

Introduction



Key points

- Among the 300-plus interstitial lung diseases, the most important are sarcoidosis, idiopathic pulmonary fibrosis, extrinsic allergic alveolitis, interstitial lung disease as a feature of connective tissue disease, drug-induced interstitial lung disease and pneumoconiosis.
- Only about one in three cases of interstitial lung disease has a known cause.
- Survival rates at 5 years range from 20% for idiopathic pulmonary fibrosis to almost 100% for cryptogenic organising pneumonia.
- The highest mortality rates are about 2.5 per 100 000 people per year, seen in the British Isles, Scandinavia, the Netherlands and Spain.
- The management of interstitial lung disease of known aetiology is, in the first place, prevention and cessation of exposure. For interstitial lung disease of unknown aetiology, treatment consists mainly of antifibrotic and anti-inflammatory drugs.

Patients with interstitial lung diseases (ILDs), also called diffuse parenchymal lung diseases, generally present with breathlessness due to impaired gas exchange as a consequence of widespread inflammation and/or fibrosis of the alveolar walls.

There are more than 300 different conditions included among the total number of ILDs. For epidemiological purposes, a practical, and therefore appealing, classification distinguishes ILDs of known cause from those of unknown aetiology (table 1). Some of these diseases, such as sarcoidosis and ILD associated with connective tissue disease (CTD), also affect other organs and this may determine the prognosis to a greater extent than the lung dysfunction.

ILDs usually have a gradual onset but can also present an acute course. Chest radiography and thoracic computed tomography (CT) typically show widespread nodular and/or fine linear ('reticular') shadowing with, at a later stage, fibrotic distortion and sometimes 'honeycombing' of the lungs. Pulmonary function testing shows a 'restrictive' (and, much less often, an 'obstructive') ventilatory defect and hypoxaemia (low blood oxygen), which is particularly seen during exercise. Diagnosis is often made using a combination of the clinical, pathophysiological, immunological and imaging (especially CT) features. For a precise diagnosis, a surgical lung biopsy with histological examination may be needed; however, even this procedure does not always give a clear answer. The microscopic

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appearance of the lung should be interpreted according to the recent American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus classification of the idiopathic interstitial pneumonias (IIPs), of which one of the commonest is idiopathic pulmonary fibrosis (IPF).

Therapy includes anti-inflammatory and antifibrotic agents, but in advanced disease it may be limited to palliative care. In ILDs resulting from known exogenous causes, it is crucial to avoid further exposure. Despite treatment, some forms of ILD, such as IPF, have a downward course, and lung transplantation may need to be considered.

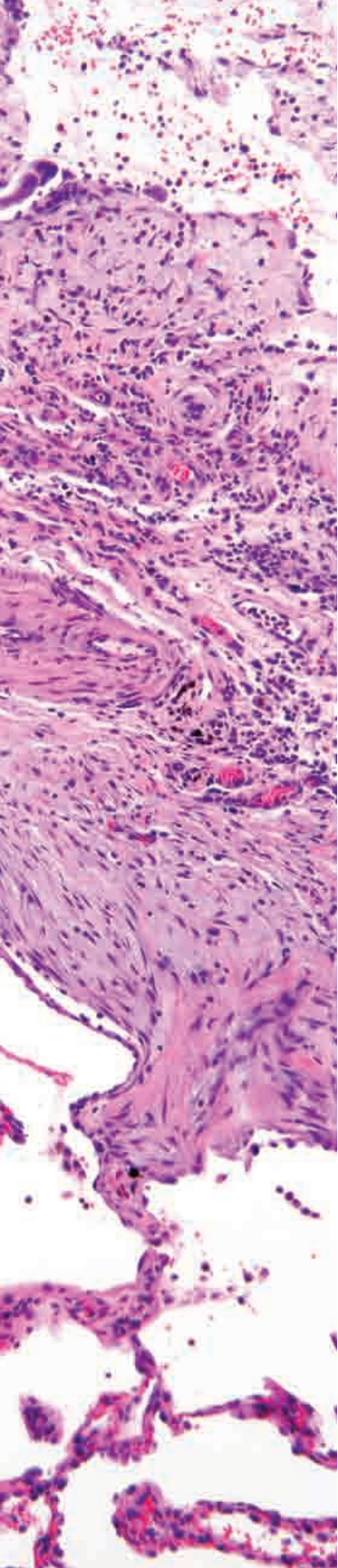
Major ILDs of known aetiology (~35% of all patients with ILDs)

- Pneumoconioses (e.g. asbestosis, silicosis)
- Extrinsic allergic alveolitis (hypersensitivity pneumonitis)
- Iatrogenic ILD caused by drugs and/or radiation
- Post-infectious ILD

Major ILDs of unknown aetiology (~65% of all patients with ILDs)

- Sarcoidosis
 - Idiopathic interstitial pneumonias, of which the most important are:
 - IPF with a histopathological pattern of usual interstitial pneumonia (~55% of IIPs)
 - Nonspecific interstitial pneumonia (~25% of IIPs)
 - Respiratory bronchiolitis ILD, occurring in smokers (~10% of IIPs)
 - Desquamative interstitial pneumonia (~5% of IIPs)
 - Cryptogenic organising pneumonia (~3% of IIPs)
 - Lymphoid interstitial pneumonia (~1% of IIPs)
 - Acute interstitial pneumonia (~1% of IIPs)
 - ILD in CTDs and in collagen-vascular diseases, of which the most important are:
 - ILD in rheumatoid arthritis
 - ILD in progressive systemic sclerosis
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Table 1 – Classification of interstitial lung diseases (ILDs). IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; CTDs: connective tissue diseases.



Comparative studies of frequency, incidence and prevalence

Registries of the epidemiology of different ILDs have been compiled in several countries. However, they remain scarce due to the difficulties that arise in obtaining a specific diagnosis as many of these conditions are rare. Many of the available data come from prospective registries of data reported by respiratory physicians, for example in Flanders (Belgium), Germany, Italy, Spain and Greece (table 2). These registries have the disadvantage that the registered populations may not be representative of the true populations of patients. They also do not necessarily represent the true overall incidence and prevalence. However, they do allow comparison of the relative frequencies of the different ILDs. The data show that the most frequent ILDs are IPF and sarcoidosis, which together comprise about 50%. The data also show some interesting differences between countries, such as lower proportions of IPF in Flanders, of sarcoidosis in Spain, of ILD associated with CTD in Germany, and of extrinsic allergic alveolitis (hypersensitivity pneumonitis) (EAA) in the Italian, Spanish and Greek registries.

In addition, in Denmark there is a population-based registry, encompassing the entire population and comparing the periods 1995–2000 and 2001–2005, which undoubtedly provides more complete data. This registry shows a lower frequency of IPF but a higher frequency of 'atypical', nonspecific fibrosis in the second period, which can, at least partly, be attributed to the new classification of the IIPs with a more specific and restricted definition of IPF.

Incidence and prevalence of specific subgroups of ILD

The most important ILDs are sarcoidosis, IPF (previously called cryptogenic fibrosing alveolitis, mainly in the UK), EAA, ILD as a feature of CTD, drug-induced ILD and pneumoconiosis (for further information on the latter, see chapter 24). These are discussed below in more detail.

Sarcoidosis

In the UK, general practice data have suggested an incidence of approximately 3 cases of sarcoidosis per 100 000 people per year (assuming a mean disease duration of 2 years). In another UK study, a similar incidence of 5 cases

	Flanders (Belgium) (1992–1996)	Germany (1995)	Italy (1997–1999)	Spain/RENIA (1998–2000)	Spain/SEPAR (2000–2001)	Greece (2004)
	Prevalent cases	Incident cases	Prevalent cases	Incident cases	Incident cases	Prevalent cases
Incident cases	Prevalent cases	Incident cases	Prevalent cases	Incident cases	Incident cases	Prevalent cases
Subjects n	362	264	1138	744	511	967
Unknown aetiology						
Sarcoidosis	112 (31)	69 (26)	344 (30)	87 (12)	76 (15)	330 (34)
IPF/IIP	62 (17)	50 (19)	417 (37)	287 (39)	215 (42)	234 (24)
COP/BOP	10 (2.3)	9 (3.4)	57 (5.0)	38 (5.1)	53 (10)	51 (5.3)
[C]EP	9 (2.2)	7 (2.7)	27 (2.3)			21 (2.2)
CTD	27 (7.5)	19 (7.2)		69 (9.3)	51 (19)	120 (12)
Vasculitis#	5 (1.4)	4 (1.5)	25 (2.2)			14 (1.5)
EG/HX	13 (3.6)	7 (2.7)	73 (7.2)	6 (0.8)	15 (3)	37 (3.8)
Exogenous aetiology						
EAA	47 (13)	32 (12)	50 (4.3)	38 (5.1)	34 (7)	25 (2.6)
Drug [†]	12 (3.3)	12 (5)	21 (1.8)		21 (4)	17 (1.8)
Pneumoconiosis ⁺	19 (5.0)	18 (6.8)		55 (7.4)		20 (2.0)
Variable aetiology						
Nonspecific fibrosis	33 (9.1)	27 (10)	124 (11)	69 (9.3)	9 (2)	82 (8.5)
Others	13 (3.8)	10 (3.8)		76 (10)		15 (1.5)

Table 2 – Comparison of the distribution of interstitial lung diseases (ILDs) in respiratory physicians' prospective registries. Data are presented as n (%), unless otherwise stated. RENIA: Registry of Interstitial Pneumopathies of Andalusia; SEPAR: Sociedad Española de Neumología y Cirugía Torácica; IPF: idiopathic pulmonary fibrosis; IIP: idiopathic interstitial pneumonia; COP: cryptogenic organising pneumonia; BOP: bronchiolitis obliterans organising pneumonia (not necessarily cryptogenic); [C]EP: (chronic) eosinophilic pneumonia; CTD: connective tissue disease; EG/HX: eosinophilic granuloma/histiocytosis X; EAA: extrinsic allergic alveolitis (hypersensitivity pneumonitis). #: Goodpasture's, granulomatosis with polyangiitis (Wegener's), Churg–Strauss, etc.; †: radiation was also included in the Italian and SEPAR registries; +: coal worker's pneumoconiosis was excluded in the Flemish, Italian and SEPAR registries.

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	Incidence per 100 000 people per year	
	1995–2000	2001–2005
Sarcoidosis	3.75	4.68
Nonspecific pulmonary fibrosis	7.49	9.76
IPF	7.27	5.28
Occupational	1.98	1.32
Environmental	0.80	0.78
CTD (and pulmonary haemorrhagic syndrome)	4.46	12.32
Total	19–27	28–34

Table 3 – Incidence of interstitial lung diseases in a population-based registry in Denmark (total population: 5.4 million). IPF: idiopathic pulmonary fibrosis; CTD: connective tissue disease.

per 100 000 people per year was found, which remained stable over time. The incidence appears to be higher in some countries (e.g. Scandinavia), in some population groups (black Americans) and in some families. In Spain, an incidence of only 1.2 cases per 100 000 inhabitants per year has been reported and similar low numbers have also been found in Portugal. International registries have, furthermore, demonstrated differences in the typical clinical presentation of sarcoidosis between various countries; for example, the benign subacute form known as Löfgren syndrome (hilar lymphadenopathy, fever, arthritis and painful cutaneous lesions called erythema nodosum) is particularly frequent in Scandinavia.

Idiopathic pulmonary fibrosis

Interpretation of the incidence and prevalence data needs to take into account the current definitions and classifications of the ATS/ERS consensus reports. In a UK study published in 1999, the estimated prevalence of IPF was 15–18 cases per 100 000 people; a median survival time from diagnosis of approximately 3 years thus corresponds to the estimated incidence of about 5 cases per 100 000 people per year obtained from several studies in the UK. While incidence and mortality data suggest that the frequency of IPF is increasing in the UK, a decrease was found in the Danish registry between 1995 and 2005.

Extrinsic allergic alveolitis (hypersensitivity pneumonitis)

A very large number of causes of EAA have been reported, such as EAA in farmers, pigeon breeders and budgerigar fanciers, and EAA due to repeated exposures to isocyanates, fungi, mollusc shells, etc. There are marked variations in the prevalence of the specific disease types between countries,

which is not only due to differences in the diagnostic criteria but also to the possible presence of industrial manufacturing plants, and to differences in local seasonal climate, geographic conditions and altitude. Smoking history is also important as patients with EAA are less likely to have been smokers than the general population. In a general-population cohort study based on a UK primary care database, a stable incidence of ~0.9 cases per 100 000 people per year (*i.e.* about 600 new cases each year) was found between 1991 and 2003.

The two most extensively studied types of EAA are farmer's lung and pigeon breeder's lung. Among Swedish farmers, the incidence of EAA is ~20 cases per 100 000 people per year. The reported prevalence across several countries varies between 4–170 per 1000 farmers, depending on local conditions and the diagnostic criteria used, while the frequency of hospital admission due to farmer's lung has been estimated in Finland and Sweden to be ~3–5 per 10 000 farmers per year. In pigeon fanciers, the prevalence of clinical disease has, in the past, been estimated at ~1 case per 1000 breeders, but more recently, a prevalence of more than 10% was reported in those with regular high exposure.

Interstitial lung disease associated with connective tissue disease

It is difficult to provide accurate data on the prevalence of ILD in CTD because this depends very much on the diagnostic methods used. Rheumatoid arthritis is estimated to occur in 2% of the population and evidence of ILD can be found using chest radiography and lung function testing in up to 20% of these patients. The prevalence of systemic lupus erythematosus is 40 cases per 100 000 people, with clinically relevant ILD in an estimated 10% of cases. The prevalence of progressive systemic sclerosis is 10 cases per 100 000 population, with pulmonary fibrosis found at autopsy in up to 75% of patients and lung function impairment seen in up to 90%.

Drug-induced lung diseases

Drug-induced lung diseases account for ~1.5–5% of all ILD (table 2), but these percentages probably underestimate the real frequency. More than 300 drugs are recognised as causing respiratory disease, particularly ILDs. Specifically, drugs such as amiodarone, bleomycin, methotrexate and nitrofurantoin, as well as radiation therapy, can all cause pulmonary fibrosis. Registration of, and information about, drug-related lung diseases has been coordinated by the Pneumotox group in Dijon, France (www.pneumotox.com) for the past two decades.

Inorganic dust-induced occupational lung fibrosis

Pneumoconioses, such as silicosis, coal worker's pneumoconiosis and asbestosis are discussed in chapter 24.

Age and sex distributions

ILD, particularly IPF and drug-induced fibrosis, occur mostly in older subjects, while sarcoidosis shows a predominance in young adults of both sexes, and in women over 50 years of age. The rarer pulmonary Langerhans' cell histiocytosis is notable for its typical occurrence in young cigarette smokers.

While IPF, EAA and inorganic dust-induced occupational ILD are more frequent in males, sarcoidosis and ILD associated with CTD are more frequent in women.

Annual mortality and survival

Extensive mortality data for the majority of European countries is available from the World Health Organization (WHO) World and Europe Mortality Databases. There are clearly differences between countries, which are partly real and partly due to differences in diagnostic and therapeutic strategies. The highest mortality rates due to ILD, of more than 2.5 per 100 000 people, are recorded in the UK, Ireland, Scandinavia, the Netherlands and Spain (figure 1).

Figure 2 shows that, among the most important ILDs, 'chronic ILD' (International Classification of Disease (ICD)-10 code J84, which includes IPF and other forms of fibrosing alveolitis) has the highest mortality rate, followed by ILD associated with CTD (ICD-10 code M32-M36). The mortality rates of sarcoidosis (ICD-10 code D86) and particularly EAA (ICD-10 code J67) are much lower. For sarcoidosis, the age-standardised mortality rate (per 100 000 people) in many countries is less than 0.15, but it is more than 0.30 in Denmark and Ireland. For chronic ILD, the mortality rate in most countries is less than 2 per 100 000 people, but it is at least 4 per 100 000 people in the UK, Ireland and Malta. For EAA, the mortality rate is below 0.05 per 100 000 people in the majority of the countries. For ILD associated with CTD, the mortality rate is generally below 0.6 per 100 000, but it is higher than 0.8 per 100 000 in Denmark and Norway.

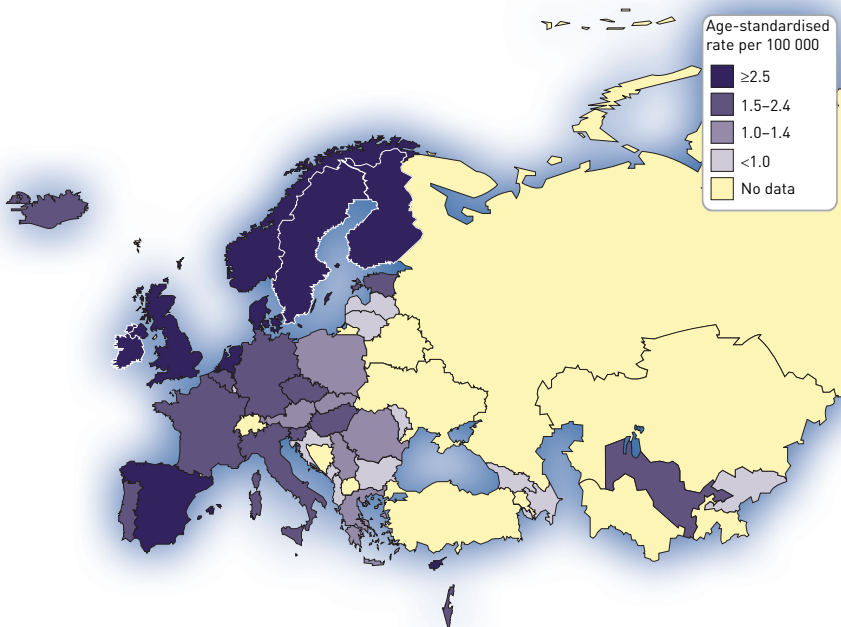


Figure 1 – Mortality rate of interstitial lung diseases. Data from the World Health Organization World and Europe Mortality Database, November 2011 update.

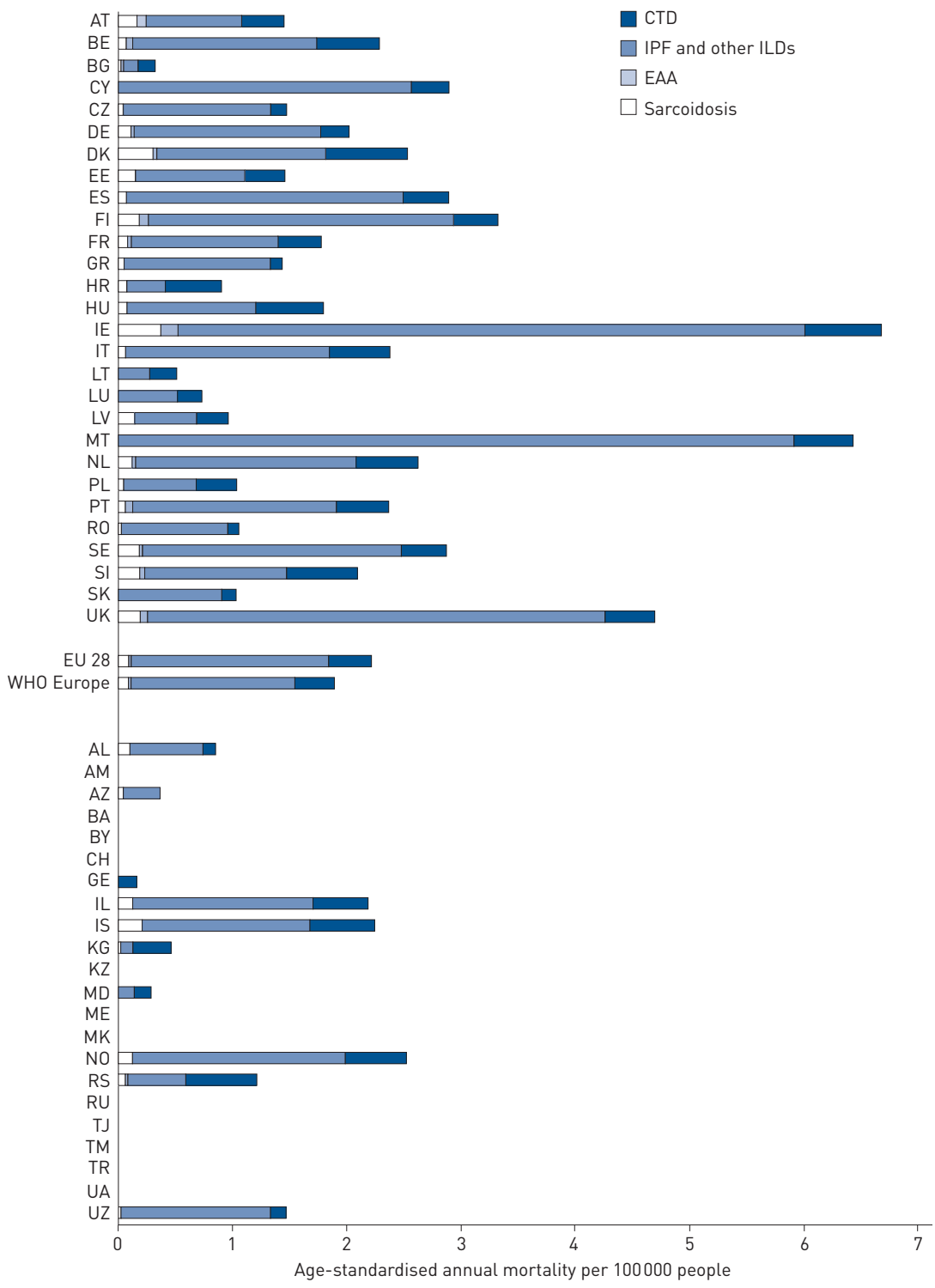


Figure 2 – Age-standardised annual mortality rates (per 100 000 people), 2005–2010, for the most important interstitial lung diseases (ILDs): sarcoidosis (International Classification of Disease (ICD)-10 code D86), chronic ILD (ICD-10 code J84; including IPF and other forms of ILD), extrinsic allergic alveolitis (EAA) (ICD-10 code J67), connective tissue disease [CTD] (ICD-10 code M32–M36). EU: European Union. Data from the World Health Organization (WHO) World and Europe Mortality Databases, November 2011 update.

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Although the WHO mortality data may be more complete than clinical registries of incidence or prevalence, they should be interpreted cautiously. Firstly, the relation of mortality data to incidence or prevalence rates varies considerably between disease conditions. About 50–70% of patients with IPF will die from this disease and thus the mortality rate should be about 50–70% of the incidence rate, but only about 5% of sarcoidosis patients will die of the disease and thus the mortality rate is only 5% of the incidence. Furthermore, for systemic diseases, such as sarcoidosis and CTD, the WHO mortality data do not distinguish whether patients had related ILD or, if present, whether the ILD contributed to death; thus the mortality rates in figure 2 only partly reflect deaths due to ILD. The WHO ICD classification may also be misleading due to peculiarities of the ICD codes, and owing to the fact that the definition of the codes changed from ICD-8 to ICD-9 and ICD-10, especially for IPF. In the figures presented in this chapter, the ICD-10 code J84 (chronic ILD) is used. This is broader than just IPF. In ICD-9, a specific disease code for IPF/cryptogenic fibrosing alveolitis (code 516.3) was introduced for the first time. Studies of the use of code 516.3 in death certificates and hospital admissions data in the UK, suggest that most patients coded as having IPF (using IDC-9 codes) do, indeed, have this disease, but that about half of the individuals known to have IPF are not coded correctly and many receive the less precise code of ‘post-inflammatory fibrosis’ (code 515). Consequently, countries with higher frequencies of post-inflammatory fibrosis tend to have lower frequencies of IPF and *vice versa*. The ICD-10 code J84 (chronic ILD) includes IPF as well as other chronic ILDs (such as other IIPs, ‘atypical’ nonspecific lung fibrosis, post-infectious ILD, drug-induced ILD) without subdivision into these entities.

Causes/pathogenesis



The cause of ILD is unknown in about 65% of patients (table 1). However, in several conditions, there is increasing evidence of the involvement of exogenous factors. Sarcoidosis is attributed to the combination of a susceptible constitution and exposure to a still unknown agent (microorganisms, inorganic material, etc.), but for the moment there is no convincing evidence of the precise causative agent(s). High exposure to metals (including brass, lead and steel) and wood dust have been shown to be risk factors for IPF.

Exogenous causes are recognised in 35% of patients with ILD, especially organic material (causing EAA), inorganic material (leading to pneumoconiosis), drug reactions and infections.

To date, human genetic studies of ILD have largely centred on descriptions of associations between certain phenotypes and known genetic loci, especially loci involved in inflammation and fibrogenesis. In the past decade, molecular genetic technology has improved greatly and complete genome scanning is now possible. In the future, more comprehensive information is expected thanks to advances in the field of functional genomics, including complementary DNA micro-array schemes and genetic bioinformatics. As a result, powerful strategies are becoming available to increase the resolution of gene mapping, even in complex diseases such as ILD.

Clinical manifestations and consequences



Typically, patients with ILD complain of breathlessness and decreased exercise tolerance. Clinical examination shows inspiratory 'crackles' audible on auscultation of the lungs. At a later stage, cyanosis and clubbing of the fingers and toes may be evident. Lung function tests show decreased lung volumes and low carbon monoxide diffusing capacity with hypoxaemia, especially on exercise. Chest radiography shows small lungs and increased interstitial markings. CT of the thorax is very important in both diagnosis and assessment, as is lung histology, if available, for revealing the characteristic patterns of ILD.

Prevention



Prevention is of great importance in conditions of known aetiology, especially pneumoconioses, EAA and iatrogenic ILD. Appropriate methods of prevention in the environment or workplace are being applied, mainly for ILDs caused by occupational exposure, but continuous vigilance remains necessary.

An ultimate goal would be better detection of susceptible subjects in order to provide specific preventive measures.

Management



The first stage of management of ILDs of known aetiology is prevention and cessation of exposure. Current therapy for ILDs of unknown aetiology consists mainly of antifibrotic and anti-inflammatory drugs and there has been an intensive search for active products in the past decade. For advanced ILD, oxygen and rehabilitation may be required, and lung transplantation may need to be considered in the later stages.

Prognosis



Evolution and survival time from diagnosis differ depending on ILD type. In addition, within a particular disease group, such as the IIPs, the prognosis may be very different depending on subclassification: although the 5-year survival rate is only about 20% in IPF, it is about 60% in lymphoid interstitial pneumonia, 80% in cellular nonspecific interstitial pneumonia and close to 100% in cryptogenic organising pneumonia. In a UK study, 5-year survival with EAA was 82% in the period 1993–2004. In sarcoidosis, 5-year survival is estimated to be well above 90%.

Morbidity and total costs

No precise data are available for morbidity or the total costs of ILD. However, it can be assumed that the costs are high for these chronic diseases, as respiratory impairment causes many patients to give up work, some need chronic home oxygen therapy, and some undergo lung transplantation.

Hospital admissions and hospital days

Extensive European hospital admission data are available from the WHO Hospital Morbidity Database. These data show that the age-standardised hospital admission rate for ILD was highest (more than 40 per 100 000 people) in Austria, Denmark, Norway, Finland, Poland and Slovakia (figure 3).

The hospital admission rate for the different subgroups of ILD varies markedly. For sarcoidosis, the WHO Hospital Morbidity Database (2011) showed that it was generally less than 5 per 100 000 people, but was more than 10 per 100 000 people in Austria, Poland and Slovakia. The admission rate for chronic ILD (including IPF) was generally less than 10 per 100 000 people, but was higher than 20 per 100 000 people in Denmark and Slovakia. For CTD, the admission rate was generally less than 15 per 100 000 people but was about 30 per 100 000 people

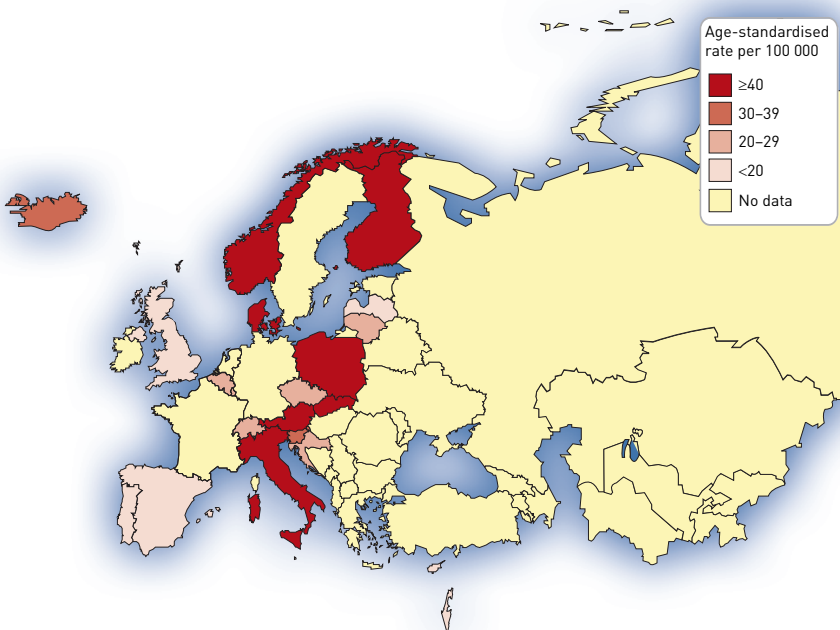


Figure 3 – Hospital admission rate of interstitial lung disease. Data from World Health Organization Hospital Morbidity Database, October 2011 update.

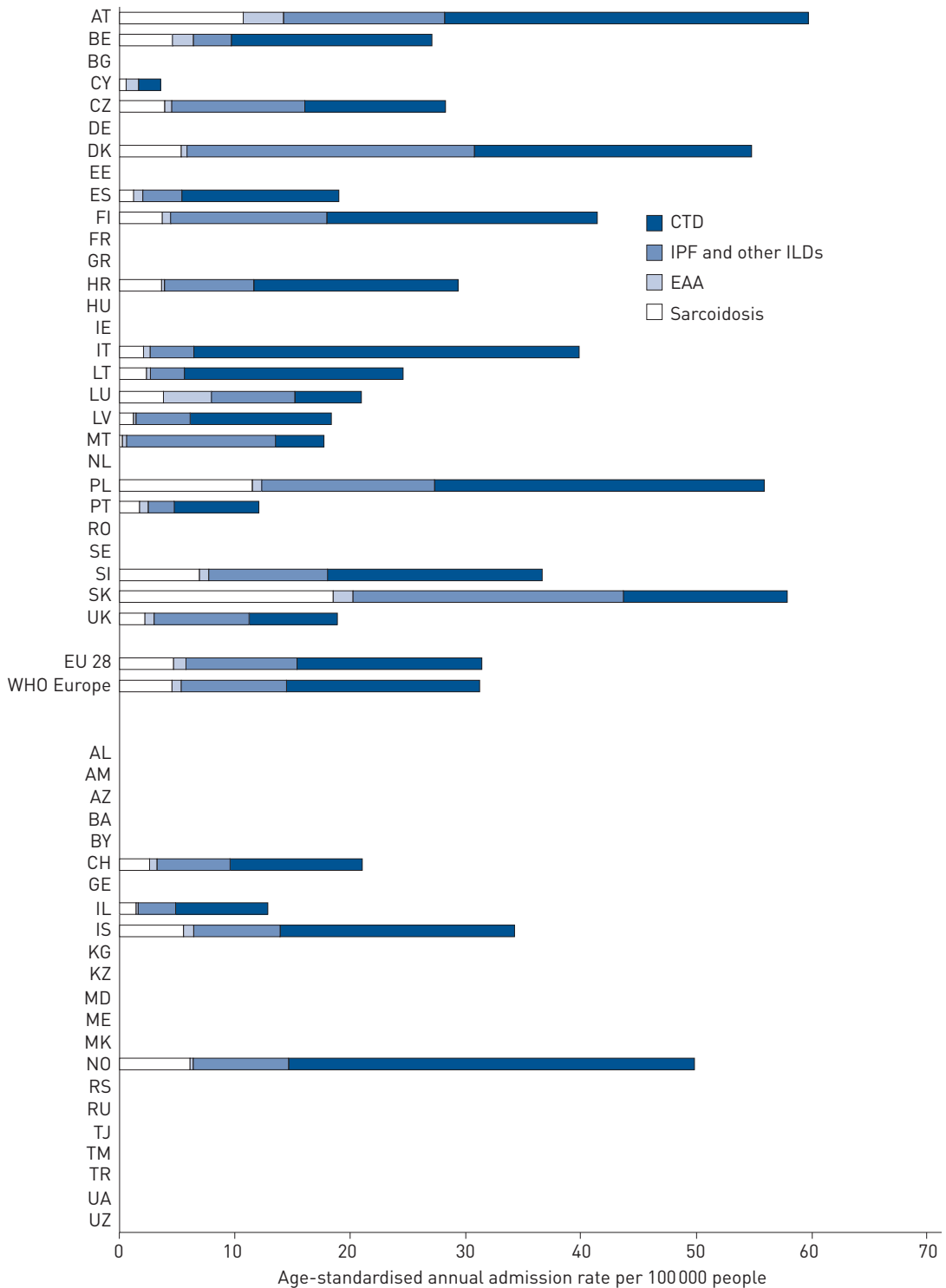


Figure 4 – Age-standardised annual hospital admissions (per 100 000) in the period 2005–2010 for the most important interstitial lung diseases (ILDs): sarcoidosis (International Classification of Disease (ICD)-10 code D86), chronic ILD (ICD-10 code J84; including idiopathic pulmonary fibrosis (IPF) and other forms of ILD), extrinsic allergic alveolitis (EAA) (ICD-10 code J67) and connective tissue disease (CTD) (ICD-10 code M32–M36). EU: European Union. Data from the World Health Organization (WHO) Hospital Morbidity Database, October 2011.

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in Austria and Norway. For EAA, the admission/discharge rate was generally very low but was more than 4 per 100 000 people in Austria and Luxembourg (figure 4).

The average length of hospital stay was generally 8–10 days; the shortest average stay was about 6 days in Denmark and Norway, and the longest average stay was 12 days in Switzerland.

Treatment costs

No precise data are available for drug/treatment costs of ILD. In the assessment of costs, the following aspects need to be taken into consideration: chronic use of anti-inflammatory drugs and antifibrotic agents (partly in clinical trials); frequent use of antibiotics; ambulatory oxygen therapy (especially lightweight, portable, liquid-oxygen containers) used in the advanced stages of the disease; and the possible cost of pulmonary rehabilitation and lung transplantation.

Working days lost

There are no exact data on working days lost due to ILD. However, the majority of patients with active ILD who are not yet retired are unable to work, mainly because of exertional breathlessness. In those with occupational ILD, avoidance of exposure and transfer to another job is the logical measure.

Research needs



There is a need for further large-scale epidemiological studies of ILDs and for clinical, basic and genetic research in ILD. Although knowledge of individual genetic susceptibility to the different ILDs and of the pathogenetic effects of exogenous agents has increased greatly, there is still much to learn. Furthermore, drug treatment of most ILDs remains unsatisfactory, although in recent years much research and several clinical trials have been carried out, particularly for IPF.

ILDs are an increasing burden on healthcare resources and many remain under the ‘orphan disease’ heading. In order to improve the efficiency of diagnostic and therapeutic management of ILD, it is necessary to plan strategically for the future with the help of a more intensive approach by national health authorities.

It is also the task of the medical profession to minimise the occurrence of iatrogenic ILDs; any such cases should be registered and communicated, for example *via* the Pneumotox website. In addition, guidelines are required for prevention, early detection and treatment of drug-induced ILDs.

Further reading



Reviews on classification, diagnosis and treatment of ILD

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