Rates and Risk Factors for Recurrent Pneumonia in Patients Hospitalized With Community-Acquired Pneumonia: Population-Based Prospective Cohort Study With 5 Years of Follow-up

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Background. The rates and risk factors for developing *recurrent* pneumonia following hospitalization with community-acquired pneumonia (CAP) are poorly understood.

Methods. We examined a population-based cohort of patients with CAP who survived hospital admission and who were free of pneumonia for at least 3 months. We collected clinical, functional, and medication-related information and pneumonia severity index (PSI). Using linked databases we followed patients for 5 years and captured any clinical episode of pneumonia 90 days or more post-discharge. We used Cox proportional hazards models (adjusted for age, sex, PSI, functional status, medications) to determine rates and independent correlates of recurrent pneumonia.

Results. The final cohort included 2709 inpatients; 43% were 75 years or older, 34% were not fully independent, and 56% had severe pneumonia. Over 5 years of follow–up, 245 (9%; 95% confidence interval [CI], 8%–10%) patients developed recurrent pneumonia, and 156 (64%) of these episodes required hospitalization. Rate of recurrence was 3.0/100 person–years and median time to recurrence was 317 days (interquartile range, 177–569); 32 (13%) patients had 2 or more recurrences. In multivariable analyses only age >75 years (adjusted P = .047) and less than fully independent functional status (12% recurrence rate with impaired functional status vs 7% for fully independent; adjusted hazard ratio, 1.7; 95% CI, 1.3–2.2; P < .001) were significantly associated with recurrent pneumonia.

Conclusions. One of 11 patients who survived CAP hospitalization had recurrent pneumonia over 5 years and those with impaired functional status were at particularly high risk. Recurrent pneumonia is common and more attention to preventive strategies at discharge and closer follow-up over the long-term seem warranted.

Keywords. recurrent pneumonia; community-acquired pneumonia; risk factors; population-based cohort.

Community-acquired pneumonia (CAP) is one of the most common reasons for hospital admission in

Clinical Infectious Diseases 2014;59(1):74-80

North America. One cost-of-illness study showed that, annually, pneumonia accounted for 4.5 million physician visits and 1.1 million hospital admissions with a cost of approximately \$8 billion per year [1]. Furthermore, patients with pneumonia incurred an additional \$15 682 in annual healthcare costs compared with patients who did not have pneumonia [2]. As such, preventing CAP is important, and it is widely held that one of the most important risk factors for pneumonia is a previous episode of pneumonia. Given how

Received 27 February 2014; accepted 2 April 2014; electronically published 11 April 2014.

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common CAP is, it is surprising that we know so little about the rates and the risk factors for an episode of recurrent pneumonia [3–6].

To our knowledge, only 4 studies have examined rates and risk factors for recurrent pneumonia in detail [3-6]. The rate of recurrent pneumonia in these studies was reported to range from 3.5% over 11 years to 9.4% over 3 years to a 20% recurrence rate over an undefined period of follow-up [5, 6]. In terms of potential risk factors for recurrent pneumonia, the focus has been on comorbidities that are believed to be associated with an increased risk, particularly heart failure, chronic obstructive pulmonary disease (COPD), diabetes mellitus, neurological disorders and swallowing dysfunction (presumably on the basis of aspiration), and underlying immune deficiencies [3-6]. Other studies have identified some lifestyle factors (ie, chronic alcoholism, current smoking), impaired functional status, and certain medications (ie, sedative hypnotics, inhaled or oral corticosteroids) as risk factors for recurrence [4, 5]. In our previous work, we demonstrated that proton pump inhibitors (PPIs) and inhaled (but not oral) corticosteroids were independently associated with recurrent pneumonia [7, 8]. El Soth et al, on the other hand, identified some protective factors, including use of angiotensin-converting enzyme (ACE) inhibitors and pneumococcal vaccination [4], although the latter finding has been difficult to replicate [9].

Sparse as these data are, these studies were generally in agreement. However, each study is subject to a number of important limitations, including [3–6] nonpopulation representativeness, being a single center, small sample sizes, lack of detailed clinical information, potentially biased recurrence ascertainment, and/or follow-up periods that are too short. Therefore, in an effort to expand the literature and try to overcome some of these limitations, we undertook the present study to better define the rates and independent correlates of recurrent pneumonia in a population-based prospective cohort study with 5 years of follow-up.

METHODS

Subjects and Setting

From 2000 to 2002, 6874 patients with pneumonia evaluated in any of the 7 emergency departments and 6 hospitals serving Edmonton, Alberta, Canada, were enrolled in a population-based clinical registry and followed for up to 5 years. The metropolitan Edmonton region has a population of more than 1 million with universal healthcare coverage provided for by more than 1000 family physicians and an annual healthcare budget of almost \$2 billion. Details and analyses related to the subgroups of patients admitted to hospitals [10, 11], transferred to intensive care units [12], or treated as outpatients [13] have been previously published. The institutional ethics review board of the University of Alberta approved the study.

In summary, all patients were managed according to a validated clinical pathway that had triage and site-of-care suggestions based on the pneumonia severity index (PSI), as well as recommendations for investigations and antibiotics. For the present study, we considered only the 3415 adults admitted to hospitals with signs and symptoms of pneumonia (defined as 2 or more of the following: cough, pleurisy, shortness of breath, temperature >38°C, crackles, or bronchial breathing on auscultation) who also had physician-reported chest radiographic findings consistent with pneumonia. The registry did not capture patients with tuberculosis, cystic fibrosis, immunocompromised status, or those who were pregnant. For our study, we also excluded patients who died in the hospital (n = 323), who had an episode of pneumonia within 90 days of discharge (n = 241, in an effort to exclude counting relapse or recrudescence of the original pneumonia or development of early nosocomial disease related to hospitalization as a recurrent episode), or who could not be linked to provincial databases to identify longer-term outcomes of mortality or recurrent pneumonia (n = 142). Thus, the final study cohort consisted of 2709 adult survivors of pneumonia hospitalizations.

Data Collection and Measurements

Research nurses prospectively collected sociodemographic, clinical, functional, and laboratory data as well as complete medication lists. Functional status was a clinical variable that was dichotomized as "independent" vs "less than fully independent," with the latter being defined as unable to mobilize and ambulate without assistance or use of assistive devices such as a cane or a wheelchair [7–12]. The PSI was calculated for each patient at the time of admission, and we used PSI classes IV and V to define "severe" pneumonia. The PSI is a well-validated tool designed to predict 30-day all-cause mortality in patients with pneumonia; it has also been used for purposes of risk adjustment [10].

Outcomes

To ascertain outcomes, we linked registry patients to provincial administrative databases that included vital statistics and all health resource utilization. The rate of successful linkage between population-based clinical registries and our provincial administrative databases generally exceeds 95% [10–13]. The primary outcome for this study was any clinical episode of recurrent pneumonia that occurred 90 days or more after hospital discharge during the 5-year follow-up period. Hereafter, we refer to this as "recurrent pneumonia." As we [7–9] and others [14–16] have previously done, we used International Classification of Diseases (ICD) 9th and 10th revision codes to identify any episode of inpatient or outpatient pneumonia as defined by

the following codes: ICD-9 480.0–487.7 and ICD-10 J10-J18. These codes have been previously validated and are considered to have very good sensitivity and very high specificity [14–17].

Analysis

Descriptive statistics using parametric or nonparametric tests as appropriate were calculated. Patient characteristics were stratified according to the presence or absence of recurrent pneumonia over the entire duration of follow-up. Cumulative incidence rates for recurrence were plotted and presented in graphical form. Censoring occurred at the time of recurrent pneumonia, death, departure from Alberta (mandating withdrawal from provincial health insurance coverage), or the end of study follow-up in March 2006. Univariable (unadjusted) and multivariable (adjusted) hazard ratios were estimated using Cox proportional hazards models. We forced age, sex, and severity of initial pneumonia according to the PSI (excluding points for age) into all models. Additional candidate variables (see Table 1) were considered for inclusion in our models based on clinical relevance, literature review, univariable association with recurrent pneumonia of P < .1, or demonstrable confounding (ie, a 10% or greater change in beta-coefficient). All first-order interaction terms were considered and none achieved nominal statistical significance (P < .1). Assessment of the proportional hazards assumptions was undertaken using log-log survivor plots and time-interaction terms, and no violations were present.

In terms of sensitivity analyses, we used multivariable logistic regression and a proportional hazards approach that accounted for the "competing risks" of mortality vs recurrent pneumonia. Finally, we examined the rates and risk factors for "early" recurrent pneumonia, that is, episodes that occurred between 30 days and 90 days after discharge from the hospital. We considered a P value of < .05 to be statistically significant and a P value between .05 and .1 to be indicative of a statistical trend. All analyses were conducted using STATA/IC version 13.0 (Stata Corp., College Station, TX).

RESULTS

Patient Characteristics

The final cohort consisted of 2709 inpatients with CAP who were discharged from the hospital and who were free of pneumonia for at least 90 days. Of this cohort, the mean age was 67 years, 43% were aged \geq 75 years, 51% were male, 34% were not fully independent, and 56% had severe (PSI, class IV or V) pneumonia at presentation (Table 1). The median follow-up time for the cohort was 3.6 years, and there were 8292 person-years at risk for the entire population studied. Over the entire duration of follow-up, 1163 (43%) patients died and 77 (3%)

Table 1. Characteristics of 2709 Survivors of PneumoniaHospitalization According to the Presence or Absence ofSubsequent Recurrent Pneumonia

		No	
	Recurrence	Recurrence	Р
Characteristic	n = 245 (%)	n = 2464 (%)	Value
Patient Demographics			
Male	119 (50.0)	1271 (51.6)	.37
Mean age (SD)	69.9 (17.4)	66.7 (18.2)	.008
Age >75 y	123 (50.2)	1049 (42.6)	.013
Markers of Frailty			
Assisted feeding	5 (2.0)	76 (3.1)	.36
Not fully independent	111 (45.3)	805 (32.7)	<.001
Nursing home resident	51 (20.8)	371 (15.1)	.018
Underweight (body mass index < 18)	5 (7.6)	46 (6.9)	.83
3+ comorbidities	67 (27.4)	710 (28.8)	.63
Lifestyle Factors			
Chronic alcoholism	21 (8.6)	195 (7.9)	.72
Current smoking	52 (21.2)	667 (27.1)	.048
Comorbidities			
Prior aspiration	8 (3.3)	148 (6.0)	.079
Heart failure	49 (20.0)	482 (19.6)	.87
Chronic obstructive pulmonary disease	84 (34.3)	874 (35.5)	.71
Dementia	17 (6.9)	137 (5.6)	.37
Diabetes mellitus	37 (15.1)	402 (16.3)	.62
Seizure	18 (7.4)	114 (4.6)	.059
Stroke	30 (12.2)	253 (10.3)	.34
Medications and Immunizations			
Angiotensin-converting enzyme inhibitors	43 (17.6)	483 (19.6)	.44
Sedative-Hypnotics	39 (15.9)	289 (11.7)	.055
Inhaled bronchodilators	85 (34.7)	839 (34.1)	.84
Inhaled corticosteroids	49 (20.0)	394 (16.0)	.11
Proton pump inhibitors	30 (12.2)	355 (14.4)	.36
Statins	24 (9.8)	248 (10.1)	.89
Pneumococcal vaccine	24 (9.8)	282 (11.4)	.44
Influenza vaccine	82 (33.5)	732 (29.7)	.22
Pneumonia-Specific Factors			
PSI			
Age-subtracted mean PSI (SD)	35.7 (24.7)	34.5 (25.7)	.47
Classes I/II	39 (15.9)	566 (23.0)	.038
Class III	54 (22.0)	521 (21.1)	
Classes IV/V (severe)	152 (62.0)	1377 (55.9)	
Chest Radiograph Finding			
Single-lobe involvement	107 (43.7)	1111 (45.1)	.67
Multilobar involvement	68 (27.8)	572 (23.2)	.11
Bilateral involvement	36 (14.7)	363 (14.7)	.99
Pleural effusion	46 (18.8)	490 (19.9)	.68

Abbreviations: PSI, pneumonia severity index; SD, standard deviation.

patients withdrew from the provincial health insurance plan and left the province.



Figure 1. Rates of recurrent pneumonia according to functional status: cumulative incidence curves.

Rates of Recurrent Pneumonia

Overall, 245 (9%; 95% confidence interval [CI], 8%–10%) patients developed recurrent pneumonia over a maximum of 5 years of follow-up and 32 (13%) of these patients had more than 1 recurrence. Of these recurrent episodes, 156 (64%) required hospitalization. The median time to recurrence was 317 days (interquartile range, 177–569 days), and the incidence of recurrent pneumonia was 3.0/100 person-years of follow-up. The 30-day case fatality rate for an episode of recurrent pneumonia was 10.2%. Of note, 3 (1.2%) of those with recurrent pneumonia were subsequently diagnosed with lung cancer, while 10 (0.4%) of those without recurrent pneumonia developed lung cancer during the follow-up period (P = .08 for difference).

Independent Risk Factors for Development of Recurrent Pneumonia

In general, patients who had recurrent pneumonia were older, frailer, had more comorbidity, and had more severe pneumonia at presentation than those who did not have a recurrence. Table 1 presents patient characteristics stratified according to the presence or absence of recurrent pneumonia. Although these tabulated data suggest several potential risk factors, in multivariable analyses adjusted for sex, initial pneumonia severity, and medications, only older age (P = .047) and functional status were independently associated with an increased risk of recurrent pneumonia. Specifically, pneumonia recurred in 111 of 916 (12%) patients with any impairment in functional status vs 134 of 1793 (7%) patients who were fully independent (adjusted hazard ratio, 1.70; 95% CI, 1.30–2.23; P < .001; Figure 1). Although not statistically significant, there was a trend toward inhaled corticosteroids (P = .065) also being independently associated with an increased risk of recurrent pneumonia

Table 2. Factors Independently Associated With Recurrent Pneumonia: Cox Multivariable Proportional Hazards Analysis

	Adjusted Hazards Batio (95%	
Factor	confidence interval)	<i>P</i> Value
Age >75 y	1.31 (1.00–1.71)	.047
Male sex	1.00 (.78–1.29)	1.00
Age-subtracted pneumonia severity index (per point)	1.00 (.99–1.01)	.27
Inhaled corticosteroids	1.34 (.98–1.83)	.11
Not fully independent (any impairment in functional status)	1.70 (1.30–2.23)	<.001

(Table 2). In terms of sensitivity analyses, using the same model as our primary analysis, both multivariable logistic regression and competing risks proportional hazards models yielded virtually identical results—the only robust and statistically significant variable associated with recurrent pneumonia was impaired functional status (adjusted odds ratio, 1.61; 95% CI, 1.21–2.14; P = .001; Supplementary Appendix Table 1 and competing risks HR, 1.58; 95% CI, 1.20–2.08; P = .001; Supplementary Appendix Table 2).

"Early" Recurrent Pneumonia

Between 30 days and 90 days post-discharge there was a 2% (70 episodes) rate of recurrent pneumonia. These were episodes that we had excluded a priori. However, if we had included them, the "overall" rate of recurrent pneumonia 30 days following hospital discharge would have been 12% (95% CI, 10%-13%). In terms of age, sex, and other characteristics, the patients with early recurrent pneumonia were very similar to the patients with recurrent pneumonia as we originally defined it (Table 3). However, it is of note that patients with early recurrence appeared more likely to have heart failure or COPD. In a multivariable Cox proportional hazards model constructed as we did for the main analysis but including these 2 additional comorbidities, we again found that any impairment in functional status was significantly associated with early recurrent pneumonia (P = .021; Table 4). Of note, inhaled steroids achieved statistical significance in this analysis (P = .032), while both heart failure (P = .12) and COPD (P = .098) demonstrated a trend toward significance (Table 4).

DISCUSSION

In a population-based prospective cohort study of almost 3000 patients who survived hospitalization with CAP, we found that 1 of 11 would have a recurrent episode of pneumonia within 5 years and that 13% would have more than 1 episode. Despite the availability of comprehensive sociodemographic, clinical, laboratory, and medication-related data, the only statistically

Table 3. Characteristics of 2709 Survivors of Pneumonia Hospitalization According to the Presence or Absence of Early (30-90 Days Post-Discharge) Recurrent Pneumonia

	Early (30–90 d)	No Early	
Characteristic	n = 70 (%)	n = 2639 (%)	P Value
Patient Demographics			
Male	38 (54.3)	1352 (51.2)	.61
Mean age (SD)	72.1 (15.1)	66.8 (18.2)	.016
Age >75 y	34 (48.6)	1101 (41.7)	.26
Markers of Frailty			
Assisted feeding	3 (4.3)	78 (3.0)	.52
Not fully independent	32 (45.7)	884 (33.5)	.033
Nursing home resident	12 (17.1)	410 (15.5)	.71
Underweight (body mass index < 18)	2 (9.5)	49 (6.9)	.64
3+ comorbidities	25 (35.7)	752 (28.5)	.51
Lifestyle Factors			
Chronic alcoholism	5 (7.1)	211 (8.0)	.8
Current smoking	12 (17.1)	707 (26.8)	.07
Comorbidities			
Prior aspiration	2 (2.9)	154 (5.8)	.29
Heart failure	22 (31.4)	509 (19.3)	.012
Chronic obstructive pulmonary disease	26 (51.4)	922 (34.9)	.004
Dementia	5 (7.1)	149 (5.7)	.59
Diabetes mellitus	16 (22.9)	423 (16.0)	.13
Seizure	2 (2.9)	126 (4.8)	.46
Medications and Immuniza	tions		
Angiotensin-converting enzyme inhibitors	16 (22.9)	510 (19.3)	.46
Sedative-Hypnotics	5 (7.1)	323 (12.2)	.2
Inhaled bronchodilators	24 (34.0)	900 (34.1)	.91
Inhaled corticosteroids	21 (30.0)	422 (16.0)	.002
Proton pump inhibitors	11 (15.7)	374 (14.2)	.72
Statins	8 (10.1)	264 (10.0)	.92
Pneumococcal vaccine	6 (8.6)	300 (11.4)	.47
Influenza vaccine	27 (38.6)	787 (29.8)	.12
Pneumonia-Specific Factors	S		
Age-subtracted mean PSI (SD)	34.4 (25.6)	40.3 (27.5)	0.06
Classes I/II	9 (12.9)	596 (22.6)	0.024
Class III	12 (17.1)	563 (21.3)	
Classes IV/V (severe)	49 (70.0)	1480 (56.1)	
Chest Radiograph Finding			
Single-lobe involvement	29 (41.4)	1189 (45.1)	.55
Multilobar involvement	21 (30.0)	619 (23.5)	.2
Bilateral involvement	11 (15.7)	388 (14.7)	.81
Pleural effusion	13 (18.6)	523 (19.8)	.8

Abbreviations: PSI, pneumonia severity index; SD, standard deviation.

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Table 4. Factors Independently Associated With Early (30–90 Days Post-Discharge) Recurrent Pneumonia: Cox Multivariable **Proportional Hazards Analysis**

Factor	Adjusted Hazards Ratio (95% confidence interval)	<i>P</i> Value
Age >75 y	0.98 (.59–1.61)	.94
Male sex	1.10 (.68–1.78)	.69
Age-subtracted pneumonia severity index (per point)	1.00 (.99–1.01)	.29
Heart failure	1.54 (.90–2.64)	.12
Chronic obstructive pulmonary disease	1.56 (.92–2.62)	.098
Inhaled Corticosteroids	1.83 (1.05–3.17)	.032
Not fully independent (any impairment in functional status)	2.15 (1.12–4.10)	.021

significant independent risk factors for recurrent pneumonia that we found in multivariable analysis were a 31% relative increase associated with older age and a 70% relative increase associated with any impairment in functional status.

The 9% incidence of developing recurrent pneumonia within 5 years (median follow-up 3.6 years) we found is similar to the 3-year recurrence rate of 9.4% reported by Garcia-Vidal et al in a study design that included 1556 patients [5]. The other studies that have examined this issue report rates as high as 13%-20%, although these estimates are likely inflated as most studies have not excluded "early" recurrences (ie, those within 30-90 days of hospital discharge) that are more likely to be relapses or recrudescence of the original CAP or acquisition of a new nosocomial pneumonia [3-6]. Including these early recurrences would have inflated our estimate to 12%, perhaps somewhat more in line with earlier published estimates. Furthermore, because losses to follow-up and durations of follow-up times are incompletely reported, some of these studies are perhaps better considered to be describing prevalence (rather than incidence) rates, which might also tend to overestimate recurrence [3, 4, 6]. The apparently higher rates in these studies may, in part, also be explained by inclusion of sicker and less representative patients drawn from single centers [3, 6].

In terms of risk factors for developing the first episode of CAP, much has been written [18-28]. In a recent literature review, Torres et al identified older age, male sex, smoking, chronic alcohol abuse, and being underweight as major nonclinical risk factors for CAP [25]. In addition, they identified preexisting medical conditions such as COPD, other chronic diseases (eg, cardiovascular disease, stroke, Parkinson disease, epilepsy, chronic renal or liver disease), dementia, and swallowing problems as increasing the risk of CAP 2- to 4-fold compared with the healthy population [25]. Some previous literature on recurrent pneumonia has also identified similar nonclinical factors (eg, current smoking, chronic alcoholism, and impaired functional status [4, 5]) and similar comorbidities (eg, COPD, neurological disease, heart failure, and diabetes [3–6]) as well as certain medications (eg, PPIs, inhaled or oral corticosteroids [5, 8]) as being risk factors for recurrent pneumonia.

Surprisingly (except for older age and impairments in functional status), none of these risk factors were independently associated with an increased risk of recurrent pneumonia in our study. Given that our study sample was larger than that of most studies that have examined this question, the comprehensiveness of our data collection, and the completeness and duration of our follow-up, we do not believe that we were examining an atypical population or overadjusting our analyses, rather, we believe that what we observed is an example of "index event bias" [29]. This phenomenon has been repeatedly demonstrated in other fields, wherein a risk factor for developing an acute condition is not a risk factor for developing a recurrence of that same condition or, indeed, the original risk factor may now be protective against recurrence [29]. Examples from other observational studies include the thrombophilia paradox (inherited thrombophilia increases the risk of a first episode of deep venous thrombosis but is not associated with recurrent thrombosis [30]) or the obesity paradox (increased body mass index is associated with coronary disease, but obesity is associated with a reduced risk of myocardial infarction) [31]. In our study, by definition, the entire cohort had already demonstrated (through a congruence of the above-mentioned risk factors) that they were at high risk of an initial episode of CAP; now that they have survived, predicting a recurrent episode appears extremely difficult.

Nevertheless, we did find that any impairment in functional status, as we defined it, was associated with a 70% increased risk of recurrent pneumonia. Coupled with our finding that older age was also a risk factor, we suspect that we captured elements of frailty that predispose to adverse events in general and to pneumonia in particular [32]. This easy-to-capture information aligns with the findings of El Solh et al who reported that impairments in basic activities of daily living were associated with an increased risk of recurrent pneumonia [4]. In addition, our findings might also indirectly corroborate other studies that suggest very modest physical activity (eg, walking 0.5–1 hour per day) is protective against developing pneumonia [18, 21].

Despite its strengths, our work has several important limitations. First, while the initial CAP episode was based on a clinical radiographic diagnosis, the recurrent episodes were based on linked administrative data. Particularly for the one-third of episodes that did not require hospital admission, it is possible that patients had only severe lower respiratory tract infections or alternate diagnoses and they may or may not have had radiographic confirmation of their illness. This is an important limitation, although prior validation studies suggest that ICDbased claim codes have very good sensitivity (74%– 93%) and very high specificity (97%-99%) for a diagnosis of pneumonia [14, 15]. In our dataset we previously demonstrated that patients with a clinical diagnosis of pneumonia without radiographic confirmation had the same rates of positive bacterial confirmation by blood or sputum, morbidity, and mortality, suggesting that a confirmatory chest radiograph may not be so critically important as often thought [33]. Second, we did not have epidemiologic (eg, community vs healthcare-acquired), microbiologic, or antibiotic treatment-related information about the recurrent episodes. Third, while we had detailed clinical data about our cohort, this information was not updated over the course of follow-up, and new risk factors may have supervened, whether increasing risk (eg, recent severe stroke) or decreasing risk (eg, starting ACE inhibitors). Last, our source population had pneumonia of sufficient severity that they were admitted to the hospital, were discharged, and survived at least 90 days in the community. Thus, this may not be a representative population, particularly as it relates to those with pneumonia treated on an outpatient basis or those with "early" recurrences.

In conclusion, 9% of inpatients who survive an episode of CAP will have a recurrent episode over the next 5 years, and those with any impairment in functional status appear to be at particularly increased risk. We believe that recurrent pneumonia is sufficiently common that more attention should be paid to preventive strategies at the time of discharge (eg, medication review, up-to-date immunizations, advice to seek medical attention sooner rather than later with development of symptoms of lower respiratory tract infection), closer follow-up of patients with signs of frailty, and perhaps a lower threshold to diagnose and treat pneumonia over the longer term in those who have survived a previous episode.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Contributions. S. R. M. and D. T. E. had full access to all study data and take responsibility for the integrity of the data and the accuracy of the analysis. All authors participated in study conception, design, interpretation, and critical revisions and have seen and approved the final manuscript. T. T. D. drafted the initial manuscript. D. L. W. and D. T. E. undertook all analyses. S. R. M., D. T. E., and T. J. M. obtained funding and supervised the study. S. R. M. will act as guarantor.

Financial support. This research was supported by grants from the Canadian Institutes of Health Research (CIHR), the Alberta Heritage Foundation for Medical Research (AHFMR), Alberta Innovates Health Solutions (AIHS), grants-in-aid from Capital Health, and unrestricted grants to T. J. M. from Abbott Canada, Pfizer Canada, and Jannsen-Ortho Canada. D. T. E. receives salary support awards from AHFMR and AIHS (Population

Health Investigator) and CIHR (New Investigator). S. R. M. receives salary support awards from AHFMR and AIHS (Health Scholar) and holds the Endowed Chair in Patient Health Management (Faculties of Medicine and Dentistry and Pharmacy and Pharmaceutical Sciences, University of Alberta).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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