Use of administrative healthcare claims to examine the effectiveness of trimethoprim–sulfamethoxazole versus fluoroquinolones in the treatment of community-acquired acute pyelonephritis in women

A. G. Carrie1-3*, C. J. Metge2,3, D. M. Collins2, G. K. M. Harding4,5 and G. G. Zhanel4

1Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta; 2Faculty of Pharmacy, University of Manitoba, Winnipeg, Manitoba; 3Manitoba Centre for Health Policy, Winnipeg, Manitoba; 4Department of Medical Microbiology, Faculty of Medicine University of Manitoba, Winnipeg, Manitoba; 5Departments of Clinical Microbiology and Medicine, St. Boniface General Hospital, Winnipeg, Manitoba, Canada

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Objective: To evaluate the effectiveness of trimethoprim–sulfamethoxazole and fluoroquinolones in the treatment of community-acquired acute pyelonephritis.

Patients and methods: We identified a population-based cohort of non-pregnant women aged 18–65 years, initially treated with trimethoprim–sulfamethoxazole or a fluoroquinolone for community-acquired pyelonephritis in an ambulatory care setting. Subjects were identified from a healthcare claims database in Manitoba, Canada for the period 15 February 1996 to 31 March 1999. Subsequent treatment failure, as evidenced by the provision of additional treatment up to 42 days post-diagnosis, was compared between the two treatments.

Results: A total of 1084 women met inclusion criteria: 653 (60.2%) treated with trimethoprim–sulfamethoxazole and 431 (39.8%) treated with a fluoroquinolone. Treatment outcomes were affected by subject age. At age 20, treatment with a fluoroquinolone resulted in a reduced probability of treatment failure compared with trimethoprim–sulfamethoxazole (odds ratio, 0.56; 95% CI, 0.33–0.97). At age 60, there was no difference in the probability of treatment failure (odds ratio, 1.61; 95% CI, 0.82–3.16). No other subject characteristics impacted comparative effectiveness; however, several characteristics increased the odds of treatment failure irrespective of the initial antibiotic. These included: recent urinary tract infection (odds ratio, 2.07; 95% CI, 1.14–3.57), recent antibiotic use (odds ratio, 1.40; 95% CI, 1.00–1.96;), and a treatment duration of less than 10 days (odds ratio, 2.18; 95% CI, 1.59–2.99).

Conclusion: Younger subjects (~20 years) treated with fluoroquinolones were less likely to experience treatment failure than those treated with trimethoprim–sulfamethoxazole. Treatment durations of less than 10 days resulted in a higher probability of treatment failure regardless of the initial antibiotic.

Keywords: outcome assessment (healthcare), health services research, insurance claim review

Introduction

Pharmaceuticals are the most rapidly increasing component of healthcare costs in Canada,1 thus the effectiveness of their use is of concern, as are methods to monitor effectiveness at the population level. Drugs whose equivalent efficacy have been demonstrated in randomized controlled trials (RCT) may exhibit differences in effectiveness when used in clinical practice. In addition, comparative effectiveness of antibiotics is expected to change over time, as a result of the evolving nature of antibiotic-resistant pathogens. Thus, refinement of population-based methods to evaluate effectiveness becomes essential.

Recent increases in resistance to trimethoprim–sulfamethoxazole among uropathogens has resulted in concern regarding its suitability for empiric treatment of urinary tract infections (UTI).2 In Canada, in 1998, approximately 19% of uropathogens exhibited resistance to trimethoprim–sulfamethoxazole, in contrast to approximately 2% to fluoroquinolones.3 Although the effectiveness of trimethoprim–
sulfamethoxazole for treatment of UTI may be compromised as a result of antibiotic resistance, much may depend on the site of infection. The potential consequences of inadequate treatment of UTI owing to antibiotic-resistant pathogens is greater in pyelonephritis, as it is an invasive infection compared with cystitis.

Equal efficacy of trimethoprim–sulfamethoxazole and fluoroquinolones in the treatment of pyelonephritis has been demonstrated in RCT. However, these studies included only a small number of subjects and excluded subjects with resistant organisms, or with characteristics known to be associated with an increased probability of harbouring resistant organisms. More recently, Talan et al. reported that ciprofloxacin provided superior treatment outcome compared with trimethoprim–sulfamethoxazole, especially in those patients infected with trimethoprim–sulfamethoxazole-resistant organisms. Superiority of fluoroquinolones over trimethoprim–sulfamethoxazole in the setting of trimethoprim–sulfamethoxazole resistance, has likewise been reported in the treatment of cystitis.

Several patient-specific characteristics have been identified as risk factors for infections with antibiotic-resistant pathogens, including recent antibiotic use, recent hospitalization, recent UTI, diabetes and increasing age. Since resistance among uropathogens to fluoroquinolones is relatively rare, compared with resistance to trimethoprim–sulfamethoxazole, we hypothesized these characteristics would negatively impact treatment outcome in subjects treated with trimethoprim–sulfamethoxazole to a greater degree than those subjects treated with a fluoroquinolone. Current recommendations for the treatment of acute uncomplicated pyelonephritis in women include trimethoprim–sulfamethoxazole or a fluoroquinolone for up to 14 days. The objectives of this study were to: (1) compare the effectiveness of trimethoprim–sulfamethoxazole and fluoroquinolones in the treatment of community-acquired pyelonephritis, and (2) identify subject-specific variables that impact the comparative effectiveness of these two agents in community-acquired pyelonephritis.

Materials and methods

Data source

To establish the effectiveness of drug treatments, as opposed to efficacy, it is necessary to observe outcomes of treatment under conditions of everyday practice. In keeping with this perspective, this study used an observational cohort design. Use of administrative healthcare claims from the province of Manitoba, Canada offered several advantages as a data source for this purpose. Manitoba is a province in central Canada, with a population of approximately 1.1 million. As Manitoba residents enjoy universal healthcare coverage, records of healthcare utilization are available for all services for all Manitobans (with a few exceptions), thus enhancing the external validity of results. Anonymized datasets used for this study included, medical claims (MC), hospital separation abstracts (HSA), and pharmaceutical claims from the Drug Programs Information Network (DPIN), accessed through the Manitoba Centre for Health Policy. MC contain records of reimbursement for services rendered by physicians, in addition to diagnostic services (e.g. laboratory, radiology) provided by private laboratories upon a physician’s order. HSA contain data on hospital stays for all Manitoba residents admitted to Manitoba and out-of-province hospitals. The DPIN contains records of prescription pharmaceutical usage by non-hospitalized residents of Manitoba. The existence of unique patient identifiers allowed for computer linkage across datasets. The reliability and validity of Manitoba’s healthcare claims for epidemiological study has been previously reported.

Identification of cohort

Non-institutionalized females, aged 18–65 years, who evidenced continuous coverage with Manitoba Health for the duration of the study period and experienced a new episode of pyelonephritis initially treated on an outpatient basis with a single antibiotic (either trimethoprim–sulfamethoxazole or a fluoroquinolone) were eligible for entry to the study cohort. Exclusion criteria included pregnancy and initial antibiotic treatment in excess of 15 days. The study period for identification of new episodes of pyelonephritis was 15 February 1996 to 31 March 1999.

Identification of new episodes of pyelonephritis was accomplished by an examination of diagnoses submitted on MC and HSA. The International Classification of Disease 9th Clinical Modification (ICD-9-CM) system is used to code for diagnoses. Three ICD-9-CM codes are relevant to infection of the urinary tract; specifically 590 (infection of the kidney), 595 (cystitis) and 599 (other disorders of the urethra and urinary tract, including urinary tract infection of unspecified site). Physician reimbursement, for outpatient visits, does not depend upon diagnostic codes submitted on MC, and thus is not expected to influence the validity of the diagnostic codes. In addition, an earlier study of pyelonephritis, conducted by one of the authors, reported that 80% of subjects identified as having pyelonephritis from the Manitoba Health database, had symptoms consistent with a diagnosis of pyelonephritis documented in the medical record.

The following case definition of acute pyelonephritis was established based on standard recommendations for a 4 to 6 week follow-up of UTI. An MC for a physician visit containing an ICD-9-CM code of 590, for a subject whose claim history contained no evidence of other healthcare claims (either MC or HSA) consistent with UTI (ICD-9-CM codes 590, 595 or 599) in the previous 42 days was defined as a new episode of pyelonephritis. The MC that identified a new episode of pyelonephritis is hereafter referred to as the initial physician visit, and the date of the initial physician visit, the index date.

Identification of initial treatment was achieved by an examination of HSA and DPIN claims. An HSA containing one of the ICD-9-CM codes 590, 595 or 599 (as the most responsible diagnosis) was assumed to reflect initial treatment if the admission date matched, or was up to 2 days subsequent to the index date. Similarly, a DPIN claim for a single systemic antibiotic was assumed to reflect initial treatment if the dispensing date matched, or was up to 2 days subsequent to the index date.

Subjects with claims for only one of the possible treatment options (hospitalization or outpatient antibiotic) were assigned that status. Further investigation was required for those subjects having claims for both antibiotic treatment and hospitalization within 2 days of the initial physician visit. A claim for hospitalization that pre-dated a claim for outpatient antibiotic treatment resulted in assignment to hospitalized status and vice versa. For subjects with more than one antibiotic claim within 2 days of the index date, the antibiotic with the earliest dispensing date was considered the single initial treatment. To ensure independence of the comparator groups (trimethoprim–sulfamethoxazole or fluoroquinolone) for statistical analysis, only the most recent episode of pyelonephritis for each subject was included.

Identification of covariate status

Identification of covariate status with regard to diabetes, recent UTI, recent antibiotic use and recent hospitalization was carried out using the following operational definitions. A subject with two or more MC for separate physician visits within 2 years, or at least one HSA containing the ICD-9-CM code 250 during the study period, was identified as diabetic. A subject with a DPIN claim for a systemic antibiotic within 90 days previous to the index date was identified as a recent antibiotic user. A subject with an HSA containing a discharge date within 90 days previous to the index date was identified as recently hospitalized. A sub-
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ject with at least one MC or HSA containing a service or discharge date within 90 days before the index date containing any of the ICD-9-CM codes 590, 595 or 599 was considered to have experienced a recent UTI.

Identification of treatment outcome (treatment failure)

Treatment failure was determined based on the presence or absence of further healthcare claims consistent with additional treatment of the initially identified infection. Thus, treatment failure (or lack of effectiveness) may result from the provision of further antibiotic treatment or hospitalization due to: persistence of infection, adverse effects or resistance documented by culture. Specifically, antibiotic-treated subjects with subsequent hospital claims within 42 days of the index date, which indicated UTI (ICD-9-CM codes 590, 595, 599) as the primary reason for hospitalization, were considered to have failed initial treatment. In the absence of hospital claims as described above, DPIN claims that indicated the receipt of further antibiotic treatment within 42 days of the index date were considered indicative of treatment failure, if therapy was deemed to be related to the initial infection. Thus, any event necessitating a change and/or addition to the initial treatment was considered evidence of treatment failure, in the manner of an intent-to-treat analysis.

Criteria to determine the likely indication for use of any additional antibiotic included: its temporal association with additional physician, laboratory, and/or hospital claims, the class of antibiotic, and the dosing schedule. Antibiotic claims within 2 days of a subsequent MC or HSA containing ICD-9-CM codes 590, 595 or 599 were considered evidence of treatment failure. Antibiotic claims which were not associated with a MC or HSA as described above, were considered evidence of treatment failure only if the antibiotic was one of trimethoprim–sulfamethoxazole, a fluoroquinolone or nitrofurantoin. Finally, recognizing the possibility of the provision of prophylactic/suppressive treatment, only those antibiotic claims providing at least two solid dosage units per day were considered evidence of treatment failure (exclusive of antibiotics for which once daily dosing is recommended).

Statistical methods

Differences between trimethoprim–sulfamethoxazole- and fluoroquinolone-treated subjects were assessed using $\chi^2$ or Wilcoxon rank sum tests as appropriate. Logistic regression was used to model the effects of initial antibiotic treatment and covariate status (age, diabetes, recent antibiotic use, recent hospitalization and recent UTI) on the probability of treatment failure. Age was entered into the model as a continuous variable; all other covariates were dichotomous. Two-way interactions between initial antibiotic therapy and each of the covariates were explored. Interaction terms which did not attain statistical significance at the 0.05 level were removed from the model. In addition to the above covariates, treatment duration was included in the model since there is evidence to suggest that the effect of treatment duration on outcome may differ between antibiotics. Exploratory data analysis identified a non-linear pattern between treatment duration (a continuous variable) and treatment failure, requiring the transformation of treatment duration to a dichotomous variable. Treatment durations of a single-dose to 9 days were defined as ‘short duration’, whereas treatment durations of 10 days or greater were defined as ‘long duration’. All $P$ values are two-tailed. Statistical analysis was carried out using Statistical Analysis System software (SAS Institute, Version 8.1).

Results

Description of final cohort

We identified 1084 women meeting inclusion criteria, of whom 653 (60.2%) received trimethoprim–sulfamethoxazole and 431 (39.8%) received a fluoroquinolone. Of the 431 subjects receiving a fluoroquinolone, 280 (65.0%) received ciprofloxacin and 151 (35.0%) received norfloxacin. Median duration of treatment was 10.0 days, however, subjects receiving treatment with fluoroquinolones had a significantly shorter duration of treatment than those treated with trimethoprim–sulfamethoxazole ($P < 0.001$) (Figure 1). Descriptive data on the final cohort is provided in Table 1.

![Figure 1. Duration of initial treatment of pyelonephritis by initial antibiotic.](image)

Table 1. Subject characteristics by initial treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>SXT ($n = 653$)</th>
<th>Fluoroquinolone ($n = 431$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>33.0 (18–65)</td>
<td>37.0 (18–65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>52 (8.0)</td>
<td>36 (8.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Recent antibiotic use</td>
<td>202 (30.9)</td>
<td>160 (37.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Recent UTI</td>
<td>40 (6.1)</td>
<td>25 (5.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>Recent hospitalization</td>
<td>53 (8.1)</td>
<td>50 (11.6)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

SXT = trimethoprim–sulfamethoxazole.

*Values are presented as number (percentage) unless otherwise indicated.

Treatment outcome

Overall, 207 (19.1%) of 1084 subjects were identified as having experienced treatment failure; 190 based on receipt of at least one additional antibiotic within 42 days of the index date, six as a result of admission to hospital for treatment of a UTI, and 11 by both admission to hospital and receipt of an additional related antibiotic therapy. Treatment failure was experienced by 124 (19.0%) of 653 subjects treated with trimethoprim–sulfamethoxazole and 83 (19.3%) of 431 subjects treated with a fluoroquinolone. Median time to treatment failure was 8.0 days, with 47% experiencing treatment failure within 1 week subsequent to index date. Median time to treatment failure was significantly shorter for subjects treated with trimethoprim–sulfamethoxazole (7 days), versus a fluoroquinolone (11.0 days) ($P = 0.02$). No difference was observed in the proportion of subjects experiencing treatment failure between the two fluoroquinolones: ciprofloxacin (18.9%) versus norfloxacin (19.9%) ($P = 0.81$).
sulfamethoxazole, although this effect did not achieve statistical significance; OR = 0.95 (95% CI, 0.68–1.33). By age 60, subjects receiving fluoroquinolones had an odds of experiencing treatment failure of 0.56 (95% CI, 0.33–0.97) times that of subjects receiving trimethoprim–sulfamethoxazole. However, by age 40, no difference in the probability of treatment failure between the two antibiotics was observed; OR = 0.95 (95% CI, 0.68–1.33). By age 60, subjects treated with fluoroquinolones appeared to have a higher probability of treatment failure than subjects treated with trimethoprim–sulfamethoxazole, although this effect did not achieve statistical significance; OR = 1.61 (95% CI, 0.82–3.16).

No other subject-specific variables evidenced differential effects on the relationship between initial antibiotic treatment and probability of treatment failure; however, several were identified as independent risk factors for treatment failure. Evidence of a recent UTI and recent antibiotic use significantly increased the odds of a patient experiencing treatment failure by a factor of 2.07 and 1.40 times, respectively. In addition, the odds of treatment failure among subjects with short duration of treatment (a single dose to 9 days), were 2.18 times that of subjects receiving long durations of treatment (10 days or more). The presence of diabetes or recent hospitalization did not significantly affect the probability of treatment failure.

**Discussion**

This study provides a measure of the effectiveness of current antibiotic use in the treatment of pyelonephritis. The proportion of subjects experiencing treatment failure, as defined by the study, was similar between the two treatments: approximately 19%. However, Talan et al. reported clinical failure of 9% and 23% for ciprofloxacin and trimethoprim–sulfamethoxazole, respectively. The few available RCT comparing trimethoprim–sulfamethoxazole and a fluoroquinolone in pyelonephritis provide little data regarding the effect of subject variables on treatment outcome. Rather, subjects with diabetes, recent antibiotic use or other complicating factors were commonly excluded from study. Thus, the results of this study provide new insight into subject variables which may affect treatment outcomes.

Risk factors for antibiotic resistance were expected to act as effect modifiers in the relationship between initial treatment and treatment outcome. However, significant effect modification was observed only with subject age. Younger subjects achieved superior outcomes with fluoroquinolones, whereas no difference in treatment outcome was observed between the two treatments in older subjects (Table 2). This finding was contrary to the expectation of greater failure in older women treated with trimethoprim–sulfamethoxazole because of their increased propensity to harbour resistant organisms. This unexpected result may be explained by consideration of prescribing decisions. In younger subjects (20 years) with pyelonephritis, patient demographics and risk factors for treatment failure may be homogenous, and thus choice between trimethoprim–sulfamethoxazole and fluoroquinolone should reflect prescribing patterns.
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and a fluoroquinolone may simply be based on physician preference. In this circumstance, the fluoroquinolone proved to be superior to trimethoprim–sulfamethoxazole in terms of success as defined by this study. Higher usage of fluoroquinolones in older subjects may have been because of a number of factors, for example, clinical severity, presence of risk factors for antibiotic resistance, previous antibiotic experiences, and/or the potential for adverse drug reactions in this patient population. This phenomenon is referred to as channelling bias and may have been responsible for the apparent lack of differential effectiveness in older subjects. While it was not possible to determine whether older fluoroquinolone-treated subjects were more clinically ill than those treated with trimethoprim–sulfamethoxazole (due to the lack of clinical data), the presence of risk factors for resistance did not exert a greater effect on antibiotic choice in older subjects. Although no other subject-specific variables evidenced significant differential effects on the relationship between initial antibiotic treatment and treatment outcome, several variables were independent risk factors for treatment failure. Subjects with recent antibiotic use and recent UTI were more likely to have experienced treatment failure; however, this was evidenced regardless of initial antibiotic. Other subject variables which were hypothesized to affect treatment outcome (diabetes and recent hospitalization) were not substantiated.

The effect of treatment duration on treatment outcome was an important finding. There are few data in the literature regarding the optimal duration of treatment for pyelonephritis. Recommendations for treatment durations of 14 days appear to be based on an early study which reported that 14 days provided as efficacious a treatment as 6 weeks.21 Subsequent to that report, few studies have addressed treatment durations for this indication. Talan et al.5 reported that 7 days of ciprofloxacin was superior to 14 days of trimethoprim–sulfamethoxazole for the therapy of acute uncomplicated pyelonephritis in women. However, this study indicates that a 10 to 15 day treatment with a fluoroquinolone provides superior outcome compared with a 7 day treatment with a fluoroquinolone.

Limitations

Although the use of administrative data has many advantages, the lack of clinical data, and the validity of diagnostic information are important limitations.22–24 The implications of the lack of clinical data, in connection with channeling bias, have been previously discussed. Owing to the many factors that may influence the validity of diagnostic codes in healthcare databases, and the construction of cohorts resulting from their use, validation of these data is important. Validation of diagnostic codes within the Manitoba Health database has been accomplished for a number of disease states, including pyelonephritis.18,25–27 Nicolle et al.18 reported 80% agreement between HSA and hospital charts for the diagnosis of pyelonephritis. However, validation of physician claims in office-based practice in Canada is complicated by increasingly stringent legislation regarding access to health information. The earlier study allowed for the assumption of similar diagnostic validity in this study; however, 80% consistency with the actual clinical diagnosis is much less rigorous than that of an RCT, and thus the inclusion of subjects who may not have had pyelonephritis. Thus, in this study, inclusion/exclusion criteria based on related claims, as suggested by several authors,16,28 were used to increase confidence in the validity of the diagnostic codes (e.g. the requirement of a DPIN claim for a systemic antibiotic within 2 days of the MC). The duration of treatment prescribed, provided further assurance of diagnostic validity. Pyelonephritis is an invasive infection compared with cystitis, and this is reflected in different recommended durations of treatment for the two infections. The current recommendation for the treatment of acute uncomplicated pyelonephritis in women is 14 days, although there is some support for treatment durations as short as 7 days.12–14 The recommended duration of treatment for cystitis in young healthy women is 3 days.12–14 As the median treatment duration identified in this study was 10 days, with 92% of subjects receiving 7–15 days of treatment, confidence in the diagnosis of pyelonephritis was further strengthened. In addition, performance of sensitivity analysis excluding subjects with less than 7 days of treatment did not change study conclusions.

Other potential limitations relate to the method used to establish treatment outcomes. Establishing a link between the need for additional hospital treatment and treatment failure was uncomplicated given that HSA provide an indication of the relative importance of a listed diagnosis to the hospital stay. However, only 17 (8.2%) of 207 treatment failures were the result of hospital admission. Establishing a link between subsequent antibiotic and treatment failure was more complicated given the lack of indication for use on the DPIN database. Although knowledge of the indication for use was strengthened by examining associated MC and HSA, a number of subsequent antibiotic claims lacked associated MC or HSA. However, it was recognized that this scenario was highly probable, as additional antibiotic treatment may have been prescribed following telephone consultation or subsequent to a physician visit not captured in the MC (e.g. care provided in a few Emergency Rooms) based on symptomatic complaints, without a follow-up culture. The decision to accept only trimethoprim–sulfamethoxazole, fluoroquinolones or nitrofurantoin as evidence of treatment failure in the situation of no associated MC or HSA may have led to underestimation of treatment failure. However, as these three antibiotics accounted for approximately 87% of initial treatment of pyelonephritis among non-pregnant women, any underestimation was expected to be small.

The decision not to include antibiotic prescriptions with less than two solid dosage units per day as evidence of treatment failure (considered antimicrobial prophylaxis or suppression) may also have resulted in an underestimation of treatment failure, since a single daily dose of trimethoprim–sulfamethoxazole or a fluoroquinolone may be appropriate treatment in situations of reduced renal function. However, this was considered unlikely since the number of additional antibiotic prescriptions with less than two dosing units per day were few, and, of these, the majority were for long durations of treatment consistent with antimicrobial prophylaxis (30–180 days).

Despite the potential limitations inherent in the use of healthcare claims to examine treatment outcomes, this study includes methodological strengths. Like all Canadians, Manitoba residents enjoy universal healthcare coverage. Therefore, records of healthcare utilization for the vast majority of the population are available for study, which facilitates highly generalizable data. Furthermore, loss to follow-up is minimized, since only subjects’ claims need be followed up rather than the subjects themselves, and finally, large numbers of subjects may be studied at minimal cost.

In conclusion, this study provided a measure of the effectiveness of trimethoprim–sulfamethoxazole and fluoroquinolones for the treatment of acute pyelonephritis in women in everyday clinical practice. Initial treatment with either agent resulted in favourable treatment outcome in greater than 80% of patients. However, fluoroquinolone treatment resulted in a significantly lower probability of treatment failure in young women. In addition, treatment durations of less than 10 days resulted in a higher probability of treatment failure regardless of the initial antibiotic.
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