OUTPATIENT TREATMENT OF COMMUNITY- ACQUIRED PNEUMONIA: EVOLVING TRENDS AND A FOCUS ON FLUOROQUINOLONES

Anita G Carrie[1,2], Anita L Kozyrskyj[3,4]

[1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, [2]Institute of Health Economics, Edmonton, Alberta, [3]Faculties of Medicine and Pharmacy, University of Manitoba, Winnipeg, Manitoba, [4]Manitoba Centre for Health Policy, Winnipeg, Manitoba

Corresponding Author: acarrie@pharmacy.ualberta.ca

ABSTRACT

Background
Increasing use of broad-spectrum antibiotics in the community, including fluoroquinolones, has been reported, despite concerns for developing antibiotic resistant organisms. Community-acquired pneumonia (CAP) is commonly treated on an outpatient basis, and recent treatment guidelines suggest only a limited role for fluoroquinolones.

Objectives
To identify evolving trends in the outpatient treatment of CAP in adults, and to identify factors associated with receipt of a fluoroquinolone.

Methods
Retrospective observational design using population-based administrative data. Initial outpatient treatment for subjects diagnosed with CAP between May 1996 and March 2002 was examined. Logistic regression was used to examine the influence of patient characteristics on the receipt of a fluoroquinolone.

Results
A total of 31,940 outpatients with CAP were identified. The proportion of patients receiving fluoroquinolones increased from 6.6% in 1996/97 to 25.2% in 2001/02. Over the course of the study, 158 (25.9%) of the 610 patients meeting the eligibility criteria for treatment with fluoroquinolones, according to treatment guidelines, received these agents. Of the 31,330 subjects who did not meet the eligibility criterion, 3,886 (12.4%) received a fluoroquinolone. Other variables that influenced the receipt of a fluoroquinolone included: age (for every 10-year increase) [OR=1.16 (1.14-1.19)], urban residence [OR=1.40 (1.30-1.51)], presentation to an emergency department [OR=0.80 (0.70-0.90)], high-level drug use (six or more different drugs in the previous year) [OR=1.50 (1.41-1.59)], and income-level (highest to lowest) [OR=1.20 (1.08-1.35)].

Conclusion
The use of fluoroquinolones for the treatment of CAP is increasing. However less than 4% of the subjects receiving fluoroquinolones met eligibility requirements according to treatment guidelines. Initiatives to increase the uptake of treatment guidelines appear warranted.

Key Words: *community-acquired pneumonia, outpatients, drug utilization, antibiotics, fluoroquinolones*

Respiratory tract infections account for the majority of antibiotic use in community practice.[1] In recent years, consumption of older narrow-spectrum antibiotics has been supplanted by an increased consumption of newer, more costly, broad-spectrum antibiotics.[1-4]

A number of patient characteristics have been reported to influence the receipt of broad-

spectrum antibiotics, including age, residence, and income.[5-7]

Fluoroquinolones, a broad-spectrum and relatively new class of antibiotics, have been reported to decrease the need for hospitalization.[8] However, there remains concern that inappropriate use of fluoroquinolones may promote further selection of antibiotic resistant pathogens, limiting the future usefulness of these agents.

Community-acquired pneumonia (CAP) is one respiratory tract infection for which broad-spectrum antibiotics such as fluoroquinolones may be appropriate dependent upon the presence of co-morbid illness and other patient-related factors.[9] Fluoroquinolones were not recommended for outpatient treatment of CAP in Canada prior to 2000. Use of other broad-spectrum agents (e.g., 2nd generation cephalosporins, b-lactam/b-lactamase inhibitor) was suggested for subjects with relevant co-morbidities.[10] Relevant co-morbidities included: chronic obstructive pulmonary disease (COPD), diabetes mellitus, renal disease, congestive heart failure, or hospitalization within the previous year. The most recent Canadian guidelines suggest only a limited role for fluoroquinolones for outpatient treatment of CAP. Specifically, fluoroquinolones are recommended only for outpatients with a history of COPD and recent consumption of antibiotics or oral steroids.[9] The extent to which these recommendations are adhered to is unknown.

The objectives of the current study were to identify evolving trends in the outpatient treatment of CAP, and to identify factors associated with receipt of a fluoroquinolone for this indication.

METHODS

This study used a retrospective observational design to examine trends in antibiotic consumption for initial treatment of CAP among adults in the outpatient setting from 1996 to 2002 in Manitoba, Canada. Manitoba Health's Health Information Privacy Committee and the Health Research Ethics Boards of the Universities of Manitoba and Alberta approved the study protocol.

Manitoba has a universal healthcare system, and healthcare claims, including those for pharmaceuticals, are available for the approximately 1.1 million residents with few exceptions. All Manitoba residents are eligible for the income-based Pharmacare program.

During the study period the income-based deductible was 2% for families with a household income less than $15,000, and 3% for those with higher income. Once the deductible has been reached, prescriptions for eligible pharmaceuticals, within that benefit year, are 100% paid by the Pharmacare program. A number of broad-spectrum antibiotics, including fluoroquinolones, have Exception Drug Status (EDS); meaning specific criteria for prescribing must be met before they may be considered eligible pharmaceuticals. If these criteria are not met, the total prescription cost is borne by the consumer. EDS criteria for fluoroquinolones and other antibiotics recommended in the treatment of pneumonia are listed in Appendix A.[11]

Demographic, diagnostic, and treatment data were obtained from anonymized healthcare claims accessed through the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy. A scrambled unique personal health information number (PHIN) allowed computer linkage across the four relevant databases: medical claims, hospital separations abstracts, pharmaceutical claims, and the registry file. Finally, Manitoba Health data were linked to aggregate income-level data from Statistics Canada.

All Manitoba residents greater than 14 years of age who were eligible for the provincial drug plan and diagnosed with CAP between May 1, 1996 and March 1, 2002, were eligible for inclusion. Subjects diagnosed with CAP were identified from medical claims using the International Classification of Disease 9th Clinical Modification (ICD-9-CM) codes for pneumonia [480-486]. Specifically, a medical claim for a physician visit containing one of the above ICD codes, for a subject having no medical or hospital claims containing these codes within the previous 30 days were identified. This visit, representing a new episode of CAP, is hereafter referred to as the index visit. Exclusion criteria included: nursing home residence, hospitalization for any reason within 14 days prior to the index visit, one or more pharmacy claims for antiretroviral therapy within the previous year, and identification of an

earlier CAP episode during the study period (i.e., only the earliest episode for each subject was retained for study).

Initial treatment of CAP was determined via an examination of hospital and pharmaceutical claims for up to seven days subsequent to the index date. Subjects having a pharmacy claim for a systemic antibiotic and no hospital claims containing the ICD codes 480-486 as the primary diagnosis, or subjects whose antibiotic claim preceded such a hospital claim were labeled as initially treated with outpatient antibiotics and comprised the study cohort. Patient characteristics expected to influence initial treatment were identified from the healthcare databases and from aggregate income-level data from Statistics Canada. These included temporal, demographic (age, gender, residence, site of care, income), and disease variables (level of co-morbidity and drug use, criterion eligibility for fluoroquinolone use).

An explanation of patient characteristics follows. Subject residence was defined as urban or rural. Subjects residing in the two major urban centers of Manitoba (Winnipeg and Brandon) were classified as urban, while the remaining subjects were classified as rural. Subjects whose index visit occurred in an emergency department were differentiated from those whose index visit occurred in a non-emergency department setting. Subjects were assigned to an income quintile, based on census data regarding the average household income of the enumeration area of residence. Income quintile 1 indicates subjects with the lowest income, and quintile 5, the highest. Co-morbidity level assignment was dependent upon the number of major ambulatory diagnostic groups (ADGs) assigned from diagnostic codes reported on medical and hospital claims in the year prior to the index date. This method of quantifying the burden of illness, based on the system developed at John Hopkins University, categorizes subjects as having a low (0-1 major ADGs), medium (2-3 major ADGs), or high (4+ major ADGs) level of co-morbidity.[12] Level of drug use was based upon the number of different prescription drugs received in the previous year (based on the 4th level of the Anatomic Therapeutic Classification System). Subjects who received less than six different drugs were classified as low level, while those with six or more were classified as high level.

Finally, subjects were classified as to whether or not they met the eligibility criterion for receipt of a fluoroquinolone. Based on ICD codes, as operationalized by Deyo et al.,[13] subjects having medical or hospital claims indicative of chronic obstructive lung disease, renal insufficiency, diabetes mellitus, or congestive heart failure within two years prior to the index date, or hospitalized within one year previous to the index date, and had a pharmacy claim for a systemic antibiotic and/or an oral corticosteroid within 100 days prior to the index date were deemed eligible for treatment with a fluoroquinolone.

Changes in the proportion of outpatients treated with specific antibiotics over the study period were examined. Differences between those subjects treated with fluoroquinolones and alternate antibiotics were assessed using chi-square or Wilcoxon rank sum tests as appropriate. Logistic regression was used to model the effects of patient variables and study year on the probability of receipt of a fluoroquinolone. All variables were included in the model regardless of their significance in univariate testing. The model was tested using the Hosmer-Lemeshow goodness-of-fit test, and the full model is reported. All statistical analysis was performed using Statistical Analysis System software (SAS Institute, Version 8.2).

RESULTS

We identified 60,016 non-institutionalized individuals with one or more new episodes of CAP during the study period. Of these, 28,075 were excluded for the following reasons: age less than 15 years (N=18,438), ineligible for provincial drug plans (N=4,225), missing data regarding residence and income (N=383), and admitted to hospital for initial treatment (N=5,029). The remaining 31,940 received outpatient antibiotic treatment of CAP, and 31,528 (98.7%) were treated with a single antibiotic.

TABLE 1 Antibiotic treatment of community-acquired pneumonia by year among subjects receiving a single antibiotic

	96/97	97/98	98/99	99/00	00/01	01/02	% change
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	96/97 – 01/02
Erythromycin	1880 (36.8)	1581 (31.7)	1744 (30.0)	1405 (22.7)	981 (19.0)	591 (13.9)	-22.9
Clarithromycin/Azithromycin	899 (17.6)	1133 (22.7)	1741 (29.9)	2273 (36.8)	2204 (42.7)	1872 (43.9)	+26.3
Penicillins	803 (15.8)	744 (14.9)	749 (12.9)	607 (9.8)	393 (7.6)	283 (6.6)	-9.2
2/3rdgeneration Cephalosporins[a]	474 (9.3)	509 (10.2)	512 (8.8)	536 (8.7)	387 (7.5)	205 (4.8)	-4.5
1stgeneration Cephalosporins[b]	398 (7.8)	335 (6.7)	338 (5.8)	307 (5.0)	145 (2.8)	88 (2.1)	-5.7
Fluoroquinolones	339 (6.6)	383 (7.7)	458 (7.9)	810 (13.1)	898 (17.4)	1073 (25.2)	+18.6
Trimethoprim-sulfamethoxazole	173 (3.4)	170 (3.4)	147 (2.5)	112 (1.8)	55 (1.1)	37 (0.9)	-2.5
Miscellaneous	145 (2.8)	134 (2.7)	135 (2.3)	131 (2.1)	99 (1.9)	111 (2.6)	-0.2
All antibiotics	**5111 (100)**	**4989 (100)**	**5824(100)**	**6181 (100)**	**5163 (100)**	**4260 (100)**	

[a] includes cefaclor, cefuroxime, cefixime, cefprozil, ceftriaxone
[b] includes cephalexin, cefadroxil, cefazolin

In the first year of the study erythromycin (36.8%), extended-spectrum macrolides (17.6%), penicillins (15.8%), and $2^{nd}/3^{rd}$ generation cephalosporins (9.3%) were the most commonly used agents for treatment of CAP. Table 1 describes changes in antibiotic consumption over the study period.

Decreased erythromycin use was coupled with an increase in the use of extended-spectrum macrolides (clarithromycin, azithromycin). In 2001/02 extended-spectrum macrolides were the most commonly employed agents for CAP, accounting for 43.9% of episodes treated with a single antibiotic.

In contrast, penicillins, cephalosporins, and trimethoprim-sulfamethoxazole all demonstrated decreased use over the study period. The use of fluoroquinolones increased from 6.6% to 25.2% over the study period, becoming the second most commonly used class of agents for CAP.

TABLE 2 Comparison of subject characteristics between those initially treated with a fluoroquinolone and other antibiotics

Subject variable	**Fluoroquinolone N (%)**	**Other N (%)**	**p**
Age in years (median)	59.0	50.0	<0.0001
Male gender	1731 (42.8)	12514 (44.9)	<0.05
Urban residence	2739 (67.7)	16780 (60.2)	<0.0001
Presentation to emergency department	333 (8.2)	2574 (9.2)	<0.05
Criterion eligibility for fluoroquinolone	158 (3.9)	452 (1.6)	<0.0001
High-level drug use	1909(47.2)	8263 (29.6)	<0.0001
Level of comorbidity			<0.0001
Low	3204 (79.2)	24207 (86.8)	
Moderate	751 (18.6)	3347 (12.0)	
High	89 (2.2)	342 (1.2)	
Total	**4044**	**27896**	

Over the course of the study 4,044 subjects received a fluoroquinolone. Compared to subjects receiving alternate antibiotics, subjects receiving fluoroquinolones were older, more likely to be female, have urban residence, and a higher level of co-morbidity and drug use (Table 2). No significant difference in the proportion of subjects receiving a fluoroquinolone between income quintiles was observed (χ^2=8.48, df=4, p=0.08).

Of the 31,940 antibiotic treated subjects, only 610 (1.9%) met the eligibility criterion for fluoroquinolone treatment. Of these 610 subjects, 158 (25.9%) received a fluoroquinolone while the remainder were treated with a variety of agents including extended-spectrum macrolides, $2^{nd}/3^{rd}$ generation cephalosporins, and erythromycin. In contrast, of the 31,330 subjects who did not meet the eligibility criterion, 3,886 (12.4%) received a fluoroquinolone.

TABLE 3. Multivariable analysis: independent predictors of receipt of a fluoroquinolone among outpatients

Subject variables	Odds Ratio (95% CI)
Age (10 years)	1.16 (1.14-1.19)
Male gender	1.00 (0.93-1.07)
Urban residence	1.40 (1.30-1.51)
Year of study	1.42 (1.39-1.45)
Presentation to emergency department	0.80 (0.70-0.90)
Criterion eligibility for fluoroquinolone use	1.84 (1.51-2.23)
High-level drug use	1.50 (1.41-1.59)
Level of comorbidity	
High	1.28 (0.99-1.64)
Medium	1.14 (1.03-1.25)
Low	1.00 (referent)
Income	
Quintile 5	1.20 (1.08-1.35)
Quintile 4	1.18 (1.05-1.31)
Quintile 3	1.02 (0.91-1.13)
Quintile 2	1.09 (0.98-1.22)
Quintile 1	1.00 (referent)

Multivariate modeling revealed that age, area of residence, level of co-morbidity, level of drug use, emergency department presentation, study year, income, and eligibility for fluoroquinolone treatment were independently associated with receipt of a fluoroquinolone (Table 3).

The odds of receipt of a fluoroquinolone among those meeting the eligibility criteria were 1.84 times that of subjects not eligible. In addition, the odds of receipt of a fluoroquinolone increased by 1.42 times yearly, and subjects in the highest income groups (income quintiles 4 and 5) were more likely to receive a fluoroquinolone than those in the lowest income group; odds ratios 1.18 and 1.20 respectively.

DISCUSSION

Recommendations for the treatment of CAP have changed in recent years to address new developments, such as increasing antibiotic resistance among causative organisms and the availability of newer antibiotic agents.[9] In general, increasing use of newer broad-spectrum agents coupled with a decrease in the use of older narrow-spectrum agents has been reported

worldwide.[1-4] Less is known regarding recent changes in populations' antibiotic consumption by indication. Our study identified changes in outpatient antibiotic use for CAP among the adult population of Manitoba over six years, and examined factors that influenced the use of fluoroquinolones for this indication.

Consistent with overall trends in antibiotic utilization, the use of older narrow-spectrum agents for treatment of CAP decreased, while the use of newer broad-spectrum agents increased. Of note was the increased consumption of extended-spectrum macrolides (clarithromycin/azithromycin), replacing erythromycin as the most commonly prescribed treatment for CAP. The improved pharmacokinetic and safety profile of the new macrolides over the older erythromycin, and the inclusion of this class of agents in the most recent treatment guidelines as an alternative to erythromycin, likely accounts for this change.

The proportion of adults with CAP treated with a fluoroquinolone more than tripled over the study period, from 6.6% to 25.2%. This is consistent with reports of fluoroquinolone use in other jurisdictions and for other indications.[14,15] However, the proportion of fluoroquinolone users observed in our study was less than the 32% reported among emergency room patients with CAP in Alberta, Canada.[16] Differences in severity of illness and drug-plan coverage between provinces may partially account for such differences.

In addition to study year a number of variables exhibited significant, although modest effects on the probability of receipt of a fluoroquinolone. Positive associations between income, urban residence, increasing age, and receipt of broad-spectrum antibiotics have been previously reported.(5-7) Greater use of fluoroquinolones among subjects with a higher level of co-morbidity, as measured by the number of ADGs and number of drugs, was expected due to the implications of possible treatment failure in this patient population. In contrast, our finding of a reduced probability of receipt of a fluoroquinolone among subjects presenting to an emergency department was in contrast to the findings of Pennie, who reported urgent care physicians were more likely to prescribe second-line antibiotics.[17] The greater propensity for subjects who met eligibility criteria for fluoroquinolone treatment to receive a fluoroquinolone (OR=1.84) was a positive finding.

However, the number of subjects who did not meet eligibility criteria for treatment with a fluoroquinolone far exceeded those who did. In addition, while 452 (74.1%) of those meeting criteria did not receive a fluoroquinolone, 3886 (12.4%) of subjects not meeting the criteria received one. Thus, overuse of fluoroquinolones was observed in a far greater number of persons with CAP than underuse, and represents a significant public health concern in terms of population numbers. As the role for fluoroquinolones in the treatment of CAP is limited, and the potential for the selection of antibiotic resistant pathogens remains, initiatives to increase the uptake of treatment guidelines to decrease unnecessary fluoroquinolone use are warranted.

Direct and indirect methods to influence prescribing have been advocated.[18] Direct approaches include administrative policies such as prescribing restrictions and financial incentives, which have met with success in lowering drug costs and improving prescribing.[19,20] A number of Canadian provinces, including Manitoba, currently employ reimbursement restrictions on fluoroquinolones prescriptions.[2,8,21]

Indirect methods to influence prescribing practices include educational initiatives such as the provision of one-to-one consultation and printed material by academic detailers, peer counseling, and information regarding prescribing practices in relation to peers.[18] These methods have also been reported to improve prescribing to varying degrees,[22-24] however, such methods need to be maintained to achieve long term results.[18] Further, the development of electronic health records and the use of e-prescribing, in conjunction with computerized decision-support tools, may prove a valuable tool to improve uptake of treatment guidelines. Combinations of several of the above strategies are thought necessary to optimize prescribing.[18,25]

Potential limitations of the current study include the use of healthcare claims to identify the cohort of interest. It is possible that a number of subjects identified did not have CAP, but rather a less invasive respiratory tract infection. However,

since few cases of pneumonia are diagnosed via microbiologic methods, these data reflect physicians' practice patterns in treating suspected or presumed pneumonia. In addition, we expected some misclassification of fluoroquinolone eligibility due misclassification of co-morbidity status and/or our liberal definition of fluoroquinolone eligibility. Validation of a similar classification system reported the agreement between administrative and medical chart data as being: very good (diabetes), good (chronic obstructive lung disease and renal disease), and moderate (congestive heart failure).[26] Thus a small amount of misclassification is likely.

In addition, we applied a liberal definition of fluoroquinolone eligibility by combining criteria from treatment guidelines published prior to and during the study period.[9,10] This included the existence of a number of co-morbidities, which would indicate the need for a broad-spectrum antibiotic in the early guidelines, in addition to recent use of systemic antibiotics or corticosteroids, as indicated in the latter guidelines. This liberal definition may have led to an overestimation of those underusing fluoroquinolones, and an underestimation of those overusing this class of antibiotics. Finally, administrative data commonly lack data on important co-morbidities (e.g., smoking status) and drug allergies/intolerances, which might be expected to influence treatment.

In summary, treatment of CAP among outpatients has changed in recent years, with a larger proportion of patients receiving newer broad-spectrum antibiotics, including fluoroquinolones. Few of those receiving fluoroquinolones met the eligibility requirement for such treatment. Observed overuse of fluoroquinolones has the potential to promote selection of resistant pathogens, which may limit the future usefulness of this class of agents.

Appendix A. Manitoba Health reimbursement criteria for antibiotics used in the treatment of community-acquired pneumonia.[11]

Drug name(s)	**Reimbursement criteria**
Amoxicillin-clavulanic acid	1. For treatment of patients not responding to alternative antibiotics (e.g. amoxicillin) 2. For treatment of patients with infections caused by organisms known to be resistant to alternative antibiotics (e.g., amoxicillin)
Azithromycin	1. For treatment of patients not responding to or intolerant of alternative antibiotics (e.g., amoxicillin and erythromycin) 2. Mycobacterial infections due to mycobacterium avium and mycobacterium intracellulare 3. Sexually transmitted diseases due to Chlamydia 4. Treatment of otitis media in patients not responding to or intolerant of alternative antibiotics (e.g., amoxicillin and erythromycin)
Cefaclor/Cefuroxime/Cefprozil	1. Step-down care following hospital separation in patients treated with intravenous cephalosporins 2. Treatment of patients with infections not responding to alternative antibiotics (e.g., amoxicillin) 3. Treatment of infections caused by organisms known to be resistant to alternative antibiotics (e.g., amoxicillin) 4. Treatment of patients known to be allergic or unresponsive to alternative antibiotics (e.g., penicillins or sulfonamides)
Clarithromycin	1. Infections not responding or intolerant of alternative antibiotics (e.g., amoxicillin and erythromycin) 2. Mycobacterial infections due to mycobacterium avium and mycobacterium intracellulare 3. In combination therapy in the treatment of H. pylori

Levofloxacin	1. Step-down care following hospital separation in patients treated with parenteral antibiotics 2. Treatment of gram-negative infections resistant to standard therapy 3. Treatment of infections in persons allergic to alternative agents (e.g., penicillins, cephalosporins, and sulfonamides) 4. Treatment of bacterial prostatitis 5. Treatment of respiratory infections in patients failing or likely to fail or intolerant of penicillins, cephalosporins, and/or macrolides 6. Treatment of diabetic foot infections
Moxifloxacin	1. Step-down care following hospital separation in patients treated with parenteral antibiotics 2. Treatment of resistant gram-positive or gram-negative infections 3. Treatment of infections in persons allergic to alternative agents (e.g., penicillins, cephalosporins, and sulfonamides) 4. Treatment of infections in patients failing or likely to fail or intolerant of penicillins, cephalosporins and/or macrolides
Ciprofloxacin/Ofloxacin	1. Step-down care following hospital separation in patients treated with parenteral antibiotics 2. Treatment of pseudomonal infections or resistant gram-negative infections 3. Treatment of resistant gonococcal infections 4. Treatment of infections in persons allergic to alternative agents (e.g., penicillins, cephalosporins, and sulfonamides) 5. Treatment of infections in immunocompromised patients 6. Treatment of diabetic foot infections and complications of orthopedic surgery 7. Treatment of chronic bacterial prostatitis

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