Pulmonary Arterial Hypertension and Interstitial Lung Diseases

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Editors

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A Clinical Guide

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wife Elise Lower,
in Memory of mother Attilia Innesti Carbone
wife Elena Bottino

Preface

Interstitial lung disease (ILD) is a broad category of lung diseases that includes more than 150 disorders characterized by scarring or fibrosis of the lungs. Even among the many types of the disease, ILD's progression can vary from person to person, and people respond differently to therapy. In the past, emphasis in treating ILDs has focused on the effect on gas exchange and loss of lung volume. This is a direct effect of the damage to the interstitium. However, an important indirect effect is on the pulmonary vasculature with resulting pulmonary hypertension. The association between interstitial lung disease and pulmonary hypertension has long been recognized, it was often associated with hypoxia and fibrosis alone. Recent studies that demonstrate response to pulmonary vasodilators stresses the vascular component of this process. In this book, we examine the various interstitial lung diseases. We also examine the incidence and outcome of pulmonary hypertension in the various interstitial diseases.

The book is divided into two main sections. The first discusses general issues. Drs. Carbone and Bottino introduce both ILD and associated pulmonary hypertension in the first two chapters of the book. The next chapter is by Drs. Meyer and Raghu, who discuss the evaluation of idiopathic interstitial lung diseases. They point out that this includes not only idiopathic pulmonary fibrosis, but other conditions such as nonspecific interstitial pneumonitis and cryptogenic organizing pneumonia. Drs. Moreira and Travis provide a detailed analysis of the pathology of the various ILDs. The pathologist often has the final say about what disease, although a comprehensive approach the clinician, radiologist, and pathologist gives a better definition of many cases. Finally, Drs. Carbone and Bottino summarize the evaluation of pulmonary hypertension. Although most of the information available is from patients with primary pulmonary hypertension, the observations can often be extended to patients with ILD.

The other section of the book deals with specific categories of disease. Dr. Lynch and colleagues discuss bronchiolitis, an increasingly recognized problem leading to airway obstruction and restriction. The use of inspiratory and expiratory high-resolution computed tomography scan has markedly enhanced the recognition of this process. Dr. Selman and his group then discuss hypersensitivity pneumonitis, a diffuse group of diseases bound together by common clinical and pathological features.

Drs. Brown and Strange discuss the collagen vascular diseases. Scleroderma has been one of the most widely studied lung diseases that can cause both interstitial lung process as well as pulmonary hypertension. In the past few years, large clinical trials have been published showing the benefits of some forms of therapy in these diseases. Dr. Martinez discusses the specific problem of pulmonary hypertension with idiopathic pulmonary fibrosis. Because idiopathic pulmonary fibrosis is associated with a high mortality, treatment for this complication may have major impact on the disease. Dr. Lee Newman examines the interstitial lung diseases associated with various occupational exposures. This divergent group can have a quite variable outcome. However, as a group it represents a major part of the differential diagnosis of all patients with interstitial lung diseases.

Dr. Baughman and colleagues discuss sarcoidosis. This multi organ disease affects the lungs in more than 90% of cases. Although most patients do well, there is a group with persistent pulmonary disease. Up to half of these patients will have pulmonary hypertension. Drs. Baughman, Lower, and Engel provide an evaluation for the disease and treatment strategies for the disease and associated pulmonary hypertension.

Finally, the editors would like to again to thank all the authors for their efforts in preparing this book. We would also like to thank Richard Lansing of Humana Press for his support.

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Abbreviations

6MWT	six minute walk test
ACCESS	A Case Control Etiologic Study of Sarcoidosis
ACCP	American College of Chest Physicians
AIP	acute interstitial lung disease
ALK1	active/like kinase type/1
ANCA	antineutrophil cytoplasmic antibody
ANP	atrial natriuretic peptide
APC	antigen-presenting cells
AR	acute rejection
ASD	atrial septal defect
ATS	American Thoracic Society
AVP_1	vasopressin receptor
BAL	broncho alveolar lavage
BCG	bronchocentric granulomatosis
BeLPT	beryllium lymphocyte proliferation test
BIP	bronchiolitis interstitial pneumonia
BMPR2	bone morphogenetic protein receptor type-2
BNP	brain natriuretic peptide
BOOP	bronchiolitis obliterans organizing pneumonia
CCB's	calcium channel blockers
CFA	cryptogenic fibrosiing alveolitis (synonymous of IPF)
CMV	cytomegalovirus
COP	cryptogenic organizing pneumonia
CPI	composite physiologic index
CRP score	clinical radiological physiological score
CVD	collagen vascular disease
CXC	chemochine
DG	diacylglycerol
DIP	desquamitive interstitial pneumonia

DLco	diffusion capacity (of the lung) for carbon monoxide (CO)
DPI	Diphenyleniodonium
ERS	European Respiratory Society
ET	endothelin
ETA	endothelin receptor
EVE	endogenous vascular elastase
FVC	forced vital capacity
FEV1	Forced expiratory volume in one second
GIP	giant interstitial pneumonia
HHT	hereditary hemorrhagic teleangectasia
HPV	hypoxic pulmonary vasoconstriction
HSCT	HEMATOPOIETIC STEM CELL TRANSPLANTATION
IIP	idiopathic interstitial pneumonia
IL	interleukin
ILD	interstitial lung disease
IP	inositol phosphate
IP3	inositol triphosphate
IPAH	idiopathic pulmonary arterial hypertension
IPF	idiopathic pulmonary fibrosis
ISHLT	INTERNATIONAL SOCIETY OF HEART LUNG TRANSPLANTATION
LIP	lymphoid interstitial pneumonia
LIGHT	Lymph toxin-like Inducible protein that competes with Glycoprotein D for Herpes virus entry mediator on T lymphocytes
LTR	lung transplant recipients
NO	nitric oxide
NSIP	non-specific interstitial pneumonia
NYHA	New York Heart Association class
Octreoscan	^{111} In-DTPA-D-Phe1-Octreotide
ODTS	organic dust toxic syndrome
PAF	platelet activating factor
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
	PDE4, and PDE 5:phosphodiesterases
PAPm	mean pulmonary artery
PCW	pulmonary capillary wedge

PFT	pulmonary functional test
PGI2	prostaglandin I2
PH	pulmonary hypertension
PIP2	inositol polyphospholipids
P_{LA}	left atrial pressure
PLC	phospholypase C
PMF	progressive massive fibrosis
PPH	primary pulmonary hypertension
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
RA	right atrial
RB/ILD	respiratory bronchiolitis-associated with interstitial lung disease
RIPID	Italian registry for diffuse infiltrative lung disorders
RV	right ventricular/ ventricle
RVH	right ventricular hypertrophy
RVSP	right ventricular systolic pressure
S6c	peptide named sarafotoxin
SACE	serum angiotensing converting enzyme
SFTPC	surfactant protein C gene SFTPC
SLE	systemic lupus erythematous
SMC	smooth muscle cells
SOD	Super oxide Dismutase
SPAM cells	pulmonary artery smooth muscle cells
sPAP	systolic pulmonary arterial pressure
SPECT	Single Photon Emission Computed Tomography
SPH	secondary pulmonary hypertension
SSc	systemic scleroderma
TBB	transbronchial biopsy
TGF/β	transforming grown factor
TIE2	endothelial-specific receptor of angiopoietin-1
TNF	tumor necrosis factor
TR	tricuspid valve regurgitation
U.I.	uptake index
UIP	usual interstitial pneumonia
VEGT	Vascular endothelial growth factor
VF	ventricular fibrillation
V/Q	ventilation/perfusion

Part I
General Principles

Chapter 1
Interstitial Lung Disease: Introduction

Roberto G. Carbone, Fabio Montanaro, and Giovanni Bottino

Introduction

Interstitial lung diseases (ILDs) are a large group of heterogeneous inflammatory fibrosing disorders comprising more than 200 entities that predominantly affect the pulmonary interstitium rather than the airspaces [1]. Significant progress in the understanding of ILD was made since the 1960, with the recognition of collagen vascular diseases, drugs, and occupational exposures as potential causes. However, a wide spectrum of pathologies, presentations, and outcomes still remain unknown. Liebow and Carrington [2] were first to classify idiopathic interstitial pneumonia (IIP) into five histologic subgroups: usual interstitial pneumonia (UIP), bronchiolitis interstitial pneumonia, desquamative interstitial pneumonia, giant interstitial pneumonia, and lymphoid interstitial pneumonia. In 1998, the classification was modified by Katzenstein and Myers [3], with UIP corresponding to Hamman–Rich Syndrome [4], respiratory bronchiolitis associated with ILD, desquamative interstitial pneumonia, nonspecific interstitial pneumonia (NSIP), and acute interstitial lung disease. The modern classification, which was recognized by the American Thoracic Society and European Respiratory Society [5], included another entity: cryptogenic organizing pneumonia (Fig. 1.1). Different ancillary diagnostic procedures, such as chest x-ray, high-resolution computed tomography (HRCT), Gallium^{67} scintigraphy, and bronchoalveolar lavage, are considered inaccurate and nonspecific in diagnosing this group of diseases, especially in the their early stages [6–11]. Imaging with radiolabeled indium-111 octreotide scintigraphy (Octreoscan, Mallinckrodt Medical, Inc., St. Louis, MO), which is used in the evaluation of patients with neuroendocrine tumours, meningiomas, astrocytomas as well as lymphomas and thymomas [12], has been proposed in the study of ILD by several clinicians and nuclear medicine specialists.

As for sarcoidosis, the use of Octreoscan was shown to be a sensitive diagnostic tool, particularly in the imaging of lymph nodes and spleen, and its use appears to enable the better identification of lung disease activity [13–15].

Recently, the authors of several studies [16–17] have proposed the use of echocardiography and cardiac catheterization as effective tools in the evaluation of pulmonary hypertension, which is a predictive factor of survival associated with

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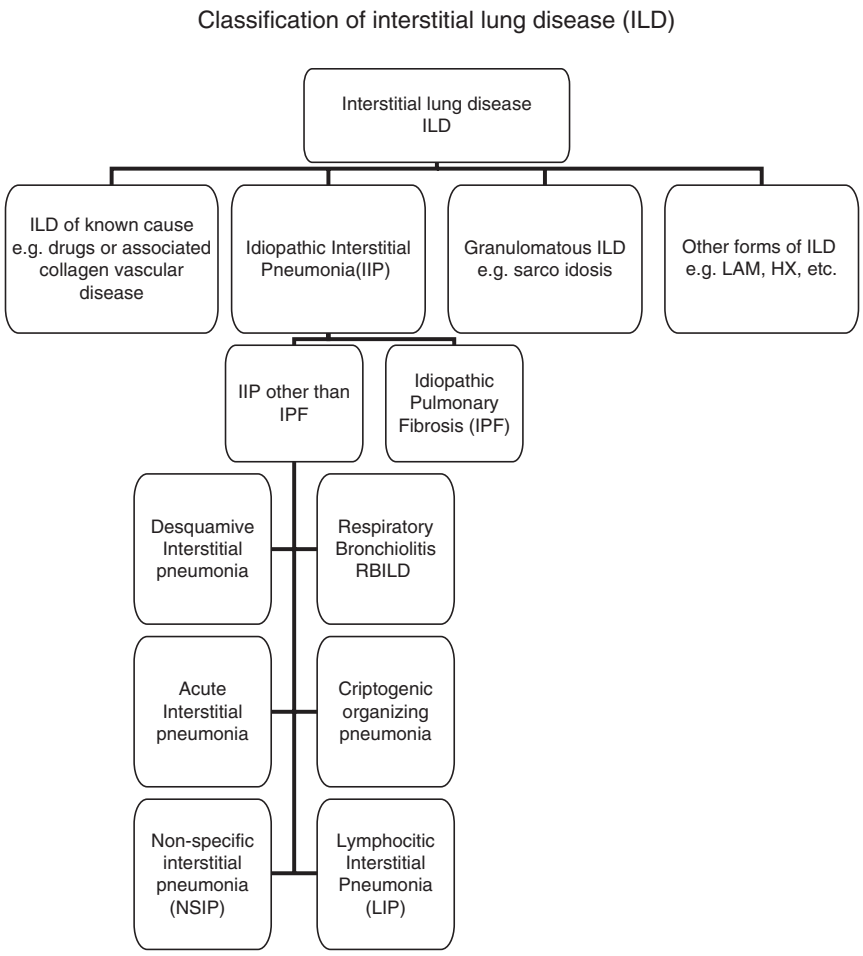


Fig. 1.1 Classification of ILD

systemic scleroderma. This hypothesis suggests a similar correlation between idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension [18].

Therapy for patients in the advanced stages of ILD has little or no benefit, which is why prompt diagnosis is important (especially with UIP or NSIP) and why lung biopsy considered the gold standard for the diagnosis. The importance of tissue morphology has been addressed in the American Thoracic Society/ European Respiratory Society / American College of Chest Physicians classification of IIP, where both histological and clinicoradiological findings with the use of HRCT are taken into account [19,20].

The difficulty in the clinical assessment and classification of ILD emphasizes the complexity of this group of diseases, which are still poorly understood and

underdiagnosed. The scope of the following two chapters is to describe (1:) the epidemiology, the genetic factors of fibrotic lung diseases, the physiology, and the pathophysiology of the pulmonary circulation in correlation with ILD; (2) the role of imaging, such as HRCT, gallium-67, Octreoscan, and echocardiography in the development of new management strategies of ILD-associated pulmonary hypertension; and (3) the utility of different imaging techniques in the clinical medical practice.

Patients suspected of ILD must be referred to a specialist as soon as possible for the following reasons: (1) the earlier patients are referred to a pulmonologist, the greater the possibility of confirming the diagnosis; (2) an accurate diagnosis is crucial, because some ILDs are treatable; (3) early referral also may ensure that the patient is an eligible lung transplant candidate; (4) early diagnosis and intervention may improve outcomes and enable the patient to be enrolled in one of the many ongoing trials for potential new therapies; and (5) a prompt diagnosis of ILD should depend upon a multidisciplinary approach, in which clinical and radiological data assessed by physicians, pulmonologists, surgeons, cardiologists, pathologists, radiologists, and nuclear medicine specialists are integrated.

Epidemiology of ILD in Europe in Comparison With the USA

As mentioned previously, ILD is a group of approximately 200 different pathologies of heterogeneous origin, with different clinical aspects and prognosis. This implies that describing the "epidemiology of ILDs" involves the descriptions of each specific pathology included in this group.

Epidemiology of ILD

The first population-based registry of patients with ILD was established in Bernalillo County (NM, USA) in 1988 [21]. During the period of 1988–1993, 460 patients with ILD were enrolled in the patient registry: 56% were prevalent cases and 44% were incident cases diagnosed during the study period. The prevalence rates of ILD were estimated to be 80.9 per 100,000 among men and 67.2 per 100,000 among women and incidence rates of 31.5 per 100,000 and 26.1 per 100,000, respectively. This study had some limitations: first, only 7% of the cases had the diagnosis confirmed by open lung biopsy; second, the autopsy population—which was used to estimate the occurrence of preclinical and undiagnosed ILD in the general population—was much younger than the control group (average ages: 42 years versus 70 years, respectively); finally, concerns regarding possible overdiagnosis or underdiagnosis in the investigated community, possible overdiagnosis because of the activity of the registry itself, and the estimated pool

of patients that could be undiagnosed were expressed by the authors but not investigated.

During the period of 1992–1996, in Flanders, a prospective registry collected information about 362 prevalent and incident cases of ILD. Cases came from 20 respiratory centers who responded to a standardized questionnaire. An incidence of 1.0 per 100,000/year was estimated [22].

In Germany, a prospective incidence registry of newly diagnosed cases of ILD started its activity in January 1995. Up to early 2000, 1,184 cases have been registered [23]. In Spain, an ILD registration was conducted on 23 pulmonary medicine centres during 1 year (Oct. 2000 to Sept. 2001). In the study period, 511 cases were registered, allowing researchers to estimate an incidence rate of 7.6 per 100,000/year [24].

In Italy, two different registries were created. The first aimed to retrospectively survey the occurrence of different ILD through a questionnaire sent to 34 respiratory centres (17 respondents). Finally, 4,169 patients were registered and validated [25]. The second Italian registry, namely the Italian registry for diffuse infiltrative lung disorders (RIPID, i.e., Registro Italiano Pneumopatie Infiltrative Diffuse), was established in 1998 with the aim of creating a national database of these disorders, providing the background for epidemiological and clinical studies of adequate sample size [26]. During the period of 1998–2005, a total of 3,152 patients had been registered. Unfortunately, the prevalence and incidence rates could not be estimated because the size of the population covered by the participating centre was not exactly estimable, with the exception of Bolzano province, where 193 newly diagnosed cases of diffuse infiltrative lung diseases were enrolled in the registry and an incidence of 2.9 cases per 100,000 was estimated in the period 1990–2004. The most frequently reported interstitial lung disorders were sarcoidosis and IPF.

The RIPID did not include a series of 128 patients diagnosed with ILD of unknown etiology who were referred to Regional Hospital, Aosta (126,000 inhabitants) in the period 1995–2004. According to the recommendations of ATS Criteria, the diagnosis was made on clinical, radiological, and histological data:59 patients were diagnosed with UIP/IPF (46.1%), 19 with NSIP (14.8%), and the remaining 50 patients (39.1%) with other ILD (including:24 with sarcoidosis, 16 with Wegener granulomatosis, and 10 with extrinsic allergic alveolitis). All diagnosis of ILD were confirmed by biopsy:42 open pulmonary biopsies, 40 video-assisted thoracoscopies, 32 percutaneous biopsies, 12 mediastinoscopies, and 2 lymph node biopsies [27].

Because incidence/prevalence data were difficult to estimate or, where estimated, were susceptible to uncontrollable biases, the comparison of the occurrence in different areas could be not informative and likely biased. On the contrary, to compare the relative frequency of different ILD subgroups could be informative (Fig. 1.2). In all the registries, the most frequent diseases were IPF (more than 30% of cases except in Flanders) and sarcoidosis, ranging from 14.9% in Spain to 35.4% in Germany.

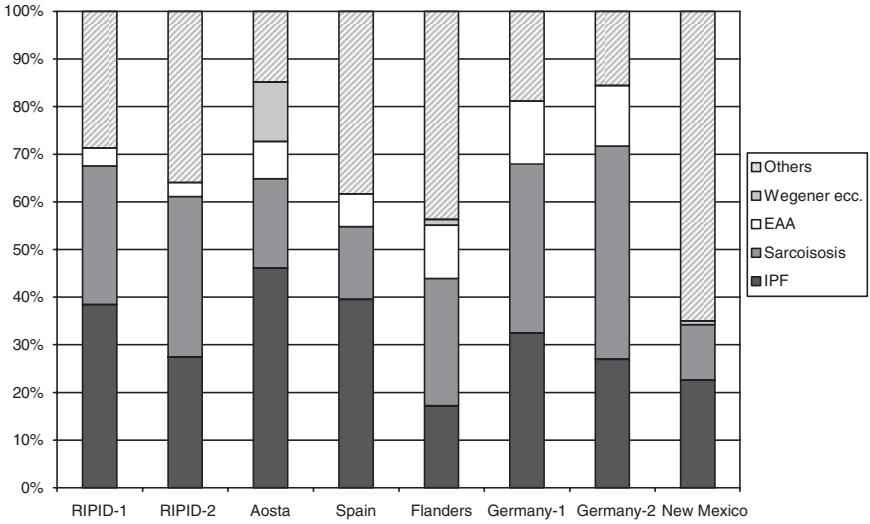


Fig. 1.2 Relative frequency of ILD subgroups in different countries

Epidemiology of ILD Subgroups

Besides general ILD registries, epidemiological investigations on specific subgroup pathologies included in the large ILD disease also have been conducted.

IPF

IPF is not a rare disease. Approximately 80,000 cases of IPF have been identified in the USA, with an estimated 30,000 new cases developing each year. The descriptive epidemiology of IPF has not been deeply investigated, and estimates are quite limited. Moreover, criteria providing the basis for these estimates often are not precisely defined. In early 1990s, prevalence estimates of IPF in the general population varied from 3 to 6 cases per 100,000 [28,29], whereas the aforementioned New Mexico's ILD registry [21] revealed a prevalence of 20.2 and 13.2 per 100,000 among men and women, respectively, and an incidence of 10.7 per 100,000 per year among men and 7.4 among women. IPF is reported to occur more commonly in men than women [28,29].

Typically, patients present between the ages of 40 and 70 years, and approximately 66% of patients are older than 60 years of age at presentation. The mean age at diagnosis is 66 years, and the prevalence for people ages 35 to 44 years is 2.7 cases per 100,000 whereas the prevalence for people older than 75 years of age exceeds 175 cases per 100,000.

The incidence of IPF increases with age, as approximately two-thirds of patients with IPF are older than 60 years of age [28,30,31], and the incidence is 160 per 100,000 among 75 years of age and older [21]. There is no valid explanation as to why IPF is a disease that occurs predominately in older people.

Limited evidence exists that the geographical location and ethnicity are related to diagnosis. There is a slight male preponderance of disease, and the age-adjusted mortality rate for white patients exceeds that for black patients. Age-adjusted rates mortality rates from IPF appear to be greater among the white population and lower among the black population [31]. A geographic variation was observed that may reflect differences in occupational and environmental exposures.

Because IPF is a chronic disease that is almost uniformly fatal, the ratio of the prevalence to the incidence can provide a crude indication of the duration of survival after diagnosis [32]. Hubbard et al. [33] investigated the rate of mortality from IPF (i.e., cryptogenic fibrosing alveolitis) in England and Wales (UK), Australia, Canada, Scotland, Germany, USA, and New Zealand to determine whether mortality was increasing or decreasing compared with that observed in other seven countries. They observed that the greatest mortality rates for CFA were observed in UK, i.e., England and Wales, followed by Scotland, New Zealand, Australia, and Canada, whereas the USA and Germany had CFA mortality rates considerably lower than those for the other countries. Mortality from CFA had increased in England and Wales, Scotland, Canada, and Australia since 1979 whereas it decreased in the USA and it was low and stable in Germany.

Concerns regarding the accuracy of IPF diagnoses were raised. In the Italian RIPID, the diagnosis of IPF was based upon a surgical lung biopsy only in 20% of cases; this percentage of pathological diagnosis was slightly lower than that reported in the Spanish register (32%) [24], whereas in the Regional Hospital of Aosta, all diagnoses were biopsy-confirmed and 33% of all patients with IIP had open lung biopsies.

Sarcoidosis

Information on sarcoidosis can be traced from general ILD registries (Fig. 1.2) or from specific analytical studies; no specific registry of patients diagnosed with sarcoidosis have been established. Sarcoidosis represented 11.6% of prevalent cases registered by Coultas et al. [21] and 7.8 percent of incident ones in the same registry. Only approximately one-third of cases patients with sarcoidosis in the RIPID had a lung surgical biopsy.

A Case Control Etiologic Study of Sarcoidosis (ACCESS) generated a large database for a series of analytical epidemiological reports. In this study, in which the authors aimed to study the etiology of sarcoidosis, newly biopsy-confirmed patients with sarcoidosis from several US regions were examined with the use of a standardized evaluation [34–36].

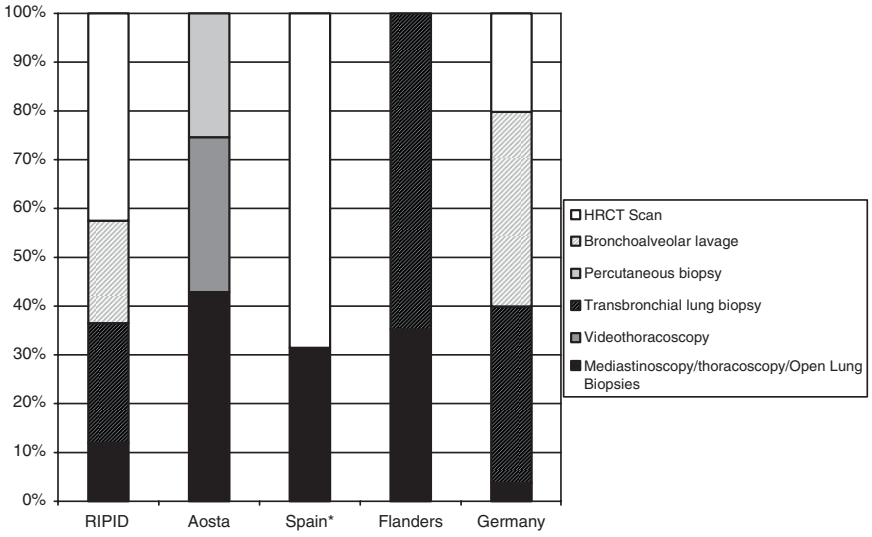
In the first report, 736 patients were considered to be representative of sarcoidosis in the USA, even if some potential recruitment biases have been identified. In this

report, organ involvement was investigated, revealing differences attributable to race, sex, and age [34]. Because of the considerable sample size of case and control relatives, Rybicki et al. [35] could demonstrate that sarcoidosis aggregates in family, confirming what was before based only on anecdotal reports. A third report based on ACCESS database was aimed to investigate the relationship between environmental and occupational factors and risk of sarcoidosis. The results of this study suggested that insecticides, agricultural environments, and exposure to microbial aerosol may be associated with sarcoidosis, whereas many other possible etiologic require further investigation [36].

Summary

The data of aforementioned registries confirmed that epidemiological registries can be useful tools to investigate rare or relatively rare disorders (e.g., sarcoidosis and IPF) to design multicentric clinical studies of adequate sample size, especially cohort and prospective studies, aimed at providing standardized diagnostic, management, and follow-up criteria with a particular regard to outcome measures such as survival and quality of life.

This consideration is a consequence of the fact that death certificates and state mortality data are neither sensitive nor accurate for describing the occurrence of ILD. Proof of that could be the apparently low mortality rates from IPF in USA when compared with other countries [37].



* IPF cases only. Both HRCT and open lung biopsies were used in combination with other diagnostic procedures.

Fig. 1.3 Diagnostic procedures in ILD in different countries

A limitation in the data of ILD registries is the limited use of biopsies. As reported in this chapter, only low percentages of cases had a histology confirmed diagnosis, whereas most diagnoses are based upon clinical observation and radiological and HRCT scan findings. Unfortunately, the accuracy of the HRCT scan is limited, as only approximately 50% of IPF diagnosis obtained in that way could be confirmed and the remaining should be inexorably wrong [7]. Therefore, the use of open lung biopsy should be the gold standard. Only Aosta Valley had all its cases histologically confirmed (Fig. 1.3). Comparability of registries included in Fig. 1.2 is limited, as RIPID included only 167 cases of 4,169 and Flanders only 71 out of 362. Finally, different diagnostic procedures for each patient have been registered in Spain.

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Chapter 2
Pulmonary Hypertension in Interstitial Lung Disease

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Genetic Factors Associated With Interstitial Lung Disease (ILD): View in Relation to Pulmonary Hypertension (PH)

The development of family registries and the banking of deoxyribonucleic acid has enabled researchers to search for a marker for familial PH on chromosome 2q 31/32. As a result, the bone morphogenetic protein factor receptor type 2 gene (BMPR2) on chromosome 2q 33, having 13 exons, was discovered. Mutations in familial PH have been reported in all exons except for 5 and 13. Humbert et al. [1] cited mutations of BMPR2 in PH associated with fenfluramine derivates. These data are concordant with the working hypothesis that gene–gene or gene–environmental interactions are required for PH. Conversely, Morse et al. [2] and Tew el al. [3], who studied patients with scleroderma and PH, did not find the presence of BMPR2 mutations.

Recently, Trembart et al. [4] have found a second PH gene in some patients with hereditary hemorrhagic teleangectasia lesions whose mutation in active/like kinase type/1 (ALK1) receptor confers a predisposition to PH and hereditary hemorrhagic teleangectasia lesions. Both BMPR2 and ALK1 genes are two receptors in the transforming grown factor (TGF)-β family. Multiple genetic causes associated with PH are summarised in Fig. 2.1.

Du et al. [5,6] have described the genetic mechanism of PH. According to their hypothesis, an unknown stimulus involved in the TGF-β receptor pathway increases angiopoietin-1 and its receptor TIE2, which decreases the BMPR1A receptor. The latter is required for the optimization of the BMPR2A receptor. Mutant forms of BMPR2A and mALK1 are associated with familial forms of PH, and both are involved in signaling through growth promoting proteins, which finally stimulate vascular smooth muscle remodelling. The study of genes associated with the risk of acquiring PH is complex from a statistical point of view. PH is probably the result of an interaction between the BMPR2 genes with environmental factors and will be continue to be a subject of future investigations.

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