

## THE EPIDEMIOLOGY OF ORGANIZING PNEUMONIA IN ICELAND.

Gunnar Gudmundsson (1)

Olafur Sveinsson (1)

Helgi J Isaksson (2)

Steinn Jonsson (1)

Halla Frodadottir (1)

Thor Aspelund (3)

1. Department of Respiratory Medicine, Allergy and Sleep, Landspítali University Hospital, Reykjavik, Iceland
2. Department of Pathology, Landspítali University Hospital, Reykjavik, Iceland
3. The Icelandic Heart Association, Kopavogur, Iceland

### Correspondence

Gunnar Gudmundsson, MD, PhD

Department of Respiratory Medicine, Allergy and Sleep

Landspítali University Hospital, E-7 Fossvogur

IS-108 Reykjavik, Iceland

Tel. +354-5436876, Fax +354-5436568, E-mail: [ggudmund@landspitali.is](mailto:ggudmund@landspitali.is)

Keywords: idiopathic interstitial pneumonia, organizing pneumonia, bronchiolitis obliterans, incidence, prognosis

Running title: Organizing pneumonia in Iceland

Publication licence: "the Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in [THORAX] editions and any other BMJPG Ltd products to exploit all subsidiary rights, as set out in our licence . (<http://thorax.bmjournals.com/ifora/licence.pdf>).

**Abstract**

Cryptogenic organizing pneumonia (COP) represents what has also been called Idiopathic Bronchiolitis Obliterans Organizing Pneumonia. In secondary organizing pneumonia (SOP) causes can be identified or it occurs in a characteristic clinical context. The aim of this study was to determine the incidence and epidemiological features of COP and SOP nationwide in Iceland over an extended period.

A retrospective study of OP in Iceland over twenty years was conducted and epidemiology and survival were studied. All pathology reports of patients diagnosed with or suspected of having COP or SOP in the period 1984–2003 were identified and all pathology samples were re-evaluated using strict diagnostic criteria.

After re-evaluation 104 patients fulfilled diagnostic criteria for OP, 58 as COP and 46 as SOP. The mean annual incidence for OP was 1.97/100,000 inhabitants. Annual incidence for COP was 1.10/100,000 and 0.87/100,000 for SOP. The mean age at diagnosis was 67 years with a wide age range. The most common causes of death were lung diseases other than OP and only one patient died from OP. Patients with OP had decreased survival compared to the general population but there was no statistical difference between COP and SOP.

The incidence of OP is higher than previously reported, suggesting that OP needs to be thought of more often than has been done in the past.

## Introduction

The diagnosis of organizing pneumonia (OP) is based on a characteristic histological pattern in the presence of certain clinical and radiological features. The histological pattern is characterized by polypoid connective tissue masses composed of myxoid fibroblastic tissue resembling granulation tissue filling the lumens of terminal and respiratory bronchioles and extending in a continuous fashion into alveolar ducts and alveoli, representing an organizing pneumonia [1]. It is called cryptogenic organizing pneumonia (COP) when no definite cause or characteristic clinical context is found [2]. In secondary OP (SOP) causes can be identified such as infection or it occurs in a characteristic clinical context such as connective tissue disorder. Recently a classification for idiopathic interstitial pneumonias has been published [2]. Cryptogenic organizing pneumonia is one of several subtypes and represents what has also been called idiopathic bronchiolitis obliterans organizing pneumonia (BOOP). Most reports of BOOP/COP are small case series or single case reports [3][4]. Therefore the epidemiology is not well described and not much is known about the incidence of these diseases. The present study compares cases of COP and SOP over a 20 year period in a nationwide study in Iceland with respect to epidemiology and outcome. The aim of this study was to determine the incidence rate, survival and causes of death for COP and SOP in Iceland over a twenty-year period, 1984–2003. This is the first nationwide survey where the incidence of both COP and SOP is determined in the same time period, using strict diagnostic criteria in a homogenous population. This is a retrospective study with no referral bias affecting the results.

## Materials and methods

### Clinical data

Information on all patients diagnosed with OP from 1984 to 2003 was obtained by specific ICD codes from computerized hospital records and from specific codes from computerized Pathology reports. The International Classification of Diseases (ICD) is designed for the classification of morbidity and mortality information for statistical purposes, and for the indexing of hospital records by disease and operations, for data storage and retrieval. ICD is published by the World Health Organization (WHO). For this study records on patients with the following codes were evaluated: J68, J70, J84 and J98. All lung specialists in Iceland (total of 14 at the end of the study period) were also asked to provide information about patients diagnosed with OP during this time period. All of them gave information on patients with OP.

Clinical data were collected from clinical records from hospitals and private offices with a standardized data sheet and were reviewed by two of the investigators. The study was approved by the National Data Protection Agency of Iceland and National Ethics Committee.

**Catchment Area.** The population of Iceland increased during the study period from 239,498 in 1984 to 289,272 in 2003 or 17.2 %. About 60% of the population lives in the capital, Reykjavik, and the greater Reykjavik area. All information regarding the size of the population, age, sex distribution and cause of death (death certificates) was obtained from the Statistics Iceland (the National Statistical Institute of Iceland).

### Pathology

All pathology specimens in Iceland are evaluated at the Department of Pathology at Landspítali University Hospital in Reykjavik and the Department of Pathology at Akureyri Regional Hospital. Both departments use the SNOMED (Systematized Nomenclature Of Medicine) coding system. The following codes were used: T26000-T28900, M45700, which is a morphologic code for OP and M40000-M49990, D7325-7705 to cover all other inflammatory and interstitial lung disorders. SNOMED is published by the College of American Pathologists. All specimens were reviewed by one pathologist (HJI) and those that were classified as OP were used for this study. All glass slides and paraffin tissue blocks are stored indefinitely. When needed recuts and special stains were made. After review some cases were excluded from the study. To make a diagnosis of OP, the pattern of organizing pneumonia had to be prominent and not an accessory finding of another well-defined pattern of idiopathic interstitial pneumonia. The diagnosis of OP was ruled out if biopsies showed prominent cellular and significant interstitial fibrosis, fibroblastic foci, granulomas, hyaline membranes, vasculitis and prominent eosinophilia [2].

### Inclusion criteria

All patients enrolled in the study were required to meet the following criteria: 1) radiologic lung infiltrates or nodules; 2) lung biopsy, transbronchial or surgical confirming OP; 3) a well documented improvement that was either spontaneous or after immunosuppressive treatment, usually corticosteroids. Clinical criteria were applied to

patients after screening of patients' records. Pathology was then evaluated. Some cases did not qualify for pathology and were therefore excluded.

Clinical criteria or the clinical context of the case were used to classify cases as SOP; if none of these criteria were met, the case was classified as COP.

Post infectious: if the patient had symptoms and signs consistent with the diagnosis of respiratory infection and positive cultures or serology or antigen detection for a known bacteria, virus or other pathogen at the time of diagnosis.

Drug related: if onset of OP was in relation to drug treatment and the drug was previously known to cause OP and no other cause could be found.

Radiotherapy related: if onset of OP was in relation to radiotherapy to the chest or surrounding area and no other cause could be found.

Rheumatologic disorder: if the patient had a previous diagnosis of rheumatologic disease and no other cause could be found.

### **Causes of death**

Three methods were used to determine the cause of death. First autopsy reports were used, secondly we used hospital records. Third: death certificates from Statistics Iceland were obtained and reviewed. Time to death was based from time of diagnosis to death.

### **Statistical analysis**

The calculation of the annual incidence per 100,000 was based on the number of inhabitants on July 1 of each year. It was assumed that the number of cases each year follow a Poisson distribution, and the incidence rates were analyzed with a Poisson regression model using age, sex and period specific population size as an offset term. The average annual increase in the incidence was estimated by a linear Poisson regression model both overall and by age-groups. The Poisson model was used to test for interaction between age group and incidence increase. Age at diagnosis was compared between time-periods by ANOVA. Mortality between patients and the population was compared using the standardized mortality ratio approach [5]. It is based on the total observed deaths versus the total expected deaths estimated by computing individual expected cumulative hazards. Survival rates for the study group were estimated using the Kaplan-Meier method. Survival rates for a reference population were based on the cohort expected survival approach by Hakulinen as outlined in [6]. Both the individual expected cumulative hazards and the expected cohort survival rates were constructed from age and sex matched survival rates in a national life table from Statistics Iceland of 1993. The significant level was set at 0.05. The data analysis for this paper was performed using SAS software version 9.1. Copyright, SAS Institute Inc.

## Results

Using the strict criteria we identified 104 patients with OP during the study period. Table 1 shows the demographic data for the patients.

Table 1. Number of patients, gender, median age of patients and mean annual incidence for OP

	Cryptogenic OP	Secondary OP	Total
Number of patients	58	46	104
Male/Female	31/27	25/21	56/48
Median age at diagnosis (range)	66 (15-87)	70 (26-83)	67 (15-87)
Mean annual incidence per 100,000			
Male	1.13 (0.79-1.62)	0.94 (0.64-1.40)	2.08 (1.60-2.71)
Female	1.06 (0.73-1.53)	0.80 (0.52-1.22)	1.86 (1.41-2.46)
Total	1.10 (0.85-1.42)	0.87 (0.65-1.16)	1.97 (1.62-2.39)

There were 58 patients with COP and 46 patients with SOP. There were similar numbers of males and females and median age at diagnosis was same in both groups. Overall the mean age was 67 with standard deviation of 14. Figure 1 shows the wide age distribution found in the study. The age range was from 15 years to 87 years. Comparing the age distribution between the time-periods 1984-1988, 1989-1994, 1995-1999, and 2000-2003 resulted in a non-significant difference ( $p=0.64$ , ANOVA). During the study period the mean age at diagnosis remained similar but was found to be higher from year 2000 as can be seen in Table 2.

Table 2. Mean age by study period

Time period	Number diagnosed	Mean age	Standard deviation
1984-1989	12	64,8	16,4
1990-1994	16	63,4	13,4
1995-1999	41	63,1	14,0
2000-2003	35	67,1	14,2

The incidence of both COP and SOP increased but COP more consistently than SOP. The incidence of OP increased significantly ( $p<0.0001$ ). The annual incidence for OP is summarized in Figure 2 by time period and age groups. The mean annual OP incidence for 1984-2003 was 1.97 (95% CI 1.63 – 2.39). During 2000-2003 the average annual OP incidence was 3.06 (95% CI 2.20 – 4.26). On average the OP incidence rose by 8.1% (4.4%-12.2%) per year as shown in Table 3.

Table 3. Average yearly increase in incidence by age group and for all

Age group	Increase in incidence	95% Confidence interval
<60	7.9%	0.8% - 15.5%
60-74	8.2%	2.0% - 14.7%

75+	8.1%	7.6% - 16.0%
All	8.1%	4.1% - 12.2%

This increase in OP incidence was not different among the age groups ( $p=0.99$ ). During the study period and follow-up 45 patients died. The most common causes of death were lung diseases other than OP. Of those chronic obstructive pulmonary disease (COPD) was most common. Other causes of death are shown in Table 4.

Table 4. Causes of death in patients with organizing pneumonia

	Total	COP	SOP
Organizing pneumonia	1	1	0
Other lung diseases	14	5	9
Heart diseases	11	5	6
Cerebrovascular diseases	4	0	4
Hematologic/oncologic diseases	13	6	7
Other causes	2	1	1
Total	45	18	27

Only one patient died from OP and had the rapidly progressive form. One patient died from steroid related complications. The mortality rates in COP and SOP were significantly higher than in the general population as shown in Figure 3. The standardized mortality in OP was 2.7 (SE 0.4). The standardized mortality ratio in COP was 2.6 (SE 0.6) and for SOP 2.9 (SE 0.6). There was no difference in mortality between COP and SOP ( $p=0.7$ ).

## Discussion

This is the first nationwide study reporting the mean annual incidence of both COP and SOP. The period 1984–2003 was chosen because of excellent computerized hospital records for both pathology and discharge diagnosis. As we did a very thorough search, we believe we succeeded in retrieving all relevant pathology reports in the time period. We believe that this study includes all cases of OP diagnosed in Iceland during the study period.

Our results show that the mean annual incidence of COP and SOP is higher in Iceland than previously reported in a more limited population [7]. This high incidence is established despite the fact that strict diagnostic criteria were used.

A study from Olmstead county in Minnesota found an age- and sex adjusted annual incidence for OP of 0.85 per person years (95% CI 0.24-1.45 per 100.000) [7]. A report on the incidence of interstitial lung diseases (ILD) in Spain showed estimated incidence of 7.6 per 100.000/year and COP was estimated to be 10.4% of cases [8]. A study from Germany showed that COP was 6.8% [9] and in Italy it was 5% of all ILD cases [10]. All of these studies are registries of patients seen by respiratory medicine centers. They are subject to selection bias and do not permit an estimate of the real incidence of COP. A study from Bernalillo county in New Mexico showed that the incidence of ILD was 32 per 100.000/year in males and 26 per 100.000/year in females [11]. They reported COP in 1 (0.5%) of 202 patients registered over 48 months. That is the only population based registry of all ILD published to date. It is however only a two-year registry unlike ours that is over 20 years.

Overall the incidence of OP is increasing during the study period. This could have many different explanations. First of all physicians were not familiar with the disease during the first part of the study period. Secondly there were increasing numbers of respiratory specialists in Iceland during the study period and more bronchoscopies were done. Thirdly there was increasing use of medications and treatments that can cause SOP during the study period that could lead to more cases. However the greatest rise in incidence during the study period was in COP rather than SOP. The fluctuations in the incidence of SOP may be in part due to that these patients are diagnosed and treated without a biopsy if physicians are confident with the diagnosis, which is less likely to occur if the diagnosis is unclear.

The age distribution in our study suggests that this is a disease that can occur from adolescence until old age but most of the patients are elderly. These results are in agreement with the study by Cazzato et al from Italy [12]. The median age in our study is similar to other studies [7].

The current study shows that mortality for OP is higher than in the general population but similar for both COP and SOP. There was a trend for a higher mortality in the SOP group than the COP group but it was not statistically significant. In the Mayo Clinic study patients with SOP had higher mortality compared to COP but for all causes it was similar [7]. One possible explanation for the difference is that we did not classify the focal nodular variant as a separate entity. It is possible that having OP sensitises the patient for premature death. One explanation could be the systemic inflammation that OP

causes which could have effect in different organs, including the cardiovascular system [3]

Our result on the causes of death for patients with COP and SOP are in agreement with the study by Lohr et al. that the most common cause of death was respiratory [7]. We describe a low mortality from the disease itself, but patients die from other respiratory causes and their underlying disease. It was common for patients in our study to have underlying lung disease when diagnosed with OP. After OP had been cured there was often continuing progression of the underlying disease such as COPD that lead to death. Deaths from treatment related complications were rare.

The fact that our study is nationwide with no reference bias, long time period of registration, excellent computerized records of all cases and long follow-up time lends strength to our results.

Among weaknesses of the study is the small population of the country and basing causes of death on death certificates, which have been found to be inaccurate for interstitial lung diseases [13]. We used cases diagnosed with surgical biopsy that has been called definite OP and cases diagnosed with transbronchial biopsy obtained by flexible bronchoscopy. It has been suggested that these cases be called probable cases [3]. By doing this we get more cases and more accurate estimate of the incidence of the disease than by using cases diagnosed with surgical biopsy alone. We are in an agreement with what has been suggested that the diagnosis of OP can be made fairly accurately with transbronchial biopsy [14].

In summary this study compares COP and SOP and estimates incidence in a nationwide population based study. The mean annual incidence is about 1.97 per 100.000 and is higher than some other studies have suggested. It is a disease that can occur in all age groups but is more common in elderly individuals. It leads to increased mortality compared to the general population but there is no difference in mortality between the cryptogenic and secondary form.

### **Acknowledgements**

This study was funded by Landspítali University Hospital Scientific Fund, Icelandic Thoracic Society Research Fund and Oddur Olafsson Memorial Fund in Iceland. The authors would like to thank all pulmonary specialists in Iceland for sharing information for this study.

### **Ethics approval**

The study was approved by the National Data Protection Agency of Iceland in Reykjavik, Iceland and the National Ethics Committee in Reykjavik, Iceland.

### **Statement of conflicting interests**

none for all the authors

### **Figure legends**

Figure 1. Age distribution for organizing pneumonia in Iceland

Figure 2. OP incidence by year and age groups.

Figure 3. Kaplan-Meier curve of observed and expected survival in 104 patients with organizing pneumonia in Iceland

**References**

1. Colby TV. Pathologic aspects of bronchiolitis obliterans organizing pneumonia. *Chest* 1992;102: 38S-43S.
2. American Thoracic Society/European Respiratory Society Classification of the idiopathic interstitial pneumonias: international multidisciplinary consensus. American Thoracic Society/European Respiratory Society. *Am J Respir Crit Care Med* 2002;165: 277-304.
3. Cordier JF. Cryptogenic organizing pneumonia. *Clin Chest Med* 2004;25: 727-738.
4. Epler GR. Bronchiolitis obliterans organizing pneumonia. *Arch Intern Med* 2001;161: 158-164.
5. Berry G. The analysis of mortality by the subject-years method. *Biometrics* 1983, 39: 173-84.
6. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. Springer 2001.
7. Lohr RH, Boland BJ, Douglas WW et al. Organizing pneumonia: features and prognosis of cryptogenic, secondary, and focal variants. *Arch Intern Med* 1997;157:1323-1329.
8. Xaubet A, Ancochea J, Morell F et al. Report on the incidence of interstitial lung diseases in Spain. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21: 64-70.
9. Schweisfurth H. Mitteilung der wissenschaftliches Arbeitsgemeinschaft fur die Therapie Lungenkrankheiten (WATL): Deutcher Fibrosereregister mit ersten Ergebnissen. *Pneumologie* 1996; 50:899-901.
10. Agostini C, Albera C, Bariffi F et al. First report of the Italian Register for diffuse lung disorders. *Monaldi Arch Chest Dis* 2001;56:364-368.
11. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Resp Crit Care Med* 1994;150:967-972.
12. Cazzato S, Zompatori M, Baruzzi G et al. Bronchiolitis obliterans-organizing pneumonia: an Italian experience. *Respir Med* 2000; 94:702-708
13. Coultas DB, Hughes MP. Accuracy of mortality data for interstitial lung diseases in New Mexico, USA. *Thorax* 1996; 51:717-20
14. Cordier JF. Organizing pneumonia. *Thorax* 2000; 55:318-328.





