

Antibiotic Therapy for Ambulatory Patients With Community-Acquired Pneumonia in an Emergency Department Setting

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Background: Little attention has been paid to the factors that influence choice of antibiotic therapy for patients with community-acquired pneumonia who are treated on an ambulatory basis in an emergency department setting.

Methods: Prospective observational study of all patients who presented to the 6 hospitals for adults in the Capital Health Authority, Edmonton, Alberta, with community-acquired pneumonia (as diagnosed by the emergency department physician) from November 15, 2000, through April 30, 2001, and who were treated on an ambulatory basis.

Results: The study population consisted of 768 patients, mean age 51 years. The antibiotics most commonly prescribed were azithromycin (36%), levofloxacin (32%), and clarithromycin (17%). Site of care differences were evident in the frequency of clarithro-

mycin ($P < .001$) and levofloxacin ($P = .01$) prescription. Multiple logistic regression analysis showed that older age, presence of chronic obstructive pulmonary disease, antibiotic therapy at the time of presentation, and site of care were factors independently predictive of levofloxacin use ($P < .05$ for all factors). Levofloxacin prescription did not follow our indications for its use in 51% of the 245 patients who were treated with this antibiotic. The failure rate (defined as admission to the hospital within 3 weeks of emergency department visit) was low (2.2%).

Conclusions: Patient factors and site of care influence the choice of antibiotic therapy in an ambulatory setting, and 50% of levofloxacin use was inappropriate according to our definition.

Arch Intern Med. 2003;163:797-802

COMMUNITY-ACQUIRED pneumonia (CAP) is a common disease in North America with significant morbidity and mortality.¹⁻³ Since the etiologic agent remains unidentified in up to 50% of cases¹⁻³ and a delay of more than 8 hours in antimicrobial therapy is associated with increased mortality,⁴ prompt empiric therapy for CAP is essential.

The treatment of ambulatory CAP is problematic. Choosing an appropriate empiric antibiotic is made difficult by the large number of possible causes of CAP, the possibility of multidrug-resistant *Streptococcus pneumoniae*, and the fact that selecting a very broad-spectrum antibiotic or misusing an antimicrobial agent can lead to antimicrobial resistance or even morbidity or mortality for the patient. In the United States, multicenter studies indicate that penicillin-resistant *S pneumoniae* accounts for 24% to 34% of all isolates with high-level resistance rates of 9%

to 14%.^{5,6} A recent study by Zhanel et al⁷ indicates that the prevalence of penicillin-resistant *S pneumoniae* is around 21.2% in Canada (14.8% intermediate and 6.4% high-level resistance rates). Furthermore, it is estimated that as many as 30% of avoidable deaths from pneumonia are due to incorrect selection of antimicrobial agents.⁸

In an effort to provide clinicians with help in the management of pneumonia, guidelines for empiric antibiotic therapy have been developed.^{9,10} The Infectious Diseases Society of America guidelines¹⁰ recommend a macrolide or doxycycline for treating ambulatory patients with CAP, but if penicillin-resistant *S pneumoniae* is suspected, a respiratory quinolone should be prescribed (levofloxacin, moxifloxacin, and gatifloxacin are currently available in Canada). Many of the recommendations in these and other guidelines are not based on data from randomized clinical trials. The updated Canadian guidelines for the management of CAP⁹ include a new cat-

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egory, "outpatient with modifying factors," which includes patients with chronic obstructive pulmonary disease (COPD) who have had antibiotic or oral corticosteroid therapy within the past 3 months. For these patients, the recommended first-line therapy is a respiratory fluoroquinolone.

There have been very few studies of the management of pneumonia in ambulatory patients in an emergency department setting. Our objectives in this study were to (1) describe the antibiotics used to treat ambulatory patients with CAP in an emergency department setting in a large Canadian city; (2) identify factors that predict the use of fluoroquinolone and levofloxacin; and (3) determine if levofloxacin is being prescribed in accordance with the published pneumonia guidelines.

METHODS

STUDY SITES

This study involved all 6 hospitals in the Edmonton, Alberta, area: 2 tertiary care hospitals, 2 hospitals that provide secondary and some tertiary care, and 2 community hospitals. This study was approved by the research ethics committee at the University of Alberta and approved for use at all 6 study sites. The population of the city of Edmonton and its surrounding municipalities is 921 000 people.¹¹

DEVELOPMENT OF PNEUMONIA PATHWAY

A multidisciplinary team consisting of internists, pulmonologists, emergency physicians, family physicians, other physicians, pharmacists, nurses, respiratory therapists, and dieticians developed a comprehensive pathway for the management of CAP. Six research nurses were hired to assist with implementing the pathway, perform data collection, and carry out follow-up phone calls 48 to 72 hours after emergency department visits. Implementation began on November 15, 2000.

STUDY POPULATION

Patients were enrolled into the pathway if they presented to the emergency department for adults of 1 of the 6 hospitals in the Capital Health Authority, Edmonton, with 2 or more symptoms or signs of CAP plus radiographic evidence of pneumonia as interpreted by the emergency department physician or internal medicine consultant. Symptoms and signs of CAP included cough (productive or nonproductive), pleuritic chest pain, shortness of breath, temperature higher than 38°C, and crackles on auscultation. Patients were excluded from the pathway if they were thought to have aspiration pneumonitis (defined as pulmonary opacities in the presence of recent loss of consciousness, vomiting, or observation of respiratory distress within 30 minutes of feeding), tuberculosis, and cystic fibrosis. Also excluded were pregnant women, nursing mothers, and immunosuppressed patients (ie, those undergoing treatment with >10 mg/d of prednisone or other immunosuppressive drug).

AMBULATORY PNEUMONIA PATHWAY

For patients whom emergency department physicians managed on an ambulatory basis, there was a preprinted prescription included in the pneumonia pathway materials that recommended as first-line therapy a macrolide or doxycycline. The

specific agent was chosen by the physician. Conversely, for patients with COPD and antibiotic or oral corticosteroid therapy within the past 3 months, a respiratory fluoroquinolone (levofloxacin) was recommended.⁹ Patients were also given a pamphlet explaining the symptoms of pneumonia and the expected course of resolution. One of the 6 research nurses carried out a follow-up phone call 48 to 72 hours after the emergency department visit to assess if the patient's condition had improved and to record any symptoms that the patient still experienced.

DATA COLLECTION AND DEFINITIONS

Trained research nurses collected data through retrospective chart review because nurses could not staff the emergency department 24 hours a day. All data relating to ambulatory patients with CAP were reviewed and queried for correction when necessary. There were 768 unique patient visits. Some patients presented multiple times, but only the initial visit was included in this study. Patients treated in an ambulatory setting were considered *outpatients*. Patients presenting to the emergency department and then hospitalized were considered *inpatients*. The Canadian guidelines for treating CAP on an outpatient basis were used so that we could determine appropriate levofloxacin prescription at discharge. Levofloxacin prescription was considered appropriate if the patient had documented COPD or was receiving antibiotic therapy at the time of presentation or both.

Patients with COPD were identified by any of the following: (1) physician-documented COPD, emphysema, or chronic bronchitis in the chart; (2) patient history consistent with chronic bronchitis (productive cough for at least 3 months of the year during 2 consecutive years); or (3) chest radiograph reports indicating COPD or emphysema. *Treatment failure* was defined as all-cause admission to a hospital within 21 days of initial treatment at one of the participating emergency departments. *Prior antibiotic therapy* meant that the patient was receiving antibiotics at the time of presentation to the emergency department. *Physician-patient volume* was classified as low (≤ 4 patients during the study period) or high (≥ 5 patients).

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS (version 10.0.5; SPSS Inc, Chicago, Ill). The *t* test was used to compare means of continuous data, and proportions were compared using the χ^2 test or Fisher exact test. All tests were interpreted using a 2-tailed significance level of less than .05. Univariate analysis of factors predicting levofloxacin use was performed with the independent sample *t* test or χ^2 as appropriate. Multivariate analysis was conducted using the logistic regression method.¹² Factors that were found to be significant by univariate analysis at $P < .05$ were included in the regression model.

RESULTS

BASELINE CHARACTERISTICS

From November 15, 2000, through April 30, 2001, a total of 1506 patients presented with CAP and were eligible to be enrolled in the pathway. A total of 768 patients (51%) were treated on an ambulatory basis, and 738 patients (49%) were hospitalized. **Table 1** summarizes some of the demographic and clinical characteristics of the ambulatory patients. The proportion of patients with

Table 1. Demographic and Clinical Characteristics for the 768 Ambulatory Patients With Community-Acquired Pneumonia

Characteristic	No. (%) of Patients
Study site	
A	203 (26)
B	86 (11)
C	125 (16)
D	110 (14)
E	150 (20)
F	94 (12)
Age, y*	
16-43	339 (44)
44-64	203 (26)
≥65	226 (29)
Sex	
Male	424 (55)
Female	344 (45)
COPD	89 (12)
Prior antibiotic therapy	163 (21)

Abbreviation: COPD, chronic obstructive pulmonary disease.

*Mean ± SD age was 51.4 ± 20.3 years.

Table 2. Antibiotic Therapy for the 163 Patients Who Were Receiving Such Therapy at Time of Presentation to Emergency Departments*

Antibiotic	No. (%) of Patients
Monotherapy	
Clarithromycin	19 (12)
Levofloxacin	17 (10)
Amoxicillin	14 (9)
Azithromycin	12 (7)
Cefuroxime	9 (6)
Erythromycin	4 (2)
Ciprofloxacin	4 (2)
Co-trimoxazole	4 (2)
Metronidazole	1 (0.6)
Doxycycline	1 (0.6)
Moxifloxacin	1 (0.6)
Penicillin V	1 (0.6)
Clindamycin	1 (0.6)
Combination Therapy	
Gentamicin and ampicillin	1 (0.6)
Penicillin and cefuroxime	1 (0.6)
Cefuroxime and clarithromycin	1 (0.6)
Levofloxacin and clarithromycin	1 (0.6)
Levofloxacin and trimethoprim and sulfamethoxazole	1 (0.6)
Levofloxacin and metronidazole	1 (0.6)
Gentamycin and cloxacillin and ceftiazone	1 (0.6)
Total	95 (58)

*Unknown antibiotics, n = 6; missing antibiotics, n = 62.

pneumonia presenting to each study site is also given in Table 1. The mean age was 51.4 years (range, 16-100 years). A total of 89 patients (12%) had COPD, and 163 patients (21%) were receiving antibiotic therapy at presentation. The antibiotics being used at presentation and the reasons for their prescription are summarized in **Table 2**. The reasons for antibiotic therapy at the time of presentation were documented for 101 patients (68%): respiratory tract infection, 57% (93 patients); urinary tract

Table 3. Antibiotic Therapy Prescribed on Discharge for the 768 Ambulatory Patients With Community-Acquired Pneumonia*

Antimicrobial Agent Class	No. (%) of Patients
Monotherapy	
Macrolides	
Azithromycin	280 (36)
Clarithromycin	133 (17)
Erythromycin	13 (2)
Lincosamides	
Clindamycin	1 (0.1)
Cephalosporins	
Cefuroxime	8 (1)
Cefaclor	1 (0.1)
Quinolones	
Levofloxacin	245 (32)
Ciprofloxacin	1 (0.1)
Moxifloxacin	4 (0.5)
Tetracyclines	
Doxycycline	4 (0.5)
Aminopenicillins	
Amoxicillin	4 (0.5)
Amoxicillin-clavulanate	2 (0.3)
Natural penicillins	
Penicillin V	1 (0.1)
Combination Therapy	
Cephalosporins and macrolides	
Cefuroxime and azithromycin	1 (0.1)
Cefuroxime and clarithromycin	1 (0.1)
Cefuroxime and erythromycin	1 (0.1)
Cephalosporins and quinolones	
Cefuroxime and levofloxacin	1 (0.1)
Cefuroxime and ciprofloxacin	1 (0.1)
Quinolones and macrolides	
Levofloxacin and azithromycin	1 (0.1)
Levofloxacin and clarithromycin	1 (0.1)
Tetracyclines and macrolides	
Doxycycline and azithromycin	1 (0.1)
Total	705 (92)

*Missing antibiotics, n = 20; unknown antibiotics, n = 32; and no antibiotic prescribed, n = 11.

infection, 2% (3 patients); gastrointestinal tract treatment, less than 1% (1 patient); and other reasons, 4% (2 patients).

ANTIBIOTICS PRESCRIBED AT DISCHARGE FROM EMERGENCY DEPARTMENT

The antibiotics prescribed most often at discharge included azithromycin (280 patients [36%]), levofloxacin (245 patients [32%]), and clarithromycin (133 patients [17%]) (**Table 3**). Fewer than 1% of patients received combination therapy, and fewer than 1% of patients received a prescription for clindamycin, ciprofloxacin, penicillin V, or cefaclor. Macrolides were prescribed for 426 patients (55%), while quinolones were prescribed for 250 patients (33%). For most of the 11 patients who were not prescribed any antibiotic on discharge, this was because they left the emergency department against medical advice. Site differences were evident in the prescription rates of clarithromycin ($P < .001$) and levofloxacin ($P = .02$).

Table 4. Demographic and Clinical Characteristics of Patients Treated With Levofloxacin Compared With Patients Treated With All Other Antibiotics

Characteristic	No. (%) of Patients		P Value*
	Levofloxacin (n = 245)	Other Antibiotics (n = 451)	
Study site			.02
A	51 (21)	132 (29)	
B	19 (8)	54 (12)	
C	39 (16)	75 (17)	
D	42 (17)	59 (13)	
E	57 (23)	83 (18)	
F	37 (15)	48 (11)	
Age, y†			<.001
16-40	61 (25)	252 (56)	
41-64	68 (28)	119 (26)	
≥65	116 (47)	80 (18)	
Sex			NS
Male	142 (58)	240 (53)	
Female	103 (42)	211 (47)	
Living arrangements			NS
Home	176 (72)	415 (92)	
Lodge/subacute	44 (18)	11 (2)	
Shelter/homeless	9 (4)	1 (0.2)	
Smoking status			NS
Smoker	36 (15)	98 (22)	
Ex-smoker	24 (10)	33 (7)	
COPD	58 (24)	18 (4)	<.001
Prior antibiotic therapy	75 (31)	67 (15)	<.001
Physician-patient volume			.08
Low	85 (35)	110 (24)	
High	156 (64)	327 (73)	

Abbreviations: COPD, chronic obstructive pulmonary disease; NS, not significant.

*Calculated using χ^2 or *t* test.

†Mean \pm SD age for levofloxacin was 61 \pm 20 years; for other antibiotics, 46 \pm 18 years.

PREDICTORS OF LEVOFLOXACIN PRESCRIPTION AT DISCHARGE

Patients who received levofloxacin were compared with those who received other antibiotics (**Table 4**). On univariate analysis, the following factors were significantly associated with levofloxacin prescription on discharge from the emergency department: older age, presence of COPD, antibiotic therapy at the time of presentation, site of care, and low physician-patient volume (**Table 5**). Physicians who saw fewer patients with CAP prescribed levofloxacin more often than physicians who saw more patients with CAP. Significant predictors of levofloxacin prescription in the multivariate model included older age (odds ratio, 1.033; $P < .001$); the presence of COPD (odds ratio, 4.623; $P < .001$); antibiotic therapy at the time of presentation (odds ratio, 2.527; $P < .001$); and site (Table 5). For each 10-year increase in age, levofloxacin prescription increased 39%.

PATIENTS WITH PNEUMONIA AND COPD

Eighty-nine (12%) of the 768 patients who presented with CAP to an emergency department and who were treated on an ambulatory basis had COPD. Most of these pa-

Table 5. Univariate and Multivariate Analysis of Factors Predicting Levofloxacin Use*

Characteristic	Univariate Analysis P Value	Multivariate Analysis P Value	Odds Ratio (95% Confidence Interval)
Age	<.001	<.001	1.033 (1.02-1.04)
COPD	<.001	<.001	4.623 (2.5-8.5)
Antibiotics at time of presentation	<.001	<.001	2.527 (1.7-3.8)
Site	.02		
A		.11	1.000
B		.37	1.368 (0.7-2.7)
C		.14	1.537 (0.9-2.7)
D		.05	1.780 (1.0-3.2)
E		.02	1.868 (1.1-3.2)
F		.01	2.223 (1.2-4.1)
Physician-patient volume	.007	.08	0.7 (0.5-1.0)

Abbreviation: COPD, chronic obstructive pulmonary disease.

*Hosmer and Lemeshow goodness of fit = 0.720; C-index = 0.765.

tients (n = 58; 65%) were prescribed levofloxacin on discharge. The other monotherapy antibiotics prescribed were azithromycin (9 patients [10%]), clarithromycin (5 patients [6%]), cefuroxime (3 patient [3%]), and erythromycin (1 patient [1%]). Additionally, 1 patient (1%) received combination antibiotic therapy with cefuroxime and clarithromycin. Under our criteria, levofloxacin was appropriately prescribed for 119 patients (49%) with CAP.

OUTCOMES

There were no deaths among the patients treated on an ambulatory basis. A total of 2.2% were subsequently admitted to the hospital within 3 weeks of the initial emergency department visit.

COMMENT

The first objective of our study was to define the antibiotic therapy used to treat ambulatory patients with CAP in an emergency department setting. We found that azithromycin (36%), levofloxacin (32%), and clarithromycin (17%) were the most commonly prescribed antibiotics. The multivariate model identified older age, the presence of COPD, antibiotic therapy at the time of presentation, and site of care to be predictors of levofloxacin prescription. Laurichesse et al¹³ in 1998 studied the management of ambulatory patients with pneumonia by a group of general practitioners in France from 1993 to 1994 and found that amoxicillin alone or in combination with clavulanic acid was prescribed most often (57% of cases), and fluoroquinolones were prescribed at a rate of 2%. In another study from France, Fantin et al¹⁴ noted that of 94 ambulatory patients with pneumonia, 33% were treated with amoxicillin monotherapy, 18% with amoxicillin-clavulanate combination, and 12% with macrolides. In a study of 610 ambulatory patients with clinically diagnosed pneumonia carried out in 9 census regions in the United States during the 1999-2000 "respiratory season," Gotfried¹⁵ found that levofloxacin was the most

commonly prescribed antibiotic (23%), while 29% of the patients received macrolides. From these studies it is evident that there are differences in the choice of antibiotic therapy for the treatment of ambulatory patients with pneumonia in France and North America.

The PORT study¹⁶ was conducted at 5 medical institutions in Pittsburgh, Pa, Boston, Mass, and Halifax, Nova Scotia, from October 1991 through March 1994 and included ambulatory patients who presented to the Harvard Community Health Plan–Kenmore Center as well as to participating hospital emergency departments. In that study, the patient population included fewer patients 65 years or older (18.4% of 944 patients) than does the present study (29.4% of 768 patients). In the PORT study, 14.3% of the 944 outpatients were said to have COPD; however, COPD was defined to also include asthma and interstitial lung disease.¹⁶ In the present study, 12% of the 768 outpatients were found to have COPD (chronic bronchitis or emphysema only). Neither study objectively defined COPD using pulmonary function tests. The failure rate of outpatient therapy in the present study was 2.2%, which is significantly lower than the reported finding of 7.5% in the PORT study ($P < .001$) under the same definition for treatment failure. Additional study is required to explain this difference. We found that 21% of the 768 outpatients were receiving antibiotics at the time of presentation, similar to the 24.2% of the 927 patients in the PORT study.¹⁶

As part of the PORT study, Gilbert et al¹⁷ described the antibiotic therapy of 927 outpatients with CAP. Twenty-three different antimicrobial agents were prescribed for at least 2% of outpatients, with 74.4% of the 927 patients receiving monotherapy and 19.3% receiving a combination of 2 antibiotics on discharge from the emergency department or from the physician's office. The 3 most commonly prescribed antibiotics were erythromycin (58.5%), clarithromycin (13.6%), and amoxicillin (12.6%). The classes of antibiotics prescribed included macrolides (73.4%), aminopenicillins (21.5%), cephalosporins (13.7%), fluoroquinolones (6.3%), and tetracyclines (5.3%). In the present study, only 4 antibiotics (vs 23 in the PORT study) were prescribed for 2% or more outpatients, and 90.2% of outpatients were discharged with antibiotic monotherapy. The classes of antibiotics prescribed in 2001 include macrolides (55%), fluoroquinolones (32.6%), cephalosporins (1.1%), tetracyclines (0.8%), and aminopenicillins (0.5%). In the 7 years since the PORT study, fluoroquinolone use to treat ambulatory CAP increased by 26.3%, aminopenicillin use decreased by 20%, and macrolide use decreased by 18.3%. It is noteworthy that the respiratory fluoroquinolones and azithromycin were not available at the time of the PORT study; clarithromycin was marketed shortly after the study began.

The second main objective of the present study was to determine how often levofloxacin therapy for ambulatory patients with CAP adhered to the Canadian guidelines. Since the design of our study did not permit us to determine if patients took oral corticosteroids or the time frame for antibiotic or oral steroid treatment, we widened our definition of appropriate levofloxacin use to include all patients with COPD (regardless of whether they had undergone treatment with antibiotics or oral steroids within the past 3 months), and included

antibiotic therapy at the time of presentation as a reasonable justification for levofloxacin prescription. When comparing our definition of appropriate levofloxacin prescription with the Canadian guidelines, we found that we actually considered more cases appropriate than the Canadian guidelines would have indicated. Therefore, our estimate of the prevalence of inappropriate levofloxacin use at 51% likely understates the magnitude of the problem.

Our study indicates that patient factors (age, presence of COPD, antibiotic therapy at the time of presentation), physician factors (experience treating pneumonia), and site of presentation (which may be a physician factor) are all predictive of levofloxacin use. There have been many studies addressing the use of clinical practice guidelines. A study by Gleason et al¹⁸ in 1997 found an adherence rate of only 46% to the American Thoracic Society guidelines in an outpatient population. Likewise, Marras and Chan¹⁹ documented a 44% rate of adherence to guidelines in their outpatient population. It is difficult to distinguish the effects of the new Canadian guidelines from those of effective detailing in the prescription rate of levofloxacin.

The treatment failure rate in our study, defined as admission to a hospital with 3 weeks of the initial visit, was low (2.2%). Fantin et al¹⁴ noted that 9 (7.6%) of 117 patients treated on an ambulatory basis subsequently required admission to the hospital. However, when the authors excluded the patients who did not have pneumonia and those who were not treated according to recommended therapy, the failure rate for those who were treated according to recommendations was 1 (2.6%) in 38. Minogue et al²⁰ found that 71 (7.5%) of 944 patients with CAP initially treated in the outpatient setting were subsequently hospitalized within 30 days. Five of these patients were offered admission at the time of the initial visit. Forty (61%) of the remaining 66 were hospitalized because of the pneumonia, and 95% of these were hospitalized within 3 weeks.

Based on these findings, it is likely that 7 or more of our patients who were subsequently admitted to the hospital were admitted because of worsening comorbid illnesses. It is apparent that more in-depth study of treatment failure in ambulatory patients with CAP is required. Twenty-one percent of our patients were already receiving antibiotics at the time of their first emergency department visit, most often for a lower respiratory tract infection. The issue, then, is why they presented to the emergency department. Ambulatory patients must be instructed on the natural course of pneumonia resolution and given information on what constitutes worsening pneumonia.

We accepted the emergency department physician's interpretation of the chest radiograph as pneumonia for purposes of the present study. Indeed, in 20% of cases, a radiologist interpreted as normal chest radiographs determined by emergency department physicians to indicate pneumonia. Interobserver variability in the interpretation of chest radiographs for the presence of pneumonia is not uncommon.^{21,22} Melbye and Dale²² studied outpatients with pneumonia. The κ coefficient for agreement between radiology residents and an expert panel was 0.50, while it was 0.59 when an expert consultant was used.

When a radiology resident and a staff radiologist read normal chest x-ray films, they agreed 76% of the time, and for patients with pneumonia agreement was 74%.

Our study has a number of limitations. Since we could not staff 6 emergency departments on a 24-hour basis, our study has the limitation of a chart review. Another limitation is that our results are region specific and may not be generalizable to other areas in North America. A major strength of our study is its comprehensiveness—we were able to include all patients in a large city who presented to the emergency department for the treatment of pneumonia.

We are providing feedback to hospitals on their performance in the pneumonia pathway on a quarterly basis. Whether this changes prescribing habits for ambulatory patients with pneumonia remains to be seen. Our data suggest that there are elements about prescribing behavior that are still poorly understood. A perfect example of this is the influence of site of care on the rate of clarithromycin and levofloxacin prescription.

Accepted for publication June 26, 2002.

Funding for this research was provided by the Capital Health Authority and by the Alberta Heritage Foundation for Medical Research, Edmonton, and by grants in aid from Janssen-Ortho, Toronto, Ontario, and Abbott Laboratories Canada, Montreal, Quebec. Additionally, Ms Malcom received a Medical Research Studentship Award from the Alberta Heritage Foundation for Medical Research.

We thank the CAP research nurses, JoAnne de Jager, RN; Linda Gardner, BScN; Lynne Korobanik, RN; Tammy Pfeiffer, BScN; Cynthia Proskow, BScN; Sue Marshall, BScN; and Fredrika Herbert, RN. In addition, we thank William Midodzi, MSc, for help with statistical analysis, and the members of EPICORE data management center at the University of Alberta Hospital.

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