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SELECTED REPORT

Comparison of registries of interstitial lung diseases in three European countries

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Comparison of registries of interstitial lung diseases in three European countries. M.J. Thomeer, U. Costabel, G. Rizzato, V. Poletti, M. Demedts. ©ERS Journals Ltd 2001.
ABSTRACT: Few published studies have compared epidemiological data on the prevalence, incidence or relative frequency of the different interstitial lung diseases. In this review, the data of such registries from three countries in Europe (Belgium, Germany and Italy) are compared with those in the USA (Bernalillo County, NM).

These registries show some striking similarities, but also discrepancies, which in part may be real, but may also be due to selection bias. Indeed, the registries in the European countries encompass the patients seen by pulmonologists, while the registry in Bernalillo County is based on a general population study in a limited area. In addition, in some studies, prevalences and incidences were registered, while in others, only prevalences or incidences were registered. Finally, most, but not all studies were prospective.

Nonetheless, the different studies showed that sarcoidosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, interstitial lung diseases due to collagen vascular diseases and not-defined (or postinflammatory) fibrosis were most frequent. In the majority of disease entities a male predominance was found. Surprisingly large differences in the use of diagnostic techniques, such as high-resolution computed tomography, bronchoalveolar lavage, open lung biopsy and transbronchial lung biopsy, were noted between the different studies.
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The interstitial lung diseases (ILDs) comprise a very large group of more than 200 entities. As outlined by DEMEDTS *et al.* [1] in this Supplement, the incidences/prevalences of several disease entities, including sarcoidosis, idiopathic pulmonary fibrosis (IPF), and some types of hypersensitivity pneumonitis, such as farmer's lung and bird fancier's lung, have been studied. Many differences in disease prevalence between countries have been found, which in part may be real, but which may also be due to selection bias in the registries.

A more global approach involves comparison of the incidences, prevalences or relative frequencies of different ILDs. The advantage of such an approach is that even in the presence of a selection bias concerning the "absolute numbers", a comparison of the relative frequencies of the different entities provides relevant data. Surprisingly few published studies have compared data on different ILD entities. In the last decade, the paper by COULTAS *et al.* [2] on a registry in the Bernalillo County, New Mexico, has been of interest because it addresses comparative frequencies of different ILDs. In the same period, ILD registries have been developed in Flanders [3–5], Germany [6], and Italy [7] (V. Poletti, Dipartemento Malattie del Torace, Ospedale, Bellaria Maggiore, Bologna, Italy, personal communication). The data from these registries are compared in this document.

Methodology of the different registries

In Flanders ($\sim 6\times10^6$ inhabitants), a registry was set up by the Society for Respiratory Health Care and Tuberculosis Control (VRGT) among the centres of respiratory medicine. A standardized questionnaire was sent to the centres, together with elaborate guidelines for classification, diagnostic evaluation, therapy and follow-up of ILDs. It was a prospective registry of incident and prevalent cases of ILDs. Between January 1992–June 1996, 20 respiratory centres responded and 362 cases were registered. These results [3–5] are summarized here.

In Germany ($\sim 80\times10^6$ inhabitants), the Scientific Working Group for the Therapy of Lung Diseases (WATL) constructed an elaborate questionnaire (also addressing diagnostic assessments), which was sent to the hospital-based chest physicians and physicians with a pulmonary practice in the country [6]. An overview of the major ILDs, based on the international classification of diseases (ICD)-9 codes [8], was added and used for classifying the cases. The recommendations of the German Society of Pneumology for the diagnostic assessment of ILDs were also added [9]. It was a prospective incidence registry of newly diagnosed cases of ILDs from January 1995. By the end of 1995, 234 questionnaires had returned from 26 centres, the results of which have already been

published [6] and are summarized in the present paper. However, the registry has continued and by early 2000, 1,184 cases have been registered. A publication of the final analysis is in preparation.

In Italy ($\sim 57 \times 10^6$ inhabitants), two different registries were set up. In the first, a questionnaire retrospectively surveying the occurence of the different ILDs was sent, in 1998, to 34 respiratory centres of whom 17 replied. In total, 4,867 patients were registered of whom 4,169 were retained. The numbers registered varied among centres from 1,607 in Milan to 16 in Caserta [7]. The first year of inclusion also varied between the centres, ranging from 1978 in Milan to 1996 in Caserta. For the second registry, the Italian Registry of Diffuse Infiltrative Pulmonary Diseases (RIPID) was set up in 1997. A data card was sent to the centres of respiratory and internal medicine and was also published in Italian scientific journals. The goals were to obtain prospective data on the distribution of incident and prevalent ILD cases, to establish a data bank for studies and to propose diagnostic and therapeutic guidelines for ILDs. By December 1999, 1,138 data cards were collected and processed (V. Poletti, Dipartemento Malattie del Torace, Ospedale, Bellaria Maggiore, Bologna, Italy, personal communication).

In Bernalillo County, New Mexico (~480,000 inhabitants), incident and prevalent cases of ILDs were prospectively recorded from October 1988–September 1990 [2]. The ILD cases were identified from four sources: pulmonary and primary care physicians (n=219), hospital discharge diagnoses, death certificates and pathology reports, including autopsies. A total of 258 prevalent cases (diagnosed before October 1988) and 202 incident cases (diagnosed since October 1988) were reported. The participating clinicians were provided with elaborate criteria for diagnosis and the data from each reported case was reviewed by a trained abstractor. The ICD-9 codes were used for classification [8].

Results and discussion

Obviously, a comparison of the registries in these different countries poses some problems. The registries in the three European countries are incomplete since only physicians engaged in respiratory disease were contacted and not all of them replied. The studies were prospective, except for one Italian registry [7], and could contain incident [6] or prevalent cases [7], or a mixture of both [2–5]. Also, the diagnostic classifications were not the same, although several used the ICD-9 code [2–6].

Table 1 shows a comparison of the distribution of ILDs in the different registries. The highest concordance is found between the registries in Flanders, Germany and the RIPID registry in Italy, except for the lower occurences of hypersensitivity pneumonitis in Italy and of IPF in Flanders. The latter, however, largely compensated for the greater numbers for not-defined fibrosis and ILDs in connective tissue disease (which apparently were not registered as a separate entity in the Italian registry). The registry in New Mexico differed, showing low values for sarcoidosis and hypersensitivity pneumonitis and high values for not-defined fibrosis. The largest numbers of case inclusions are found in the Italian registries, but the retrospective survey [7] was skewed by the number of cases and the number of years among the different centres. This may explain the unexpectedly high percentage of sarcoidosis cases in this registry because more than one-third of all cases came from a sarcoidosis centre.

In the European registries, stage I sarcoidosis was also included, while the New Mexico registry probably

Table 1. – Comparison of distribution of interstitial lung diseases in different registries

	Flanders*		Germany#	Italy		New Mexico§	
	Prevalent	Incident	Incident	Prevalent¶	Prevalent+	Prevalent	Incident
Total number	362	264	234	4169	1138	257	202
Sarcoidosis	112 (31)	69 (26)	83 (35)	2199 (53)	344 (30)	30 (12)	16 (7.8)
IPF (UIP, DIP, LIP)	62 (17)	50 (19)	76 (32)	805 (19)	417 (37)	58 (23)	63 (31)
BOOP	10 (2.3)	9 (3.4)	16 (6.8)	26 (0.6)	57 (5)	0	1 (0.5)
(C)EP	9 (2.5)	7 (2.7)	0	42 (1.0)	27 (2.3)	3 (1.2)	1 (0.5)
Connective tissue disease	27 (7.5)	19 (7.2)	5 (2.1)	125 (3.0)		33 (13)	18 (8.9)
Goodpasture, Wegener, Churg Strauss	5 (1.4)	4 (1.5)	2 (0.8)	62 (1.5)	25 (2.2)	2 (0.8)	7 (3.5)
Hypersensitivity pneumonitis	47 (13)	32 (12)	25 (11)	162 (3.9)	50 (4.3)	0	3 (1.5)
Drug/radiationƒ	12 (3.3)	12 (5)	6 (2.6)	87 (2.1)	21 (1.8)	6 (1.9)	7 (3.5)
Eosinophil granuloma/histiocytosis X	13 (3.6)	7 (2.7)	0	34 (0.8)	73 (7.2)	2 (0.8)	0
Pneumoconiosis**	19 (5.0)	18 (6.8)	6 (2.6)	417 (10)		36 (14)	21 (10)
Fibrosis (postinflation, not defined)	33 (9.1)	27 (10)	12 (5.1)			83 (32)	61 (30)
Others	13 (3.6)	10 (3.8)	0	210 (5.0)	124 (11)	5 (1.9)	4 (1.9)

Data are presented as n (%). Type of study (month/yr): *: prospective (January 1992–June 1996); #: prospective (January 1995–December 1995); ¶: retrospective (1978–1998); +: prospective (Italian Registry of Diffuse Infiltrative Pulmonary Diseases (RIPID), 1997–1999); §: prospective (October 1988–September 1990); ƒ: radiation was not included in the registries in Flanders and Germany; **: coal workers' pneumoconiosis was excluded in Flanders registry and in the RIPID project. IPF: idiopathic pulmonary fibrosis; UIP: usual interstitial pneumonia; DIP: desquamative interstitial pneumonia; LIP: lymphoid interstitial pneumonia; BOOP: bronchiolitis obliterans organizing pneumonia; (C)EP: (chronic) eosinophilic pneumonia.

Table 2. – Number of lung biopsies (% of cases) contributing to diagnosis

	New Mexico		Flanders	
	Transbronchial	Open	Transbronchial	Open/VATS
Total	33	6.9	23	18
Occupation/hypersensitivity	13	0	25	10
			26	15
Drugs/radiation*	50	0	50	0
Connective tissue disease	11	11	0	7
IPF	38	11	21	38
Pulmonary fibrosis**	25	0	27	18
Sarcoidosis	81	0	26	7

IPF: idiopathic pulmonary fibrosis; VATS: video-assisted thoracoscopy. *: radiation was only included in the Mexican registry; **: corresponding with international classification of diseases (ICD)-9 code 515.

only included sarcoidosis stage II–IV, although this is not clearly stated. This could partly explain the low prevalence and incidence of sarcoidosis found in New Mexico. Prevalence of IPF (including usual interstitial pneumonia (UIP), desquamiative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP)) ranged between 17% (Flanders) and 37% (RIPID, Italy). The difference may be partly explained by the fact that in Flanders, but not Italy, the indeterminate and postinflammatory fibroses and connective tissue diseases were registered as a separate category. The recent classification for IPF [10] was not used in any of the registries. It is likely, therefore, that UIP, DIP, nonspecific interstitial pneumonia (NSIP) and possibly LIP were included as IPF. The frequency of hypersensitivity pneumonitis or extrinsic allergic alveolitis ranged widely, which to some extent is expected, as argued in the Review by BOURKE *et al.* [11] in this Supplement. It is perhaps still surprising that no prevalent cases of hypersensitivity pneumonitis were registered in New Mexico and only a low percentage were registered in the RIPID registry. The high percentage of not-defined fibrosis in the New Mexican registry is probably related to the fact that primary care physicians also recorded cases (which may have been investigated less extensively) and the fact that less surgical lung biopsies had been performed than in Flanders, for example (see table 2).

Age and sex distribution of the ILDs were presented in two and three registries respectively, and are shown in table 3. In New Mexico and Flanders there was a slight predominance of male patients (especially in ILDs due to occupational exposure and/or hypersensitivity pneumonitis), whereas there was a female predominance in Germany. Mean ages for the whole group were highest in New Mexico, but in this registry, no details were provided for the different disease entities. Ages for the different disease groups were relatively similar in Flanders and Germany. Drug-induced ILDs were found in the oldest patients in Flanders, particularly due to amiodarone and nitrofurantoïne, which is consistent with the fact that these drugs are most often prescribed to the elderly.

Clinical and lung function characteristics were reported in the registries in Germany and Flanders and are shown for the most frequent types of ILDs in table 4. Never-smokers were clearly more frequent in extrinsic allergic alveolitis (EAA, hypersensitivity pneumonitis) than in IPF or sarcoidosis. Crackles and dyspnoea, but also cough, were, as expected, much less frequent in sarcoidosis than in EAA and IPF, with fever occurring more often in the former. Lung function tests, including diffusing capacity, were most disturbed in IPF and least disturbed in sarcoidosis; as expected, the forced expiratory volume in one second/vital capacity (FEV_1/VC) ratio was slightly decreased in sarcoidosis and hypersensitivity pneumonitis. The latter mainly included pigeon breeder's disease in Flanders.

The use of several diagnostic procedures was registered in the German, Flemish and the Italian

Table 3. – Sex and age distribution of interstitial lung diseases in different registries

	New Mexico		Flanders	Germany
	Prevalence	Incidence	Prevalence	Incidence
Total	136:122 (69)	106:96 (69)	205:157 (52±17)	105:129 (51±15)
Occupation/HP	35:1 (-)	21:3 (-)	46:20 (55±14)	15:16 (50±15)
Drugs*	2:4 (-)	6:4 (-)	7:5 (70±13)	3:3 (-)
Connective tissue disease	12:21 (-)	7:11 (-)	15:12 (63±13)	0:5 (-)
IPF	34:24 (-)	36:27 (-)	36:26 (57±16)	35:41 (61±12)
Sarcoidosis	14:16 (-)	3:13 (-)	59:53 (44±14)	36:47 (40±12)
Others	39:56 (-)	33:38 (-)	42:41 (-)	16:22 (-)

Data are presented as male:female (mean age) or (mean age±SD). HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; (-): not available. *: in New Mexico radiation pneumonitis was also included.

Table 4. – Characteristics of interstitial lung diseases at diagnosis

	Total	Sarcoidosis	HP	IPF
Clinical data (Germany)				
Cough	69	55	77	78
Dyspnoea on exercise	57	28	77	75
At rest	13	?	16	21
Crackles	38	4	55	66
Fever	?	27	13	7
Current smoker	19	27	7	21
Never-smoker	56	55	74	50
Lung function (Flanders)				
Vital capacity	82±22	91±20	81±20	66±21
FEV_1/VC	0.8±0.1	0.7±0.1	0.7±0.2	0.8±0.1
$D_{L,CO}$	57±23	78±21	49±17	39±14

Data are presented as % or mean % predicted±SD. HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; FEV_1: forced expiratory volume in one second; VC: vital capacity; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; ?: no data available. Total: includes all registered interstitial lung diseases, not only sarcoidosis, HP and IPF.

studies, which are listed in table 5. The frequencies of application of mediastinoscopic, thoracoscopic or open lung biopsies were rather low. Interestingly, in Italy, high-resolution computed tomography (HRCT) was most frequently used, while in Germany, transbronchial biopsies and bronchoalveolar lavage (BAL) were the most commonly applied investigations. These differences have apparently not led to marked differences in the registered distribution of ILDs in these countries (see table 1).

Information on the diagnostic values of transbronchial (TBB) compared with thoracoscopic (video-assisted thoracoscopy (VATS)) or open lung biopsy in the different ILDs were reported in the studies in New Mexico and Flanders (table 2). Overall, histological diagnosis was only obtained in a minority of cases. Open or thoracoscopic lung biopsies contributed more often to diagnosis in the Flemish than the New Mexican registry, while the opposite was true for TBB. Interestingly, a positive TBB in sarcoidosis was obtained in more cases in the New Mexico registry than the Flanders registry. In IPF and pulmonary fibrosis, diagnosis was based on open or VATS lung biopsies much more often in the Flanders than the New Mexico registry. TBB, as well as open/VATS biopsies, also contributed much more to a specific diagnosis in the registry in Flanders. The large number of so-called "diagnostic" TBB in IPF, particularly seen in New Mexico, should be interpreted with caution because this type of biopsy does not allow a specific diagnosis of IPF to be made, but only excludes other diagnoses.

Table 5. – Number of procedures irrespective of contribution to diagnosis

	RIPID	Germany	Flanders
HRCT scan	71	43	*
Transbronchial biopsy	41	77	46
BAL	35	85	*
Mediast/thoracoscopy/ open lung	20	8	25

HRCT: high-resolution computed tomography; BAL: bronchoalveolar lavage; Mediast: mediastinoscopy; RIPID: Italian Registry of Diffuse Infiltrative Pulmonary Diseases. *: not registered.

The findings in tables 4 and 5 are consistent with current guidelines [10, 12, 13] that suggest that ILDs may, in some instances, be diagnosed on the overall clinical presentation, including HRCT and BAL, and that open or thoracoscopic lung biopsy is required in a minority of cases. However, no audit of diagnoses was undertaken to exclude the possibility of erroneous diagnosis in patients that did not undergo surgical biopsy.

Conclusions

Comparison of the registries in the three European countries and New Mexico highlights marked similarities but also apparent dissimilarities between countries in the distribution of the different interstitial lung diseases. Since the designs of these studies were different, it is unclear whether these differences in distribution represent real differences in occurrence of interstitial lung disease among countries or are in part due to a selection bias by the type of registry or the applied diagnostic procedures. These registries also demonstrate the difficulties and challenges encountered when reliable incidence or prevalence data of this very complex and rather infrequent group of diseases are searched for. A more global prospective approach with consistent inclusion criteria is required.

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