EFFECTIVENESS AND COST-EFFECTIVENESS OF ANTIBIOTIC TREATMENTS FOR COMMUNITY ACQUIRED PNEUMONIA (CAP) AND ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS (AECB)

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ABSTRACT

Background
The antibacterial activity, tolerability profile and duration of treatment associated with antibiotics are important therapy attributes when considering treating patients for lower respiratory tract infections (LRTIs), such as community acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB).

Objectives
To investigate the effectiveness and cost-effectiveness of oral antibiotics used in the treatment of LRTIs.

Methods
A cohort of inhaled corticosteroids users who were diagnosed with a LRTI and dispensed a prescription for one of the antibiotics under study on the same day as the diagnosis was selected from the administrative health databases of the Régie de l'assurance maladie du Québec (RAMQ). The risks of treatment failure were estimated using a logistic regression analysis. Treatment failure was defined as another prescription for any antibiotic, an emergency room visit or hospitalization for LRTIs, or death, in the 20 days following the dispensation of the first antibiotic prescribed. A cost-minimization analysis was performed in which only the drug costs related to the first antibiotic filled were considered.

Results
A total of 3,610 episodes of LRTIs were studied. There were no significant differences between antibiotics in terms of their respective adjusted odds ratios for rates of failure. However, the lower cost associated with azithromycin was significantly different from the costs associated with any other antibiotic ($p<0.0001$).

Conclusion
Clinical effectiveness appears to be similar amongst second line antibiotics that are commonly used in the treatment of LRTIs in the community. Using a cost-minimization analysis, azithromycin appears to be the most cost-effective antibiotic treatment in this setting.

Key Words: *Treatment effectiveness; cost effectiveness; lower respiratory tract infection; azithromycin*

The lower respiratory tract infections (LRTIs), community acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB), are very common diseases. The morbidity and mortality associated with LRTIs place a large burden on medical and financial resources. The primary determinant of the total costs for treating LRTIs is the need for hospitalization of some

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patients due to the severity of the infection or failure of the initial oral antibiotic therapy.[1-5]

Consequently, the cost and effectiveness of the initial oral antibiotic therapy plays an important role in attempting to reduce the total cost associated with LRTIs. The initial oral antibiotic therapy of patients whose clinical severity does not warrant immediate hospitalization is usually empirical since it is initiated when cultures and antibacterial resistance profiles are not yet available. Aside from the obvious importance of an antibiotic's activity against the LRTI causative pathogens, a favourable tolerability profile and a simple dosing and administration schedule are also significant attributes of the antimicrobial of choice since these variables may influence treatment compliance.[2,3] Numerous published randomized controlled clinical trials document the safety and the efficacy of the antibiotics available for the treatment of LRTIs and those results provide guidance to practitioners. However, those trials are not the most appropriate measures to assess the effectiveness (i.e., real life efficacy) of a drug treatment due to their rigid study designs and to the experimental and artificial conditions in which they are carried out.

Effectiveness of a drug product is of relevant interest to health care decision makers as it depicts efficacy in real life situations integral to the concept of population heterogeneity. Therefore, the objective of this study was to investigate the effectiveness and the cost-effectiveness of currently used antibiotic regimens in the context of real life community treatment of LRTIs.

METHODS

Source of data

Data from the administrative databases of the Régie de l'assurance maladie du Québec (RAMQ) were used. The accuracy and comprehensiveness of the RAMQ pharmaceutical data have been validated by Tamblyn et al.[4] As such, the database has been extensively utilized in observational studies that led to numerous peer-reviewed publications.[5,6,7]

Study cohort

A cohort of income security recipients who were dispensed at least one prescription for inhaled corticosteroids between 1991 and 1997 were selected. This sub-group was chosen because LRTIs are more prevalent in patients who suffer from asthma and/or chronic obstructive pulmonary disease (COPD).[8] The index date for inclusion in the cohort was defined as the first dispensed prescription for an inhaled steroid on or after January 1, 1991.

An episode of LRTI was defined as: 1) the presence of a diagnosis of LRTI[*] along with a prescription for 20 days or less of one of the antibiotics under study dispensed on the same day as the medical visit for LRTI; 2) no history of LRTI, nor of dispensed antibiotics within 20 days prior to the initial LRTI diagnosis; and, 3) data availability for at least one year prior to the initial LRTI diagnosis in order to allow for the assessment of certain co-morbid factors. As an episode of LRTI represented the unit of analysis considered for this study, a single individual could contribute more than one episode.

Outcome and exposure to antibiotics

Failure to the antibiotic treatment was defined as a prescription for any other antibiotic, an emergency room visit or a hospitalization for LRTI, or death (based on all cause mortality status), in the 20 days following the initiation of the first antibiotic prescribed. The antibiotics under study were divided into four categories: azithromycin, clarithromycin, ciprofloxacin and other second line antibiotics defined as amoxicillin/clavulanic acid, cefaclor, cefprozil, cefuroxime axetil and ofloxacin. This categorization was chosen based on the recommended second-line agents in treatment guidelines effective at the time of the cohort definition period.

RESULTS

A total of 3,610 episodes of LRTIs were identified from the cohort of users of inhaled corticosteroids.

[*] The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used to identify LRTI episodes. The codes used to identify AECB episodes are: 466.0, 490.0-490.9, 491.0, 491.1, 491.2, 491.8, 491.9. The codes used to identify CAP episodes are: 481.0-481.9, 482.0, 482.1, 482.2, 482.3, 482.4, 482.8, 482.9, 483.0, 483.1, 483.8, 485.0-485.9, 486.0-486.9.

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Among the 3,610 episodes of LRTIs, 16% were initially treated with azithromycin, 28% with clarithromycin, 11% with ciprofloxacin, and 45% with other second line antibiotics. The demographics of patients in the treatment groups are presented in Table 1.

Although no statistically significant differences were observed, the group treated with azithromycin and clarithromycin appears to be younger and consists of a higher proportion of females in comparison to the ciprofloxacin and the other second-line antibiotic treatment group.

TABLE 1 Baseline characteristics and failure events with antibiotic treatments

	Azithromycin	Clarithromycin	Ciprofloxacin	Other antibiotics§
N	591	1006	402	1611
Age, mean (SD)	42 (13)	43 (13)	48 (11)	47 (12)
% Male*	21.5	19.4	25.9	26.1
Duration of antibiotic, days, mean (SD)	5.0 (0.9)	9.9 (1.4)	9.7 (1.5)	9.9 (1.5)
Failure events, n (%)				
ER visit for LRTI	12 (2.0)	29 (2.9)	19 (4.7)	48 (3.0)
Hospitalisation for LRTI	0 (0.0)	0 (0.0)	3 (0.7)	6 (0.4)
℞ for another antibiotic	85 (14.4)	158 (15.7)	64 (15.9)	244 (15.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Total**	97 (16.4)	187 (18.6)	86 (21.4)	300 (18.6)

§ Other second line antibiotics (amoxicillin/clavulanic acid,cefaclor, cefprozil,cefuroxime axetil and ofloxacin)
*The percentage of male in the cohort of corticosteroid users selected at RAMQ is 40.6%.
** The Chi-square test for difference between rates of failure is associated with a p-value of 0.27.

The rates of failure to each antibiotic treatment are also presented in Table 1. For example, among the 591 LRTIs episodes initially treated with azithromycin, within the 20 days following treatment initiation, 2% experienced an emergency room visit, 14.4% filled an additional prescription for an antibiotic while none died nor were hospitalized. Although the overall risk of failure is slightly lower for azithromycin than for the other treatment groups, the difference is not significant (p=0.27).

A logistic regression analysis was performed to assess the probability of failure associated to each of the index antibiotics controlling for age, sex, and other variables that characterize subjects' heath state quality (i.e., use of inhaled and oral corticosteroids, number of hospital days, number of emergency room visits and of outpatient

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consultations in the year prior to the dispensation of the index antibiotic). The results of the logistic regression analysis presented in Table 2 demonstrate that the subject's age, their use of oral corticosteroids and their number of emergency room visits in the previous year were found to increase the risk of failure to the initial oral antibiotic therapy. Consistent with the crude rates of failure described in Table 1, the risk of failing with the index antimicrobial therapy was lower with azithromycin compared to the other groups but the difference did not reach statistical significance. The consistency of results amongst the different models would suggest that there was no confounding by severity.

TABLE 2 Risk of failure - results of the logistic regression analysis

		Complete Model		**Final model**	
	Crude OR	Adjusted OR	95 % C.I.	Adjusted OR	95 % C.I.
Antibiotics					
Azithromycin	Reference	Reference		Reference	
Clarithromycin	1.16	1.14	(0.87, 1.50)	1.14	(0.87, 1.49)
Ciprofloxacin	1.39	1.28	(0.92, 1.78)	1.29	(0.93, 1.79)
Other§	1.17	1.11	(0.86, 1.44)	1.11	(0.86, 1.43)
Age					
16-24		Reference		Reference	
25-39		1.40	(0.96, 2.06)	1.53	(1.05, 2.24)
≥ 40		1.18	(0.81, 1.72)	1.34	(0.93, 1.93)
Gender					
Female		Reference		NI	
Male		1.10	(0.90, 1.34)		
Oral corticosteroids**					
0		Reference		Reference	
≥ 1		1.41	(1.12, 1.77)	1.51	(1.22, 1.86)
Inhaled corticosteroids**					
0					
1-6		Reference		NI	
≥ 7		0.91	(0.75, 1.11)		
		1.06	(0.78, 1.44)		
Medical outpatient visits**					
0					
1-12		Reference		NI	
≥ 13		0.33	(0.63, 2.82)		
		1.96	(0.91, 4.20)		
ER visits**					
0		Reference		Reference	
≥ 1		1.17	(0.97, 1.40)	1.28	(1.07, 1.52)
Hospitalisation days**					
0		Reference		NI	
1		0.94	(0.74, 1.19)		
≥ 2		1.03	(0.84, 1.26)		

§ Other second line antibiotics (amoxicillin/clavulanic acid, cefaclor, cefprozil, cefuroxime axetil and ofloxacin)
** Assessed within the year preceding the episode of LRTI
NI: not included in the final model

The similar effectiveness among the four treatment groups analysed was thus used to justify conducting a cost-minimization analysis. This cost-minimization analysis considered only the acquisition cost of the initial antibiotic treatment since no statistical differences in the utilization of

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other healthcare resources such as hospital stays, emergency room visits or dispensation of other antibiotics were observed between treatment groups at the index LRTI episode. The result of this cost-minimization evaluation presented in Table 3 demonstrates that the cost of a treatment episode is significantly lower with azithromycin (i.e., an average of $10.87 lower) in comparison to the cost associated with any of the other treatments (p<0.0001).

TABLE 3 Cost-minimization analysis

Antibiotics	Mean dispensed prescription cost (SD)	Incremental cost: Azithromycin as reference	95% C.I. for multiple comparisons**
Azithromycin	$28.91 ($2.84)	Reference	Reference
Clarithromycin	$34.32 ($12.50)	$5.41	$3.83; $7.00
Ciprofloxacin	$47.39 ($8.67)	$18.48	$16.50; $20.45
Other[§]	$37.62 ($14.05)	$8.71	$7.24; $10.18

[§]Other second line antibiotics (amoxicillin/clavulanic acid, cefaclor, cefprozil, cefuroxime axetil and ofloxacin)
**A confidence interval not including 0 means that the cost of the antibiotic is statistically higher than the cost of azithromycin.

CONCLUSION

This study demonstrated that the risk of failure among currently used antibiotics were not statistically different. A cost minimization analysis indicated that the cost associated with the azithromycin study group was significantly lower than the costs associated with any of the other antibiotics under study. The lower cost associated with azithromycin is due to the significantly shorter duration of azithromycin treatment compared to other antimicrobial therapies under study.

It is instrumental that physician's selection of antibiotic fulfills the condition of optimizing treatment success under the constraints that relate to the uncertain etiology of the respiratory infection and to the uncertain patient compliance behaviours vis-à-vis the recommended therapy. As such, the results of this study are useful to understand the real life outcomes associated with antimicrobial treatment whereby the effectiveness of commonly used agents appears equivalent even after adjusting for various comorbidity indicators.

This study warrants further investigations involving more representative populations and more definite ascertainment of the risk of failure and of certain confounding variables important in the realm of LRTIs. Nevertheless, the study reveals that azithromycin, which is a widely prescribed antimicrobial in Canada, appears as being a cost-effective treatment strategy for lower respiratory tract infections such as community acquired pneumonia and acute exacerbation of chronic bronchitis.

FUNDING

This work was funded through a research grant from Pfizer Canada Inc. Lucie Blais is the recipient of a New Investigator salary support grant from the Canadian Institutes for Health Research (CIHR).

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