomes are detailed in Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150067/-/DC1).

Patients

We studied a cohort of older women with relatively low estimated glomerular filtration rate (based on a validated algorithm of diagnosis codes for chronic kidney disease;[19] see Appendix 2) who received a prescription for 1 of 4 oral antibiotics: nitrofurantoin, ciprofloxacin, norfloxacin or trimethoprim–sulfamethoxazole. All of these antibiotics are frequently considered first-line therapy for urinary tract infections.[20] We restricted the cohort to patients over 65 years of age, as we had accurate information on the outpatient drugs dispensed to patients in this age group. We excluded older men because of the possibility that urinary tract infection in men may be complicated by prostatic obstruction. The date of the prescription of the study antibiotic served as the index date (cohort entry date). We studied a second cohort of women with relatively high estimated glomerular filtration rate (determined by the absence of codes for chronic kidney disease). In Ontario, the validated algorithm for patients with relatively low estimated glomerular filtration rate (i.e., chronic kidney disease) identifies older adults with a median estimated glomerular filtration rate of 38 (interquartile range [IQR] 27–52) mL/min per 1.73 m^2, whereas absence of codes for chronic kidney disease identifies those with a median rate of 69 (IQR 56–82) mL/min per 1.73 m^2.[19] In an additional analysis, we studied a subpopulation of women whose baseline serum creatinine values were available for direct calculation of estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula. At a recent consensus conference, this formula was described as the most accurate method for estimating glomerular filtration rate and was deemed appropriate for use in drug dosing (with recognition that all equa-

tions provide similar estimates when the glomerular filtration rate is low).[21]

We excluded the following patients from all cohorts: those in their first year of eligibility for prescription drug coverage (age 65), to avoid incomplete medication records; those with prescriptions for any antibiotic in the 120 days before the index date, to avoid including continuing treatments for the same urinary tract infection; those with more than one antibiotic prescription on the index date; those who had been discharged from a hospital or had an emergency department visit in the 2 days before the index date, to ensure that antibiotic use was newly initiated in a nonhospital setting (in Ontario, patients continuing antibiotic treatment initiated in hospital would have their oral outpatient prescription dispensed on the same day or the day after hospital discharge); those with a history of end-stage renal disease, because of their minimal urine output; those without evidence of urine being cultured in the 2 days before or on the day after the antibiotic prescription, to ensure that included patients were being treated for a urinary tract infection (submission of a urine sample for culture was accurately recorded in our data sources, but culture results were not available); those in a long-term care facility, because antibiotic use and resistance may be higher in these patients;[22,23] and those with characteristics suggesting complications associated with the urinary tract infection, specifically visit to a urologist, history of kidney stones and antibiotics not prescribed by a general practitioner. For patients with multiple eligible prescriptions, the first eligible prescription was included in the study.

Outcomes

We assessed 2 measures of treatment failure in the 14 days following prescription of an antibiotic: receipt of a second antibiotic indicated for urinary tract infection (from the list of antibiotics presented in Appendix 2) and hospital presentation (either an emergency department visit or hospital admission) with a urinary tract infection. In a validation study conducted in Denmark, ICD-10 hospital diagnosis codes for urinary tract infection had sensitivity of 61%, specificity of 95% and positive predictive value of 54%.[24] We used a similar set of codes to identify urinary tract infection, accounting for small differences between the Canadian and Danish ICD-10 coding structures (see Appendix 2). Treatment success was not directly recorded in our datasets, so we selected the 2 specified measures because patients with failure of treatment for urinary tract infection would likely receive a new antibiotic prescription or would present to a health care facility with ongoing symptoms (or both). All comparisons were made between nitrofurantoin (reference group) and the other study antibiotics (ciprofloxacin, norfloxacin and trimethoprim–sulfamethoxazole).

Statistical analyses

We compared baseline characteristics between those with a prescription for nitrofurantoin and those with a prescription for ciprofloxacin, norfloxacin or trimethoprim–sulfamethoxazole, using the standardized difference.[25,26] This metric describes the difference between group means relative to the pooled standard deviation; differences greater than 10% are considered meaningful.[25] We used multivariable logistic regression analyses to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We adjusted for 11 prespecified potential confounders: age, year of cohort entry, rural residence, duration of initial antibiotic prescription ($\leq$ 7 d v. > 7 d), number of antibiotic prescriptions in the previous 5 years, number of urine samples cultured in the previous 5 years, number of unique medications and presence of dementia, stroke, diabetes mellitus and urinary incontinence. To account for clusters of patients within prescribing physicians, we reran the analysis treating the prescribing physician as a random effect. We performed a similar analysis in the subpopulation of women with calculated values of estimated glomerular filtration rate to evaluate antibiotic effectiveness across different levels of kidney function. ORs can be approximated as relative risks, given the incidences observed. We conducted all analyses with SAS version 9.3 (SAS Institute Inc.). In all outcome analyses, we considered 2-tailed p values below 0.05 as marking statistical significance.

Results

Baseline characteristics

We identified 9223 women with relatively low estimated glomerular filtration rate and 182 634 women with relatively high estimated glomerular filtration rate for whom 1 of the 4 study antibiotics was prescribed (cohort selection is described in Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150067/-/DC1). Overall, baseline characteristics were similar across the 4 antibiotic groups in each of the 2 cohorts (Table 1 and Table 2; most standardized differences < 10%). In both cohorts, nitrofurantoin was the most commonly prescribed antibiotic (40.5% and 38.7% of prescriptions, respectively). The median dose of nitrofurantoin was 200 (IQR

Table 1: Baseline characteristics of patients with relatively low estimated glomerular filtration rate

Characteristic	Drug; no. (%) of patients*				Standardized difference relative to nitrofurantoin, %†		
	Nitrofurantoin *n* = 3739	Ciprofloxacin *n* =1989	Norfloxacin *n* = 2032	TMP–SMX *n* = 1463	Cipro-floxacin	Norflox-acin	TMP–SMX
Age, yr, mean ± SD	78 ± 7	79 ± 7	79 ± 7	78 ± 7	3	8	1
Year of cohort entry							
2002–2005	609 (16.3)	310 (15.6)	610 (30.0)	386 (26.4)	2	33	25
2006–2009	1414 (37.8)	771 (38.8)	828 (40.7)	539 (36.8)	2	6	2
2010–2013	1716 (45.9)	908 (45.6)	594 (29.2)	538 (36.8)	0	35	19
Rural residence‡	367 (9.8)	183 (9.2)	232 (11.4)	221 (15.1)	2	5	16
Prescription supply of 3–7 d	2999 (80.2)	1483 (74.6)	1610 (79.2)	1130 (77.2)	14	2	7
Health care use, mean ± SD§							
Primary care visits¶	12.59 ± 10.69	13.82 ± 11.86	13.58 ± 11.98	12.67 ± 10.80	11	9	1
Emergency department visits	4.66 ± 4.66	4.65 ± 4.82	4.63 ± 4.39	4.90 ± 4.59	0	1	5
Hospital discharges	2.55 ± 2.14	2.55 ± 2.10	2.84 ± 2.46	2.79 ± 2.29	0	13	11
Urine cultures	8.10 ± 6.71	9.18 ± 8.24	9.07 ± 8.91	8.04 ± 7.40	14	12	1
Prior antibiotic prescriptions							
0	295 (7.9)	137 (6.9)	129 (6.4)	133 (9.1)	4	6	4
1 or 2	803 (21.5)	372 (18.7)	397 (19.5)	310 (21.2)	7	5	1
3 or 4	722 (19.3)	362 (18.2)	405 (19.9)	273 (18.7)	3	2	2
≥ 5	1919 (51.3)	1118 (56.2)	1101 (54.2)	747 (51.1)	10	6	1
Comorbidities**							
Coronary artery disease††	1842 (49.3)	1029 (51.7)	1073 (52.8)	742 (50.7)	5	7	3
Dementia	549 (14.7)	306 (15.4)	279 (13.7)	202 (13.8)	2	3	3
Diabetes mellitus‡‡	1086 (29.0)	617 (31.0)	571 (28.1)	416 (28.4)	4	2	1
Heart failure	986 (26.4)	606 (30.5)	621 (30.6)	412 (28.2)	9	9	4
Peripheral vascular disease	106 (2.8)	57 (2.9)	85 (4.2)	63 (4.3)	0	7	8
Stroke	171 (4.6)	108 (5.4)	87 (4.3)	87 (6.0)	4	1	6
Urinary incontinence§§	153 (4.1)	96 (4.8)	98 (4.8)	55 (3.8)	4	4	2
Baseline medications¶¶							
No. of unique medications, mean ± SD	8.31 ± 4.18	8.72 ± 4.25	8.13 ± 4.09	8.02 ± 4.25	10	7	4
ACE inhibitor	1497 (40.0)	768 (38.6)	829 (40.8)	595 (40.7)	3	2	1
ARB	1015 (27.1)	561 (28.2)	522 (25.7)	332 (22.7)	2	3	10
β-Blockers	1632 (43.6)	912 (45.8)	887 (43.6)	627 (42.9)	4	0	2
Calcium-channel blocker	1781 (47.6)	952 (47.9)	946 (46.6)	676 (46.2)	0	2	3
Loop diuretic	969 (25.9)	600 (30.2)	563 (27.7)	382 (26.1)	9	4	0
Potassium-sparing diuretic	334 (8.9)	181 (9.1)	202 (9.9)	148 (10.1)	1	3	4
Thiazide diuretic	896 (24.0)	441 (22.2)	488 (24.0)	360 (24.6)	4	0	2
Prescriber characteristics							
Sex, female	1431 (38.3)	597 (30.0)	546 (26.9)	478 (32.7)	4	6	4
Time since graduation, yr, mean ± SD	23.75 ± 10.85	26.01 ± 11.23	27.65 ± 10.26	22.85 ± 10.88	20	37	8

Note: ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blocker, SD = standard deviation, TMP–SMX = trimethoprim–sulfamethoxazole.
*Unless otherwise indicated.
†Standardized differences are less sensitive to sample size than traditional measures for testing hypotheses. They provide a measure of the difference between groups divided by the pooled SD, where a value greater than 10% is considered to represent a meaningful difference.[25]
‡Municipalities with population < 10 000 were considered to be rural.
§Health care use (except for primary care visits) was assessed as the mean number of visits by a patient in the preceding 5 years.
¶Primary care visits were assessed as the mean number of visits by a patient in the preceding year.
**Comorbidities were assessed for the preceding 5 years.
††Coronary artery disease includes undergoing coronary artery bypass graft surgery or percutaneous coronary intervention and diagnosis of angina.
‡‡Diabetes mellitus was assessed through use of oral hypoglycemic medications and insulin prescriptions in the preceding 120 days.
§§Urinary incontinence was assessed through prescriptions for overactive bladder medication in the preceding 120 days.
¶¶Baseline medications were assessed for the preceding 120 days.

Table 2: Baseline characteristics of patients with relatively high estimated glomerular filtration rate

Characteristic	Drug; no. (%) of patients*				Standardized difference relative to nitrofurantoin, %†		
	Nitrofurantoin *n* = 70 758	Ciprofloxacin *n* = 29 095	Norfloxacin *n* = 45 116	TMP–SMX *n* = 37 665	Cipro-floxacin	Norflox-acin	TMP–SMX
Age, yr, mean ± SD	75 ± 7	75 ± 7	76 ± 7	75 ± 7	3	8	1
Year of cohort entry							
2002–2005	18 091 (25.6)	7 037 (24.2)	20 452 (45.3)	15 383 (40.8)	3	42	33
2006–2009	25 745 (36.4)	11 588 (39.8)	16 078 (35.6)	12 958 (34.4)	7	2	4
2010–2013	26 922 (38.0)	10 470 (36.0)	8 586 (19.0)	9 324 (24.8)	4	43	29
Rural residence‡	7 522 (10.6)	3 171 (10.9)	5 025 (11.1)	6 589 (17.5)	1	2	20
Prescription supply of 3–7 d	57 679 (81.5)	21 331 (73.3)	35 385 (78.4)	29 476 (78.2)	20	8	8
Health care use, mean ± SD§							
Primary care visits¶	8.99 ± 7.9	9.37 ± 8.1	9.26 ± 8.0	8.50 ± 7.4	5	4	7
Emergency department visits	3.19 ± 3.7	3.25 ± 3.5	3.04 ± 3.2	3.12 ± 3.4	3	8	3
Hospital discharges	1.77 ± 1.3	1.85 ± 1.5	1.81 ± 1.4	1.81 ± 1.4	8	4	4
Urine cultures	5.08 ± 6.3	5.72 ± 7.1	5.55 ± 6.6	4.41 ± 5.6	16	12	19
Prior antibiotic prescriptions							
0	12 159 (17.2)	4 208 (14.5)	6 639 (14.7)	7 034 (18.7)	7	7	4
1 or 2	20 718 (29.3)	7 818 (26.9)	12 634 (28.0)	11 716 (31.1)	5	3	4
3 or 4	14 083 (19.9)	5 696 (19.6)	8 943 (19.8)	7 488 (19.9)	1	0	0
≥ 5	23 798 (33.6)	11 373 (39.1)	16 900 (37.4)	11 427 (30.3)	11	8	7
Comorbidities**							
Coronary artery disease††	19 573 (27.7)	9 053 (31.1)	13 941 (30.9)	10 328 (27.4)	8	7	1
Dementia	5 421 (7.7)	2 290 (7.9)	3 325 (7.4)	2 618 (7.0)	1	1	3
Diabetes mellitus‡‡	9 413 (13.3)	4 171 (14.3)	5 429 (12.0)	4 603 (12.2)	3	4	3
Heart failure	5 695 (8.0)	2 654 (9.1)	4 009 (8.9)	2 998 (8.0)	4	3	0
Peripheral vascular disease	495 (0.7)	220 (0.8)	360 (0.8)	276 (0.7)	1	1	0
Stroke	1 337 (1.9)	588 (2.0)	918 (2.0)	672 (1.8)	1	1	1
Urinary incontinence§§	2 205 (3.1)	892 (3.1)	1 381 (3.1)	1091 (2.9)	0	0	1
Baseline medications ¶¶							
No. of unique medications, mean ± SD	5.02 ± 3.60	5.36 ± 3.75	4.97 ± 3.53	4.69 ± 3.44	9	1	9
ACE inhibitor	19 334 (27.3)	7 926 (27.2)	12 606 (27.9)	10 429 (27.7)	0	1	1
ARB	10 638 (15.0)	4 899 (16.8)	6 192 (13.7)	4 715 (12.5)	5	4	7
β-Blocker	16 878 (23.8)	7 258 (24.9)	11 170 (24.8)	8 778 (23.3)	3	2	1
Calcium-channel blocker	17 724 (25.0)	7 600 (26.1)	11 242 (24.9)	8 764 (23.3)	2	0	4
Loop diuretic	4 392 (6.2)	2 210 (7.6)	3 105 (6.9)	2 264 (6.0)	5	3	1
Potassium-sparing diuretic	3 619 (5.1)	1 625 (5.6)	2 860 (6.3)	2 241 (6.0)	2	5	4
Thiazide diuretic	13 726 (19.4)	5 256 (18.1)	8 855 (19.6)	7 871 (20.9)	3	1	4
Prescriber characteristics							
Sex, female	26 409 (37.3)	8 036 (27.6)	12 297 (27.3)	10 813 (28.7)	21	12	18
Time since graduation, yr, mean ± SD	23.69 ± 10.8	26.60 ± 10.8	27.54 ± 10.1	23.90 ± 11.1	12	15	1

Note: ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker, SD = standard deviation, TMP–SMX = trimethoprim–sulfamethoxazole.
*Unless otherwise indicated.
†Standardized differences are less sensitive to sample size than traditional measures for testing hypotheses. They provide a measure of the difference between groups divided by the pooled SD, where a value greater than 10% is considered to represent a meaningful difference.[25]
‡Municipalities with population < 10 000 were considered to be rural.
§Health care use (except for primary care visits) was assessed as the mean number of visits by a patient in the preceding 5 years.
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††Coronary artery disease includes undergoing coronary artery bypass graft surgery or percutaneous coronary intervention and diagnosis of angina.
‡‡Diabetes mellitus was assessed through use of oral hypoglycemic medications and insulin prescriptions in the preceding 120 days.
§§Urinary incontinence was assessed through prescriptions for overactive bladder medication in the preceding 120 days.
¶¶Baseline medications were assessed for the preceding 120 days.

200–200) mg/day, and the median duration of antibiotic therapy was 7 (IQR 7–7) days.

Outcomes

Among patients with relatively low estimated glomerular filtration rate, receipt of ciprofloxacin or norfloxacin was associated with lower likelihood of receiving a second antibiotic during the follow-up period relative to nitrofurantoin (Table 3; ciprofloxacin v. nitrofurantoin: 6.5% v. 13.8%, OR 0.44, 95% CI 0.36–0.53; norfloxacin v. nitrofurantoin: 6.5% v. 13.8%, OR 0.44, 95% CI 0.36–0.53); the distribution of second antibiotic prescriptions is presented in Appendix 4 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150067/-/DC1). Similarly, receipt of ciprofloxacin or norfloxacin was associated with lower likelihood of a hospital encounter with a urinary tract infection during the follow-up period relative to nitrofurantoin (ciprofloxacin v. nitrofurantoin: 1.1% v. 2.5%, OR 0.41, 95% CI 0.25–0.66; norfloxacin v. nitrofurantoin: 1.2% v. 2.5%, OR 0.46, 95% CI 0.29–0.72). Receipt of trimethoprim–sulfamethoxazole was associated with a lower incidence of both outcomes relative to nitrofurantoin (12.6% v. 13.8% and 2.1% v. 2.5%, respectively), but neither comparison was statistically significant.

The patterns were similar for patients with relatively high estimated glomerular filtration rate (Table 3). Receipt of a prescription for ciprofloxacin or norfloxacin was associated with lower likelihood of treatment failure than was the case with nitrofurantoin. Receipt of trimethoprim–sulfamethoxazole was associated with lower likelihood of receiving a second antibiotic indicated for urinary tract infection relative to nitrofuran-

Table 3: Treatment failure in patients with relatively low and relatively high eGFR

Indicator of failure* and drug	No. with event/ total no. of patients (%)		OR (95% CI)	
			Unadjusted	Adjusted†
Relatively low eGFR‡				
Second prescription				
Nitrofurantoin	516/3 739	(13.8)	1.00	1.00
Ciprofloxacin	130/1 989	(6.5)	0.44 (0.36–0.53)	0.43 (0.35–0.53)
Norfloxacin	133/2 032	(6.5)	0.44 (0.36–0.53)	0.44 (0.36–0.54)
TMP–SMX	184/1 463	(12.6)	0.90 (0.75–1.08)	0.92 (0.77–1.10)
Hospital encounter with UTI				
Nitrofurantoin	95/3 739	(2.5)	1.00	1.00
Ciprofloxacin	21/1 989	(1.1)	0.41 (0.25–0.66)	0.40 (0.25–0.64)
Norfloxacin	24/2 032	(1.2)	0.46 (0.29–0.72)	0.45 (0.28–0.71)
TMP–SMX	31/1 463	(2.1)	0.83 (0.55–1.25)	0.81 (0.53–1.22)
Relatively high eGFR§				
Second prescription				
Nitrofurantoin	7 759/70 758	(11.0)	1.00	1.00
Ciprofloxacin	1 713/29 095	(5.9)	0.51 (0.48–0.54)	0.50 (0.47–0.53)
Norfloxacin	2 734/45 116	(6.1)	0.52 (0.50–0.55)	0.54 (0.52–0.57)
TMP–SMX	3 683/37 665	(9.8)	0.88 (0.84–0.92)	0.93 (0.89–0.97)
Hospital encounter with UTI				
Nitrofurantoin	863/70 758	(1.2)	1.00	1.00
Ciprofloxacin	241/29 095	(0.8)	0.68 (0.59–0.78)	0.65 (0.56–0.75)
Norfloxacin	272/45 116	(0.6)	0.49 (0.43–0.56)	0.51 (0.44–0.58)
TMP–SMX	412/37 665	(1.1)	0.90 (0.80–1.01)	0.93 (0.83–1.05)

Note: CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio, TMP–SMX = trimethoprim–sulfamethoxazole, UTI = urinary tract infection.
*The follow-up time was the 14 days following antibiotic dispensing.
†Analyses were adjusted for age, year of cohort entry, rural residence, duration of initial antibiotic prescription (≤ 7 d v. > 7), prior number of antibiotic prescriptions, prior number of urine cultures, number of unique medications, dementia, stroke, diabetes mellitus and urinary incontinence.
‡Cohort with relatively low eGFR: the algorithm of database codes identified patients with a median eGFR of 38 (IQR 27–52) mL/min per 1.73 m^2.[19]
§Cohort with relatively high eGFR (absence of chronic kidney disease): the algorithm of database codes identified patients with a median eGFR of 69 (IQR 56–82) mL/min per 1.73 m^2.[19]

toin but was not significantly associated with a hospital encounter involving urinary tract infection. The larger sample size for patients with relatively high estimated glomerular filtration rate resulted in narrower 95% CIs than for those with relatively low estimated glomerular filtration rate. Also, as expected, patients with relatively high estimated glomerular filtration rate had a lower incidence of treatment failure.

Additional analyses

The primary associations proved robust in multiple additional analyses. First, we adjusted for 11 relevant confounders and found no meaningful difference from the unadjusted results for all outcomes (Table 3). Second, when we treated the prescribing physician as a random effect, we found no appreciable change in the estimates of risk relative to the primary analyses. Third, we identified a subpopulation of 48 195 women for whom baseline serum creatinine values were available (obtained a median of 120 [IQR 46–219] d before prescription of an antibiotic) for whom 1 of the 4 study antibiotics was prescribed for a urinary tract infection. These patients were divided into 3 categories according to glomerular filtration rate, as used for nitrofurantoin prescribing recommendations in the literature: below 40 mL/min per 1.73 m^2 (3268 patients), 40–60 mL/min per 1.73 m^2 (10 981 patients) and above 60 mL/min^1 per 1.73 m^2 (33 946 patients).[7,8] Baseline characteristics were similar across the 4 antibiotic groups in each of these categories (see Appendix 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150067/-/DC1). Similar to the results of the primary analysis, in all 3 groups, receipt of ciprofloxacin or norfloxacin was associated with lower likelihood of receiving a second antibiotic in the follow-up period relative to nitrofurantoin (see Appendix 6, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150067/-/DC1). There was no significant interaction between the 3 categories of estimated glomerular filtration rate and outcomes (p for interaction = 0.4 [second antibiotic] and 0.4 [hospital presentation]). We also examined the risk of hospital admission with adverse events; however, because of the limited sensitivity of the relevant codes and low event rates, meaningful comparisons were not possible.

Interpretation

Nitrofurantoin is currently considered unsuitable for patients with reduced estimated glomerular filtration rate.[7] In this study, nitrofurantoin was the antibiotic most commonly prescribed for urinary tract infection in older women, irrespective of estimated glomerular filtration rate. The rate of treatment failure was higher among patients who received nitrofurantoin than among those who received other antibiotics, such as ciprofloxacin. This difference was evident regardless of patients' estimated level of kidney function.

Our results are consistent with those of 2 other recent studies, which showed that the effectiveness of nitrofurantoin was unaffected by reduced estimated glomerular filtration rate in routine care.[9,10] Also, in patients in the current study who had relatively low estimated glomerular filtration rate, nitrofurantoin was not associated with a significantly higher risk of treatment failure than was trimethoprim–sulfamethoxazole, consistent with the findings of Geerts and associates.[10] Furthermore, we found that ciprofloxacin and norfloxacin were associated with a lower rate of treatment failure than nitrofurantoin in patients with both lower and higher estimated glomerular filtration rate. These results may be explained by drug pharmacokinetics and bacterial resistance patterns. Nitrofurantoin undergoes more enzyme degradation and has a significantly shorter half-life than the fluoroquinolones,[3] which may affect antibiotic effectiveness. Furthermore, whereas *Escherichia coli* generally exhibits low resistance to nitrofurantoin (1.4% of isolates in Ontario during our study period),[27] the same cannot be said for other bacteria causing urinary tract infection.[28] In Ontario, the resistance of *E. coli* to trimethoprim–sulfamethoxazole during our study period was 16.8%, whereas resistance to fluoroquinolones was 7.1%,[27] which may explain some of the associations observed when we compared nitrofurantoin with trimethoprim–sulfamethoxazole.

Given these findings, a review of multiple sources of information is needed to define optimal prescribing for urinary tract infection in general practice. The use of nitrofurantoin for patients with relatively low estimated glomerular filtration rate may relieve the pressure to prescribe fluoroquinolones, a valuable antibiotic class the widespread empiric use of which may promote bacterial resistance.

Our study had several strengths. This was a large population-based study that addressed certain limitations of previous research, including inadequate control for confounders and small sample sizes; for example, in our study, the sample of patients with reduced estimated glomerular filtration rate who received nitrofurantoin was nearly 20 times the size of a corresponding sample in a prior study.[10] The use of Ontario's health care databases and definition of a patient population with universal prescription drug coverage yielded a representative sample of older women

for whom the antibiotics of interest had been prescribed. This allowed us to estimate risks with good precision and excellent external validity. Furthermore, we focused on events that occurred soon after (within 14 days of) antibiotic initiation, which allowed us to be more confident about attributing observed effects to the type of antibiotic used. Finally, we compared the effectiveness of nitrofurantoin with that of other antibiotics recommended as first-line treatment for urinary tract infection, which adds to the clinical relevance of the study.

Limitations

Our study had some limitations. First, we identified urinary tract infection on the basis of urine cultures ordered and restricted the analysis to antibiotics recommended for this type of infection. Although we feel this approach is reasonable, we would have preferred to use data on patients' symptoms and bacterial culture results, along with antibiotic sensitivities. Consequently, we may have missed patients with a urinary tract infection for whom urine culture was not ordered. To ensure generalizability, we confirmed that the patients included in our study were similar to those for whom the same antibiotics were prescribed without evidence of urine culture (see Appendix 7, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.150067/-/DC1). Furthermore, we recognize that resistance to nitrofurantoin could have resulted in subsequent prescription of an alternative antibiotic. However, we expect the number of patients in this situation to be low, given low resistance to nitrofurantoin during the study period. Second, as with any observational study, we may have failed to account for unmeasured confounders. Nonetheless, the 4 antibiotic groups were very similar at baseline, and adjustment for known confounders did not meaningfully alter the observed associations. Third, concordant patterns in adverse drug events would have strengthened our results, but these events were poorly coded, and there were too few events to perform meaningful analyses. Fourth, we had a limited number of patients with very low estimated glomerular filtration rates (i.e., < 20 mL/min per 1.73 m^2); as such, additional studies are warranted in this patient population, including those receiving dialysis. Fifth, given the data available, we were able to study only older patients with a urinary tract infection. Patients in this cohort also had an important history of urine culture, which may not be representative of the general population. Therefore, younger women and women with less frequent urinary tract infections may be more likely to have a successful outcome, regardless of the antibiotic prescribed. Finally, our data sources recorded the antibiotics dispensed, but we had no knowledge of patients' adherence with their medications. Any major differences in adherence between the antibiotic groups might have affected our outcomes.

Conclusion

Among older women with urinary tract infection, treatment failure was more common with nitrofurantoin than with other antibiotics, regardless of estimated level of kidney function. In this study, the presence of mild to moderate reductions in estimated glomerular filtration rate did not justify avoidance of nitrofurantoin.

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Affiliations: Division of Nephrology, Department of Medicine (Singh, Gandhi, McArthur, Moist, Jain, Liu, Garg), and the Department of Epidemiology and Biostatistics (Gandhi, Moist, Liu, Garg), Western University, London, Ont.; Institute for Clinical Evaluative Sciences (McArthur, Moist, Jain, Garg), Toronto, Ont.; The Ottawa Hospital Research Institute (Sood), University of Ottawa, Ottawa, Ont.

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