Invasive pneumococcal disease in patients with an underlying pulmonary disorder

M. Inghammar[1,2], G. Engström[3], G. Kahlmeter[4], B. Ljungberg[1], C.-G. Löfdahl[2] and A. Egesten[2]

1) *Section for Infection Medicine, Department of Clinical Sciences Lund, Lund University, Skåne University Hospital,* 2) *Section for Respiratory Medicine and Allergology, Department of Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund,* 3) *Cardiovascular Epidemiology Research Group, Department of Clinical Sciences Malmö, Lund University, Skåne University Hospital, Malmö and* 4) *Department of Clinical Microbiology, Central Hospital, Växjö, Sweden*

Abstract

Chronic pulmonary disease is a recognized risk factor for invasive pneumococcal disease (IPD). However, previous studies have often not been large enough to allow detailed analyses of less prevalent pulmonary diseases, and findings regarding case fatality have been inconsistent. We examined the associations between an underlying pulmonary disease and IPD, and the impact of these diseases on the case fatality rate. Patients with IPD $\geq$18 years of age, between 1990 and 2008, were identified in microbiological databases. The associations between IPD and the pulmonary diseases were assessed using conditional logistic regression, comparing IPD cases to ten control subjects per case, randomly selected from the general population (matched for gender, year of birth and county of residence). Adjustments were made for other co-morbidities, level of education and socio-economic status, 4085 cases of IPD and 40 353 controls were identified. A more than four-fold increased risk of IPD was seen in chronic obstructive pulmonary disease, a doubled risk in asthma and a five-fold increased risk in subjects with pulmonary fibrosis. In univariate analysis, sarcoidosis and bronchiectasis were associated with a two-fold to seven-fold increase in the risk of IPD, but there was no statistical support for the associations when adjustments for confounders were made. No increased risk was seen in subjects with a history of pneumoconiosis or allergic alveolitis. The mortality following IPD was not increased in patients with chronic obstructive pulmonary disease, asthma, pulmonary fibrosis or bronchiectasis. Several chronic pulmonary diseases increase the risk of IPD but mortality following IPD seems not to be affected.

Keywords: Asthma, chronic obstructive pulmonary disease, epidemiology, pneumococcal infections, pulmonary fibrosis, sarcoidosis
Original Submission: 30 September 2012; **Revised Submission:** 10 December 2012; **Accepted:** 26 January 2013
Editor: M. Paul
Article published online: 7 March 2013
Clin Microbiol Infect 2013; **19:** 1148–1154
10.1111/1469-0691.12182

Corresponding author: M. Inghammar, Department of Infectious Diseases, Skåne University Hospital, SE-221 85 Lund, Sweden
E-mail: Malin.Inghammar@med.lu.se

Introduction

Streptococcus pneumoniae is an encapsulated Gram-positive pathogen with the potential to cause invasive disease. It is a major cause of community-acquired pneumonia and bacterial meningitis. In Sweden, invasive pneumococcal disease (IPD) has been a notifiable disease since 2004, and around 1500 cases are reported annually to the Swedish Institute for Communicable Disease Control, corresponding to an annual incidence of 15–19 cases/100 000 inhabitants [1].

Chronic obstructive pulmonary disease (COPD) and, recently, asthma [2] are recognized risk factors for acquiring IPD, but risk estimates published in previous studies are often based on case series or studies with aggregated denominator data on co-morbidities, and have in many cases, not been large enough to allow multivariate analysis or detailed analysis of less prevalent pulmonary diseases [3,4]. In addition, it is not clear whether an underlying pulmonary disease increases the risk of death following IPD [3,5,6].

In this large population-based case–control study, nested in the population of southern Sweden, an area with around 1.6 million inhabitants, we examined the association between a

history of chronic pulmonary disease and IPD, and the effect of underlying pulmonary diseases on mortality following IPD, comparing IPD cases with randomly selected control subjects from the general population.

Methods

Ethics

The study was approved by the Lund University Research Ethics Committee (203/2008, 223/2009, 398/2011).

Setting

Swedish health care is publicly financed, with few private care-givers in secondary care. A unique, lifelong ten-digit personal identity number assigned to each person living in Sweden provides the possibility of cross-referencing information in national databases.

Case retrieval and control selection

All individuals $\geq$18 years of age, living in southern Sweden, showing growth of *S. pneumoniae* in a culture from a normally sterile site (e.g. blood, cerebrospinal fluid, pleural effusion) were identified in the databases at the seven microbiological laboratories covering the area (Kristianstad 1991–2008, Lund 1991–2008, Malmö 1990–2008, Halmstad 1995–2008, Kalmar 1990–2008, Karlskrona 1994–2008 and Växjö 1987–2008). For each case, ten control subjects were randomly selected from the general population, matched for gender, year of birth and county of residence on 31 December the year before the diagnosis of IPD. All cases and controls were cross-referenced to national databases to obtain personal information on vital status, and information on level of education and socio-economic status.

Co-morbidity

Through linkage with the National Inpatient Registry and the Cancer Registry information was obtained on all available hospital discharge and cancer diagnoses. The Inpatient Registry has been operating in southern Sweden since the early 1970s, apart from the counties of Kronoberg (1987) and Blekinge (1984). It came into operation nationwide in 1987. Visits to hospital outpatient clinics and emergency departments have been recorded nationwide since 2001.

The following chronic pulmonary diseases were taken into consideration: COPD, asthma, pulmonary fibrosis, sarcoidosis, bronchiectasis, allergic alveolitis and pneumoconiosis registered >30 days to 5 years before the first IPD diagnosis or the corresponding date in control subjects. In addition, we noted discharge diagnoses of other non-pulmonary diseases conferring increased risk of IPD, liver disease, renal failure, heart failure, cerebrospinal fluid leakage, rheumatoid arthritis and other connective tissue diseases, alcohol-related diseases, diabetes mellitus, haematological and non-haematological cancer, human immunodeficiency virus infection and immunodeficiency [4]. Codes for transplantation and splenectomy were noted for the total Inpatient Registry period up to 30 days before index. The specific codes according to the International Classification of Diseases can be found in the Supplementary information, Appendix S1.

Chart review

General validation studies of the Inpatient Registry indicate that coverage is above 98% and that almost 90% of the diagnoses reported are correct [7]. We have previously validated the diagnosis of COPD in the Inpatient Registry in this cohort. The degree of certainty of the diagnosis varied, but < 10% were considered misclassified or having an uncertain COPD diagnosis [8]. A subset of the other pulmonary diagnoses from the four major hospitals in the county of Skåne (Helsingborg, Kristianstad, Lund and Malmö), was validated against the original medical records. The estimated diagnostic accuracy was as follows: asthma (n = 198) 80%, sarcoidosis (n = 17) 95%, pneumoconiosis (n = 7) 100%, pulmonary fibrosis (n = 41) 85% and bronchiectasis (n = 13) 85%.

Statistical analyses

Chi-squared tests, Fisher's exact test and t-tests were used to assess the risk factors for IPD and risk factors for in-hospital mortality and death within 28 days of IPD diagnosis. The associations between IPD and underlying pulmonary diseases were assessed using conditional logistic regression. Separate models were fitted for each pulmonary disease. Adjustments were made for other chronic non-pulmonary diseases, total duration of hospital stay, level of education and socio-economic status. Interactions between disease status, age at inclusion, gender and time since the previous hospital visit for pulmonary disease, on outcome were assessed by examining odds ratios in different strata of the covariates and by including interaction terms in the fully adjusted models.

The associations between death within 28 and 90 days of IPD diagnosis and underlying lung disease were assessed using logistic regression, adjusted for age, gender, clinical presentation and other co-morbidities. Likelihood ratio tests were performed to test for differences and interactions. All analyses were performed using STATA/SE (version 10.1 for Windows; StataCorp LP, College Station, USA).