ORIGINAL ARTICLE 10.1111/j.1469-0691.2009.02918.x

# Aetiology of, and risk factors for, recurrent community-acquired pneumonia

**C. Garcia-Vidal[1], J. Carratalà[1], N. Fernández-Sabé[1], J. Dorca[2], R. Verdaguer[3], F. Manresa[2] and F. Gudiol[1]**

1) *Infectious Disease,* 2) *Respiratory Medicine and* 3) *Microbiology Services, Institut d'Investigació Biomèdica de Bellvitge-Hospital Universitari de Bellvitge (IDIBELL), University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain*

## Abstract

Recurrent community-acquired pneumonia (CAP) requiring hospitalization is a matter of particular concern. However, current information on its prevalence, aetiology and risk factors is lacking. To address these issues, we performed an observational analysis of a prospective cohort of hospitalized adults with CAP. Recurrence was defined as two or more episodes of CAP 1 month apart within 3 years. Patients with severe immunosuppression or local predisposing factors were excluded. Of the 1556 patients, 146 (9.4%) had recurrent CAP. The most frequent causative organism was *Streptococcus pneumoniae*, both in patients with recurrent CAP and in those without recurrence. *Haemophilus influenzae*, other Gram-negative bacilli and aspiration pneumonia were more frequent among patients with recurrent CAP, whereas *Legionella pneumophila* was rarely identified in this group. Independent factors associated with recurrent CAP were greater age, lack of pneumococcal vaccination, chronic obstructive pulmonary disease (COPD) and corticosteroid therapy. In a sub-analysis of 389 episodes of pneumococcal pneumonia, the only independent risk factor for recurrence was lack of pneumococcal vaccination. Recurrence of CAP is not a rare clinical problem and it occurs mainly in the elderly, patients with COPD, and those receiving corticosteroids. Our study provides support for recommending pneumococcal vaccination for adults at risk of pneumonia, including those with a first episode of CAP.

**Keywords:** Chronic obstructive pulmonary disease, community-acquired pneumonia, pneumococcal pneumonia, pneumococcal vaccination, recurrence

**Original Submission:** 29 November 2008; **Revised Submission:** 4 February 2009; **Accepted:** 5 February 2009

Editor: M. Paul

**Article published online:** 10 August 2009

*Clin Microbiol Infect* 2009; **15:** 1033–1038

**Corresponding author and reprint requests:** J. Carratalà. Infectious Disease Service, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain
**E-mail: jcarratala@ub.edu**

## Introduction

Community-acquired pneumonia (CAP) is one of the most common infections [1]. More than four million adults per year in the USA present with CAP, and at least 20% of these will need hospitalization. This represents a substantial societal burden in terms of mortality, morbidity and economic cost [2]. The average cost of an episode of CAP in the USA in a hospitalized patient has been estimated as $6000–7000 [3]. While most patients experience a single episode of CAP, some have recurrent episodes; in fact, Osler regarded recurrence in pneumonia as more common than in any other acute infectious disease. In the pre-antibiotic era, the incidence established for recurrent CAP ranged between 13.6% and 22% of episodes. Nevertheless, since the introduction of antibiotics and vaccination, recurrent CAP has received scant attention [4–6].

Clinicians are well aware that aging, cigarette smoking, heavy alcohol intake, and conditions such as chronic obstructive pulmonary disease (COPD) predispose to CAP development [7]. Furthermore, local pulmonary disorders, conditions predisposing to aspiration, and innate or acquired immunodeficiency are well-known causes of recurrent pneumonia [8–10]. This prospective study was designed to determine the prevalence and aetiology of recurrent CAP, and the risk factors for recurrence, in a large cohort of hospitalized adults who were not severely immunosuppressed and who did not have local predisposing factors.

## Methods

### Setting, patients, and study design

The study was carried out in a 900-bed university hospital for adults in Barcelona, which serves an area of 1 100 000 inhabitants and admits approximately 24 000 patients per

year. In Catalonia, a region in the northeast of Spain with a population of approximately seven million people, 23-valent polysaccharide pneumococcal vaccine is recommended for people aged ≥65 years and in younger persons with medical conditions that place them at increased risk.

From 1995, all patients with CAP requiring hospitalization have been prospectively recorded at our institution, and have been the subject of previous studies [11–15]. In the present investigation, all non-severely immunosuppressed adults hospitalized with CAP from January 1, 1995 through December 31, 2005 were analysed. Patients with neutropenia, immunoglobulin deficiencies, HIV infection, and those who underwent transplantation or splenectomy, as well as those who were receiving immunosuppressant treatment and/or high-dose corticosteroids (>20 mg/day of prednisone or its equivalent) were not included. Cases in which the time elapsed since the initial diagnosis of pneumonia to the current study was less than 3 years were not included. Patients who died (≤30 days after hospitalization) and those who had a new episode of CAP requiring hospitalization <1 month or >3 years after the first episode were excluded. We also excluded patients with local predisposing factors, including bronchial stenosis or compression, bronchiectasis, or endoluminal lesions such as foreign bodies or malignancy.

Patients who received a diagnosis of CAP were divided into two groups: patients who experienced two or more episodes of pneumonia within a 3-year interval separated by an asymptomatic period of at least 1-month, and those who did not have any recurrence requiring a new admission in the study hospital within 3 years of pneumonia diagnosis. These groups are referred to as recurrent pneumonia and non-recurrent pneumonia, respectively. This prospective, longitudinal and observational study was approved by the Ethics Committee of our institution.

#### Clinical evaluation and follow-up

At the initial visit, before empirical antibiotic therapy was started, the clinical history and the results of complete physical examination were recorded. Two sets of blood samples were obtained and cultured and, when available, a sputum sample was evaluated by use of Gram staining and culture. Urinary antigen detection tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed if indicated by the attending physician. Paired serum samples during the acute and convalescent phases of infection (separated by a 3–8 week interval) were also obtained for serological studies.

Antibiotic therapy was administered according to the hospital guidelines, which recommended the administration of a $\beta$-lactam (ceftriaxone or amoxicillin-clavulanate) with or without a macrolide or a fluoroquinolone. Combination therapy was recommended for patients with clinical suspicion of *Legionella* or an atypical pathogen, or in the absence of a demonstrative sputum Gram stain. Levofloxacin monotherapy was allowed for selected cases. Concordance of antibiotic therapy was examined for all cases with an aetiological diagnosis, according to susceptibility test criteria for classical respiratory pathogens.

Patients were seen daily during their hospital stay by one or more of the investigators, who provided medical advice when requested and recorded demographic characteristics, underlying disease, clinical features, vaccination status, causative agents, therapy, and outcomes. A long-term follow-up visit took place 1 month after discharge. Pneumococcal vaccination was then offered to all unvaccinated patients.

#### Definitions

Community-acquired pneumonia was defined as the presence of a new infiltrate on a chest radiograph plus one or more of the following: fever (temperature ≥ 38.0°C) or hypothermia (temperature < 35.0°C), new cough with or without sputum production, pleuritic chest pain, dyspnea, and altered breath sounds on auscultation. Tobacco abuse was recorded when a patient had smoked more than ten cigarettes per day for at least 1 year preceding the study, as was alcohol consumption when a patient had consumed more than 80 g of alcohol daily for at least 1 year preceding the study.

#### Vaccination status

Vaccination status was assessed from interview with the patients or their relatives and review of hospital and personal health records (vaccination card). A patient was considered to have been pneumococcal-vaccinated if 23-valent polysaccharide pneumococcal vaccine had been administered in the 5 years before admission, as documented in the records of the hospital and primary healthcare centre. A patient was considered to be influenza-vaccinated if influenza vaccine had been administered during the year prior to admission.

#### Microbiological studies

The investigation of pathogens in blood, normally sterile fluids, sputum and other samples, was performed by standard microbiological procedures. *Streptococcus pneumoniae* antigen in urine was detected by using a rapid immunochromatographic assay (NOW assay; Binax Inc, Portland, Maine, USA). *Legionella pneumophila* serogroup 1 antigen in urine was detected by an immunochromatographic method (NOW *Legionella* Urinary Antigen Test; Binax Inc). Standard serological methods were used to determine antibodies against the