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Childhood asthma

Introduction ⓘ

Key points

- Although childhood asthma has historically been more prevalent in western than eastern Europe, the difference is diminishing as rates in the East rise.
- A British survey reported that 13% of carers of asthmatic children had given up work to care for the child.
- Approximately 60% of school-aged asthmatic children have allergies, particularly to animal dander, house dust mites and moulds, as well as plant pollens.
- Asthma typically begins much earlier in life than other chronic diseases, and consequently imposes a high lifetime burden on individuals, their caregivers and the community.
- Although asthma can usually be controlled, there are currently no proven methods of prevention or cure.

Asthma is the commonest chronic disease in childhood. Due to the various different phenotypes of childhood asthma, it has been difficult to agree on a clear definition of the condition and instead an operational description is used: 'Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.' (Global Initiative for Asthma, 2012). However, in children <5 years of age, clinical symptoms of asthma are variable and nonspecific, and a symptoms-only approach that defines various wheezing phenotypes has been recommended.

Epidemiology

Prevalence and incidence, and changing patterns of asthma with age

The prevalence of childhood asthma increased markedly in Europe in the second half of the 20th century. This is exemplified by published studies of asthma in schoolchildren in Norway, which have

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" *Asthma mortality in children is low and over recent years it has decreased in most European countries* "

reported an increase in prevalence from 0.4% in 1948 to 12.3 % in the mid-1990s and 20% in a study performed in 2004, although the most recent study, in 2008, reported a levelling off to 17.6% (figure 1). The increase was initially most marked in western Europe. The questionnaires developed for the International Study of Asthma and Allergy in Childhood (ISAAC) have provided a common tool for assessing the prevalence of asthma and wheezing disorders in children. In the ISAAC study performed in 1997, the highest prevalence of childhood asthma in Europe was found in the British Isles, with the prevalence of 'asthma ever' (lifetime prevalence of asthma) ranging from 1.6% in Albania to 20.7% in the UK for 13–14-year-old children, and from 1.4% in Estonia to 22.9% in the UK among 6–7-year-olds, with markedly increasing rates across Europe from East to West (figure 2). This East-to-West difference has diminished over recent years with a relative increase in lifetime prevalence in eastern Europe compared with the West; this may be related to simultaneous changes in lifestyle in eastern Europe. Figure 3 shows the prevalence rates of current wheezing in the ISAAC study phase III (data collected 2002–2003) in various centres in Europe.

The prevalence, causes and clinical presentation of asthma all vary with age. Many children first develop symptoms during infancy, but many cease wheezing in early
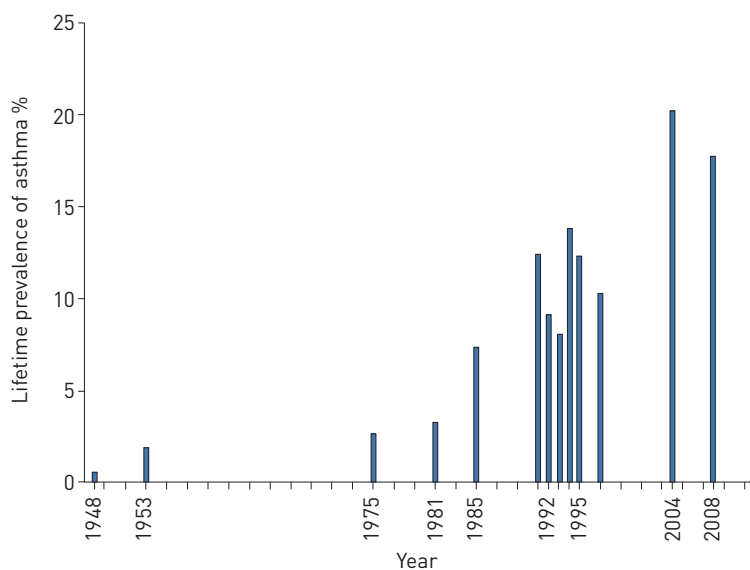

Figure 1 – Lifetime prevalence of asthma among Norwegian schoolchildren, 1948–2008.
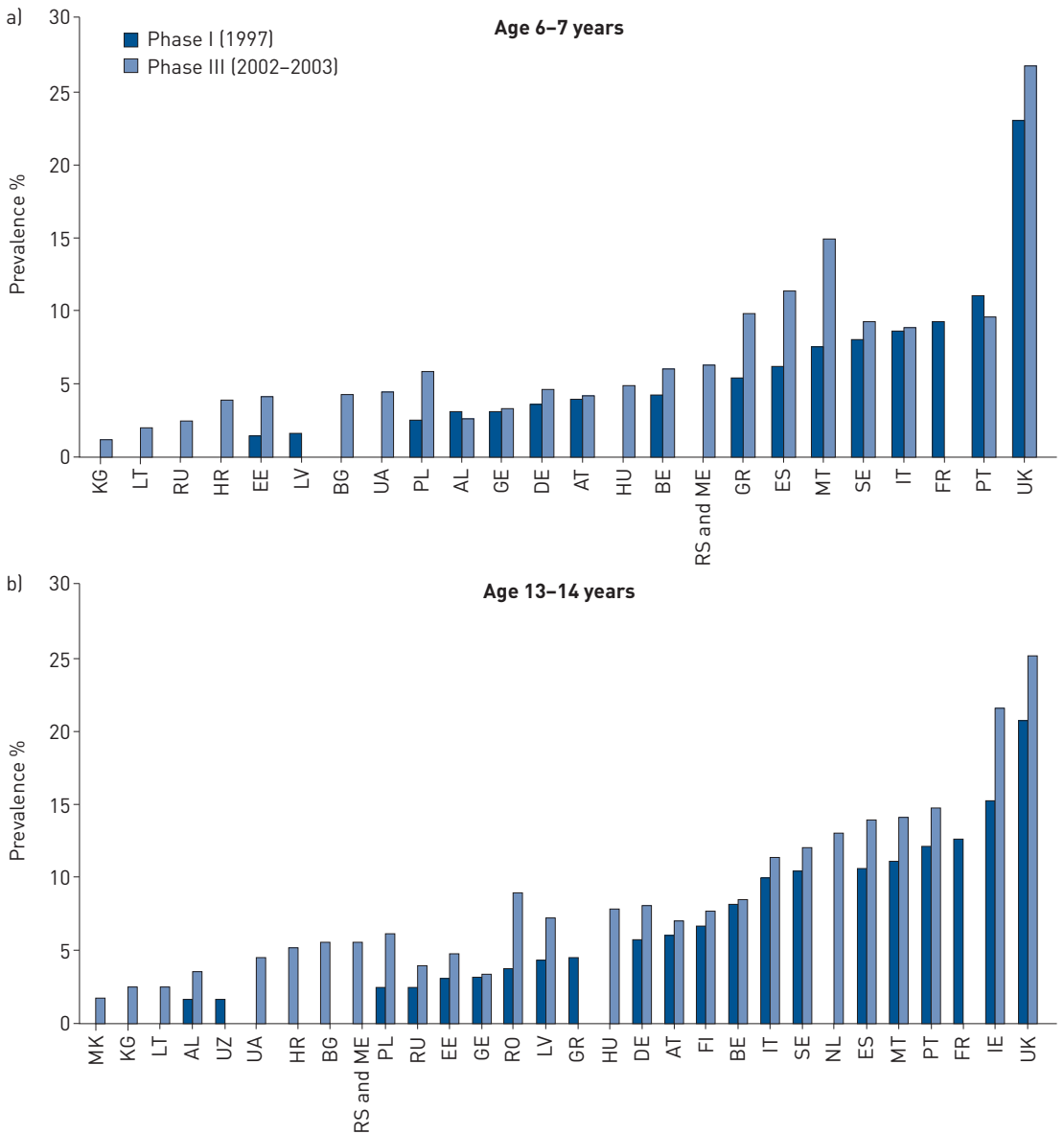
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Figure 2 – Lifetime prevalence of asthma in a) 6–7-year-old and b) 13–14-year-old children in 1997 and 2002–2003. Source: International Study of Asthma and Allergy in Childhood phases I and III.

childhood. Asthma can appear *de novo* throughout life, but it starts most commonly in early childhood, as illustrated in figure 4. This Canadian study reported that asthma affected approximately one-third of the population at some time between the ages of 4 and 80 years, much like diabetes or malignant disease. However, asthma starts much earlier in life than other disorders and thus has a lifelong impact on quality of life and health costs. The economic consequences of asthma are therefore particularly high due to its frequent early onset.
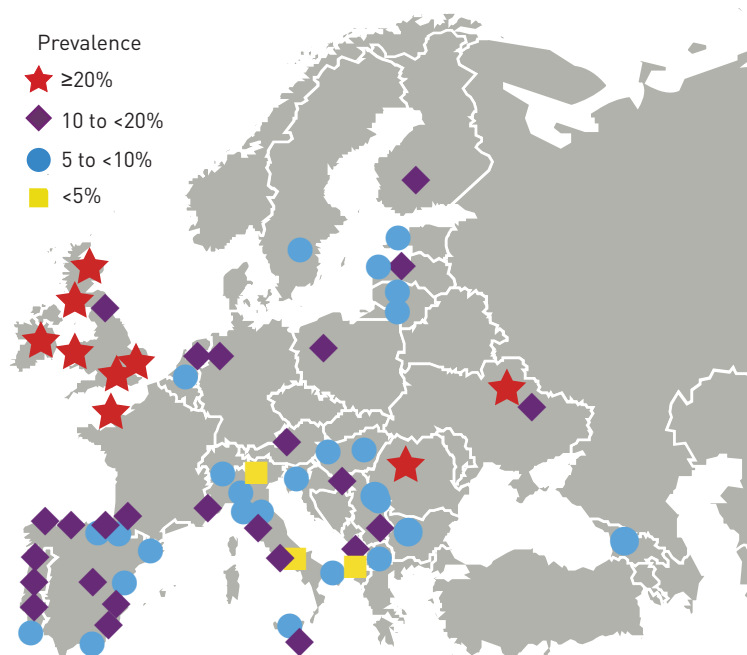
Figure 3 – Prevalence of current wheezing in children in centres across Europe. Reproduced and modified from Lᴀɪ *et al.*, 2009, with permission from the publisher.

Mortality

Asthma mortality in children is low and over recent years it has decreased in most European countries. Historically, mortality was highest among the youngest children, lower during school age, and then increased from puberty to adulthood.

In Denmark, a significant upward trend in asthma mortality was seen between 1973 and 1987. This was due solely to increasing mortality in the 15–19-year-old age group. From 1988 to 1994, the mortality rate among children aged less than 19 years decreased in general. In Norway, mortality among children ≥ 5 years of age has been consistently low since 1960, while in children < 5 years of age the mortality rate decreased until 1990 and was then as low as in the older age-groups. In contrast, in Russia an increasing mortality rate among children < 5 years of age was reported, from 0.06 per 100 000 in 1980 to 0.11 per 100 000 in 1989; there was, however, no increase among 5–34-year-old asthmatic subjects.

In the Netherlands, asthma mortality declined among 5–34-year-olds between 1980 and 1994, remaining stable among other age groups, whereas in England there was no change in asthma mortality among children aged 0–14 years from 1980 (0.389 per 100 000) to 1990 (0.387 per 100 000) compared to a 24% reduction in mortality for all causes. A further reduction in asthma mortality was seen in five European countries (France, Germany, Italy, Spain and the UK) between 1994 and 2005 among children and young adults (aged 5–34 years). Nevertheless, in 2004, there still remained 6700 possibly preventable deaths at all ages in these five countries.

In Sweden, the rate of asthma deaths among children and young adults (aged 1–34 years) decreased between 1994 and 2003. It was, however, remarkable that nine of the 12 deaths in the population aged <19 years were due to anaphylaxis, with asthma caused by food allergy.
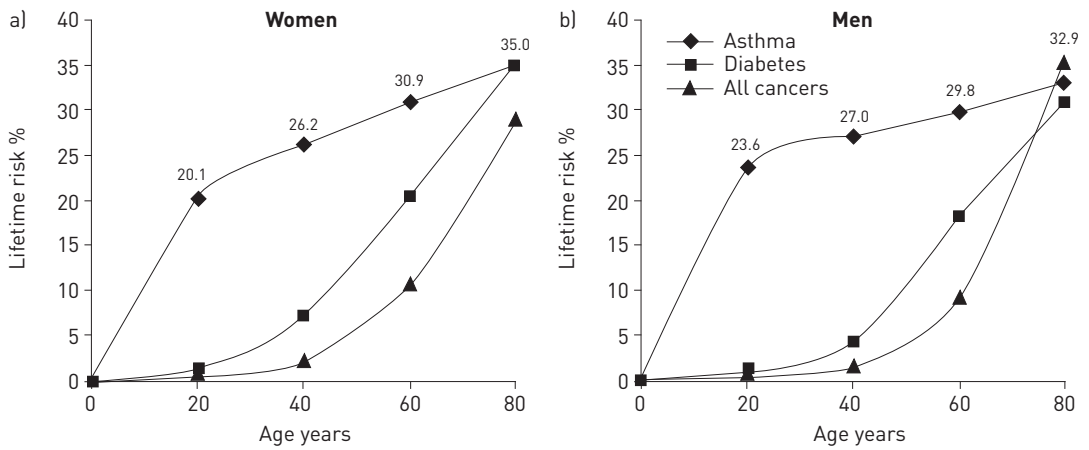
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Figure 4 – Lifetime risk of developing chronic diseases from birth in a) women and b) men. Reproduced from To *et al.*, 2010, with permission from the publisher.

When comparing childhood asthma mortality between countries, there are noteworthy correlations between the prevalence of asthma symptoms and asthma mortality as well as hospital admissions for asthma. Any reduction in prevalence may therefore have an impact upon asthma mortality. The decreasing mortality rate of asthma during childhood seen in most countries over the past two decades is probably due to the more widespread use of inhaled corticosteroids (which, even in low doses, have been shown to decrease mortality), together with improved treatment of acute asthma attacks.

Recent data (2004–2010, from the World Health Organization (WHO)) for children aged 0–14 years show that mortality is generally very low in Europe, with little difference between countries, implying better control of the condition with improvements in treatment.

Morbidity

Asthma morbidity is a major burden for the child, his/her family and the community. Asthma attacks are very frightening for the child and due to the resulting disruption of life and reduced physical ability there is an emotional, as well as economic, impact of the disease. The social burden of asthma is considerable, not only on the sick child but also on parents, siblings and the household in general. In England, 69% of parents or partners of parents of asthmatic children reported taking time off from work because of the child's asthma, while 13% had given up their jobs completely. In assessing quality of life in asthmatic children, it is important also to assess the quality of life of the caregivers.

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Severe problematic asthma that is poorly responsive to the common asthma treatments has been reported in approximately 4.5% of children with current asthma.

Direct healthcare costs for childhood asthma arise from consultations in both primary and secondary care, as well as hospital admissions (figure 5) and treatment costs. In some, but not all, countries, hospital admissions have fallen in recent years (see above), but greater use of both inhaled and oral agents has increased the expenditure on asthma drugs. A number of new drugs have recently been introduced, thereby increasing the drug-related cost. In particular, the use of inhaled steroids has increased markedly in recent years.

Although loss of working days is not directly applicable to children, absence from school is a comparable consequence. Good European studies are difficult to find, but one US study reported 10.1 million days' absence from schools due to asthma in 1 year, extrapolated from a study of 17 000 families.

Causes/pathogenesis ?

Environmental

Asthma results from an interaction between different environmental and genetic factors. The environmental influences begin during pregnancy: allergic sensitisation has been described before birth, and several studies have demonstrated reduced lung function in newborn infants of smoking mothers compared to those of nonsmoking mothers. Smoking increases the risk of both asthma and poorer lung function
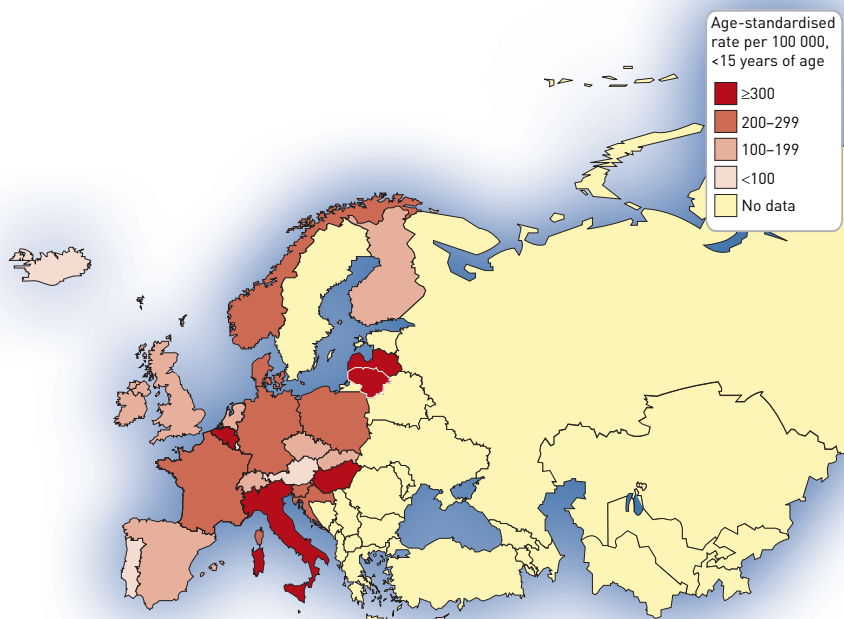

Figure 5 – Hospital admission rate for asthma in children. Data from World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

throughout childhood. All children should have the right to an environment free from tobacco smoke products both before and after birth.

Lifestyle changes have been linked to the increased prevalence of asthma, and especially allergic asthma. Studies from Russian and Finnish Karelen show a much higher prevalence of asthma and allergic diseases in the Finnish population compared with the Russian.

Respiratory virus infections are the major cause of acute bronchiolitis in infancy and of acute asthma attacks among older asthmatic children (more on childhood viral infections can be found in chapter 16). 1.5–2% of all children are hospitalised due to respiratory syncytial virus (RSV) bronchiolitis during the first 2 years of life, and approximately 60% of these children later develop asthma. At 13 years of age, more than 40% of children hospitalised in infancy with acute RSV bronchiolitis still have symptoms and bronchial hyperresponsiveness. From 2 years of age, rhinovirus infections are the most frequent precipitators of acute asthma. With modern techniques of virus diagnosis (*e.g.* those based on PCR), approximately 65% of all asthma attacks in schoolchildren have been reported to be due to rhinovirus infection, and when all types of virus infections are included it has been estimated that 85% of acute asthma attacks are precipitated by respiratory virus infections.

From 2 years of age and especially during school years, inhalant allergy becomes increasingly important for childhood asthma. Approximately 60% of all school-aged asthmatic children are allergic. The most important allergens vary according to climate, but in all European countries animal dander is among the most frequent allergens in asthma. In a warm and humid climate, house dust mites and moulds are also of major importance, and, depending upon climate, the seasonal allergens (birch, grass and mugwort pollen) play a role. Allergen exposure may cause acute asthma exacerbations, and even in the absence of an exacerbation, may increase airway inflammation and bronchial hyperresponsiveness.

Allergens may be encountered both outdoors and indoors, and house dust mites and animal dander are particularly important perennial indoor allergens. Occupational agents play a minor role during childhood, but several types of allergy may influence the choice of education in relationship to later working life. Kindergartens and schools are the working environment of children, and the need for a healthy indoor environment in such institutions should be emphasised. Special consideration should be given to the increased risk of respiratory infections, especially in kindergartens. In schools, precautions may be taken to reduce allergen exposure for

allergic asthmatic children. Emphasis should also be put upon mastering exercise-induced asthma in gymnastic lessons and physical training.

Genetic

Asthma, and one of its major causes, allergy, have strong hereditary traits. During recent years, much effort has been put into genetic family studies in order to identify genetic markers. A large number of markers with possible relationships to asthma and airway inflammation have already been identified, but these vary between populations. There has also been increased focus upon epigenetics: the finding that environmental influences may cause DNA methylation and histone formation, and thus change and inactivate the influence of specific genes, has given insight into how the environment may interact with genes, and has shown that this interaction may even be transferred from mother to child.

Furthermore, hereditary traits have been found to influence the response to asthmatic drugs. Examples include β_2-receptor sensitivity and responsiveness to inhibitors of leukotriene synthesis.

Exercise

Throughout childhood, but increasingly during school age, exercise is an important cause of asthma exacerbations (exercise-induced asthma). It has been reported that 30% of all asthmatic children suffer from restriction of physical activity and it is very important to teach asthmatic children to master exercise, by education, advice related to 'warming up' and medical treatment.

Clinical manifestations and consequences

Phenotypes

As previously discussed, asthma often starts in early childhood with acute attacks or exacerbations provoked by respiratory viral infections. Attention has focused on different asthma phenotypes especially during infancy and pre-school age, with diagnostic labels such as early wheeze, transient wheeze and late-onset wheeze, describing the longitudinal outcome of wheezing during early childhood. However, such retrospective labelling is not useful in predicting the prognosis. Recurrent wheezing during pre-school years often improves during school years and puberty. However, longitudinal cohort studies show that respiratory symptoms and bronchial obstruction often recur after the age of 16–20 years.

Most cases of asthma during childhood are mild or moderate and can be optimally controlled with treatment. However, a proportion have severe problematic asthma even during childhood, with lack of response to treatment with inhaled corticosteroids.

Exercise-induced asthma is particularly common in children and, if untreated, it may reduce activity and impair fitness. A major goal of all international guidelines for treating childhood asthma is to master exercise-induced asthma.

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Prevention

Several efforts have been made to prevent the development of asthma. These can be divided into: primary prevention, the aim of preventing symptoms and signs of allergy and asthma from occurring at all; and secondary prevention of asthma in a predisposed child who has, for example, atopic dermatitis. Tertiary prevention is the prevention of symptoms in an affected child. Prolonged feeding with breast milk may prevent respiratory infections but probably not asthma.

It is important to avoid exposure to tobacco smoke products. Since lung function is decreased in the newborn children of smoking mothers, it is especially important for such children to avoid worsening the impairment by taking up smoking in adolescence and young adulthood. In high-risk children, trials have been performed to reduce exposure to allergens, especially house dust mites and animal dander, but the efficacy of such measures remains to be proven. Although allergic sensitisation is related to early allergen exposure, low exposure to animal dander and house dust mite do not seem to reduce the occurrence of bronchial asthma in the general population.

Trials of pharmacological prevention have been performed using antihistamines, but so far the effect seems limited. It has been proposed that early introduction of anti-inflammatory drugs like inhaled steroids may influence the long-term development of asthma, but this remains to be proven.

Asthma education and asthma schools are important tools for educating patients, enabling them to take proper precautions before taking part in different activities.

> *Physical activity is of prime importance in childhood asthma, and should be encouraged*

Management

Modern guidelines for treating childhood asthma distinguish between controlling and relieving treatment. Among the controlling treatments, inhaled corticosteroids are the most important drugs and enable most children and adolescents with asthma to lead a normal life. In most cases, inhaled corticosteroids also control exercise-induced asthma, allowing participation in physical activity and sports. High doses of inhaled steroids may impair growth but only to a small extent (1–2 cm in height at most), and usually in the early phase of treatment. Adrenal suppression can occur with high doses, and hypoglycaemic convulsions have been reported. Recently, an inhaled corticosteroid has been introduced as a pro-drug,

which depends for its effect on enzymatic activation in the respiratory epithelium. The lack of systemic side-effects makes such agents particularly suitable for childhood asthma.

Inhaled β2-agonists are important reliever medication, for both acute and chronic asthma. Combination treatment consisting of an inhaled corticosteroid and an inhaled long-acting β2-agonist has proved to be very effective in adult asthma care, but in childhood asthma and especially in pre-school children, the treatment response has not been as good. Children should be monitored carefully to assess the response to treatment, and treatment that proves to be ineffective should be stopped. This also applies to leukotriene antagonists, which are remarkably effective in some patients, both as controller and reliever treatment, but there is a high percentage of non-responders. Anticholinergic therapy, in particular ipratropium bromide, is also effective as a bronchodilator in children and may have an additive effect to inhaled β2-agonists. Anticholinergic treatment seems to have a special place as pre-medication before exercise in children with exercise-induced asthma and in treatment of asthmatic adolescents with an athletic career. The anti-immunoglobulin (Ig)E monoclonal antibody omalizumab has proved effective for some patients with severe allergic asthma, but, again, some fail to respond, emphasising the need for careful follow-up. Other novel treatments are currently being investigated.

Asthma care involves much more than just pharmacological treatment, although this is a very important part of the treatment plan. Participation in physical activity is of prime importance in childhood asthma and should be encouraged.

Prognosis

Childhood asthma most often starts before school age. During puberty, many children – especially boys – experience improvement, but later in life the symptoms of asthma often recur. During early life, boys more frequently have asthma; after 10 years of age, however, girls more frequently develop asthma, often with greater severity. However, with modern asthma treatment and care, most asthmatic individuals are able to lead a normal, healthy life. The lifetime risk of asthma is approximately 35%, with most cases occurring early in life, and many requiring lifelong medical follow-up and medication, and thus having an impact on health costs. Early childhood asthma and, in particular, severe childhood asthma increase the risk of chronic airway obstruction in adult life.

Future developments

Based on the current situation, a further increase in the prevalence of asthma is anticipated, particularly in eastern European countries where acquisition of a Western lifestyle has already been shown to increase the prevalence of childhood asthma to as much as 20%. Furthermore, as there appears to be a cohort effect on the increased prevalence of asthma in childhood, an increase is likely among adults (especially young adults) in the near future. Greater use of anti-inflammatory drugs, and the possible development of more effective drugs, may reduce the acute morbidity of asthma and the need for acute hospital admissions. New drugs targeting pathways in the inflammatory processes may improve therapy, but this remains to be shown. However, there will be

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an increasing need for specialist diagnosis and monitoring of asthmatic patients especially at an early stage of the disease, with the aim of reducing its long-lasting effects.

Research needs

Further research is needed on all aspects of childhood asthma, including clinical as well as basic and genetic research. In particular, more data are needed on the environmental and genetic causes of childhood asthma in order for society to be able to take preventive measures.

Asthma cannot be cured with current treatment, but we can reduce morbidity and improve our mastery over the illness. There is a need for research into new treatment approaches, especially in young children. In many countries in Europe the resources for independent research in this area are limited, and cooperation between centres, with the creation of networks of centres of excellence, should be encouraged.

> " *Several studies have demonstrated reduced lung function in newborn infants of smoking mothers* "

Summary of research needs

- Cohort studies: follow-up studies from birth to adulthood of entire cohorts, taking into consideration:
  - Environmental factors: including outdoor and indoor pollution, the influence of infections and allergen exposure in early childhood and the long-term effects of anti-inflammatory treatment;
  - Genetic factors of importance for asthma and airway inflammation: repeated sampling over time of DNA in birth cohorts enabling longitudinal studies on epigenetics as well as long-term tracking from birth to adulthood of lung function, bronchial responsiveness and markers of airway inflammation.
- Basic research into the aetiology and pathogenesis of asthma, allergy, airway inflammation, bronchial hyperresponsiveness and exercise-induced asthma.
- Intervention studies to evaluate primary and secondary preventive measures, including attempts to prevent/reduce respiratory epithelial barrier damage.
- Epidemiological studies to enable more comprehensive Europe-wide monitoring of asthma prevalence, morbidity and hospitalisation.
- Clinical studies to develop new treatment modalities.
- International studies comparing quality of asthma care and health economics in order to optimise the quality of asthma care throughout Europe.

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Further reading

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Adult asthma

Key points

- In Europe, about 30 million children and adults less than 45 years old have asthma.
- In western Europe, the prevalence of asthma increased in the latter part of the 20th century, but it now appears to be levelling off in many countries; the UK and Ireland have some of the highest rates of asthma in the world.
- Adults with asthma include those who have had asthma since childhood, those in whom it apparently resolved but has subsequently recurred and those who have developed asthma *de novo* in adult life.
- Asthma can develop in the elderly but, because of similar clinical features, it may be difficult to distinguish asthma from COPD in older individuals.
- Most patients with asthma can be managed successfully in primary care according to widely accepted guidelines, but a significant proportion require specialist referral and supervision.

Asthma is a chronic inflammatory disease of the airways that causes recurring episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. Three terms are used to describe the course of asthma: asthma control, asthma severity and asthma exacerbations. Asthma control is assessed by symptoms, activities of daily living and quality of life. It also includes the likelihood of loss of control, exacerbations, decline in respiratory function, and the side-effects of treatment. Asthma severity describes the difficulty in controlling asthma with treatment, reflecting the level of treatment required and the activity of disease during treatment. Asthma exacerbations are episodes of worsening of symptoms that necessitate additional treatment: asthma is severe if systemic corticosteroid treatment is needed and it requires treatment in hospital or in an emergency room.

Asthma is a common disease that affects people of all ages in all countries of Europe. Most commonly it arises in childhood and may persist into adulthood (see chapter 11). In perhaps two-thirds of children with asthma, the disease remits in the early teenage years, only to relapse, in about a third of these cases, in adulthood. Less commonly, the disease begins for the first time in adulthood. Thus, adult asthma may represent persistent or relapsed childhood disease or true incident 'new' adult disease. Adult asthma is frequently associated with allergies and/or accompanied by other allergic conditions such as hayfever.

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"

Epidemiology

There is no widely applicable diagnostic test for asthma, and assessment of its frequency and determinants is based on responses to questionnaires, simple tests with imperfect sensitivity and specificity, and the outcome of medical care such as hospital attendances and drug prescriptions. Because asthma tends to remit and may relapse, it can be difficult to distinguish prevalent (or recurrent) disease from that which is truly incident. Most measures of frequency probably reflect prevalent asthma, *i.e.* that which is present at, or over, a particular time. Because the symptoms of asthma are not specific to the disease, they can be confused with those of other respiratory diseases, particularly, in later life, chronic obstructive pulmonary disease (COPD).

In the whole of Europe, about 30 million children and adults under 45 years of age have asthma. In most European countries, the prevalence and perhaps incidence of asthma increased substantially at some time between 1950 and 2000 but, at least in western Europe, the increase has levelled off in the past decade. Figure 1 shows the estimated

Asthma data available online

ec.europa.eu/health/major_chronic_diseases/diseases/asthma/index_en.htm
A public health summary of asthma provided by the European Commission with links to statistical data.

www.laia.ac.uk/pubs/sevasth.pdf
A summary of the epidemiology of severe asthma in Europe.

www.ginasthma.org/
Website of the Global Initiative for Asthma (GINA).

www.bohrf.org.uk/downloads/OccupationalAsthmaEvidenceReview-Mar2010.pdf
An evidence-based review of the recognition, management and prevention of occupational asthma.

www.efanet.org/wp-content/documents/SASSevereAsthmaBackgrounder050307.pdf Briefing document on asthma from the European Federation of Allergy and Airways Diseases Patients Associations.

current prevalence of asthma in European countries among adults aged between 18 and 44 years. The rates of disease tend to be higher in northern and western countries where the prevalence may be higher than 10%. Unlike childhood disease, adult asthma tends to be more common in females.

Causes/pathogenesis

Most adult asthma has its origins – and causes – in childhood; the sharp rise in the prevalence of childhood disease in most European countries in recent decades indicates important environmental determinants acting on a genetically susceptible population, a process commonly referred to as gene–environment interaction. The nature of the relevant drivers remains unclear, but the distribution of the disease suggests that they are associated with a 'Western' environment, possibly reflective of urbanisation and less exposure to microorganisms that are protective against asthma and allergy (the 'hygiene hypothesis'). Genome-wide association studies have identified a handful of asthma genes that account for only a small fraction of the heritability of asthma, but epigenetic silencing and activation of genes involved in asthma are likely to be other important mechanisms that determine susceptibility to asthma and that underlie gene–environment interactions (see chapter 3).

Immunopathological studies of the airways in asthma have pointed to the presence of a T-helper type 2 (Th2)-associated inflammatory process involving cytokines such as interleukin (IL)-4, IL-5 and IL-13 with a predominant eosinophilic inflammation, associated with features of airway remodelling (airway fibrosis, increased smooth muscle mass and epithelial fragility). Better understanding of the inflammatory processes has paved the way for novel, specifically targeted therapies.

Clinical manifestations

Adults with asthma present with a spectrum of signs and symptoms that vary in severity from patient to patient, and within the same patient over time. Some patients complain of very few mild symptoms while others present with more severe symptoms despite having only mild airflow obstruction. Airway function should be measured routinely by tests such as forced expiratory volume in 1 second (FEV1) or peak expiratory flow (PEF).

The clinical manifestations of asthma include recurrent episodes of wheezing, chest tightness, cough and shortness
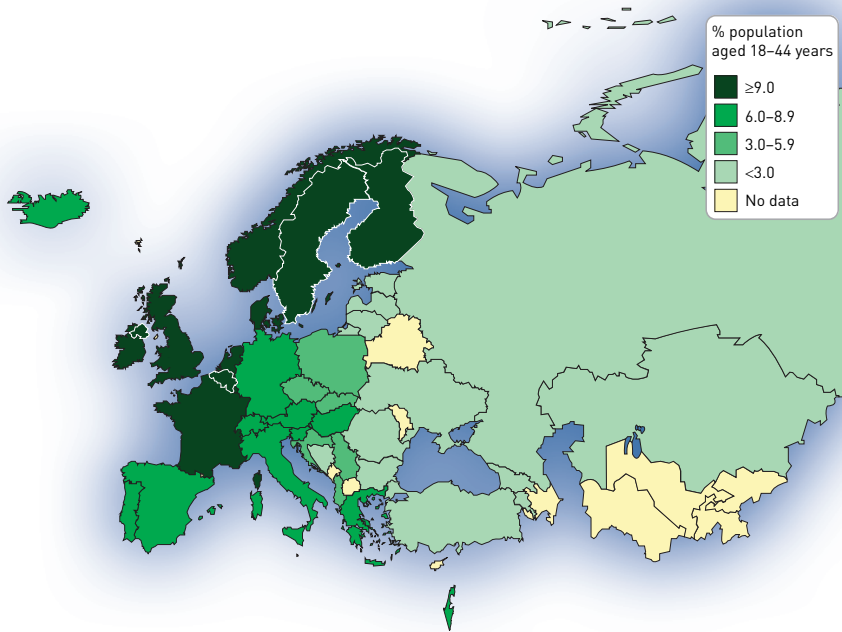
Figure 1 – Prevalence of asthma ever in adults aged 18–44 years. Data from World Health Organization World Health Survey, 2002–2004. Sɪɢᴜʀᴋᴀʀʟssᴏɴ *et al.*, 2011; Polish Multicentre Study of Epidemiology of Allergic Diseases; European Federation of Allergy and Airways Diseases Patients Associations; Serbian Health Insurance Fund; the Swiss Study on Air Pollution and Lung Disease in Adults; Pʀɪꜰᴛᴀɴᴊɪ *et al.*, 1999; Organisation for Economic Co-operation and Development.

of breath. The symptoms are often worse at night or on waking from sleep. Usually, they resolve spontaneously or with the inhalation of a reliever medication. In other cases, they may worsen over hours or minutes, leading to more severe airflow obstruction and an 'attack' or exacerbation of asthma that is relieved only by extra medication. Some very severe episodes are life-threatening, although death from asthma in adulthood is uncommon (figure 2) and in most European countries mortality rates are falling.

Exacerbations of asthma are mostly provoked by respiratory infections – usually viral in origin – and are especially common in winter and shortly after the return of children to school after the summer holiday. In adults with allergic asthma (as indicated by the co-presence of rhinitis and conjunctivitis), symptoms are provoked by exposure to the relevant allergen(s), commonly those in house dust or from pets, or encountered at work. Other common triggers include physical exertion (particularly in cold, dry air) and traffic pollution. Certain drugs such as ß-adrenergic blockers and nonsteroidal anti-inflammatory agents can provoke asthma. A rare, but characteristic form of adult-onset asthma presents with nasal polyps and symptoms provoked by taking aspirin or similar nonsteroidal anti-inflammatory agents; its mechanism is unclear. Asthma exacerbations remain the main reason for admission of people with asthma to hospital. While rates of hospital admission have gradually fallen in recent years, they remain high, particularly in the UK, Spain and Belgium (figure 3).

One important type of disease that arises in adulthood is occupational asthma, which is induced by airborne agents encountered in the workplace. Occupations in which there is a high risk of occupational asthma include baking, spray painting, chemical processing,
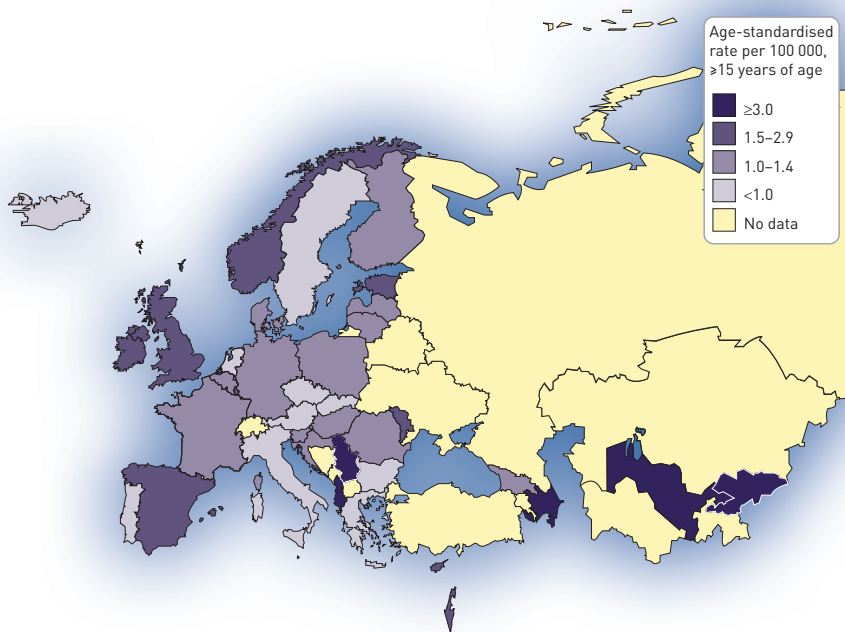
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Figure 2 – Mortality rate of asthma in adults. For some countries, data are missing due to deaths being reported for asthma and chronic obstructive pulmonary disease combined. Data from World Health Organization World and Europe Detailed Mortality Databases, November 2011 update.
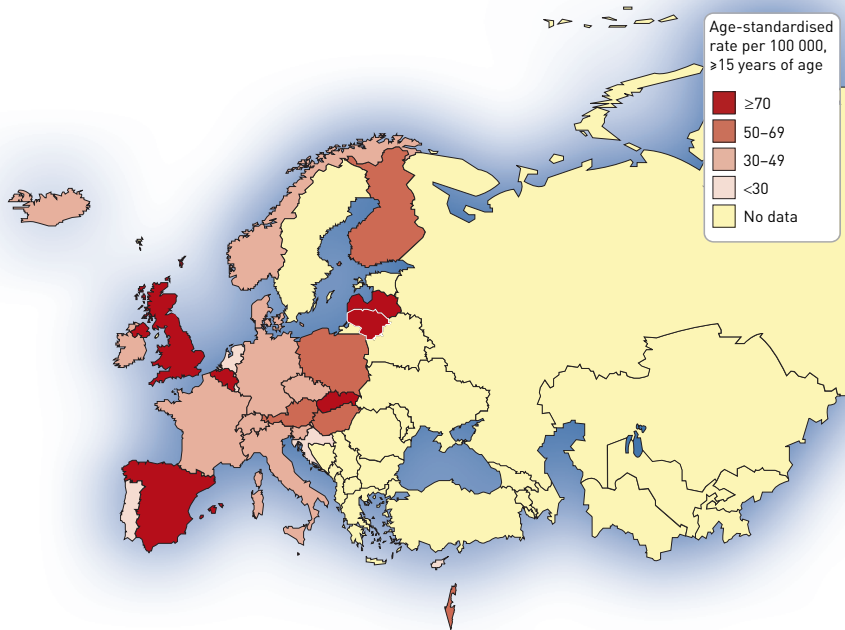

Figure 3 – Hospital admission rate for asthma in adults. Data from World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

detergent manufacture and hairdressing. In addition, adults with asthma of unknown origin may find that irritant exposures or physical exertion at work exacerbate their disease. It is estimated that, in these ways, some 15% of all adult asthma is 'work related' (see chapter 24).

Prevention

In most adults with asthma, the origins of the disease are unknown and therefore it is difficult to know what measures can be taken to prevent its development. One important exception is occupational asthma, which can generally be prevented effectively by careful control of relevant exposure in the workplace. In general, prevention or control of asthma symptoms and exacerbations is usually possible with current asthma medication.

Management

There is currently no cure for most types of adult asthma, and the primary goals of management are: 1) to achieve and maintain control of symptoms; and 2) to prevent asthma exacerbations. In many cases, it is also possible to improve and/or maintain respiratory function, to retain normal activity levels, to prevent the development of irreversible airway narrowing and to prevent deaths from asthma. Clearly, it is also desirable to avoid short- and long-term adverse events from asthma medication.

Management starts with the identification of factors that trigger or worsen asthma. Avoiding passive or active smoking, exposure to high levels of airborne allergens or environmental pollution, and certain medications that may provoke asthma can each help improve control. Appropriate patient education and self-management are important aspects of care; in many countries, this is efficiently delivered and supervised by specialist asthma nurses.

Pharmacological treatment comprises 'controller' medication, exemplified by inhaled corticosteroids (ICS), with or without long-acting β_2-agonists (LABA), and 'reliever' medication taken as required to relieve symptoms, exemplified by short-acting β_2-agonists (SABA). The amount of treatment is adjusted according to the severity and frequency of asthma symptoms. Patients' needs for treatment may change over time and treatment should be adjusted accordingly.

Mild asthma is usually controlled using SABA alone and on demand, or by the addition of low doses of ICS. Asthma of moderate severity can be controlled with a combination of low- or high-dose ICS with LABA. More severe asthma may necessitate the addition of other controller medications such as leukotriene inhibitors and slow-release theophylline. Oral corticosteroids may be needed intermittently for treatment of exacerbations, or on a daily basis in those with the most severe disease. In some countries, anti-immunoglobulin (Ig)E antibody treatment is now available as an additional therapy for patients with severe allergic asthma.

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Using established treatment guidelines, most adult patients with asthma can be managed adequately in general practice, but those with more severe disease, and particularly those who present with recurrent exacerbations of asthma, are managed in hospital clinics. The rate of acute hospital admission for asthma varies widely across Europe (figure 3) but in most countries admission is less common than it used to be, probably reflecting improvements in the delivery of asthma care and the increased use of ICS therapies.

Medication use in Europe

In the Asthma Insights and Reality (AIRE) study of seven western European countries, published in 2002, 2083 adults and children with asthma or their parents were surveyed about their asthma by telephone interview. In this survey, 12–18% of children and 15–28% of adults were classified as having severe persistent asthma. However, in the severe category, only 14–83% of children and 8–49% of adults were being treated with ICS therapy. The country with the highest use of ICS in both children and adults was Sweden. Because it would be expected that all patients with severe persistent asthma would be taking ICS, the survey indicated that there was severe undertreatment of asthma, the major reason perhaps being the lack of uniform application of asthma management guidelines across these countries.

However, in both France and the UK, there is evidence that the number of prescriptions for anti-asthma drugs more than doubled between 1980 and 1990, particularly for SABA and ICS. In the UK, the number of prescriptions for ICS in 1980 was approximately 1.2 million, increasing to 7 million in 1992. In a cross-sectional review of treatment carried out in five large general practices in the UK, 54% of adult patients with asthma were prescribed SABA alone, with most of the remainder using various combinations of additional drugs; 8% were using no treatment at all. Over the previous year, 14% had received 10 or more prescriptions for SABA/LABA and 13% had been prescribed at least one course of oral corticosteroids. Both of the latter occurred more frequently in patients taking more prophylactic treatment, indicating that there is a group of individuals, albeit relatively small in number, who have asthma that is refractory to the best available treatments.

> " *Death from asthma in adulthood is uncommon and in most European countries mortality rates are falling* "

Prognosis

Most adults with asthma achieve good or very good control of their disease and are able to lead a normal life, punctuated

only by the need to take small amounts of regular medication and by occasional exacerbations. A small subgroup of about 10% of adults with asthma have persisting symptoms and exacerbations despite taking adequate treatment at the highest doses; the impact of this severe or 'difficult-to-control' asthma is often significant and many of these patients struggle at home and at work, and are prone to the adverse side-effects of treatment, particularly those associated with oral corticosteroids at high doses. Asthmatics of particular concern are those who smoke or are exposed to passive smoking, which can make asthma worse. The challenge of severe asthma is to find ways of controlling the frequency of exacerbations and reversing the chronic airflow obstruction that are the most frequent hallmarks of this condition, despite the use of optimal anti-asthma treatment.

The most important long-term consequence of asthma is the development of persistent airway narrowing, which is non- or poorly responsive to treatment; it is unclear whether this is preventable by regular treatment with controller therapies. Death from asthma, although very uncommon in Europe, can occur in adults with all forms of the disease, especially if treatment has been suboptimal.

Future developments and research needs

Asthma is common in European adults and in many countries it is more common than it used to be. There remains a pressing need to understand its origins – in most cases in childhood – so that effective primary prevention can be devised. Where its causes are known – notably in occupationally induced disease – greater efforts need to be made in the regulation and control of causative exposures.

Propagation of good asthma care in Europe

Current medications are generally very effective but require appropriate availability and means of delivery. The establishment of national and international guidelines has been instrumental in improving the care of adults with asthma, through better education of medical practitioners, involvement of asthma-trained nurses and the implementation of standardised treatment regimens. In some countries, such as Finland and France, the active participation of government health departments has led to important improvements in asthma control with consequent reductions in morbidity, mortality and costs attributable to the disease, demonstrating that focused, national programmes can work and are probably cost-effective. In any such programme, it would be important to address three particular issues that contribute to the continuing burden of asthma. 1) Are all patients who need treatment receiving and taking adequate controller medication? 2) Are patients with persistent uncontrolled asthma being adequately monitored and investigated as to the cause of the poor control? 3) Are the co-existing factors associated with asthma being treated or addressed, such as cigarette smoking or secondary smoke exposure, allergies, sino-rhinitis and obesity?

Difficult-to-control severe asthma

Difficult-to-control severe asthma can be subdivided into: 1) untreated severe asthma caused by poor access to medical care and asthma therapies; 2) difficult-to-treat,

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severe asthma resulting from poor management or poor patient adherence to treatment; and 3) treatment-resistant asthma for which control is not achieved despite the highest level of recommended treatment (refractory asthma and corticosteroid-resistant asthma) or for which control can be maintained only with the highest level of recommended treatment with a risk of side-effects.

New therapeutic approaches are needed for the category of patients with treatment-resistant asthma. First, we need a better understanding of its pathophysiology and its relation to the various phenotypes of adult asthma with respect to clinical presentation, functional abnormalities and features of airway inflammation and remodelling. Several distinguishable phenotypes of adult asthma have been described: for example, those with the most severe disease, requiring treatment with two or more controller medications, have a later age of onset, the greatest degree of airflow obstruction and the poorest bronchodilator response. Another characteristic of some types of severe asthma is the presence of a persistently high number of eosinophils in the sputum, despite high-intensity treatment. This type of asthma would be expected to respond to novel therapies targeting eosinophils, such as anti-IL-5 antibody treatments. Thus, the importance of defining phenotypes lies in matching them with novel, specific therapies that would benefit the individual patient.

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Chronic obstructive pulmonary disease

Key points

- 5–10% of adults aged over 40 years have COPD, with a higher prevalence in men than women.
- The key risk factor for chronic obstructive pulmonary disease is tobacco smoke, but occupational exposures, pollution and genetic factors play a role.
- The most important symptoms of chronic obstructive pulmonary disease are breathlessness on exertion and chronic cough with or without phlegm, but fatigue, anorexia and weight loss can arise as the disease progresses.
- Treatment is multimodal, including smoking cessation, medical treatment with bronchodilators as well as inhibitors of inflammation, physical exercise and oxygen therapy.

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is usually progressive and associated with a chronic inflammatory response in the airways and lungs to noxious particles or gases. The persistent airflow limitation results from a combination of diffuse small airway disease and destruction of the lung parenchyma (emphysema).

COPD is a syndrome with many phenotypes. They have been poorly defined and knowledge of their specific aetiology, pathogenesis, management and meaningful outcomes is limited. Chronic bronchitis (defined as cough and phlegm for at least 3 months per year in 2 consecutive years) may precede or coincide with airway narrowing but may also be seen in patients without COPD.

The diagnostic criterion for COPD is based on spirometry confirming a reduction in the ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC). Severity is graded as shown in table 1. There is, however, ongoing discussion about the most appropriate spirometric criterion to use, either reduction of the ratio of FEV_1/FVC below a fixed value (usually 70%) or below the lower limit of normal FEV_1/FVC for the age and sex of the subject. Since even in healthy individuals the FEV_1/FVC ratio declines with age, use of the former criterion rather than the latter can result in overdiagnosis of COPD in the elderly and underdiagnosis in younger subjects.

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> " *The risk of developing COPD is inversely related to socioeconomic status based on education or income* "

ATS/ERS criteria	
Mild	FEV_1/VC <5th percentile of predicted and $FEV_1 \geqslant 70\%$ pred
Moderate	FEV_1/VC <5th percentile of predicted and FEV_1 60–69% pred
Moderately severe	FEV_1/VC <5th percentile of predicted and FEV_1 50–59% pred
Severe	FEV_1/VC <5th percentile of predicted and FEV_1 35–49% pred
Very severe	FEV_1/VC <5th percentile of predicted and FEV_1 <35% pred
GOLD criteria	
Mild (stage I)	FEV_1/FVC <0.70 and FEV_1 >80% pred
Moderate (stage II)	FEV_1/FVC <0.70 and 50%≤FEV_1<80% pred
Severe (stage III)	FEV_1/FVC <0.70 and 30%≤FEV_1<50% pred
Very severe (stage IV)	FEV_1/FVC <0.70 and FEV_1 <30% pred or FEV_1/FVC <0.70 and FEV_1 <50% pred and chronic respiratory failure

Table 1 – Classification and severity staging of airflow obstruction according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. FEV_1: forced expiratory volume in 1 second; VC: vital capacity; % pred: % of predicted value; FVC: forced vital capacity. Reproduced from BAKKE *et al*., 2011.

COPD is a major burden to many individuals, societies and healthcare budgets throughout the world. Its impact is expected to rise both in industrialised and developing countries in the decades to come, partly due to continued exposure to risk factors for COPD and partly due to an ageing world population. People who live longer are more likely to experience the consequences of long-term exposure to COPD risk factors.

The aim of this chapter is to describe the epidemiology, risk factors, clinical picture, management, and future trends of COPD in Europe.

Epidemiology

Europe, as defined by the World Health Organization (WHO), has a population of approximately 750 million in 54 countries, among which there are large differences in population structure and health services and great environmental heterogeneity. Europe should therefore be an ideal region in which to explore environmental as well as

Hospitalisation rates for COPD are heavily dependent on the average age of the population in the community and the organisation of emergency units, as well as the availability of hospital beds

genetic influences on the mortality, prevalence, incidence and hospital admission rate of COPD. Several large single-centre population studies of COPD in Europe have been in progress for some time: since 1972 in Oslo, Norway; since 1976 in Copenhagen, Denmark; since 1980–1982 in the Po river delta, Italy; and since 1985 in northern Sweden and in Bergen, Norway. In addition, multicentre surveys of COPD in single countries have been conducted in Switzerland and Spain, and studies have been coordinated across many European countries simultaneously in the European Community Respiratory Health Survey (ECRHS) and the Burden of Obstructive Lung Disease (BOLD) study. However, estimates of mortality, hospital admissions, prevalence and incidence are still lacking from many European countries in 2012.

The data in this chapter are based on the International Classification of Disease, 10th revision (ICD-10) codes J40–J44 and J47, chronic obstructive pulmonary diseases and bronchiectasis (which have much in common). The diagnostic codes J45 and J46 (asthma and status asthmaticus) have generally not been included. Differences in coding may be a cause of variations both within regions of a country and between countries, as combinations of these diseases are not uncommon. Some physicians responsible for recording cause of death still use the diagnosis of asthma/status asthmaticus instead of COPD and both under- and overdiagnosis of COPD are frequent on death certificates as well as in clinical practice.

Mortality

Overall, the COPD mortality rate for men and women in Europe, age-standardised to the European Standard Population, is about 18 per 100 000 inhabitants per year. The variation of age-standardised mortality rates is, however, more than 10-fold among the 39 countries that provided data on mortality to the WHO (figure 1). Data are scarce from countries in eastern Europe. There is a general trend for countries with higher prevalence of cigarette smoking to have higher mortality from COPD. According to the WHO, in 1997, COPD was the cause of death in 4.1% of men and 2.4% of women in Europe. However, in Denmark, deaths due to COPD are more frequent in women than in men.

It is noticeable that over a short period of time there has been a substantial decline in death rates from many causes, including cardiovascular disease, but for COPD mortality, this tendency to decline started much later in some countries.

Hospital admission

Hospital admission rates for COPD are available for 31 European countries, with the majority of data coming from
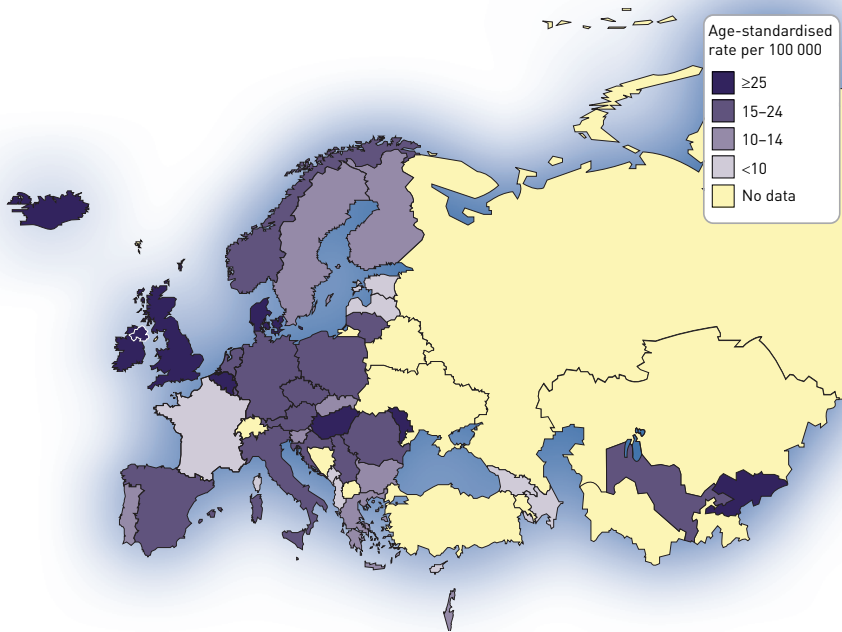
Figure 1 – Mortality rate for chronic obstructive pulmonary disease (COPD). Data from World Health Organization World and Europe Mortality Databases, November 2011 update. Data for some countries are missing because mortality data for asthma and COPD are not reported separately.

western Europe. The average age-standardised admission rate for COPD is about 200 per 100 000 people per year, being highest in Denmark, Hungary, Romania, Turkey, Macedonia, Austria, Germany, Belgium, Spain and Ireland, and lowest in Switzerland, France, Portugal, Slovenia, Croatia and Latvia. The variation in admission rates is as high as 10-fold between European countries (figure 2). Hospitalisation rates for COPD are heavily dependent on the average age of the population in the community and the organisation of emergency units, as well as the availability of hospital beds. In western and central Europe there has been a steady decrease in the overall number of hospital beds as a result of changes in the structure of healthcare. Predictors of exacerbations and hospital admissions for COPD include a previous history of exacerbations, more severe disease, impaired quality of life and the presence of comorbidities. In several countries in northern Europe, the admission rates are higher in women than men. A study including 234 hospitals in the UK showed an in-hospital mortality of 7% and a 90-day mortality of 15% following admission for COPD exacerbations. More than 50% of COPD patients discharged from hospital after an exacerbation are readmitted within a year.

Incidence and prevalence

Precise estimates of incidence of spirometry-defined COPD are lacking for most countries in Europe. A population-based study in Norway showed an overall incidence of 1% per year in 18–74 year olds during 9 years of follow-up. The incidence did not vary according to sex; it increased with increasing age; and it was 10 times higher in smokers than in never-smokers. More than 100 studies of COPD prevalence have been published since the 1970s and most estimates from large-scale studies are between 5% and 10%. These studies vary in survey methods, diagnostic criteria, analytical approaches and age distribution of the populations examined, making comparison between study results difficult.
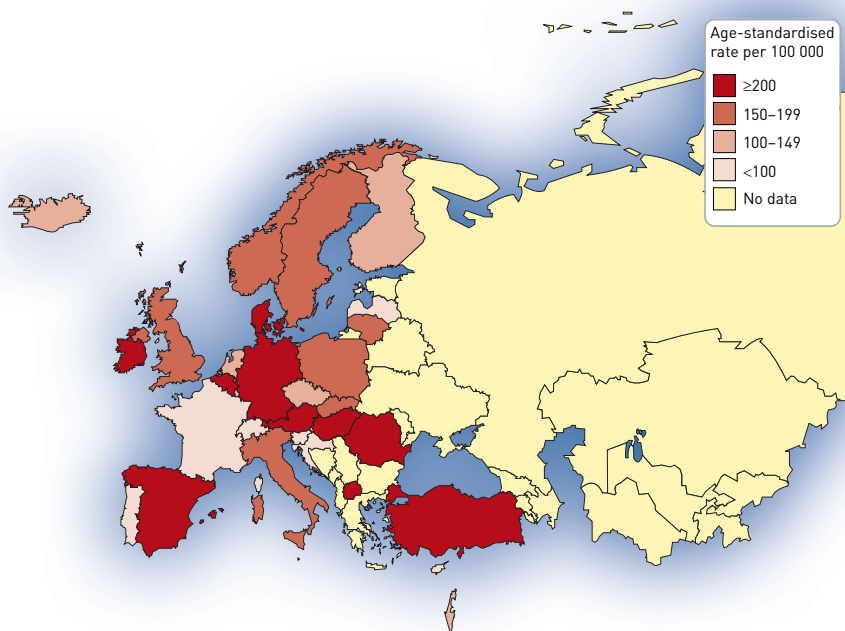
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Figure 2 – Hospital admission rate for chronic obstructive pulmonary disease (COPD). Data from World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update. The following countries supplied data to Eurostat that cover both COPD and bronchiectasis: Germany, France, Hungary, Ireland, Macedonia, the Netherlands, Romania, Sweden and Turkey.

The international, population-based BOLD study aims to use standardised survey methods and a spirometric criterion for COPD, enabling direct comparison between study populations. The prevalence of spirometry-defined COPD (FEV_1/FVC < 0.7, FEV_1 < 80% of predicted value) is about 10%. It varies considerably between European countries (figure 3). This may partly be due to small sample sizes in the studies and partly due to age distribution and different environmental exposures. The prevalence of COPD is higher in men than in women (figure 3). All studies show a clear increase of prevalence with age. In people aged > 70 years, the prevalence of COPD is about 20% in men and 15% in women.

Causes/pathogenesis

COPD is a chronic inflammatory process in the lower airways and the lung parenchyma caused by many factors that trigger and maintain inflammation. An imbalance between proteases and anti-proteases may be a contributory factor.

Tobacco smoke

The most important and modifiable aetiological factor for COPD is smoking.

Smokers have a higher prevalence of respiratory symptoms and lung function abnormality, a greater annual rate of
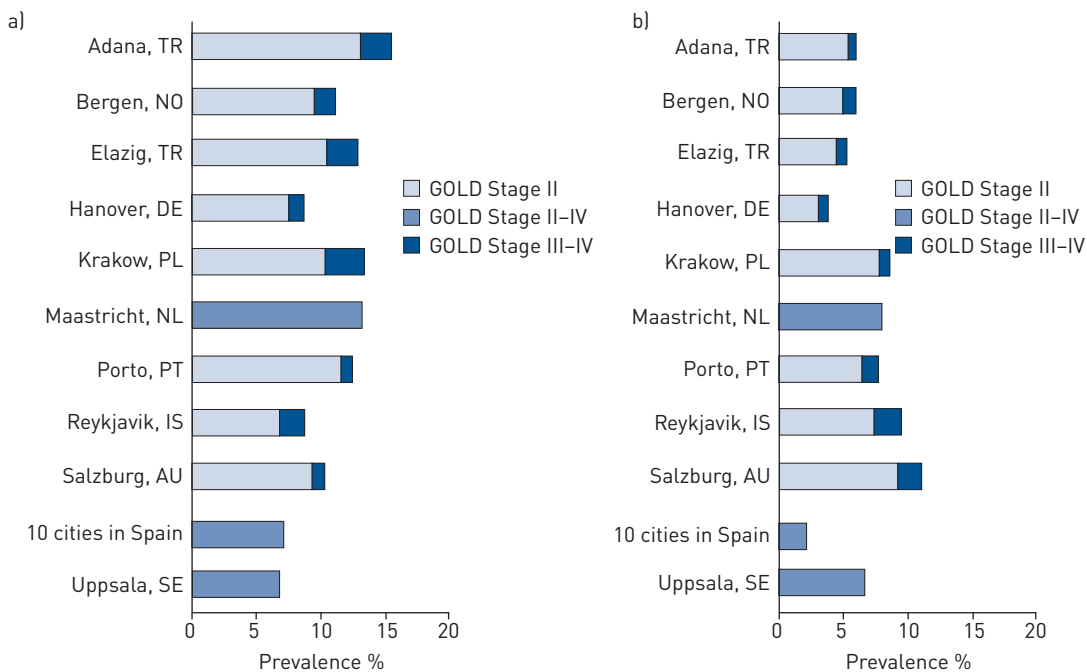
Figure 3 – Prevalence of chronic obstructive pulmonary disease (COPD) in a) men and b) women aged ≥40 years in European cities, by Global Initiative for Obstructive Lung Disease stage, ranked by national prevalence of current smoking. Data from multiple publications resulting from the Burden of Obstructive Lung Disease (BOLD) study.

decline in FEV_1, and higher death rates from COPD than nonsmokers. Women may have more symptoms than men for the same number of pack-years smoked. About 40–50% of lifelong smokers will develop COPD, compared with only 10% of never-smokers. Passive exposure to cigarette smoke may also contribute to respiratory symptoms and impaired lung function in schoolchildren. However, not all smokers develop clinically significant COPD, which suggests that genetic factors may modify individual risk. The proportion of the risk of COPD attributable to smoking has been estimated as 40–60%, depending on how many risk factors have been taken into account.

Although never-smokers are less likely to have COPD and have less severe COPD than ever-smokers, never-smokers nonetheless comprise about one-quarter of those classified with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II+ COPD.

Occupational airborne exposure

Several studies show that 30–40% of the general population report having been exposed to airborne pollutants at work (for further information, see chapters 7 and 24). When the exposure is sufficiently intense or prolonged, occupational dust, chemicals and vapours can cause COPD independently of cigarette smoking. Studies of general populations and working groups show that about 15–20% of COPD cases are due to occupational exposure. In never-smokers, the fraction of COPD attributable to occupational exposure is estimated to be 30%. A variety of occupations may represent an increased risk of COPD, such as mining, agriculture, and textile, paper, wood, chemical, and food processing.

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Outdoor and indoor pollution

A high level of urban air pollution is harmful to individuals with COPD, as it can result in exacerbations and a poorer quality of life (for further information on air pollution, see chapter 6). The role of outdoor air pollution in Europe in causing COPD is unclear. The relative importance of short-term, high peak exposures compared with long-term, low-level exposures is not known. Heavy indoor air pollution caused by the use of biomass fuel is a risk factor for the development of COPD.

Socioeconomic status

The risk of developing COPD is inversely related to socioeconomic status based on education or income. The effects of various indicators of socioeconomic status may differ between men and women, and socioeconomic status may also reflect factors such as nutrition, overcrowding and air pollution, as well as genetic determinants.

Early life environmental factors

Smoking mothers, frequent respiratory infections and asthma in childhood, and bronchial hyperreactivity are important risk factors for COPD. The proportion of the risk of COPD attributable to these early childhood events may be as great as that attributable to smoking (see also chapter 4).

Genetic factors

The best documented genetic risk factor for COPD is hereditary α_1-antitrypsin deficiency (see also chapter 3). However, in most populations, homozygous α_1-antitrypsin deficiency is found in fewer than five people per 10 000. Polymorphisms of many genes or combinations of genes may increase (or decrease) the risk of an individual developing COPD. Individual genes may be related to specific phenotypes of COPD. Single genes, such as the gene encoding matrix metalloproteinase (MMP)-12, may be related to decline in lung function. Genome-wide studies of gene expression and genetic variation have provided exciting new avenues for future investigation and potentially new approaches to risk prediction and therapy.

Clinical manifestations

The most important symptoms of COPD are breathlessness on exertion and chronic cough with or without phlegm. The dyspnoea usually worsens over time but is often not present in mild or moderate COPD. The cough may be dry or productive. Cough and phlegm often precede dyspnoea on exertion by

> " *Smoking cessation is the most important intervention that affects the prognosis of the disease* "

many years. Other symptoms include wheezing and chest tightness. As the disease progresses and reaches the severe stages, fatigue, weight loss and anorexia may increase. To establish the diagnosis of COPD, lung function measurement by spirometry is necessary.

A characteristic of COPD is exacerbations or episodes of acute worsening of the respiratory symptoms. The most common causes of exacerbations are viral or bacterial infections. Increased air pollution also appears to precipitate exacerbations of COPD. Some patients are particularly prone to exacerbations while others are not. Two or more exacerbations during the previous year is the most important indicator of a future exacerbation.

Exacerbations accelerate the decline in lung function that characterises COPD, resulting in reduced physical activity, poorer quality of life, and an increased risk of death; they are also responsible for a large proportion of the healthcare costs attributable to COPD.

Patients with COPD often suffer from other diseases (comorbidities). The comorbidities may share common risk factors with COPD, in particular cigarette smoking. They may also represent extrapulmonary manifestations or complications of COPD, such as muscle dysfunction due to inactivity. Comorbidities may be secondary to treatment of COPD; for example, osteoporosis due to oral corticosteroid treatment. The most common comorbidities in COPD are ischaemic heart disease, anxiety and depression, osteoporosis, skeletal muscle dysfunction, gastro-oesophageal reflux, anaemia, lung cancer, diabetes and metabolic syndrome. Comorbidities contribute to the overall severity and manifestations of the disease. They can occur in mild, moderate or severe COPD and they increase the risks of hospitalisation and mortality of COPD independently.

The clinical effects of COPD show considerable inter-individual variation, depending on which respiratory symptoms predominate, the frequency of exacerbations, the level and rate of lung function decline and the amount of emphysema, as well as comorbidities. Various subtypes of the disease are often termed phenotypes of COPD.

Prevention

Identification and reduction of exposure to risk factors are important steps in the prevention and treatment of COPD. All individuals who smoke should be encouraged to quit regardless of their disease status. In addition, smokers without COPD should be offered smoking-cessation advice.

Preventing passive smoking in fetal and early life is important to reduce the risk of COPD in adult life. Smoking cessation is the most cost-effective form of both primary and secondary intervention in COPD. On a global scale, reduction of exposure to smoke from indoor biomass combustion, particularly among women and children, is important to reduce the prevalence of COPD.

Prevention of COPD exacerbations is important: influenza and pneumococcal vaccination as well as treatment with inhaled long-acting bronchodilators and inhaled corticosteroids all work to reduce exacerbations and hospitalisations for COPD.

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Management

A COPD management programme includes the following four components: assessment and monitoring of disease; reduction of risk factors; management of stable COPD; and management of exacerbations. The goals of COPD management are to relieve symptoms, prevent disease progression, improve exercise tolerance, improve health status, prevent and treat complications and exacerbations, reduce mortality and prevent or minimise side-effects from treatment.

Important components of management are smoking cessation, medical treatment with bronchodilators as well as inhibitors of inflammation, physical exercise and, in advanced disease, oxygen therapy (see chapter 28).

Early rehabilitation after exacerbations is important (see chapter 29). The most effective component of pulmonary rehabilitation is physical exercise.

In the future, better classification of the different phenotypes of COPD is likely to enable implementation of personalised treatment, in which the characteristics of the patient together with the severity of the disease are the keys to choosing the best treatment option.

Comorbidities should be assessed at all stages of COPD. Differential diagnosis can often be difficult, as comorbidities with symptoms commonly seen in COPD may be overlooked, for instance heart failure or lung cancer causing breathlessness or depression presenting with fatigue. In general, any comorbidity should be treated as in patients who do not have COPD.

Prognosis

COPD is a chronic, progressive disease showing great variation in its natural history. Spirometry providing data on FEV_1 and FVC is the most common measure of disease progression. A large cohort of patients with COPD of GOLD stage II+ followed up every 6 months for 3 years showed a mean annual decline in FEV_1 of 33 mL. An annual decline in FEV_1 >40 mL was seen in 38% of the patients, while 8% showed an average annual increase of 20 mL. Current smoking and emphysema are related to more rapid decline in FEV_1.

In addition to rapid decline in FEV_1, factors that indicate a poor prognosis in established COPD are frequent exacerbations, respiratory insufficiency, nutritional status and comorbidities.

Smoking cessation is the most important intervention that affects the prognosis of the disease.

Future developments

There is a great deal of room for improvement in COPD care in Europe, and current trends suggest the following developments are possible and desirable.

- More accurate data on illness, exacerbations, natural history, cost and deaths, particularly in eastern Europe, will provide a stronger foundation for fighting COPD.
- Studies of the effectiveness of current prevention, education, medication, rehabilitation and terminal care will help to spread best practice and drive higher standards of COPD care.
- New therapeutic modalities will inhibit the decline in lung function.
- As smoking remains the key risk factor for COPD, several measures will reduce the burden of disease: more effective smoking cessation interventions and techniques to prevent people from starting to smoke; better surveillance of harmful occupational exposures; and protection in early childhood against harmful exposure and events that affect the lung.
- Governments, industry and the general public need to be made aware of the high burden of COPD in Europe. European countries should implement common strategies for effective prevention, diagnosis and treatment of this disabling and life-threatening disease.

Research needs

Research is needed in six key areas related to COPD.

- As smoking rates in Europe are declining, the relative importance of other risk factors to COPD will increase. There is a need to know how this will affect the clinical manifestations and prognosis of the disease.
- Although spirometry is a prerequisite in COPD studies, more extensive characterisation of disease than that offered by spirometry is required. Novel imaging techniques and biomarkers offer the potential to characterise subgroups, or phenotypes, of COPD.
- Limited data are available about the prevalence, incidence and natural history of various phenotypes of COPD, and their economic burden on European societies.
- Our knowledge of the pathogenesis of COPD and how this can be modified is still limited. Novel molecular and genetic techniques offer promising possibilities for gaining important knowledge on disease mechanisms, which opens up possibilities for development of new drugs.
- Cohort studies should be conducted to assess the long-term natural history of COPD and its phenotypes.
- The lungs are extremely exposed to the environment. There are few data on how global warming will affect the risk factors for, and eventually the incidence of, COPD.

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Cystic fibrosis

Introduction

Key points

- Newborn screening for cystic fibrosis leads to a reduction in prevalence, as couples are empowered to make better-informed reproductive choices.
- Adult patients as well as children should be cared for by multidisciplinary teams in specialist cystic fibrosis centres, equipped to understand and manage all aspects of the disease.
- 'CF lung attacks', *i.e.* periods of acute worsening of respiratory symptoms, negatively affect quality of life, accelerate decline in lung function and worsen prognosis.
- Median life expectancy is now in the mid-30s and it is likely this will increase.
- Although most of the morbidity and mortality caused by cystic fibrosis are still due to respiratory disease, complications affecting other bodily systems are becoming more prominent as life expectancy increases.

Cystic fibrosis (CF) is the commonest lethal inherited disease of white races, but it should be noted that in multi-racial Europe, no ethnic group is exempt from the disease, although prevalence varies across the continent. It is usually caused by the absence, dysfunction or reduced numbers of the multifunctional CF transmembrane regulator (CFTR) protein. Mature CFTR is produced after complex post-transcriptional and post-translational processing, which has implications both for prognosis and modern, genotype-specific, therapy. The protein has a key function in regulating the amount of water in the airway surface liquid. If the CFTR protein is not working normally, clearance of bacteria and particles from the lungs is impaired. Either correcting the dysfunction of this protein or dealing with the downstream consequences is key to developing therapies that will modify the natural history of CF.

Epidemiology

The most comprehensive and up-to-date collection of epidemiological data for CF across Europe is the registry maintained by the European Cystic Fibrosis Society (ECFS) (www.ecfs.eu). Data are submitted to the registry by both national CF registries and individual CF centres throughout Europe. The registry collects data from 25 000 CF patients in 21 countries and produces annual summary reports.

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" *There is a pressing need to ensure that adult services are established all over Europe, offering the same high standards of multidisciplinary care as paediatric clinics* "

The current report, covering 2008–2009, contains details on 18 999 patients. The 2007 report contains data on 20 204 patients. However, these datasets are likely to suffer from under-reporting. For example, the UK contribution of 4408 patients in the 2007 report (the third-largest in the registry) is likely to be at least 2000 short of the true figure. A high priority must be to resource this database so that data on all CF patients across Europe can be captured.

There are marked age-related changes in resource use, with older patients having more morbidity and requiring more expensive medications and other resources, including noninvasive ventilation. It is important to note that diagnosis by screening is associated with lower healthcare costs.

Prevalence and incidence

Figure 1 shows the prevalence of CF by country within Europe. Table 1 shows the number of patients reported to the ECFS Patient Registry in either the 2008–2009 or 2007 reports, and the age distribution of CF patients. Many countries have at least 90% case ascertainment, but in some countries this figure is much less. A more detailed analysis of the registry data between January 2003 and December 2007 by McCormick *et al.*, 2010 (see Further reading), covered 29 025 patients, 25 126 from European Union (EU) countries (as of 2003) and 3809 from non-EU countries. In the EU cohort, 11 742 (47%) were aged over 18 years, emphasising that CF is increasingly becoming a disease of adults. However, only 1205 (5%) were aged over 40 years. There is therefore a pressing need to ensure that adult services are established all over Europe, offering the same high standards of multidisciplinary care as paediatric clinics. There were proportionately more 'elderly' CF patients in the 2003 EU countries compared with the non-EU countries (figure 2). This is not due to ascertainment bias (milder phenotypes being diagnosed in the EU): when the analysis was repeated just for CF patients homozygous for the severe mutation ΔF508 (deletion of a phenylalanine residue at position 508 in the protein), the findings were the same. Reasons for the better prognosis and lower mortality could include the lower median age at diagnosis in the EU, and better socioeconomic conditions.

It is intriguing to note that in countries where newborn screening for CF has been introduced, there has been a decline in the prevalence of CF. This may at least in part be due to diagnosis of the first CF child in the family before a second one is conceived, thus giving couples reproductive choices after the birth of a first CF child.

	Patients n	Estimated coverage# %	Age years		
			Mean	Median	Range
EU28 countries					
AT	352	39	13.1	11.9	0.2–55.5
BE¶	1129	>90	20.4	18.5	0.0–68.5
BG+	95		14.2	13.4	0.2–52.3
CZ¶	507	100	17.2	15.8	0.1–55.5
DE¶	5048	90	19.9	18.5	0.0–71.5
DK¶	451	100	21.8	20.4	0.2–61.3
ES	740	30	17.0	14.9	0.1–57.8
FR¶	5640	90	19.1	16.5	0.0–79.6
GR	92	20	16.1	15.9	2.0–41.4
HU¶	555	90	15.8	15.4	0.2–60.9
IE¶,§	1021	90	18.6	18.1	0.4–58.7
IT	539	14	24.6	24.6	0.8–60.4
LV	29	>90	11.6	10.2	1.2–27.0
NL¶	1249	97	21.1	18.6	0.1–70.5
PT	117	42%	14.4	12.4	0.0–49.5
SE¶	578	85–90	22.5	20.2	0.2–71.1
SI	66	75	13.1	11.9	0.3–54.1
UK¶,+	4408		19.9	18.7	0.1–75.7
Non-EU28 countries					
BY+	145		12.9	12.7	0.4–33.4
CH	190	24	10.3	10.5	0.2–32.3
ILf	533	90	20.2	18.2	0.0–64.5
MD¶	41	100	9.6	8.0	0.4–22.7
RS	122	>90	13.0	11.0	1.0–44.4

Table 1 – Cystic fibrosis (CF) in Europe: age distribution, 2009. EU: European Union. #: the estimated percentage of CF patients living in a country who are included in the national registries/national data collections. One individual centre might include almost all patients for some countries (*e.g.* Latvia and Serbia); ¶: national CF registry established; +: 2007 data reported for Bulgaria, UK and Belarus; §: 2008 data reported for Ireland; f: although not officially a national registry, all centres in Israel participate and so considered a registry. Data from the European Cystic Fibrosis Society (ECFS) Patient Registry 2007 and 2008–2009 reports.

Annual mortality

Mortality rate varies with age and is likely to be about 1–2% per year overall. In 2009, there were more than 800 CF patients across Europe living with transplanted lungs. There were 133 CF lung transplants performed in 2009, compared with 108 in 2007. However, it is thought that these numbers are likely to be
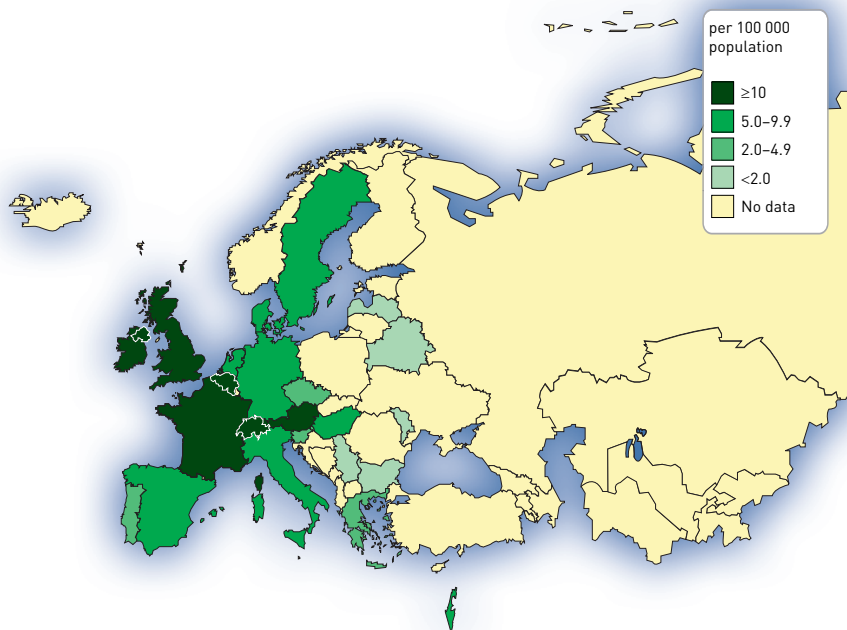
Figure 1 – Estimated prevalence of cystic fibrosis. Data from the 2007 and 2008–2009 reports of the European Cystic Fibrosis Society.

an underestimate as in some countries patients are transferred to a transplant centre and so are not known to their CF registry. Data on liver transplantations performed each year are more difficult to ascertain, but they are performed significantly less often than lung transplants in CF patients – only seven liver transplants were performed in CF patients in 2009, making a total of 93 patients living with transplanted livers in 2009 across Europe.

Causes/pathogenesis

Genetic

CFTR is a widely expressed, multifunctional protein. Its best-known function, that of a chloride channel, is responsible for the abnormal sweat test and is also responsible for some disease manifestations such as electrolyte depletion and heat exhaustion. However, it is naïve to believe that the same functions are responsible for all disease manifestations, and there is increasing evidence that dysregulation of the epithelial sodium channel ENaC is more likely responsible for the pulmonary disease. Recently, the nomenclature of CFTR gene mutations has been revised (www.cdc.gov/dls/genetics/rmmaterials/pdf/HGVSNomenclature.pdf); however, this chapter uses the old nomenclature because it is also used in the ECFS reports. CFTR mutations have been divided into six classes (table 2): classes I–III are severe, associated with pancreatic insufficiency; classes IV–VI are mild and pancreatic sufficient. A combination of a mild and severe mutation predicts a mild (pancreatic sufficient) phenotype. However, there is considerable individual variation within genotypes, which has been related to modifications within the CFTR genetic locus itself, modifier genes elsewhere in the karyotype, and environmental factors; these are the subject of active research. Predicting prognosis in an individual from his or her genotype is not possible.

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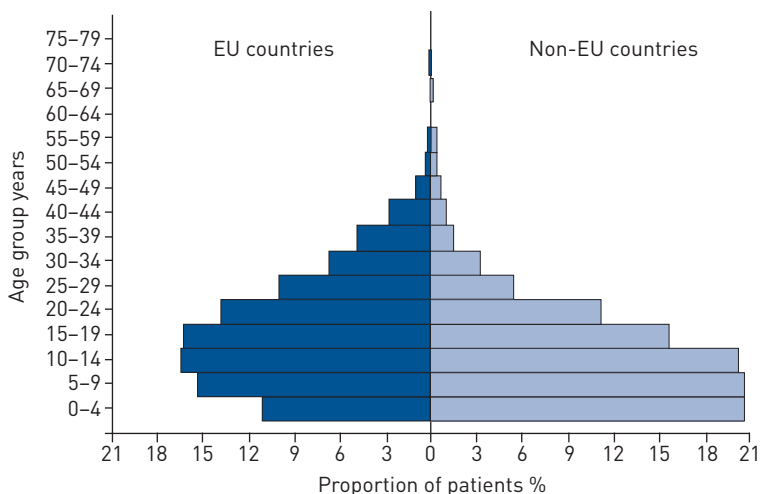PRACTISING RESPIRATORY MEDICINE IN EUROPE

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Figure 2 – Population pyramid of mean age of patients with cystic fibrosis in European Union (EU) and non-EU countries (2003 EU classification). Bulgaria, Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Romania, Slovakia and Slovenia are included in non-EU countries in this figure. Reproduced from McCormick *et al.*, 2010, with permission from the publisher.

Mutation class has implications for treatment development. Whereas current therapy is aimed at the downstream consequences of CFTR dysfunction, such as bronchial infection and pancreatic destruction, treatment will in future be aimed at correcting the underlying molecular abnormality. Treatment will be either independent of mutation class (gene therapy, the efficacy of which is thought unlikely to vary with underlying CF genotype) or specific to mutation class. Examples of the latter include the orally active compound PTC124, which overrides premature but not physiological stop codons (class I mutations); molecular chaperones ('correctors') to prevent intracellular

Class	Description	Example mutation
Class I	No CFTR synthesis (mutation inserts premature stop codon)	G542X
Class II	CFTR processed incorrectly and does not reach apical cell membrane	ΔF508
Class III	CFTR reaches apical membrane but channel regulation is abnormal	G551D
Class IV	CFTR reaches apical membrane but channel open time is reduced	R334W
Class V	Reduced CFTR synthesis	R117H
Class VI	CFTR reaches apical cell membrane but has a shortened half-life due to more rapid turnover	1811+1.6kbA>G

Table 2 – Classes of cystic fibrosis transmembrane regulator (CFTR) mutation.

degradation of abnormal CFTR (class II mutations); and potentiators, to increase the activity of CFTR at the cell surface (class III mutations, but may also need to be applied to class II mutations in combination with molecular chaperones). Some of these strategies are likely to be applicable to other genetic diseases.

There are regional variations in gene frequency across Europe. In summary, homogeneity is greatest in central, western and north-eastern Europe, where 10 mutations account for more than 80% of CF chromosomes; it is much less in, for instance, Spain, Bulgaria, Turkey and Greece, where 25 mutations must be determined in order to detect 85% of CF chromosomes. This is important for a number of reasons. Firstly, if newborn screening is to be implemented, using PCR for gene detection, the panel of genes that is most useful will vary across Europe. Secondly, if a diagnostic genetics laboratory is set up, then their routine screening panel will be different in different parts of Europe. Thirdly, comparisons of survival must take account of genetic variation: countries with a higher prevalence of mild mutations (classes IV–VI) might be expected to have better survival curves than those with more severe mutations. Comparisons between countries can be facilitated by studying groups from each with the same homogeneous genotype, usually homozygous ΔF508. Finally, it should be noted that of about 1900 mutations so far identified, fewer than 50 are definitely disease producing. The ongoing CFTR-2 project should help to elucidate this, and the project website gives useful information about unusual mutations (www.cftr2.org).

Environmental

Adverse environmental circumstances, particularly passive and active exposure to tobacco smoke, may worsen CF, but there are no known environmental causes of the disease. However, it is estimated that environmental circumstances contribute at least as much to the prognosis as CFTR gene class and modifier genes.

Occupational

Low socioeconomic status is associated with an adverse outcome at all ages. In the USA, CF patients always reliant on Medicaid (a health programme for families and individuals with a low household income) had a three-fold greater risk of dying at every age than those who never relied on Medicaid, underscoring the adverse effects of poor socioeconomic conditions.

Others

Exceptionally rare cases of phenotypic CF with apparently completely normal CFTR gene sequences have been described. It is possible that these cases relate to mutations in one of the many genes encoding proteins with which CFTR interacts during processing, or that interact functionally with mature CFTR. Mutations in the sodium channel ENaC, which is downregulated by CFTR, have been associated with a CF-like disease.

Clinical manifestations and consequences

Diagnosis of CF

Diagnosis is increasingly by newborn screening, measuring immunoreactive trypsin (iRT) and one or more ethnically appropriate genes on the routine heel-prick sample

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taken from the baby at 7–10 days of life. Diagnosis should always be confirmed with a sweat test. In patients with suspicious symptoms, diagnosis can almost always be made by a sweat test performed in an experienced centre (> 98% of cases), and the sweat test should be the first-line investigation. It should be noted that false-positive and false-negative tests will invariably occur at inexperienced centres. There are rare cases of genuine CF with equivocal or even normal sweat electrolytes. In these cases, ancillary diagnostic methods are needed, including genetic testing and measurement of transepithelial potential differences (*in vivo* in the nose, the usual method; in the lower airway; or *in vitro* on a rectal biopsy). These tests are only available in very few centres. Diagnostic algorithms have been published in Europe and the USA; they are very similar (see Further reading).

A further diagnostic issue is the spectrum of 'CFTR-related' disorders, and their relationship with CF. It is known that patients with idiopathic bronchiectasis, congenital bilateral absence of the vas deferens, idiopathic (non-alcoholic) pancreatitis, and severe sinusitis (all conditions seen in established CF) have a higher prevalence of CF mutations than would be expected; and indeed, in some adults, these are actually the first presentation of true CF. Most usually, the patient has a single CF mutation, a normal sweat test, and a single-organ manifestation such as bronchiectasis. In time, in some subjects, a second disease-producing mutation may be discovered, confirming the diagnosis of CF. The remainder are classed as having a CFTR-related disorder; in practice, the treatment of the single organ manifestation is driven by the nature of the disease, not by the diagnostic label.

Manifestations of CF

The basic details of the disease are described in standard books and monographs. When first described, CF was considered a pulmonary and digestive disease; now, it is known to affect most body systems. The important manifestations of CF, especially in longer-surviving patients, are shown in table 3.

Most of the morbidity and mortality of CF is still due to respiratory disease. The lungs are essentially normal at birth, but soon become chronically infected and inflamed. The conventional view is that the initial pathogens are usually *Staphylococcus aureus* and *Haemophilus influenzae*. Subsequently, chronic infection with *Pseudomonas aeruginosa* becomes established in most patients, although the prevalence of chronic infection is being reduced by attention to prevention of cross-infection in hospitals, and aggressive eradication regimes at the time of first isolation. This conventional view is having to be widened. Firstly,

Lower airway	Chronic infection, especially with *Staphylococcus aureus*, *Haemophilus influenzae* and, in particular, *Pseudomonas aeruginosa*, together with a widening range of other Gram-negative rods; acute exacerbations; atypical mycobacterial infection; bronchiectasis; haemoptysis; pneumothorax; allergic bronchopulmonary aspergillosis
Upper airway	Nasal polyps, sinusitis, rarely mucocele
Liver	Biliary cirrhosis, portal hypertension, gall stones, bile duct stricture
Gastrointestinal comorbidity and complications	Severe constipation, distal intestinal obstruction syndrome, Crohn's disease, coeliac disease, giardiasis, cow's milk protein intolerance, increased incidence of malignancy
Endocrine pancreatic failure	Insulin deficiency, which adversely impacts on clinical state before frank diabetes mellitus develops
Bone disease	Related to: CF itself (CFTR is expressed in bone), malabsorption of vitamin D and vitamin K, immobility, poor calcium intake, pubertal delay, gonadal failure, and the systemic effects of pro-inflammatory cytokines
Genito-urinary	Infertility due to bilateral absence of the vas deferens, stress incontinence, vaginal candidiasis
Sweat gland	Electrolyte depletion in the sweat (pseudo-Bartter's syndrome)

Table 3 – Multi-organ complications of cystic fibrosis (CF). CFTR: CF transmembrane regulator.

the aggressive use of antibiotics has led to the emergence of other Gram-negative bacilli, including the *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, *Achromobacter xylosidans* and *Pandoria apiospermum*. Secondly, the use of anaerobic cultures has shown that lower airway flora contain at least as many anaerobes as *P. aeruginosa*. Finally, molecular microbiology (16s rRNA, for example) has shown a far more diverse bacterial and fungal flora in the lower airways of CF patients than was previously suspected. It is unclear whether the CF airway is intrinsically pro-inflammatory in the absence of infection, or whether there is an exaggerated response to infection or some other dysregulation of the control and resolution of infection. What is clear is that the intense inflammatory response is itself harmful, and, combined with chronic infection, leads to bronchiectasis, cor pulmonale and death from respiratory failure unless the patient receives a lung transplant.

In addition to chronic infection, there are periods of acute deterioration of respiratory symptoms, termed 'pulmonary exacerbations', or better, 'CF lung attacks'. There is no agreed definition of a pulmonary exacerbation, despite the fact that reduction in frequency is commonly used as an end-point in clinical trials. They are common, and effects include: 1) a marked adverse effect on quality of life; 2) failure to recover baseline lung function in up to one-third of exacerbations; 3) an association with accelerated deterioration in lung function; and 4) an adverse impact on prognosis. Other important respiratory complications include allergic bronchopulmonary aspergillosis, pneumothorax (which carries a bad prognosis because of associated severe lung disease), massive haemoptysis, and lung or lobar collapse.

Many patients have malabsorption of nutrients caused by pancreatic insufficiency from diagnosis; ultimately, 85% of patients become pancreatic insufficient. Malabsorption

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should not be assumed to be due to pancreatic disease: coeliac disease, inflammatory bowel disease and the complications of neonatal surgery may all lead to steatorrhoea (an excess of fat in the faeces). A relatively common intestinal complication is distal intestinal obstruction syndrome (DIOS), caused by accumulation of thick tenacious secretions and malabsorbed fat in the terminal ileum. This must be distinguished from constipation, to which CF patients are also prone. Another more unusual gastrointestinal complication is biliary cirrhosis leading to portal hypertension.

As patients survive longer, systemic complications become more prominent. These include: CF-related diabetes, which eventually affects nearly half the pancreatic-insufficient CF population; bone disease leading to pathological fractures; and, particularly in women, stress incontinence.

Finally, although standard advice is that CF carriers are as healthy as the general population, there is a higher prevalence of CFTR mutations (*i.e.* more carriers) in groups of patients with single organ, CF-like disease.

Impact of CF on the individual

The diagnosis of CF, whether in the patient him/herself or a family member, may have a considerable economic impact. In particular, a woman who has become the mother of a CF child may refocus her career intentions, and opt to remain at home caring for the CF child rather than pursuing a career. Although many young people and adults with CF are in full-time education or employment, progression of the disease may curtail these activities. A spouse or parent may need to give up work, and rely on social security payments, as the patient becomes sicker. The other main fiscal costs for adults are time off work, community support and, for the rare really ill child, home tutoring. In the UK, adults will attain an employment rate that is 80% of that seen in a control population matched for age and sex. Half of CF adults are in paid employment, and around a quarter are in full-time education (www.cfstudy.com). However, calculating the costs of CF to society should also take account of loss of productive working years in individuals with CF and their carers.

Costs of CF treatments: impact on health services and society

The costs of care vary with the stage of the illness, being highest in the year following diagnosis, and again rising later as the disease worsens. The vast majority (90%) of patients will use pancreatic enzyme replacement supplements, and many will use rhDNAse and nebulised antibiotics

(tobramycin or colomycin), each costing several thousand euros per patient per year. These antibiotics are also now available in dry powder delivery devices, but this has not brought down the cost. Newer treatments are likely to be even more expensive. The emerging issue of the costs of genotype-specific treatments will be discussed in detail later.

It should also be noted that there are marked regional differences in the use of expensive treatments, suggesting that cost may be a factor in what patients receive. rhDNase was used in between 2% (Hungary) and 87% (Belgium) of patients in 2007, and nebulised antibiotics in 5% (Hungary) to nearly 50% (UK, Belgium, Germany). Chronic oral macrolide use ranges 0–35%.

The costs of treatment escalate as the patient becomes sicker. Treatment of lung disease is likely to involve repeated courses of expensive intravenous antibiotics. Patients being treated for atypical *Mycobacteria* are prescribed particularly expensive medications. As respiratory disease worsens, home oxygen and noninvasive ventilation may be required, and eventually very prolonged hospital stays are likely. Maintenance of good nutrition may require placement of a gastrostomy for supplemental enteral feeds. Treatment of CF-related diabetes, liver disease and bone disease adds to the rising costs, and these may culminate in the costs of lung transplantation.

Costs of emerging treatments: a new challenge

The cost of illness is likely to increase greatly with the advent of novel, expensive medications. Ivacaftor (VX-770) is a class III channel-opening small molecule, which has been tested in CF patients carrying at least one copy of the G551D mutation in a recent double-blind, placebo-controlled, 24-week trial. Patients receiving the active compound saw an increase of more than 10% in forced expiratory volume in 1 second (FEV1) (a key measurement of lung function), were half as likely to have a pulmonary exacerbation, gained on average 2.7 kg in weight, and, almost incredibly, halved their sweat chloride concentrations. This medication is licensed in the USA, where it costs $294 000 (about €220 000) per patient per year. The impact will depend initially on the country prevalence of CF, and the percentage of patients who carry the G551D mutation (Ireland has the highest prevalence, with 7.6% of its total CF population carrying G551D). In the UK, if all of the 5% of the CF population who carry at least one copy of G551D were prescribed the medication, the cost would be €75 million per year, raising the cost of CF care by about 50%. It is likely that VX-770 will be useful in other class III mutations, and possibly in some more common mutations in combination with a corrector such as VX-809, which facilitates the trafficking of misfolded class II mutations such as ΔF508 to the apical cell membrane. Strategies will be needed to decide who will benefit from these novel small molecule therapies, and how they will be financed.

Prevention

Complete prevention would only be possible if universal carrier screening were possible and acceptable to the public. Screening would have to be genetic, but there would always be the likelihood of missing rare variants. Experience is that in any case, take-up of carrier screening offered in an antenatal clinic is low, in the absence of a family history. Newborn screening should facilitate a reduction in prevalence. In the first instance, there is an opportunity for the couple to test future pregnancies for CF;

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and secondly, genetic testing (targeted at the genes found in the affected baby) can uncover other at-risk couples in the extended family, also enabling antenatal diagnosis.

Management

Management of CF

The bedrock of pulmonary management is: 1) the aggressive use of oral, intravenous and nebulised antibiotics to prevent and treat infection; 2) airway clearance, including exercise and the choice of a number of physiotherapy techniques; 3) avoidance of active and passive smoking; and 4) full immunisation, including influenza annually. Mucoactive agents employed include rhDNAse, hypertonic saline and mannitol. Macrolide antibiotics have been shown to be beneficial, although the exact mechanism has not been determined. Other anti-inflammatory drugs are more controversial. Pancreatic insufficiency is treated with pancreatic enzyme replacement therapy, sometimes supplemented by gastric acid-lowering strategies such as H_2 receptor antagonists and proton pump inhibitors; DIOS may require gastrograffin orally or by enema, or intestinal lavage with Klean-Prep (Helsinn). CF-related diabetes is treated with insulin. The reader is referred to standard texts for more detailed discussions of treatment options for the less usual complications.

Patterns of care

Care in a specialist CF centre is essential. Definitions of what constitutes a 'centre' are neither evidence based nor uniformly agreed. The definition will be modified according to local needs; what is feasible in a densely populated urban area will be impracticable in a country with a very dispersed population. In such cases, core expertise may need to be collected in a central location, supporting more distant centres with clinic visits, telemedicine, and the implementation of agreed treatment protocols. The ideal CF centre should include the following:

- A critical mass of patients sufficient to maintain expertise; ideally a minimum of 100 paediatric or adult patients, though this may not be possible in many parts of Europe.
- A core multidisciplinary team (MDT) of CF specialist health professionals, or, in satellite centres, professionals who among their other commitments will ensure that they maintain competence in CF, with particular attention to continuing professional development. This group will comprise: at least two appropriately trained specialist paediatricians or adult physicians; clinical

> " It is estimated that environmental circumstances contribute at least as much to the prognosis as gene class transmembrane regulator gene class and modifier genes "

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nurse specialists; physiotherapist; dieticians; a social worker; a psychologist; a pharmacist; and administrative support.
- Enough personnel for cross cover during periods of annual and study leave.
- Other medical and paramedical staff with experience of CF; for example, ward nurses who understand the requirements of the condition.
- Expertise throughout the MDT in the complications of CF and the specialised procedures required by people with CF, or at least access to a major centre in the country that is able to manage these.
- Support of staff from other specialist services with experience in management of the related issues that arise in patients with CF, such as ear, nose and throat specialist expertise, endocrinology, obstetrics and surgery.
- Access to diagnostic and specialist laboratory facilities, particularly microbiology. Some services (genetics, for example) may be provided off-site at a national referral centre.
- Facilities for inpatient and outpatient treatment, including an appropriate number of beds for people with CF.
- Regular audit of practice.

Guidelines for management have been published, and the reader is referred to the websites of the ECFS (www.ecfs.eu), the UK CF Trust (www.cftrust.org.uk) and the North American CF Foundation (www.cff.org); all these organisations have published useful consensus and standards of care documents.

Prognosis

The steady improvement in prognosis over several decades is related temporally to various advances in management strategies (figure 3). Undoubtedly these innovations have contributed to improving survival, but the less spectacular progress made by CF multidisciplinary teams making incremental gains by better application of basic treatments has also contributed greatly. Currently median survival is to the mid-30s, but a recent paper has predicted median survival into the mid-50s for men and into the
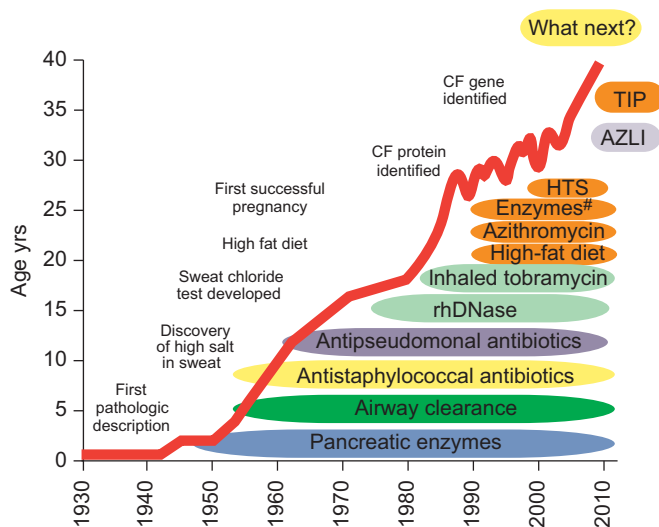

Figure 3 – Schematic illustration of how the introduction of novel cystic fibrosis (CF) therapies influenced patient survival over the decades. HTS: high throughput screening; AZLI: aztreonam for inhalation solution; TIP: tobramycin inhalation solution. #: enteric-coated pancreatic enzymes. Reproduced and modified from ELBORN, 2013.

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mid-40s for women. The discrepancy in mortality between men and women has been described before. The gap begins after childhood and may be related to a greater mortality rate in CF women developing diabetes compared with nondiabetic women and all CF men. This gap is closing, probably due to the earlier and more aggressive use of insulin. The underlying mechanisms of the interactions between sex and insulin deficiency are not known.

A number of factors are leading to an improved prognosis, to which early detection and improved treatments contribute. Increasingly mild clinical CF phenotypes are being detected and incorporated into survival curves, thus prolonging apparent life expectancy. Nonetheless, it is anticipated that life expectancy for all patients with CF will increase over time.

Future developments

Immediate needs

There are a number of basic standards of diagnosis and care that need to be implemented across Europe.

- We must ensure that CF is diagnosed early throughout Europe, preferably by newborn screening; and that everyone in Europe has access to appropriate diagnostic testing, performed by experienced personnel.
- We must ensure that every CF patient is genotyped, in order to determine eligibility for novel small molecule therapies.
- Having been diagnosed, it is essential that from diagnosis, every CF patient in Europe has access to CF specialist centre care by the full MDT and all necessary medications. This last is an ambitious goal because CF medications are expensive and currently many European countries cannot afford them.
- On reaching adulthood, it is essential that patients are treated in a CF unit experienced in CF care. This is a pressing need: adult CF clinic development has lagged behind paediatrics in many parts of Europe.

Medium-term needs

It is clear that the predictions in the previous edition of this book have not all been fulfilled! We should aim to achieve the following:

- Universal newborn screening in Europe.
- Evidence-based care for newborn-screened babies,

driven by the performance of randomised controlled trials with appropriate end-points. There is currently only one (a negative trial of hypertonic saline) that is of a satisfactory standard. This aim is in the mainstream of the European Union drive for medicines for children.

- Access to all evidence-based CF medications across Europe, eliminating regional inequalities.
- All European CF patients being seen regularly at a fully staffed, fully equipped CF centre; this is particularly necessary, and particularly far from being achieved, in adult patients. There is clear evidence that specialist centre care is beneficial.
- Increased use of care in the community and telemedicine to minimise hospital contacts.
- A fully funded, comprehensive registry which captures data on all European patients.

Recent trends will necessitate changes in the provision of care:

- Increased longevity will mean a radical rethink about the burden of care. A well adult who happens to have CF with minimal impact is not likely to want to take many therapies or perform as much airway clearance as the sick CF patient.
- Increased longevity will also mean we need to detect and deal with new emerging infections and new iatrogenic complications, such as antibiotic allergy and subtle long-term medication side-effects.
- New treatments will increase the financial costs of care: new products will build on old concepts, such as novel inhaled antibiotics and mucolytics; more therapies will address the basic defect (gene therapy, for example) and PTC124 for class I mutations.
- More attention must be paid to extrapulmonary complications. There will be pressure on diabetic and endocrine clinics, and obstetric services for pregnant women with CF.
- There will be increased demands for lung transplant services, which will mean optimising the donor supply, novel techniques to salvage donor lungs previously thought to be untransplantable, living related donation, and ultimately a transgenic large mammalian source.

Research needs and unanswered questions

The paradigm shift from treating the downstream consequences of CFTR dysfunction, such as infection with antibiotics, to addressing the fundamental consequences of the molecular defect, is likely to gather momentum, and more designer molecules to treat other classes of mutations are urgently needed.

Currently, the UK CF Gene Therapy consortium (www.cfgenetherapy.org.uk) is carrying out the first therapeutic gene therapy trial (*i.e.* 'Does it help the patient?' rather than 'Can we get the gene to be expressed in the human airway?'). It seems likely that the results will stimulate further refinements in this area, leading to further big trials.

A huge research need is to find meaningful surrogate end-points for clinical trials. Thankfully, in CF the annual mortality is low and the average decline of spirometric

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indices is slow, but this implies that neither of these conventional end-points is useful. Other possibilities include: more sophisticated lung function tests, such as lung clearance index; markers of inflammation in blood, induced sputum or breath condensate; expression of CFTR mRNA and protein; and electrophysiological tests. The choice will vary depending on the clinical trial question. Validating these biomarkers is an ongoing and important research task.

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Bronchiectasis

Introduction

Key points

- Patients with bronchiectasis typically have chronic airway infection, punctuated by acute exacerbations and accompanied by progressive airflow obstruction.
- Bronchiectasis occurs in cystic fibrosis (CF), primary ciliary dyskinesia and primary immunodeficiencies and is also associated with systemic diseases, including inflammatory bowel disease and rheumatoid arthritis.
- Computed tomography is often necessary for confident diagnosis of bronchiectasis.
- Management of non-CF bronchiectasis is largely based on evidence extrapolated from studies in CF and COPD.

Bronchiectasis means dilatation of the airways; this occurs patchily due to scarring and is usually associated with mucosal thickening, mucus plugging and a variable degree of lung over-inflation. Bronchiectasis is associated with a range of common and rare diseases, some of which impact on mucociliary clearance and immunity. Mucus clearance and local defence mechanisms against microorganisms are critically important in keeping the lungs free of infection. When they are impaired, repeated infection causes damage which further impedes the clearance of mucus. The airway dilatation and consequent impairment of mucociliary clearance combine to further increase susceptibility to repeated infection in the lungs, resulting in chronic infection in some cases. The abnormal airway anatomy, chronic infection and mucus retention result in a slow decline in respiratory function. In the early stages of the disease, even with significant evidence of bronchiectasis on computed tomography (CT), spirometry may be normal; in advanced disease, functional evidence of airway obstruction is usual. The apparent paradox of the structural bronchodilatation of airways but functional evidence of diffuse narrowing, largely reflects the different generations of airways involved; there may be irregular bronchodilatation of medium-sized airways but airflow is determined more by the smaller airways, which are narrowed due to chronic inflammation and scarring.

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> *"There is an urgent need to determine the optimal long-term therapies that maintain lung function and quality of life, and reduce exacerbations"*

As a diagnostic term, bronchiectasis is sometimes prefixed by non-cystic fibrosis (non-CF) to exclude this specific cause from that associated with another condition or in which no cause is identified. Bronchiectasis is, however, primarily a pathological description of the airways; although an aetiological diagnosis can only be established in some patients with definite CT radiological evidence of the condition, bronchiectasis is a useful diagnostic term as patients share a common symptomatology.

Epidemiology

The prevalence and incidence of bronchiectasis are not known accurately. Prevalence has been estimated to be from 0.013 cases per 100 000 population in 1954 in the UK and 0.5 per 100 000 in Finland in 1998, to 4 per 100 000 in people aged 18–34 years, rising to 272 per 100 000 in over those over 75 years of age in the USA in 2005. In New Zealand, the reported prevalence is 3.7 per 100 000 population but this varies according to ethnicity. Bronchiectasis is particularly common in children of Pacific Island descent compared with European children. In a sample of 5% of Medicare data in the USA, the 8-year period prevalence of bronchiectasis was 1106 cases per 100 000 population, and in this study the prevalence of bronchiectasis increased by about 8.7% per year of life. This report also suggested a higher prevalence in Asian- compared to African- and European-Americans.

In Europe, age-standardised hospital admission rates vary from less than 2 to more than 6 per 100 000 population (figure 1). This is lower than the estimated average annual age-adjusted hospitalisation rate in a US study, which found 16.5 hospitalisations per 100 000 population and an increase of 2.4% among men and 3.0% among women between 1993 and 2006. In the US study, women and people aged > 80 years had the highest rate of bronchiectasis-associated hospitalisations. The differences between the USA and Europe perhaps reflect the quality of available data.

Prognosis in people with bronchiectasis is not clear, but it is definitely related to lung function and the presence of infection, particularly *Pseudomonas aeruginosa*. A study from the UK suggests that the number of deaths due to bronchiectasis is increasing at 3% per year.
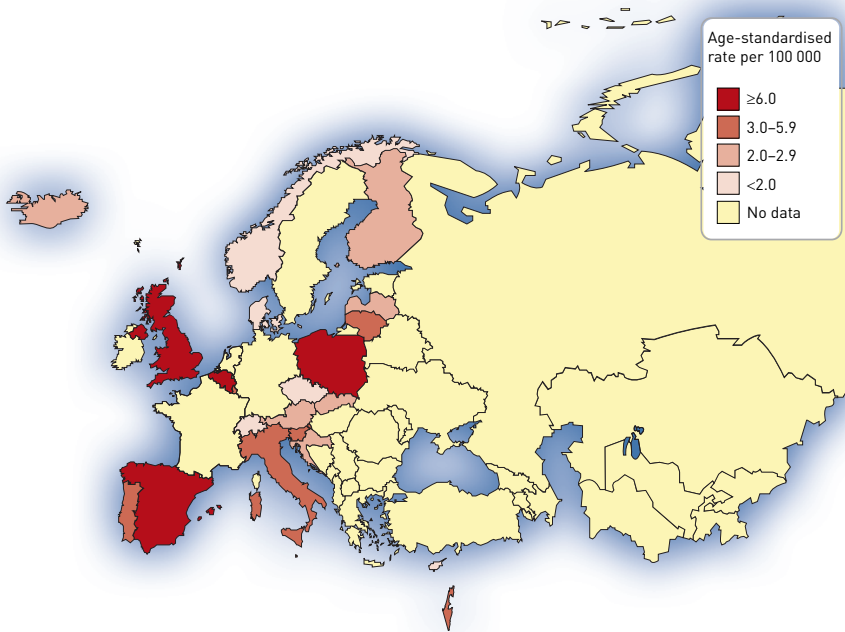
Figure 1 – Hospital admission rate for bronchiectasis. Data from the World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update. Data are not shown for the following countries where bronchiectasis is reported in combination with chronic obstructive pulmonary disease: Germany, France, Hungary, Ireland, Macedonia, the Netherlands, Romania, Sweden and Turkey.

Causes/pathogenesis   ?

The way in which bronchiectasis develops in the airways is poorly understood. The primary cause is not known in conditions other than CF, primary ciliary dyskinesia (PCD) syndromes and primary immunodeficiency syndromes. In CF, impairment of mucociliary clearance is the result of abnormal airway hydration due to CF transmembrane regulator (CFTR) mutations. In PCD it is due to abnormal structure and function of cilia. In other groups of patients with bronchiectasis, it is assumed that infection and/or perturbed innate or acquired immunity are important factors, with secondary impairment of mucociliary clearance.

In established disease, there is a vicious cycle of inflammation driven by neutrophils, recurrent or persistent infection, primarily with *Haemophilus influenzae* and injury to epithelium and bronchial and bronchiolar structures (figure 2). The anatomical damage further impairs mucociliary clearance; inflammation through proteases impairs some important aspects of innate immunity in the airways, causing further persistence of this vicious cycle. While this process is widely accepted as a paradigm for the condition, there are a number of key parts of the pathway which are poorly understood.
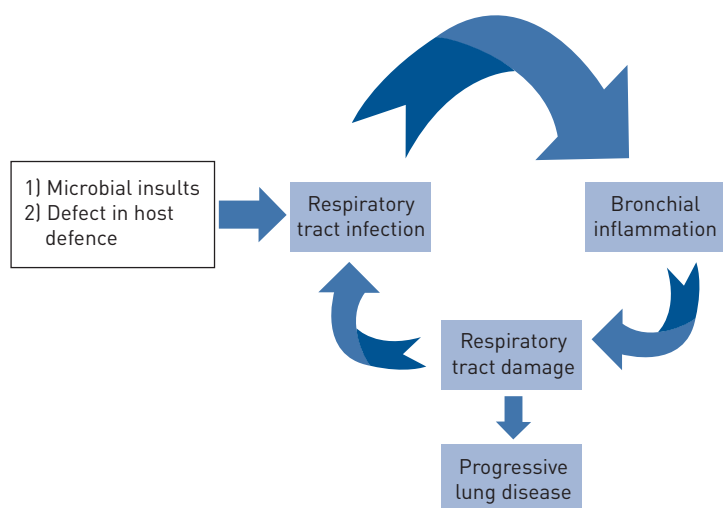
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Figure 2 – The vicious cycle of infection and inflammation leading to progressive lung disease in bronchiectasis.

In people with bronchiectasis, a diagnosis of an underlying associated condition can be made in about 50% of cases. Many studies of diagnosis begin by excluding people with CF, and in some diagnostic and treatment guidelines the condition is labelled as non-CF bronchiectasis, to capture all of the other conditions. However, there is no intrinsic pathological difference between bronchiectasis associated with CF and bronchiectasis due to other conditions. In general, in CF, lung disease is more aggressive and associated with a higher prevalence of Gram-negative infection, particularly with *P. aeruginosa*. Bronchiectasis is almost universal in people with CF (see chapter 14). It is also a common complication of PCD and primary immune deficiency disorders, particularly common variable and X-linked immunodeficiency associated with reduced blood concentrations of immunoglobulin (Ig)G. Bronchiectasis also occurs, uncommonly but with increased frequency, in a number of systemic immune conditions, particularly rheumatoid arthritis and inflammatory bowel disease. Bronchiectasis is associated with infection due to HIV, non-tuberculous mycobacteria and *Mycobacterium tuberculosis*. The pathophysiological connection between these conditions and bronchiectasis is poorly understood. However, in many patients with a diagnosis of bronchiectasis, there is no clear association with another underlying disease. Childhood infections, such as whooping cough (pertussis) and measles, have been considered as strongly associated or causative. However, problems with recall bias make it very difficult to know the importance of this association.

Bronchiectasis may also complicate a range of other lung diseases: it can be identified in some patients with chronic obstructive pulmonary disease (COPD), severe asthma and interstitial lung disease. In these conditions, bronchiectasis is usually found in the context of severe disease and is then not considered the primary disease. However, when it occurs alongside these conditions, it is associated with a higher incidence of infective pulmonary exacerbations and some of the management strategies used for primary bronchiectasis may be effective.

Clinical manifestations and consequences

Bronchiectasis causes cough, usually productive of sputum. This may occur daily or less frequently in patients with early disease. These regular symptoms are punctuated

by episodes of pulmonary exacerbation, often associated with culture of a potentially pathogenic organism in sputum. It is generally unclear whether these are new infections or a resurgence of chronic infection. It may be that both are important precipitants. The exact cause of pulmonary exacerbations is not well understood; however, these episodes are associated with a change in sputum colour towards green, along with an increase in cough frequency and sputum volume. This is sometimes complicated by minor haemoptysis. Individuals may feel more breathless and some will have systemic symptoms of infection, such as fever, fatigue and general malaise. Pulmonary exacerbations are associated with disease severity, and though there is no direct data for bronchiectasis, exacerbations are likely to contribute to a decline in lung function.

Chest crackles are heard on clinical examination, though in mild disease there may be no abnormal clinical signs. Finger clubbing is classically associated with bronchiectasis, but it is now a rare manifestation in this condition. Forced expiratory volume in 1 second (FEV_1) is frequently used for clinical monitoring to assess the severity of functional abnormality. In general, however, FEV_1 changes little during exacerbations and its value as an outcome measure in clinical trials and in clinical monitoring has been questioned. As disease progresses, there is a continuing reduction in spirometric volumes. In some patients, over-inflation of the lungs is prominent and this has been associated with higher mortality.

High-resolution CT is the diagnostic modality that defines bronchiectasis. Plain chest radiography is insufficiently sensitive for diagnostic purposes. There are a number of scoring schemes for reporting severity using CT, which are rarely used in clinical practice but are important for clinical research purposes. Other diagnostic tests should seek to systematically identify underlying causes such as CF, PCD, impaired immune function, allergic bronchopulmonary aspergillosis and α_1-antitrypsin deficiency.

Prevention

It has been suggested that the widespread application of vaccination programmes in childhood, particularly against measles and pertussis, should cause a significant reduction in the prevalence of bronchiectasis. However, there are no data to support this association. In a recent systematic review of the long-term consequences of childhood pneumonia, bronchiectasis was uncommon, and asthma and COPD were more common. In addition to universal childhood vaccination,

> *There is a great lack of clinical trials in bronchiectasis to guide treatment*

it would be prudent to recommend careful treatment of episodes of childhood pneumonia and immunisation against influenza and pneumococcus in appropriate individuals of any age.

Many patients with bronchiectasis have a significant delay in diagnosis and may be labelled as simply having lower respiratory tract infections or an alternate respiratory diagnosis of COPD or asthma. In these cases it is not clear whether earlier specific diagnosis would improve outcomes, but the diagnosis should be considered in all patients presenting with persistent cough productive of sputum. In CF, there is good evidence that the natural history of bronchiectasis can be positively affected by effective antibiotic therapy and drugs that improve mucociliary clearance (see chapter 14). Such evidence is not available in non-CF bronchiectasis.

Management

The principles of management of bronchiectasis are outlined in table 1. There is a great lack of clinical trials in bronchiectasis to guide treatment. These therapeutic choices have been extrapolated from COPD or CF treatment regimes, with variable levels of success. Some small investigator-led randomised controlled trials have been published, but there are insufficient data to recommend definitive therapies based on robust clinical trials. Regular airway clearance is a logical treatment and is supported by some small studies. Airway clearance, undertaken once or twice daily using methods such as the active cycle of breathing technique or a resistance device such as Acapella (Smiths Medical) or Flutter (Axcan Scandipharm Inc.), is a reasonable regimen. Inhaled β_2-agonists may be helpful in managing associated airflow obstruction. There is some evidence to support the use of inhaled corticosteroids to reduce sputum volume and possibly the frequency of exacerbations in patients with *P. aeruginosa* infection. There are strong published data supporting the use of macrolides in CF and oral macrolides may also be of value in reducing exacerbations in non-CF bronchiectasis. Three randomised placebo-controlled trials of macrolide treatment have demonstrated a reduction in pulmonary exacerbations and an improvement in lung function (FEV1). This treatment should be considered in all patients with bronchiectasis who have had two or more exacerbations in the previous year. The use of inhaled antibiotics has been extrapolated from CF data. In individuals in whom chronic *P. aeruginosa* infection is identified, long-term antibiotics are often used. There are no therapies licensed for use in this condition, but off-label colistin, gentamicin and tobramycin are frequently used. In patients with newly isolated *P. aeruginosa*, eradication regimes are frequently applied based on experience from CF.

Treatment of pulmonary exacerbations should include increased airway clearance and the commencement of antibiotics. Choice of antibiotic is largely empirical, though previous sputum bacteriology results can be useful in deciding. For the common organisms, such as *H. influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Streptococcus pneuomoniae*, oral antibiotics are usually sufficient. In contrast, for patients chronically infected with *P. aeruginosa*, combination therapy with an extended-action β-lactam and aminoglycoside is recommended. Surgery has a limited role in the management of bronchiectasis, mainly in localised disease. Occasionally, haemoptysis is sufficiently frequent or severe to warrant treatment by embolisation of the relevant bronchial artery or arteries.

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Improving airway clearance	Mechanical airway clearance (ACBT, PEP devices, autogenic drainage) Inhaled hypertonic saline Inhaled mannitol[#]
Reducing bronchoconstriction	Short- and long-acting β_2-agonists
Reducing inflammation	Inhaled corticosteroids Oral azithromycin[#]
Treating infection	Oral antibiotics for exacerbations Inhaled colistin/aminoglycoside for eradication or long-term suppression

Table 1 – Therapies for bronchiectasis. (Many of these therapies are used but none are approved by European Medicines Agency to support their long-term use in bronchiectasis.) ACBT: active cycle of breathing technique; PEP: positive expiratory pressure. [#]: recently reported phase 3 clinical trials.

> *A diagnosis of an underlying associated condition can be made in about 50% of cases*

Prognosis

The prognosis of bronchiectasis is undefined. One UK study has shown evidence of some increase in bronchiectasis as a certified cause of death. A number of factors contribute to poorer outcome, such as low FEV1 and *Pseudomonas* infection.

Future developments

Bronchiectasis is one of the most neglected diseases in respiratory medicine. Currently there is no clear definition or classification of the condition and very little is known about its true prevalence or its impact on length and quality of life. There are no specifically licensed therapies and few specialist clinical services. Significant research is needed in order to improve the quality of care of patients with this condition.

Research needs

There are clear research needs in order to develop an evidence base for understanding the pathophysiology of bronchiectasis. In clinical research, there is an urgent need to determine the optimal long-term therapies that maintain lung function and quality of life, and reduce exacerbations. The optimal treatment interventions for exacerbations also require further study.

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Paediatric respiratory diseases

Introduction

Key points

- About one-quarter of primary care consultations among children relate to respiratory complaints.
- There is no effective vaccination programme for respiratory syncytial virus, the most common cause of bronchiolitis and lower respiratory tract infections in the first year of life.
- Community-acquired pneumonia is not a serious threat to most children in western Europe but mortality rates are more than 10 times higher in some eastern European contries.
- There are clear differences in infant and childhood mortality from respiratory disease between western, central and eastern Europe.
- Vaccination has markedly decreased the rate of respiratory infections such as pertussis, measles, *Haemophilus influenzae*, and pneumococcus in all European countries.

This chapter covers various respiratory diseases in children, with particular focus on acute infections, perinatal lung disease and bronchopulmonary dysplasia, tuberculosis (TB) and congenital respiratory disorders, and immunisation against the common infections of childhood. Asthma (chapter 12) and cystic fibrosis (chapter 14) in children are covered elsewhere.

In cross-sectional surveys in 1987 and 2001 in the Netherlands, the most frequent reason for children consulting a general practitioner was respiratory morbidity, accounting for about 25% of all consultations by children (figure 1). About 10% of consultations are for asthma, with the other main respiratory diseases being bronchiolitis, acute bronchitis and respiratory infections. Furthermore, a recent US report showed that pneumonia, asthma and acute bronchitis are consistently the three leading diagnoses in children (excluding the newborn) admitted to hospital for any cause. Recent comparable European data are not available but it can be assumed that similar conclusions apply, at least to western European countries. It is also likely that the burden of respiratory disease is even higher in eastern European countries. The Dutch survey also demonstrates that the burden of respiratory morbidity in a western European country fluctuates with time: it depends, for example, on unpredicted epidemics such as Mexican influenza, changes in vaccination programmes, development of antibiotic resistance and variations in climate. It also implies that in children, the cost of first-line care for

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> " *In children, the cost of first-line care for respiratory tract problems, together with skin conditions, represents about half of the total cost of first-line healthcare* "
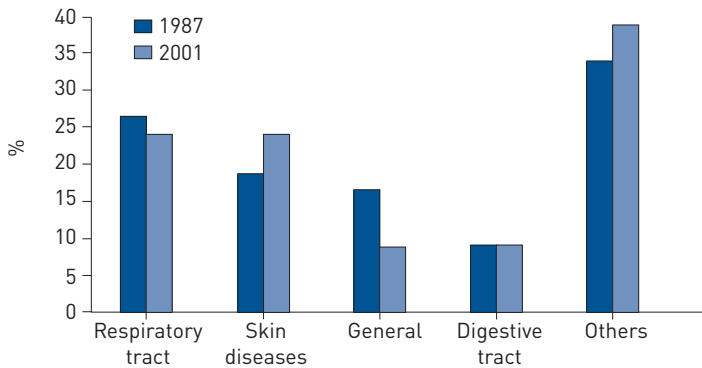

Figure 1 – Consultations for respiratory tract problems, skin diseases, digestive tract diseases, general complaints and other diseases at general practitioners for children in 1987 and 2001. Reproduced and modified from OTTERS *et al.*, 2005, with permission from the publisher.

respiratory tract problems, together with skin conditions, represents about half of the total costs of first-line healthcare.

Acute bronchiolitis

Bronchiolitis is usually the result of viral inflammation of the very small airways (bronchioles). In affected children of less than 2 years of age it is characterised by rapid breathing, chest retraction and wheezing.

Respiratory syncytial virus (RSV) infection is the most important cause of bronchiolitis and other lower respiratory tract infections during the first year of life, and is also one of the major causes of hospital admissions in infants under 1 year of age. Affected children characteristically present with symptoms of a viral infection with mild rhinorrhoea, cough, and, on occasion, a low-grade fever. Within 1 or 2 days, these symptoms are followed by rapid respiration, chest retraction and wheezing. The infant may be irritable, feeding poorly and vomiting. Other causative viruses for bronchiolitis are human meta-pneumovirus, rhinovirus, adenovirus and influenza virus. Prevalence studies have shown that up to 50% of infants are infected by RSV by their first birthday and almost 100% by 2 years of age, with the highest prevalence during the winter. In the first year of life, the hospitalisation rate for RSV infection, *i.e.* bronchiolitis, has been reported to be 1–2% of all infants and 10–15% in high-risk infants. Intensive care admissions for bronchiolitis are high, as recently reported in a retrospective study in
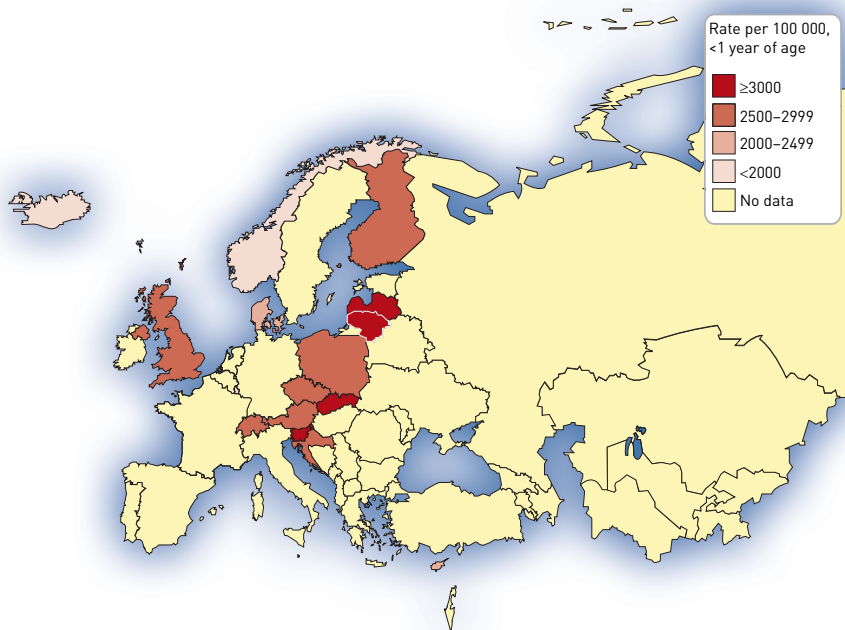
Figure 2 – Hospital admission rates for acute bronchitis and bronchiolitis in infants. Data from the World Health Organization Hospital Morbidity Database, October 2011 update.

France of 467 children admitted to 24 paediatric intensive care units (PICUs); 75% were aged less than 2 months, 76% had positive RSV tests and about one-third required noninvasive and/or mechanical ventilation. Six of the infants died. More than 50% of the neonates had a predisposing condition such as prematurity, respiratory disease including bronchopulmonary dysplasia (BPD) and congenital heart disease.

Hospital admission rates for acute bronchitis and bronchiolitis combined in children less than 1 year of age vary between countries and are particularly high in the Baltic states (Lithuania and Latvia), Finland, and the UK. For most European countries, however, this information is not available (figure 2).

Mortality from bronchitis and bronchiolitis in western Europe is generally low, but in many countries in eastern Europe, mortality rates for these diseases are unexpectedly and alarmingly high, as shown in figure 3.

The development of a vaccine to prevent RSV bronchiolitis has thus far not been successful. Furthermore, it is unclear how early in life such a vaccine should be administered. It is reasonable to assume that an RSV vaccination programme would have to start before the conventional vaccination programme against common childhood infections, *i.e.* before the age of 2 months.
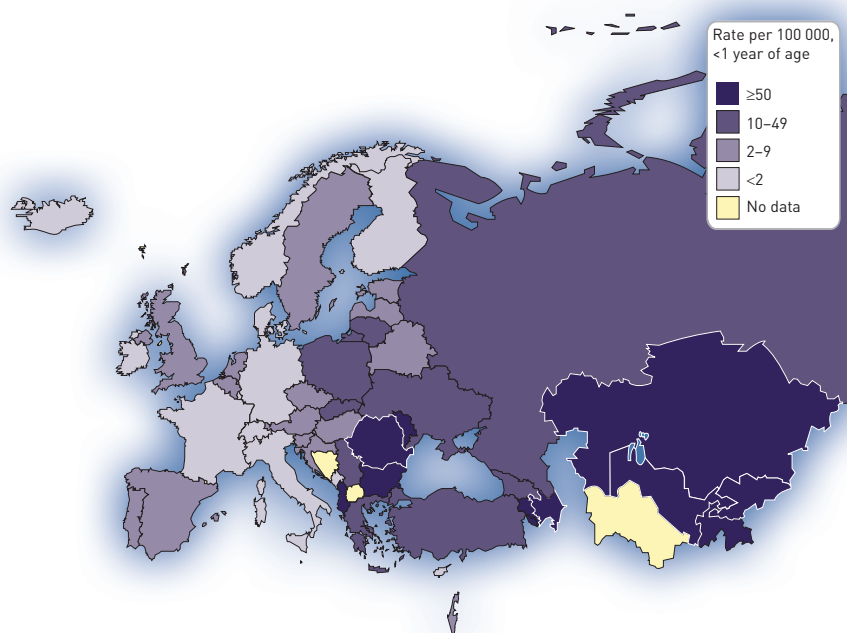
Figure 3 – Mortality rate for acute bronchitis, bronchiolitis and pneumonia combined in infants. Data from the World Health Organization World and Europe Mortality Databases, November 2011 update.

The monoclonal antibody palivizumab has been proven to reduce severe RSV infections in high-risk infants and protection appears to extend beyond the current monthly dosing. However, studies indicate that its cost-effectiveness is low. The high costs of prophylaxis with palivizumab mean it is not available in many European and low-income countries.

It is important that a reliable and highly effective vaccine and a prevention programme becomes available in the future, especially for high-risk infants. A reduction of the number of deaths due to failure of therapy in bronchiolitis, especially in eastern European countries, should be the aim of future European health programmes.

Perinatal respiratory diseases and BPD

The perinatal period, *i.e.* the period from birth (and especially premature birth) to the 28th day of life, is the period of greatest mortality. Pre-term birth is the major determinant of neonatal mortality and morbidity. In the modern era, with survival of extremely premature infants (gestational age of ≤ 26 weeks) and low-birthweight infants, post-neonatal mortality contributes significantly to the infant mortality rate.

In a US survey in 2002, the neonatal mortality rate was 6.9 per 1000 babies born at 35–36 weeks, 18.5% in babies born at 30–34 weeks, and 28.5% among babies born at < 30 weeks. In a recent follow-up of 100 infants born at 23 weeks, 60 died prior to hospital discharge, most from respiratory failure. There is an increasing trend to initiate resuscitation and treatment at an earlier gestational age; however, it is concerning that this results in an increasing proportion of children with long-term respiratory and/or neurological impairment.
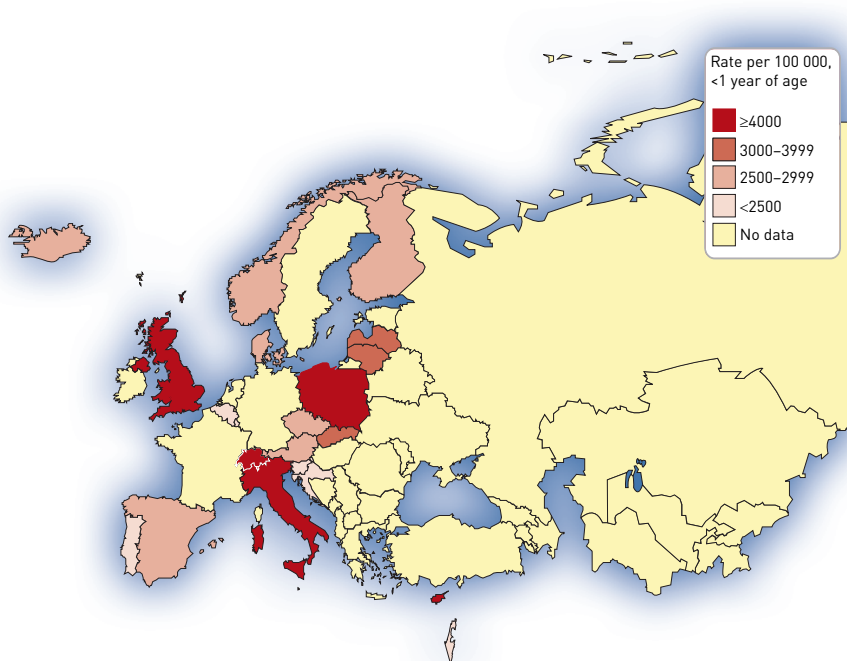
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Figure 4 – Hospital admission rate for perinatal respiratory disorders in infants. Data from the World Health Organization Hospital Morbidity Database, October 2011 update.

Hospital admission rates for perinatal respiratory disorders are presented in figure 4. It is unfortunate that data are not available from all countries, but it can be expected that, as in Switzerland, the UK, Italy, Poland and Cyprus, rates will increase across Europe and worldwide owing to the trend to start treatment at an earlier gestational age.

Another concern is the number of perinatal deaths in Europe (figure 5). Differences between western, central and eastern Europe are clearly apparent and may reflect variation in the quality of care available for these children. Also, more advanced equipment and expensive medication, such as surfactant, may not be available in some countries, whose health and budgetary priorities differ from those of western Europe.

One important long-term consequence of prematurity is BPD, or chronic lung disease of prematurity (CLD). This can be defined as oxygen dependency at 36 post-menstrual weeks. It is one of the most important complications of prematurity, with a reported incidence of 23% of infants born at 28 weeks, increasing to 73% of infants born at 23 weeks. It is characterised by prolonged respiratory support, compromised lung function and recurrent respiratory infections during the first year of life. Furthermore, BPD is considered an independent risk for and is associated with neurodevelopmental impairment.
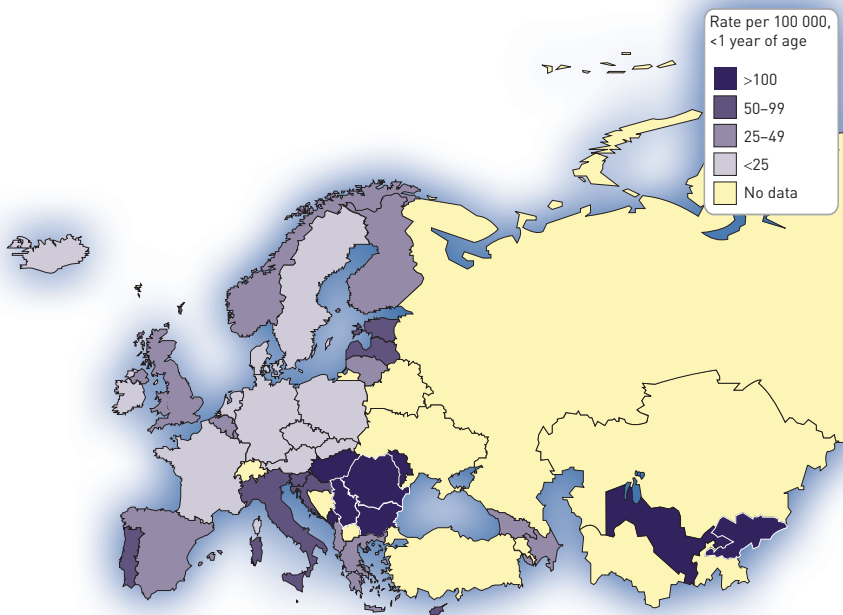
Figure 5 – Mortality rate for perinatal respiratory disorders in infants. Data from the World Health Organization World and Europe Detailed Mortality Databases, November 2011 update.

Overall, therefore, there is concern about both the short- and long-term respiratory, but also developmental, consequences of treatment of very premature children. Attention needs to be paid to developing new and effective medication for children born with immature lungs. Until now, treatment for BPD has not been effective. There is a particular need to focus on the improvement of care for premature infants with these conditions in central and eastern Europe. Although lung function in children with BPD improves with age, impairment of lung function persists into adulthood, with impaired exercise capacity, airflow limitation and airway hyperreactivity. One has to take into account that these measurements are only available in children who are able to perform lung function tests. Since only limited data about the burden and the long-term effects of prematurity and BPD are available, the development of a European databank to study the costs, the cost-effectiveness and the long-term effects of treatment of these infants should be a priority so that information is available about the number of infants with BPD in each country and the long-term effects of extreme prematurity. In addition, guidelines for the treatment of these infants are needed, perhaps developed in conjunction with health organisations in other continents.

Severe community-acquired pneumonia in children

Community-acquired pneumonia (CAP) is common among children all over the world, but its incidence and mortality rate are significantly higher in developing countries than in the industrialised world. It is estimated that about 151 million new episodes a year occur among children < 5 years of age in the developing world, with an incidence of 0.29 episodes per child-year and a mortality rate of 1.3–2.6%, or a mortality rate of > 2 million per year. In industrialised countries, the total number of new episodes
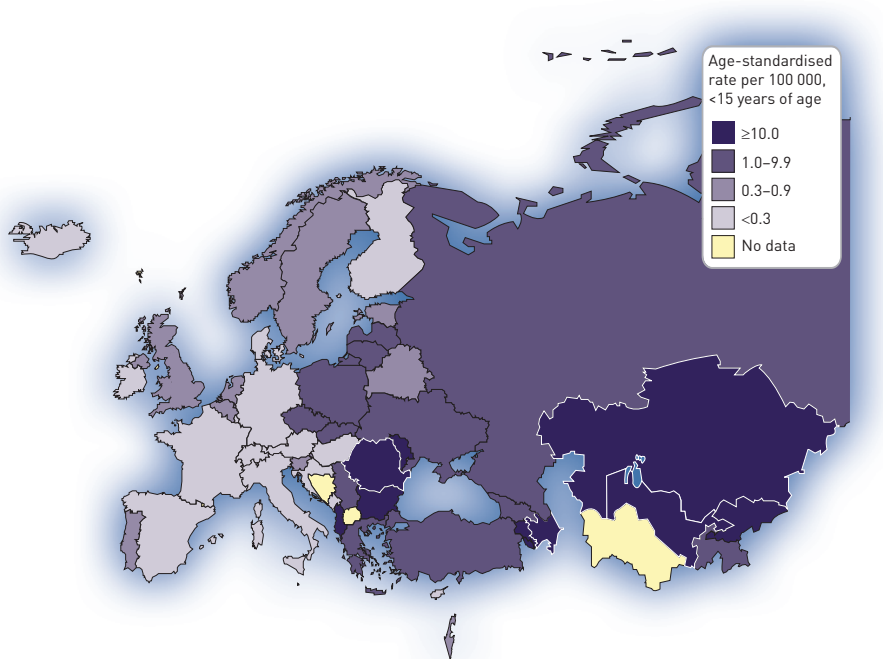
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Figure 6 – Mortality rate for pneumonia in children. Data from the World Health Organization World and Europe Mortality Databases, November 2011 update.

in the same age group is about 4 million (an incidence of 0.05 episodes per child-year), with an extremely low risk of mortality in otherwise healthy children. In the industrialised world, CAP mortality is a relatively important risk only in subjects with severe chronic underlying diseases.

Global variation in CAP prevalence and mortality results from a number of factors, including malnutrition, crowding, low birthweight, pre-existing HIV infection, the effectiveness of immunisation programmes (especially pneumococcal and *Haemophilus influenzae* immunisation) and variation in the incidence of measles.

Mortality rates vary considerably within Europe, and are highest in eastern European countries (figure 6).

The reasons for these differences within Europe are not clear, but they may include variations in the number of HIV-infected children and other underlying disease such as TB, as well as the presence of multidrug-resistant bacteria, poor immunisation rates and/or admission to hospital at a late stage of the disease.

In the future, it is important to identify and register the causes of the differences in mortality rates between European countries, and to set up an intervention programme.

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Tuberculosis in children

Childhood TB has been neglected for decades and has long been an overlooked area within global TB control. Poor ascertainment and reporting of cases of TB prevent accurate estimation of the European burden of disease in children.

TB in children most commonly results from household contact with someone with active TB, and represents ongoing transmission of *Mycobacterium tuberculosis* in the community. Infants and young children have an increased risk of infection following exposure and progress more readily from infection to active TB. In the absence of intervention, infants have a 50–60% risk of disease in the first year following infection. Young children more commonly present with disseminated disease and miliary TB and have an increased risk of death. Even low bacillary loads in children can lead to acute and severe illness, be it respiratory or disseminated; this is particularly the case in children less than 2 years of age. The generally accepted assumption is that qualitative and quantitative differences in the immune responses to mycobacterial infection between adults and children determine the outcome.

The total number of childhood TB cases in Europe in 2010 was about 11 000, with 3365 reported cases in children aged 0–4 years and 7549 reported cases in children from 5–15 years. The proportion of TB cases differs greatly between western and eastern European countries. The proportions of children with TB in eastern Europe aged 0–4 years and 5–15 years are expected to be two and four times higher, respectively, than those in western Europe.

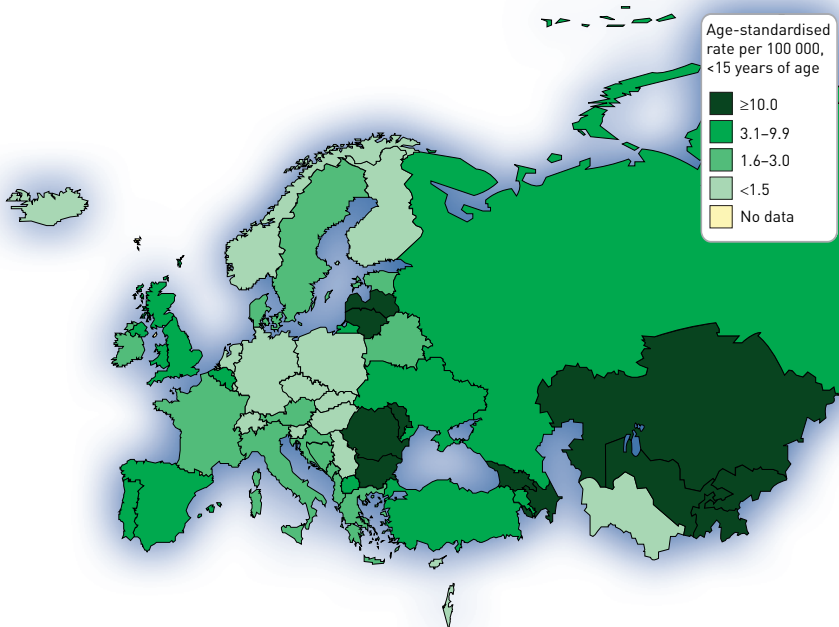The geographical distribution of TB in children is presented in figure 7.

Figure 7 – Tuberculosis cases in children, notified in 2010. Data from European Centre for Disease Prevention and Control, 2012.

The exact number of children with TB in eastern European countries is not known, but of greater concern is the lack of information regarding multidrug-resistant (MDR) and extensively drug-resistant (XDR) cases in children in Europe. Outside Europe, the highest rates of paediatric MDR-TB are reported in low-income countries and in some regions the incidence of MDR-TB has risen sharply in the past two decades. For instance, in Western Cape, South Africa, the proportion of culture-confirmed cases of MDR-TB has tripled in the past 15 years from 2.3% to 7.3% of all TB cases.

Given the overwhelming burden of TB and the vulnerability of young children to active TB disease, it is surprising that TB does not feature among the leading causes of death in children. The explanation might be the protection afforded by the bacille Calmette–Guérin (BCG) vaccination, although the protective efficacy of BCG is suboptimal.

Confirmation of the diagnosis of TB in children may be difficult, since collecting specimens of spontaneously produced sputum is problematic, although gastric aspiration and sputum induction (with or without laryngopharyngeal suction) are feasible alternative methods of collection. The tuberculin test and the interferon-γ release assay fail to differentiate *M. tuberculosis* infection from active disease, especially in vaccinated children. When a combination of clinical, radiological, laboratory and histopathological findings are consistent with a diagnosis of TB and there is epidemiological evidence of exposure to TB, an accurate diagnosis is possible in most cases.

In the future, better and more simple diagnostic tests must be developed to enable a rapid and 100% reliable diagnosis of TB. Furthermore, information on the prevalence and incidence of TB, MDR-TB and XDR-TB in children is urgently required for the whole European continent.

More information on TB can be found in chapter 17.

Immunisation

Immunisation programmes are very effective in preventing childhood respiratory infecions and, depending on the country in question, usually have a coverage of about 90%. The number of cases of infections included in the immunisation schedule, such as pertussis, measles, *H. influenzae*, and pneumococcus, has decreased considerably over the past 20 years in all European countries.

Pertussis, or whooping cough, is an acute respiratory infection caused by the bacterium *Bordetella pertussis*. It is
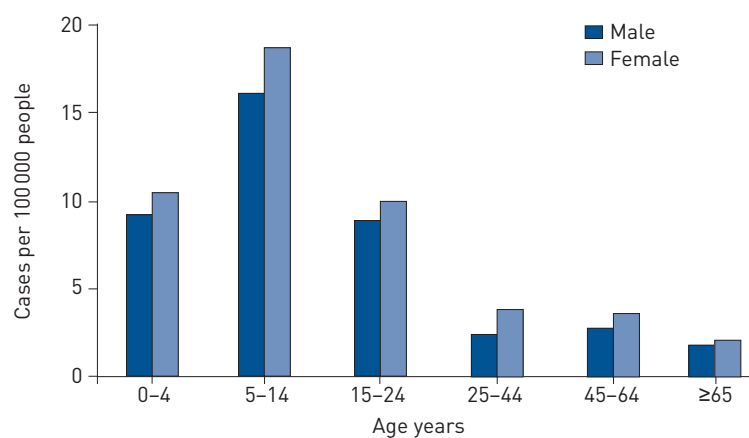
Figure 8 – Rates of reported confirmed pertussis cases, by age and sex in European Economic Area countries, 2009. Reproduced and modified from European Centre for Disease Prevention and Control, 2011.

an endemic infection common to children everywhere and is included in the primary immunisation schedule of all European Union countries. It is often unrecognised, and increasingly may occur in adults. After immunisation, the symptoms of pertussis are mostly mild and result in a prolonged period of coughing (weeks to months). However, in neonates, pertussis can be life-threatening and can result in prolonged periods of intensive care.

Despite the high immunisation coverage, cycles of outbreaks of pertussis have continued to occur, because neither infection nor immunisation produces lifelong immunity to pertussis, in the same way that they do for diseases such as measles. *B. pertussis* continues to circulate in a manner similar to that of the pre-vaccine era. Outbreaks have been reported in all European countries, especially in infants and children (figure 8). Urgent requirements are: the development of vaccines resulting in lifelong immunity; a focus on public awareness of the symptoms of the disease and the danger of contagion, especially in relation to contact with newborns.

Measles is an acute illness caused by the measles virus of the genus *Morbillivirus*. It is one of the most contagious diseases, and clusters and outbreaks of the disease are common. Infection can cause significant disability and death. One of the most common and serious complications is measles pneumonia, which develops in 5–10% of children with measles. It is caused by direct invasion of the lungs by the measles virus (primary measles pneumonia) or may occur due to a secondary infection by other viral or bacterial pathogens.

More information on immunisation can be found in chapter 26.

Congenital respiratory disorders

The incidence of congenital disorders of the respiratory tract is low and their effects are particularly seen during the first year of life. Congenital disorders can be subdivided into abnormalities of the thorax, specifically the diaphragm (hernia of the diaphragm), the lung (lung sequestration, cystic adenomatoid malformation, bronchogenic cyst, foregut cyst), the blood supply (aberrant vascularisation, double arch of the aorta), the airways (tracheal rings, tracheomalacia, tracheal atresia) and the larynx and oral cavity. Investigation and management of these diseases is usually organised in specialised centres.

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Childhood tuberculosis has been neglected for decades and has long been an overlooked area within global TB control

Primary ciliary dyskinesia is an inherited disorder characterised by specific ultrastructural defects of cilia that are associated with impaired ciliary motion and mucociliary clearance. It results in ineffective clearance of mucous secretions and inhaled particles, including bacteria. The disease is characterised by recurrent or persistent rhinitis, sinusitis, otitis media and bronchitis. The predominant pulmonary complication is bronchiectasis (see chapter 15). The incidence of the disease is low and often the diagnosis is difficult to assess. Therefore, both diagnosis and treatment should be organised in experienced centres.

In general, children with congenital respiratory disorders should be admitted to a specialised centre at an early stage as prompt assessment and, if necessary, treatment, are often important in determining survival.

General remarks

Most childhood respiratory diseases have a high morbidity and/or mortality and healthcare needs to become more focused on these diseases. It is concerning that there are huge differences between European countries. The European Union should move to address these differences and should also pay attention to the increasing burden of respiratory disease caused by prematurity across all countries.

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Tuberculosis

Introduction

Key points

- Each year, almost 400 000 new cases of TB are diagnosed in Europe, and more than 40 000 people die of the disease.
- TB is particularly problematic among the countries of the former Soviet Union, where multidrug-resistant TB is also highly prevalent.
- The proportion of TB cases with HIV infection among all TB cases tested for the virus in the WHO European region is increasing by 20% a year.
- The World Health Organization's Stop TB Strategy is a comprehensive public health approach to controlling the disease.
- There have been significant advances in diagnostic techniques for TB, but there remain logistical and financial obstacles to their widespread adoption.
- TB treatment is complex and takes many months, using a combination, usually of four drugs.

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis*, an organism belonging to the *M. tuberculosis* complex, which also includes other genetically related mycobacteria.

M. tuberculosis mycobacteria need to be distinguished from nontuberculous mycobacteria (NTM), which are widely distributed in the environment (soil, water) and can sometimes cause disease but are not transmitted from human to human. Using modern molecular techniques, more than 150 different species of NTM have now been identified. Epidemiological data from some industrialised countries suggest that cases of disease due to NTM are increasing and that NTM disease may even exceed the incidence of TB in countries in which TB incidence is low. The most important NTM is *M. avium*, which can particularly cause disease in patients with HIV/AIDS; in total, however, more than 40 NTM species have been reported to cause pulmonary disease, mostly in patients with impaired immune systems or an underlying lung disease, such as chronic obstructive pulmonary disease (COPD), bronchiectasis or cystic fibrosis. These organisms are generally less susceptible to antibiotics than *M. tuberculosis*, and the decision to treat an individual with a long-term combination of antibiotics depends upon the clinical picture and the causative NTM. Cervical lymphadenopathy (swollen lymph nodes in the neck) caused by *M. avium* complex is the prevailing manifestation in HIV-negative children, and surgical removal of the nodes is the treatment of choice, combined with antibiotics where necessary.

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> " *27 countries are classified as 'high multidrug-resistant-TB burden' countries, the top 13 of which are states of the former Soviet Union* "

TB is an important clinical and public health problem worldwide. Although its incidence and prevalence have declined notably in high-income countries over the past century, they have increased in low- and middle-income countries, owing to the emergence of strains resistant to several antimycobacterial drugs and to co-infection with HIV/AIDS.

Epidemiology

Global burden

In 2011, the global incidence of TB was estimated by the World Health Organization (WHO) to be 125 cases of TB per 100 000 people, which is equivalent to 8.7 million newly diagnosed patients (incident cases). Of the 8.7 million new cases, 12–14% (*i.e.* 1.0–1.2 million people) were HIV positive; these people were mainly African (79% of the total TB/HIV co-infected individuals). The total number of people with TB (prevalent cases) in 2010 was estimated to be 12 million (range 10–13 million), equivalent to 170 cases per 100 000 people globally. The number of prevalent cases has trended downwards since 1990; the same is true for the incidence of new cases, although there was a slight increase in the latter at the beginning of the 21st century.

The total number of patients dying of TB in 2011 was estimated to be 1.4 million (range 1.3–1.6 million), corresponding to a rate of 20 deaths per 100 000 people. The mortality rate of TB patients who were HIV negative was 14 per 100 000 in 2011 (a mortality rate of 15%), equivalent to an estimated 990 000 deaths (range 840 000–1.1 million); an estimated 430 000 HIV-positive people with TB (range 400 000–460 000) died in the same year (a mortality rate of 39%).

Epidemiology in Europe

In 2011, the estimated incidence of TB in the WHO European region was 42 per 100 000 people, with an estimated total of 380 000 incident cases. Overall, the TB notification rate has declined since 2007, from 56.3 per 100 000 inhabitants to 42 per 100 000 in 2011, a decrease of 27%.

The four countries with the highest TB notification rates (which include both incident cases and people who have relapsed) in the WHO European region in 2011 were Kazakhstan, Moldova, Georgia and Kyrgyzstan, with 118, 119, 105 and 103 cases per
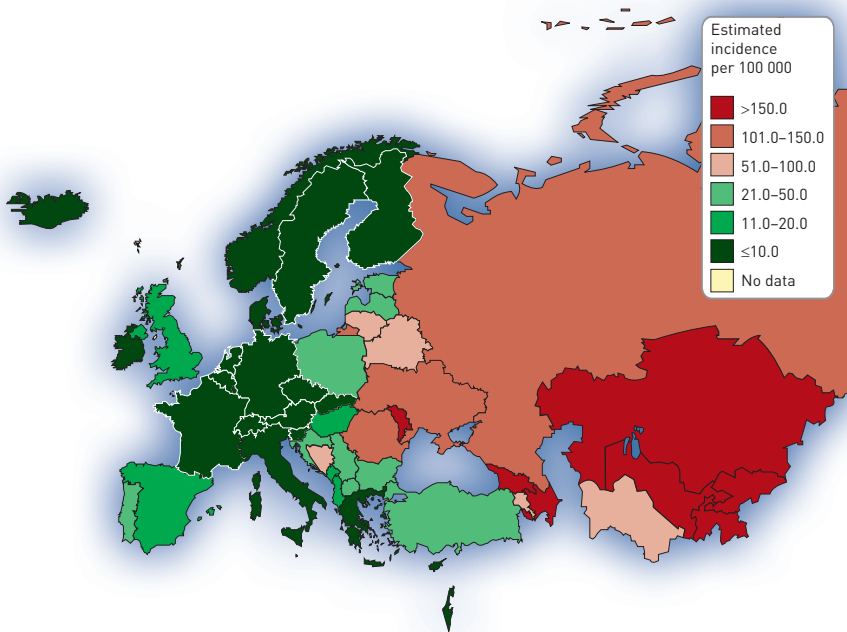
Figure 1 – Estimated incidence of tuberculosis. Reproduced and modified from European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe, 2013, with permission from the publisher.

100 000 inhabitants, respectively. A TB notification rate of 50–100 per 100 000 inhabitants was reported in seven states, including several former Soviet Union countries; the 11 countries with new/relapsing case-notification rates above 50 per 100 000 account for about 76% of the total number of notifications in Europe. Conversely, 32 western and central European nations notified less than 20 cases per 100 000 inhabitants. Estimated TB incidence is detailed in figure 1.

26% of notified TB cases in the European Union (EU)/European Economic Area (EEA) were foreign-born; in Israel, Norway and Sweden, this proportion was more than 85% of the total (figure 2). More than two-fifths (41%) of newly notified patients were 25–44 years of age. 16 countries reported a male-to-female ratio of > 2, due to males being more exposed to risk factors for developing TB such as HIV infection, smoking, alcohol abuse and homelessness.

In 2011, 12 751 (56.5%) European patients co-infected with TB and HIV were detected, out of an estimated 22 554 coinfected cases in the WHO European region. The proportion of TB cases with HIV infection among all TB cases tested for the virus in the WHO European Region is increasing by 20% per year (from 2.8% in 2006 to 6.5% in 2011). TB/HIV co-infected patients made up more than 10% of the total TB notifications in Luxembourg (40%), Ireland (20.2%), Ukraine (18.5%), Malta (16.7%) and Estonia (15%) (figure 3).
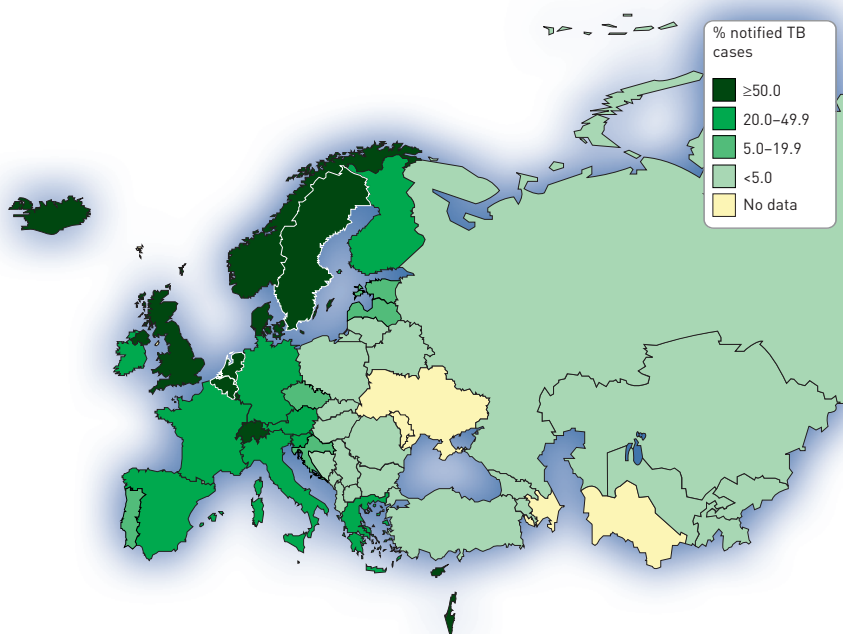
Figure 2 – Percentage of foreign-born cases among notified tuberculosis (TB) cases. Reproduced and modified from European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe, 2013, with permission from the publisher.

The estimated TB prevalence in Europe in 2011 was 55.9 cases per 100 000 inhabitants, corresponding to 502 763 patients. There is a strong gradient from East to West, and non-EU/EEA countries showed sharply higher rates than EU/EEA countries (104.4 *versus* 18.4 cases per 100 000 inhabitants, respectively).

The overall estimated TB mortality rate in Europe in 2011 was 4.9 deaths per 100 000 inhabitants, equivalent to 44 304 deaths in total; it was much higher in non-EU/EEA countries than in EU/EEA countries (10.1 *versus* 0.9 per 100 000 inhabitants, respectively) (figure 4). Among the EU/EEA member states, only Lithuania and Romania had death rates higher than 5 per 100 000 inhabitants, whereas more than 10 people per 100 000 inhabitants died of TB in Kyrgyzstan, Kazakhstan, Russia, Tajikistan, Moldova and Ukraine.

Drug-resistant tuberculosis

An important epidemiological and public health issue is the global emergence and spread of multidrug-resistant TB (MDR-TB), caused by *M. tuberculosis* strains resistant to at least isoniazid and rifampicin, the most efficacious anti-TB drugs. In 2006, an even more severe form of drug-resistant TB was described in several settings; this was defined as extensively drug-resistant TB (XDR-TB), caused by MDR-TB strains resistant to any fluoroquinolone and to at least one injectable second-line drug (kanamycin, capreomycin, amikacin).

The WHO estimated that the global prevalence of MDR-TB cases in 2011 was 630 000. 27 countries were classified as 'high MDR-TB burden' countries, the top 13 of which were states of the former Soviet Union. Belarus and Kazakhstan reported the highest MDR-TB prevalence among both new and previously treated TB cases. Overall, the highest proportions of MDR-TB among both new (15.1%) and previously treated (44%)
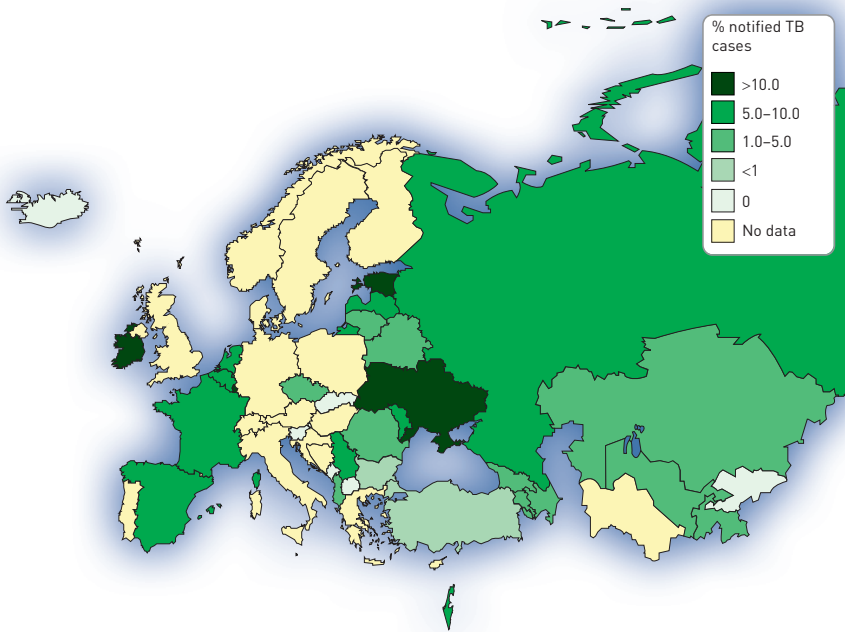
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Figure 3 – Percentage of tuberculosis (TB) cases with HIV co-infection. Reproduced and modified from European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe, 2013, with permission from the publisher.

TB patients were detected in Europe out of all WHO regions; however, the burden of MDR-TB among previously treated TB cases was unequally distributed, being greater than 50% in Belarus, Estonia, Kazakhstan, Moldova, Russia, Tajikistan, Ukraine and Uzbekistan. Figure 5 shows the proportion of notified MDR-TB cases. Almost 12% of MDR-TB cases had XDR-TB. Unfortunately, drug-susceptibility testing (DST) to ascertain MDR-TB status is carried out worldwide in less than 4% of new TB cases and 6% of previously treated cases; furthermore, treatment tailored to MDR-TB was started in only 23% of confirmed MDR-TB cases globally in 2011.

Causes/pathogenesis

TB is a mainly airborne infectious disease caused by *M. tuberculosis*. Organisms are spread by droplets in the air from individuals with active TB ('contagious patients') who cough, sneeze, sing or speak. The highest risk of acquiring TB infection is among individuals intensively exposed at a short distance for a prolonged period of time ('close contacts').

Following infection, one of two clinical outcomes is possible: 1) early development of active disease (so-called 'primary TB'), which occurs particularly in small children and immunocompromised patients); and 2) latent TB infection (LTBI), which occurs in the majority of infected individuals. The
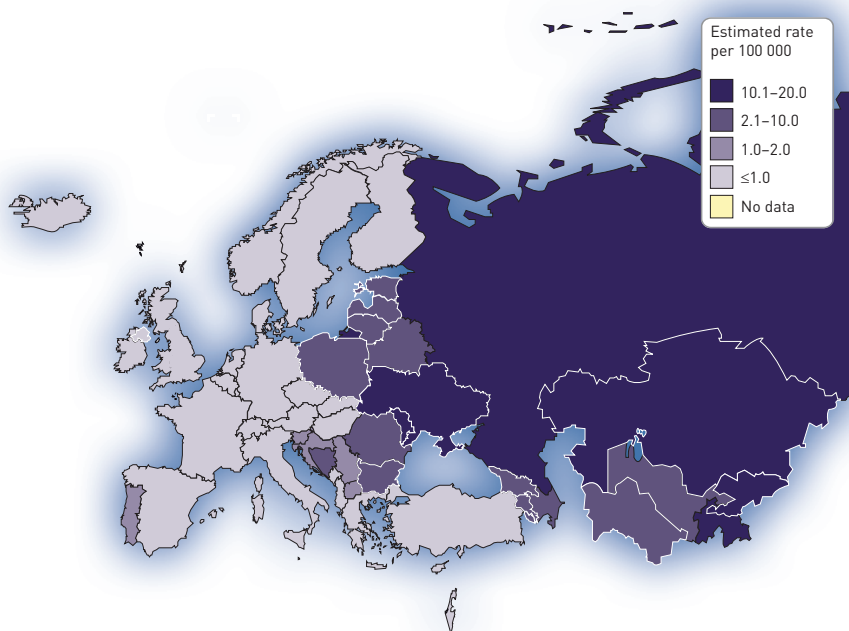
Figure 4 – Estimated mortality rate of tuberculosis. Reproduced and modified from European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe, 2013, with permission from the publisher.

lifetime risk of developing clinical TB after infection is 5–10% in the immunocompetent. The cumulative risk of developing TB is correlated with the age at primary infection: it is estimated that children who are infected after close contact with a contagious case have a 30–50% risk of developing TB. Furthermore, several medical, social and environmental conditions impairing the immune system can increase the risk of active TB: HIV/AIDS, diabetes mellitus, chronic renal failure, silicosis, exposure to immunosuppressive drugs, tobacco smoking and malignancy. Preventive drug treatment of infected individuals at higher risk of reactivation can significantly decrease the probability of them developing active TB.

Poor clinical and public health management of individuals with latent or active disease can favour the emergence and spread of MDR-TB. This is, in essence, a man-made phenomenon caused by inadequate treatment, including human errors related to any phase of the drug-delivery process involving regimen choice (for instance, the addition of a single drug to a failing regimen, prescription of low quality-assured drugs) and duration, drug dose, treatment adherence, infection control and other determinants (such as poverty and difficult access to the healthcare system). Inadequate drug treatment may promote the selection of pre-existing resistant strains or the emergence of new resistant strains.

Clinical manifestations and consequences

While any organ of the human body can be affected by TB, in HIV-negative individuals pulmonary disease is the most frequent clinical manifestation (70–80% of cases). Extrapulmonary involvement (for instance, meningitis or lymphadenitis) occurs in 20–30% of patients, sometimes accompanied by pulmonary disease; in settings with high HIV prevalence, this proportion can be higher.

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> *Children who are infected after close contact with a contagious case have a 30–50% chance of developing TB*

Pulmonary and/or extrapulmonary TB can occur many years after exposure to an individual with infectious TB, provoked by temporary or permanent immunological impairment; only on rare occasions do symptoms develop after primary infection.

The most frequent symptoms of active disease are fever, anorexia or reduced appetite, weight loss, night sweats and persistent cough (*i.e.* lasting more than 21 days), usually productive of purulent and/or blood-stained sputum. Occasionally, patients complain of localised thoracic pain due to pleural inflammation; in extensive and long-lasting pulmonary disease, patients may complain of breathlessness (dyspnoea) and of coughing up blood (haemoptysis).

Prevention and control

The first, and to date, only licensed vaccine against TB was introduced in 1921 in order to reduce the incidence of pulmonary disease: it consisted of an attenuated strain of *Mycobacterium bovis* (*M. bovis* bacille Calmette-Guérin (BCG)). Experimental studies in different geographical areas showed it to be highly efficacious in the prevention of meningitis and disseminated disease (so-called 'miliary TB') in children, whereas it provides unpredictable immunity against pulmonary disease. Currently, it is prescribed to neonates in endemic countries where there is a risk of being infected shortly after birth (see chapter 26, figure 4). In Europe, several countries (for instance, Austria, Denmark, Germany and Spain) have discontinued their mass universal vaccination programmes. However, several non-EU/EEA countries such as Belarus and Uzbekistan recommend three BCG vaccinations, with the last dose given during adolescence. Some European countries continue to suggest BCG vaccination for individuals at particular risk of being infected (such as healthcare workers).

Due to the narrow target of the BCG vaccine, the WHO advises that the best preventive approach is to focus on interrupting transmission, by case-finding and antibiotic treatment of infectious cases.

The WHO public health approaches, the DOTS (Directly Observed Treatment, Short course) strategy and Stop TB strategy, launched in 1996 and 2006, respectively, aimed to reduce the global burden of TB and have changed the global epidemiological situation. Over the past decade, they have contributed to the achievement of the United Nations Millennium Development Goals, related to the reduction of 1990 TB prevalence and mortality by 50%, by 2015.
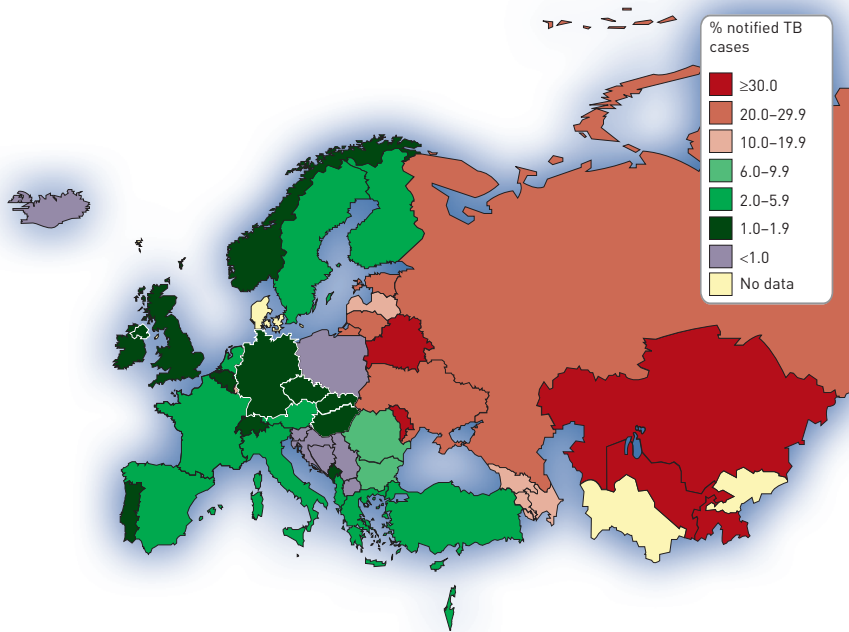
Figure 5 – Percentage of multidrug-resistant tuberculosis cases among tuberculosis (TB) patients with drug sensitivity results. Reproduced and modified from European Centre for Disease Prevention and Control/WHO Regional Office for Europe, 2013, with permission from the publisher.

The Stop TB strategy, a revised and updated public health approach, added new components in the fight against TB, to take account of the new epidemiological features of the disease, particularly TB/HIV co-infection and the rise of MDR-TB (table 1).

The fight against TB/HIV co-infection relies on HIV diagnosis and anti-HIV therapy and on the application of the '3 Is': intensified case finding, infection control, and isoniazid preventive therapy for latent infection.

In order to combat the MDR/XDR-TB epidemic, a WHO-convened Task Force developed a specific global MDR-TB and XDR-TB Response Plan in 2007–2008, and in 2009 a governmental conference launched the Beijing Call for Action. Recommendations were developed for the control of XDR-TB, including the following:

- Prevent XDR-TB through basic strengthening of TB and HIV control.
- Improve the management of individuals suspected to be affected by XDR-TB through accelerated access to laboratory facilities with rapid DST for rifampicin and isoniazid resistance.
- Strengthen the management of XDR-TB through adequate use of second-line drugs and patient-centred approaches to ensure support and supervision.
- Better protection of healthcare workers against infection.
- Implement XDR-TB surveillance activities through the network of supra-national and national reference laboratories.
- Initiate advocacy, communication and social mobilisation activities to inform and raise awareness about TB and XDR-TB.

However difficult it is to reach, the ultimate goal of international and national public health activities is the elimination of TB, decreasing the incidence of new infectious cases (*i.e.* those with a positive result on direct microscopic examination of the sputum) to less than 1 per 1 million population by 2050.

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1. **Pursue high-quality DOTS expansion and enhancement**

   Secure political commitment, with adequate and sustained financing

   Ensure early case detection and diagnosis through quality-assured bacteriology

   Provide standardised treatment with supervision, and patient support

   Ensure effective drug supply and management

   Monitor and evaluate performance and impact

2. **Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations**

   Scale up collaborative TB/HIV activities

   Scale up prevention and management of MDR-TB

   Address the needs of TB contacts, and of poor and vulnerable populations, including women, children, prisoners, refugees, migrants and ethnic minorities

3. **Contribute to health system-strengthening based on primary healthcare**

   Help improve health policies, human resource-development financing, supplies, service delivery and information

   Strengthen infection control in health services, other congregate settings and households

   Upgrade laboratory networks, and implement the PAL

   Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health

4. **Engage all care providers**

   Involve all public, voluntary, corporate and private providers through PPM approaches

   Promote use of the ISTC

5. **Empower people with TB, and communities through partnership**

   Pursue advocacy, communication and social mobilisation

   Foster community participation in TB care

   Promote use of the Patients' Charter for TB Care

6. **Enable and promote research**

   Conduct programme-based operational research and introduce new tools into practice

   Advocate for and participate in research to develop new diagnostics, drugs and vaccines

Table 1 – The World Health Organization-recommended strategy for tuberculosis (TB) control (the Stop TB strategy). DOTS: Directly Observed Treatment, Short course; MDR-TB: multidrug-resistant TB; PAL: Practical Approach to Lung Health; PPM: public–private mix; ISTC: International Standards for TB Care. Reproduced and modified from World Health Organization, Global Tuberculosis Control 2011, with permission from the publisher.

Management

Accurate bacteriological diagnosis prior to starting anti-TB drugs is the best clinical and public health approach to TB: this is based on microscopic examination, solid or liquid culture and rapid or conventional DST. The latter is required to optimise the antibiotic combination, taking into account the resistance pattern of the isolated mycobacteria.

The turnaround time for direct microscopy of a sputum smear is 1 day; however, its diagnostic sensitivity is affected by the concentration of mycobacteria in the sample. This can be improved by centrifugation and by collection of at least two sputum specimens on different days (particularly early in the morning).

Due to the suboptimal sensitivity and specificity of microscopic examination, definite diagnosis requires trying to grow mycobacteria in culture. The mean time for detection of *Mycobacterium* complex is 3 weeks. New diagnostic methods such as nucleic acid amplification tests can reduce the time to presumptive bacteriological diagnosis, thereby increasing the pre-culture probability. Recently, similar techniques have been used for the rapid detection of resistance to MDR-defining drugs. The GeneXpert (Cepheid), for example, a new molecular technique, based on a nucleic acid amplification test, can detect whether TB and resistance to rifampicin (considered a reliable marker of MDR-TB) are present in less than 2 hours. It was recently endorsed by WHO because of its higher sensitivity (it detects from ~70% to > 90% of cases) and specificity (> 90% of uninfected patients will have a negative test); however, at present, cost limits the availability of this innovative technique in low-income countries.

Chest radiography and computed tomography are useful tools to complement bacteriological examinations in the diagnosis of TB. Radiography is commonly used to screen individuals with a significantly higher risk of TB than that of the general population (such as prisoners or contacts of infectious cases) and individuals with symptoms suggestive of TB.

Immunological tests, such as the tuberculin skin test and the recently introduced interferon-gamma release assays, are helpful for the diagnosis of latent TB but cannot replace bacteriological diagnosis of active TB.

The aims of anti-TB therapy are to cure the patient and to avoid the transmission of mycobacteria to other people. Treatment is characterised by an intensive phase (2 months) and a continuation phase (4 months). For new cases, the intensive phase usually includes four drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) and is designed to eliminate actively growing, as well as semi-dormant, mycobacteria. The continuation phase, based on the combination of isoniazid and rifampicin, kills residual mycobacteria.

MDR- and XDR-TB require the use of second-line drugs, which are more expensive, toxic and difficult to manage. Treatment is prescribed for at least 20 months (with an intensive phase of at least 8 months) and should rely on at least four effective drugs.

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Prognosis

TB prognosis can be affected by numerous factors: coexistent HIV/AIDS, age, chronic comorbidity (for instance, diabetes mellitus, silicosis or cancer), exposure to immunocompromising drugs, smoking, drug and/or alcohol abuse, malnutrition and MDR/XDR-TB status. More scientific evidence is needed in order to understand the role of social determinants on the outcome of disease.

The majority of untreated patients with pulmonary disease die within 1.5 years of developing the first symptoms. The 10-year case fatality rate for untreated HIV-negative sputum smear-positive patients is 53–86% (with an average of 70%); in sputum smear-negative individuals, the rate is 20%. The average duration of the disease from the first symptoms to cure or death, is about 3 years. Unfortunately, failure and death rates are high in MDR- and XDR-TB – the treatment success rate is often less than 50%.

Research needs

The main recent development in TB is represented by the introduction of diagnostic rapid molecular methods (such as GeneXpert), as previously mentioned. Through international support, the vast majority of countries with intermediate and high TB incidence and MDR-TB prevalence (including those of the former Soviet Union) are implementing these new techniques at a central, regional and local level. The main challenge at present is to ensure that countries are able to set up and maintain the equipment, manage the large number of newly diagnosed MDR-TB cases, and ensure quality treatment and clinical management, adequate infection control and prevention of further drug resistance.

Global and European control (and, eventually, elimination) of TB will only become possible when significant advances in prevention and treatment are also achieved through better vaccines and drugs. A strong public health approach aimed at correctly applying the WHO-recommended strategy of TB control (the Stop TB strategy) is also necessary, in order to ensure the effectiveness of new therapeutic drugs is not lost, as has already occurred for first- and second-line anti-TB drugs in many countries.

"*Most untreated patients with pulmonary TB die within 1.5 years of developing the first symptoms*"

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Future developments

Among the three weapons used in the fight against TB (vaccines, diagnostics and drugs), the most spectacular improvement recently has been in the diagnostic field. Rapid molecular tests are available to identify, within a timeframe of less than 2 hours to 1 day, whether a biological sample includes *M. tuberculosis*, and whether the strain is resistant to MDR- or XDR-TB defining drugs.

The challenge now is represented by the development of model programmes in former Soviet Union countries, where innovative diagnostic and treatment algorithms (involving new drugs) are being scientifically validated and integrated within a strong public health policy. To pursue elimination, innovative treatment regimens involving new drugs will need to be validated to treat LTBI and TB, and model programmes demonstrating feasibility, efficacy, and cost-effectiveness need to be implemented. This is a preliminary step to the strengthening of the elimination strategy to which Europe has been committed since 1990 but which it has never embarked upon. Pre-registration trials are evaluating the therapeutic impact of new, short-length regimens, as well as the safety, tolerability and efficacy of new drugs for the treatment of MDR-TB.

New vaccines, when available, will increase the chances of complete elimination of TB in Europe. Currently, only a few vaccines are under advanced clinical evaluation. Of particular interest are the listeriolysin-expressing BCG construct, and vaccines that utilise a viral delivery system.

Further advances should allow identification of surrogate markers to better validate the efficacy of therapeutic and preventive products. The present development pipelines for new TB diagnostics, drugs and vaccines are outlined in the WHO Global Tuberculosis Report 2012.

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Acute lower respiratory infections

Key points

- Community-acquired pneumonia is the most frequent cause of death from infection in Europe.
- The majority of patients with pneumonia are treated at home, but about 1 million are hospitalised annually in the EU.
- On average, in Europe, approximately 80% of isolates of *Streptococcus pneumoniae*, the most frequently identified cause of pneumonia, are now resistant to commonly used penicillin and macrolide antibiotics.
- Influenza usually affects the very young and the old, but the H1N1 pandemic hit younger adults particularly hard.

Acute lower respiratory infections are a leading cause of sickness and mortality both in children and adults worldwide. Unfortunately, acute lower respiratory infections are not uniformly defined and this may hamper a true appreciation of their epidemiological importance. From an epidemiological point of view, the definition of acute lower respiratory infections usually includes acute bronchitis and bronchiolitis, influenza and pneumonia.

Acute bronchitis can be defined as an acute illness that occurs in a patient without chronic lung disease. Symptoms include cough (productive or otherwise) and other symptoms or clinical signs that suggest lower respiratory tract infection with no alternative explanation (*e.g.* sinusitis or asthma).

Bronchiolitis is the most common lower respiratory tract infection and the most common cause of admission to hospital in the first 12 months of life (see chapter 16).

Incidence

The incidence of acute bronchitis in adults is high, between 30 and 50 per 1000 people per year. This means that in Europe, approximately 16 500 000 adult cases are seen each year in primary care. The clinical syndrome lasts approximately 2 weeks and has a clear impact on daily activities.

Age-standardised admission rates for acute bronchitis and bronchiolitis in Europe are shown in figure 1.

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"
Attack rates during seasonal influenza epidemics can vary considerably, but usually 5–20% of the population is affected
"

Age-standardised rate per 100 000, ≥15 years of age

- ≥100
- 50–99
- 25–49
- <25
- No data
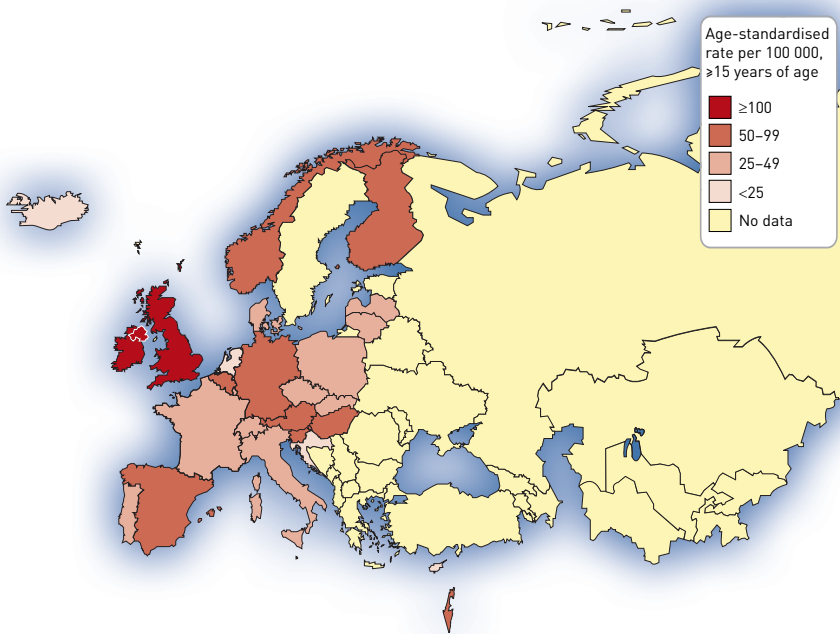
Figure 1 – Hospital admission rate for acute lower respiratory infections (including acute bronchitis and bronchiolitis but excluding pneumonia) in adults. Data from the World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

Causes and pathogenesis

Identifying causative pathogens for acute bronchitis is quite difficult and most clinical studies report identification in less than 30% of cases. Almost 90% of cases are related to viruses – such as adenovirus, coronavirus, parainfluenza, influenza and rhinovirus – and less than 10% to bacteria, such as *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.

Respiratory syncytial virus (RSV) is the most common cause of severe acute respiratory infection (*i.e.* bronchiolitis) in children (see chapter 16). Despite the generation of RSV-specific adaptive immune responses, RSV infection does not confer protective immunity in humans and recurrent infections are common.

Clinical manifestations and consequences

Acute bronchitis is a self-limiting infection in most cases, with symptoms typically lasting about 2 weeks.

RSV bronchiolitis is usually mild and self-limiting; however, some children experience more severe illness and require hospital admission, and some will need ventilatory support. Differences in innate immune function in response to the respiratory virus, as well as differences in the geometry of the airways, may explain some of the variability in clinical pattern (see chapter 16).

Management

European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines indicate that cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute bronchitis in primary care.

Antibiotics are not usually indicated for the treatment of acute bronchitis, especially in younger patients in whom bacterial infection is not suspected (see chapter 16).

Influenza

Influenza usually occurs during annual epidemics and occasional pandemics, the most recent pandemic being in 2009. Rates of infection are highest among children, with rates of serious illness and death highest in individuals over 65 years of age, children under 2 years of age, and persons of any age who have medical conditions that predispose to increased risk of complications from influenza. More than 90% of influenza-related deaths occur in patients in the older age group. Underlying medical conditions that increase the risk of hospitalisation with seasonal influenza include diabetes and cardiovascular, neurological and chronic respiratory diseases, such as asthma.

Incidence

There are varying estimates of the number of people infected by influenza every year, the resulting burden of ill health and premature death, and the degree to which these burdens can be reduced, but it is agreed that influenza is a significant threat to public health.

The attack rates during seasonal influenza epidemics can vary considerably from year to year, but usually some 5–20%

of the population is affected. The impact of influenza in different age groups varies considerably between epidemics. Usually, winter epidemics affect each country for 1–2 months and, across Europe, epidemics last for about 4 months. The epidemiology and clinical features of influenza can differ during pandemics, depending on the characteristics of the virus and on the level of immunity to a virus that by definition is different from those circulating in previous influenza seasons. This was the case during the 2009 influenza A (H1N1) pandemic, where the highest incidence of infection and disease was in younger individuals (*i.e.* those less than 65 years of age).

Figure 2 shows the case-load during the H1N1 pandemic in Europe.

Post-influenzal bacterial pneumonia is a major cause of morbidity and mortality associated with both seasonal and pandemic influenza.

Causes and pathogenesis

Influenza in humans is caused by three major families of RNA viruses: influenza A, B and C. They are usually classified according to differences in the antigenic properties of their external coat. Influenza A viruses, clinically the most important, are further divided into subtypes based on two proteins on the external coat, the haemagglutinin (HA) (H1–H16) and neuraminidase (NA) (N1–N9) proteins. Type B viruses cause somewhat less severe illness, and type C viruses do not cause significant human disease, so only type A and B viruses are of concern. Another important challenge is the emergence of influenza virus strains resistant to antivirals.

Clinical manifestations and consequences

Influenza viruses can cause disease among persons in any age group but the frequency of infection is highest in children. Rates of serious illness and death are highest among individuals over 65 years of age, children less than 2 years of age and persons of any age who have medical conditions that increase the risk of complications from influenza. Uncomplicated influenza is characterised by the abrupt onset of constitutional and respiratory signs and symptoms (*e.g.* fever, myalgia (muscle pain), headache, malaise, nonproductive cough, sore throat and rhinitis). Among children, otitis media, nausea and vomiting are also commonly reported with influenza infection. Uncomplicated influenza typically resolves after 3–7 days in most people. However, influenza virus can cause primary influenza viral pneumonia, exacerbate underlying medical conditions (*e.g.* pulmonary or cardiac disease), lead to secondary bacterial pneumonia, sinusitis and otitis media, or contribute to co-infections with other viral or bacterial pathogens.

Management

Two classes of antivirals, the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (laninamivir, oseltamivir, peramivir, and zanamivir), are currently approved for the prevention and treatment of influenza; several other classes of antivirals and immune modulators are also under investigation.

Pneumonia

Community-acquired pneumonia (CAP) is a major respiratory disease with a high prevalence in the general population, clinical heterogeneity and variable severity. Both

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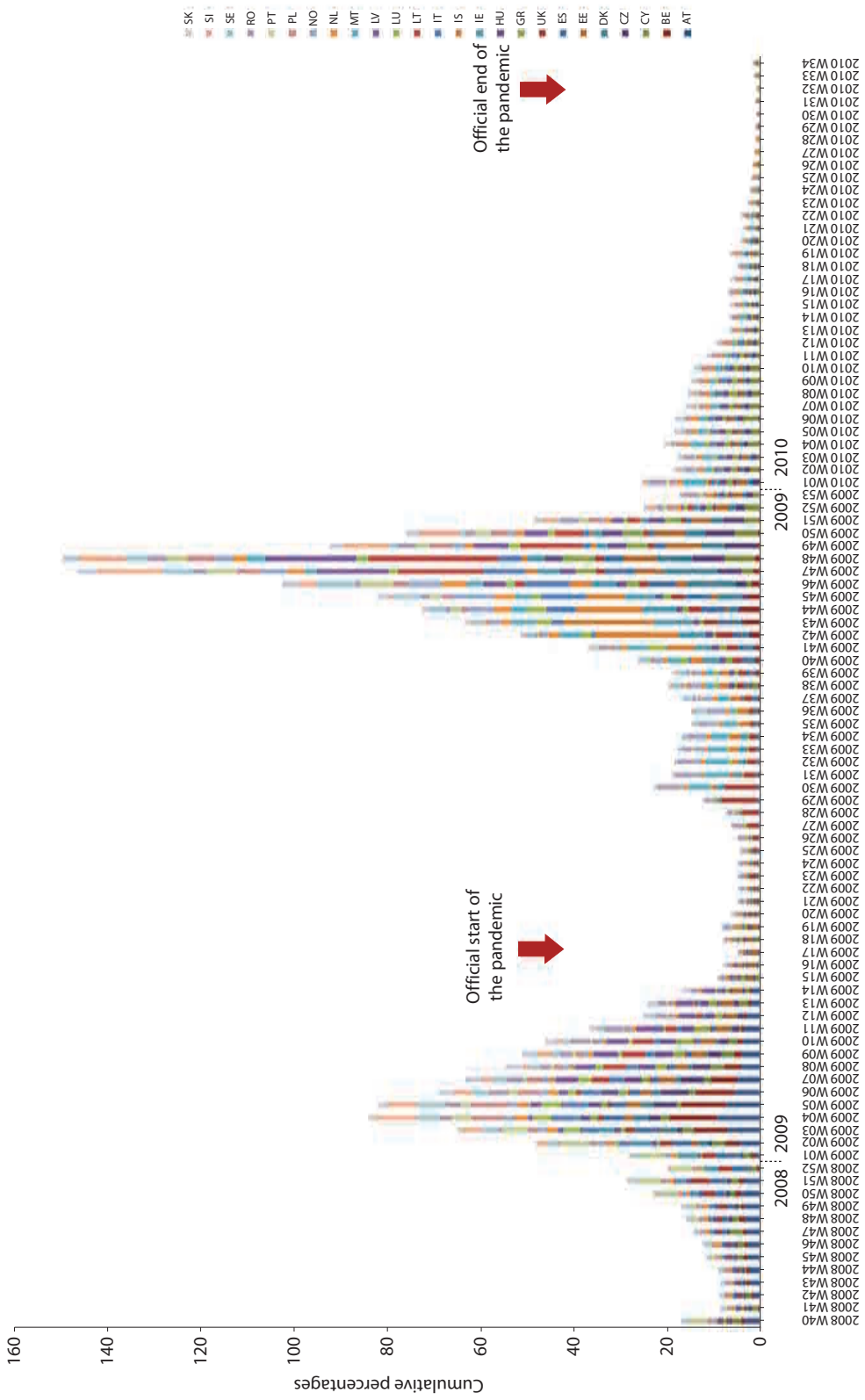PRACTISING RESPIRATORY MEDICINE IN EUROPE

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Figure 2 – Aggregate percentages of weekly reported influenza-like illness for 25 European Union member states, from week 40, 2008, to week 34, 2010. Data for each country are presented as the percentage of total cases over the whole 100-week period reported in a given week. Reproduced from European Centre for Disease Prevention and Control, 2010.

in the USA and in Europe, CAP is the most frequent cause of death due to infection and it has implications for healthcare systems worldwide. Pneumonia usually causes symptoms for 3–4 weeks, and daily activities may be impaired for a further 3 weeks on average. The reported incidence of pneumonia varies considerably from country to country and study to study, with a consistently higher incidence in very young children and elderly adults. In Europe, the mean age of the population is increasing sharply, and this is likely to lead to a significant increase in pneumonia hospital admissions and costs.

Pneumonia that occurs 48 h or more after hospital admission, and which was not incubating at the time of admission, is defined as hospital-acquired pneumonia (HAP), while pneumonia that arises more than 48–72 h after endotracheal intubation is defined as ventilator-associated pneumonia (VAP).

Incidence

The overall incidence of CAP in general practice in Europe is reported to range 1.7–11.6 cases per 1000 people per year in adults (table 1). In the European Union (EU), about

Country	Study period	Age years	Cases per 1000 population
Finland	1981–1982	15–29	4.2 M; 4.6 W
		30–44	5.6 M; 5.9 W
		45–59	9.8 M; 7.0 W
		60–74	25.0 M; 9.0 W
		>75	65.2 M; 19.6 W
		>60	33.0 M; 11.8 W
Spain	1993–1995	15–39	1.2 M; 1.0 W
		40–64	1.8 M; 1.4 W
		>64	5.2 M; 1.9 W
		All ages	1.6
	1999–2001	15–44	0.8 M; 0.6 W
		45–64	1.4 M; 0.7 W
		65–74	3.2 M; 1.6 W
		>75	8.7 M; 3.0 W
		All ages	1.6 M; 0.9 W
	2002–2005	65–74	3.0 M; 2.2 W
		75–84	5.3 M; 2.8 W
		>85	10.0 M; 7.9 W
		All ages	4.2 M; 2.9 W
Italy	1999–2000	15–44	0.9
		45–64	1.6
		>64	3.3
		All ages	1.7 M; 1.7 W
Germany	2003	>18	8.7

Table 1 – Pneumonia incidence in Europe in the outpatient setting. M: men; W: women. Reproduced and modified from WELTE *et al.*, 2012, with permission from the publisher.

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3 370 000 cases are expected annually. Hospitalisation rates differ widely between European countries, ranging from 20–50%, meaning that there are about 1 million hospital admissions for CAP per year in the EU. Age-standardised hospital admission rates for pneumonia are shown in figure 3. It is important to note that while most patients are treated on an outpatient basis, most studies are based on hospitalised patients and the true extent of pneumonia is not known.

The incidence of HAP is ~0.5–2.0% among all hospitalised patients, and while it is the second-commonest nosocomial infection, it is first in terms of mortality (ranging from 30% to more than 70%). The incidence in different hospitals and different wards of the same hospital varies considerably.

Causes and pathogenesis

The main organisms causing CAP in Europe are shown in figure 4. *Streptococcus pneumoniae* is the most frequent causative agent of pneumonia in Europe.

Antibiotic resistance is one of the major threats undermining the treatment of respiratory infections, with potentially important clinical and economic implications. Data from the European Antimicrobial Resistance Surveillance Network (EARS-net) show that in Europe almost 10% of *S. pneumoniae* strains are resistant to penicillin and 15% to macrolide antibiotics (figure 5). Moreover, new difficult-to-treat bacteria are emerging in pneumonia, *e.g.* methicillin-resistant *Staphylococcus aureus* (MRSA) and several Gram-negative bacteria (*e.g.* multidrug-resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*), particularly in elderly patients living in long-term care facilities. However, data from European studies generally suggest a low frequency of multidrug-resistant organisms (< 10%) in patients from the community with pneumonia. Viral and mixed viral–bacterial infections are reported in about 10–20% of CAP cases.

Gram-negative pathogens are the main cause of HAP. *P. aeruginosa*, *Acinetobacter baumannii*, microorganisms belonging to the family *Enterobacteriaceae* (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *etc*.) and, under certain conditions, microorganisms such as *Haemophilus influenzae*, are involved in HAP aetiology. Among Gram-positive pathogens, *S. aureus*, *Streptococcus* spp. and *S. pneumoniae* are the most common agents, accounting for 35–39% of all cases. Nonbacterial pathogens such as *Aspergillus* spp. and viruses (cytomegalovirus) have been described. There are significant geographical differences in the rates of antibiotic resistance between European areas and even within countries, from one hospital to another.
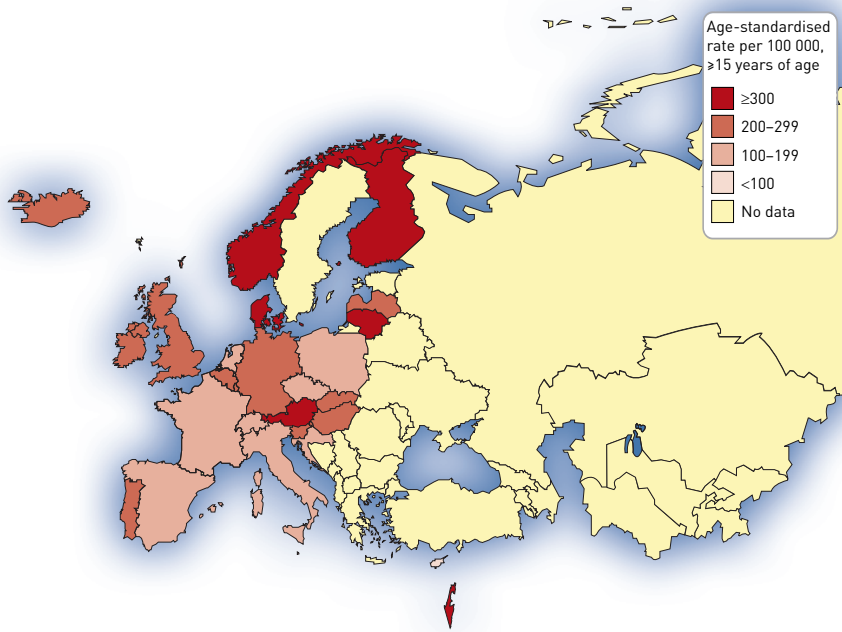
Figure 3 – Hospital admission rate for pneumonia in adults. Data from the World Health Organization Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

In neutropenic patients, Gram-negative bacteria are the main pathogens, being responsible for about 70% of cases; fungal and mixed infections are involved in about 10% and 10–15% of cases, respectively.

HIV infection impairs humoral immunity by causing quantitative and functional defects in CD4+ lymphocytes, leading to an increased risk of bacterial infections, with *S. pneumoniae* and *H. influenzae* being the most frequent pathogens. The incidence of fungal infections, mainly caused by *Pneumocystis jiroveci*, increases when the patient's CD4+ count is below 200 cells·mL^{-1}.

In the past decade, outbreaks of new infectious agents have been reported. One of these outbreaks was caused by the severe acute respiratory syndrome (SARS)-coronavirus (CoV), a pathogenic coronavirus that emerged from a zoonotic reservoir and was associated with severe respiratory syndromes with a high mortality rate. The prompt global response to this outbreak, which stopped the spread of the disease, demonstrated the importance of intensive international collaborative efforts as well as timely and thorough investigations.

Clinical manifestations and consequences

Pneumonia is defined as an acute illness with cough and at least one of the following: new focal chest signs; fever of more than 4 days' duration or dyspnoea/tachypnoea, without other obvious cause; and radiographic evidence of lung shadowing that is likely to be new. Sepsis and cardiovascular complications are the main cause of early treatment failure, *i.e.* in the first 3 days after admission. Early and appropriate antibiotic treatment is associated with a better outcome.

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Figure 4 – Frequency of isolation of causative organisms of community-acquired pneumonia in selected European countries. *S. pneumoniae*: *Staphylococcus pneumoniae*; *H. influenzae*: *Haemophilus influenzae*; *M. pneumoniae*: *Mycoplasma pneumoniae C. burnettii*: *Coxiella burnetii*. Data from WELTE *et al.*, 2010.

The dramatic shortage of new antibiotics, together with the increasing number of resistant bacteria, is a threat to the global population

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a)
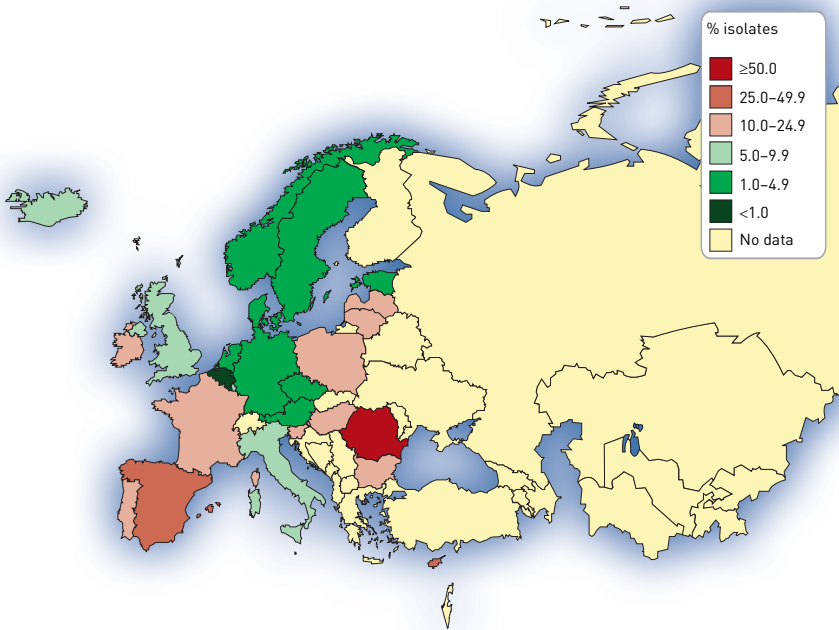
b)

Figure 5 – Percentage of *Streptococcus pneumoniae* isolates resistant to a) penicillin and b) macrolides. Data from European Centre for Disease Prevention and Control, 2011 data (accessed January 2013).

Management

Antibiotics are the treatment of choice for pneumonia, both in the outpatient and hospital setting. The ERS/ESCMID guidelines indicate different antibiotic approaches according to setting, risk factors and severity. The appropriate use of antibiotics is a vitally important intervention in the effort to reduce antibiotic resistance rates.

Prognosis

Age-standardised mortality rates for pneumonia are shown in figure 6. The risk of death from pneumonia increases with age. A Finnish study showed a six-fold increase in incidence between the ages of 30–44 years and 75 years or older. In Portugal, case fatality rates were 4.5% for patients aged 18–50 years, 19.4% for those aged more than 50 years and 24.8% for those aged more than 75 years. A UK study reported case-fatality rates of 5.6% in those aged less than 65 years and 47.2% for those aged more than 85 years. The study also found a 12-fold greater likelihood of death within 30 days of hospital admission for adults aged more than 85 years compared with those aged less than 65 years.
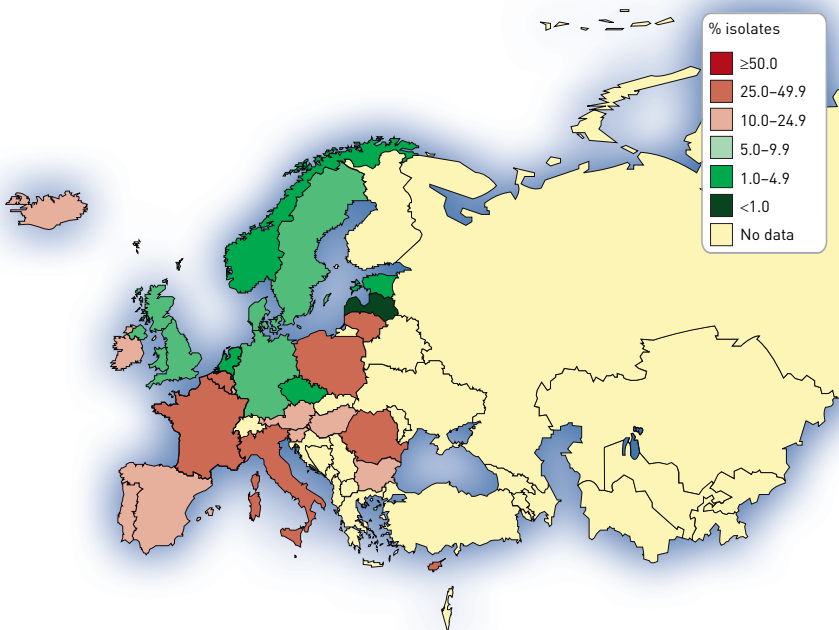
Over the past century, human life expectancy has increased dramatically in developed countries. In 2004, the EU had approximately 455 million inhabitants, of whom one-sixth were over 65 years of age (Eurostat 2004). If current trends in fertility, mortality and migration rates continue, the population is expected to peak in 2023, at which time one-third of the population will be over 65 years old. Clearly, the burden of pneumonia will be even more important in the years to come.

Variables associated with pneumonia mortality
Over 65 years of age
Female sex
Use of oral corticosteroids
Pneumonia due to more than one organism
Pleural effusion
Intensive care unit admission
Atypical pneumonia
Hospital-acquired pneumonia
Recent hospitalisation
Serious underlying disease
Acute renal failure
Bacteraemic pneumonia
Ineffective initial therapy
Multilobar involvement
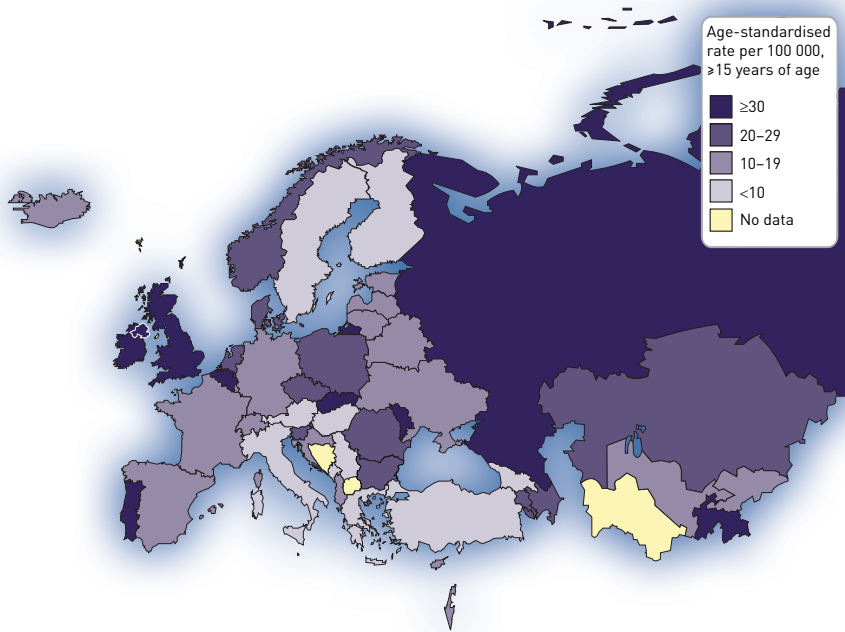Impaired alertness
Septic shock

Figure 6 – Mortality rate for pneumonia in adults. Data from the World Health Organization World and Europe Mortality Databases, November 2011 update.

The risk of pneumonia-related mortality increases three-fold if pneumonia is due to *S. pneumoniae*, with a mortality rate ranging from 6.4% to more than 40% in the different settings of out-, in- and intensive care unit patients. Mortality does not seem to be related to antibiotic resistance. Pneumococcal pneumonia is accompanied by bacteraemia (bacteria detectable in the blood) in 10–30% of cases.

Patients with pneumonia who survive hospitalisation may still experience adverse outcomes after discharge, including readmission and death due to a relapse of pneumonia or other causes. Early readmission rates range 8–46%, with readmission particularly occurring in patients who show signs of instability at discharge and contributing considerably to medical resource use and costs. In patients with pneumonia, the mortality rate within 90 days after discharge can be as high as 14%; even at 1 year, mortality is still considerably higher after hospitalisation with pneumonia than in the general population or in those hospitalised for other reasons. CAP is also associated with a significant increase in the risk of cardiovascular events and death from cardiac causes.

Intensive care unit admission criteria for pneumonia patients are highly variable between European countries, and the admission rate ranges 3–5% in Italy to more than 10% in Belgium.

Prevention

Population protection by immunisation against infection has been one of the major achievements of public health. The importance and role of influenza and *S. pneumoniae* immunisation are discussed in chapter 26. Currently, there is no immunisation available for RSV, although a number of vaccines have been tested and/or are currently under consideration.

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Future developments

There is a need to develop new or more effective immunisations against respiratory bacteria and viruses, particularly for the prevention of RSV and pneumococcal infections.

Only a few new families of antibiotics are in the pipeline for bacterial respiratory infections. The dramatic shortage of new antibiotics, together with the increasing number of antibiotic-resistant bacteria, is a worrying threat to the global population and a critical challenge for healthcare institutions. New therapeutic strategies, such as monoclonal antibodies acting against different strains of multidrug-resistant bacteria, must be developed.

The future of microbiology will determine many of the advances in respiratory medicine. For example, molecular bacteriology is being revolutionised by the next generation of sequencing methodologies; molecular virology should follow.

Areas of focus in the future should be the development of mechanisms for boosting host defence and innate immunity so that antivirals and antibacterials will be less necessary.

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Lung cancer

Introduction

Key points

- Lung cancer is the biggest cancer killer in Europe, accounting for approximately 20% of all cancer deaths and for the loss of 3.2 million disability-adjusted life-years annually in Europe.
- More than a quarter of lung cancer cases occur among the under-60s.
- Despite recent advances in surgery, chemotherapy and radiotherapy, seven out of eight patients die within 5 years of diagnosis. However, recent advances in understanding the biology of lung cancer are resulting in promising new targeted therapies.
- Smoking is by far the most important cause of lung cancer, accounting for 90% of cases in men and 80% in women. Reducing smoking and therefore eventually reducing the incidence of lung cancer requires sustained government action.

Lung cancer was a rare disease at the start of the 20th century, but exposure to new causative agents and an increasing lifespan have contributed to make lung cancer a pandemic of the 20th and 21st centuries. Lung cancer is the biggest cancer killer in Europe, accounting for approximately 20% of total cancer deaths. It remains the leading cause of cancer deaths worldwide, with 1.38 million deaths in 2008 (376 000 in Europe alone). Even though an extensive list of risk factors has been well characterised, and lifestyle changes have occurred regarding tobacco consumption, particularly in men in western Europe, lung cancer remains a huge health problem. The relevant International Classification of Disease (ICD) codes (used to code and classify mortality data from death certificates) are ICD-10 C33 (neoplasm of the trachea) and ICD-10 C34 (neoplasm of bronchus and lung).

Unfortunately, lung cancer usually becomes manifest late in its natural history, so that curative treatment is not possible in up to 90% of cases. In Europe, the overall 5-year survival for men with lung cancer is only 11.2% and for women it is 13.9%. Research has aimed to identify patients with early-stage disease in the hope of improving survival and developing individualised therapies for patients with advanced disease. Prolonging survival and improving quality of life for patients presenting with inoperable lung cancer are also subjects of current research.

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" *It is now recognised that patients with different subtypes of cancer respond differently to treatment, and it is possible to tailor treatment according to the tumour subtype* "

Epidemiology

Incidence

The World Health Organization (WHO) and the Organisation for Economic Cooperation and Development (OECD) provide comprehensive data on the epidemiology of lung cancer in Europe and worldwide. In 2008, there were an estimated 1.6 million new cases worldwide, representing 12.7% of all new cancers. Men are more frequently affected worldwide (1.1 million *versus* 0.5 million cases in women), with higher rates in central–eastern and southern Europe, North America and eastern Asia. In some Western countries where the tobacco epidemic reached its peak by the middle of the 20th century (*e.g.* the UK, Finland, and the USA), lung cancer rates have been decreasing slowly in men and plateauing in women.

Lung cancer is the second most common malignancy following prostate cancer in men of OECD countries. Figure 1 shows lung cancer incidence across Europe for men and women combined; figure 2 illustrates the marked difference in incidence between the sexes. In men in the European Union (EU), the highest rates are seen in Hungary (109.5 cases per 100 000 males), Poland (104.5 per 100 000) and Estonia (91.5 per 100 000). In women, Denmark (49.5 cases per 100 000 females), Hungary (39.8 per 100 000) and the UK (38.7 per 100 000) have the highest rates. Among non-EU countries, the highest reported incidence is seen in Armenia (111.1 per 100 000) in men and in Iceland (48.0 per 100 000) in women (figure 2).

Even though lung cancer incidence in women is generally lower than that in men, worldwide, lung cancer is now the fourth most common cancer in women (513 000 cases in 2008, 8.5% of all cancers) and the second most common cause of death from cancer (427 000 deaths, 12.8% of total cancer deaths). It has been estimated that in the UK in 2008, the lifetime risk of developing lung cancer was one in 14 for men and one in 19 for women. The incidence of lung cancer also varies within countries: in the UK, it is higher in Scotland and northern England, reflecting the historically higher rates of smoking in these areas. In Europe, the 388 753 lung cancer cases in 2008 had the following age distribution at diagnosis: approximately 6% were below 50 years of age, 20% were 50–59 years of age, 29% were 60–69 years of age, and 44% were over 70 years of age.
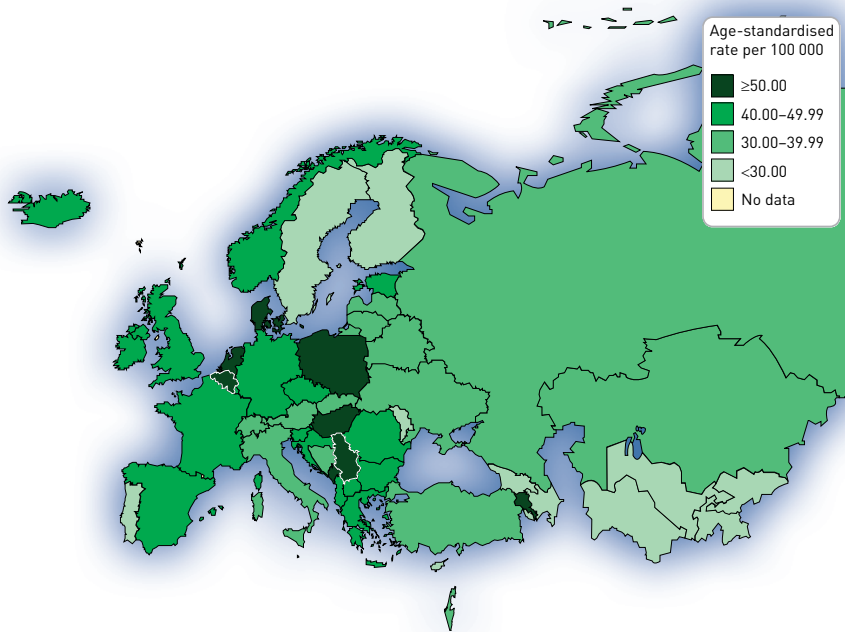
Figure 1 – Incidence rate of lung cancer. Data from FERLAY *et al*., GLOBOCAN 2008 v2.0, 2010.

Annual mortality

Figure 3 shows lung cancer mortality in Europe. Hungary showed the highest mortality rate of all European countries with an average of 65.9 deaths per 100 000 population, followed by Denmark with 52.3 deaths per 100 000 and Serbia with 51.3 deaths per 100 000. The lowest death rates in the EU were seen in Portugal and Cyprus (23.8 per 100 000). Lower mortality rates were reported in Tajikistan (6.5 per 100 000) and Uzbekistan (8.9 per 100 000); however, the efficiency of case reporting systems in those countries is unclear.

Morbidity from lung cancer

Most patients with lung cancer presenting to healthcare settings have symptoms or signs of the disease. However, these clinical features are nonspecific in their onset and are often attributed initially to benign causes by both patients and healthcare providers. This often results in a delay before patients seek medical attention and a further delay before the practitioner initiates any diagnostic tests.

The most common symptoms and signs are cough, weight loss and dyspnoea, followed by chest pain, haemoptysis, bone pain, finger clubbing and hoarseness. Less common are weakness, superior vena cava obstruction, dysphagia, wheezing and stridor.
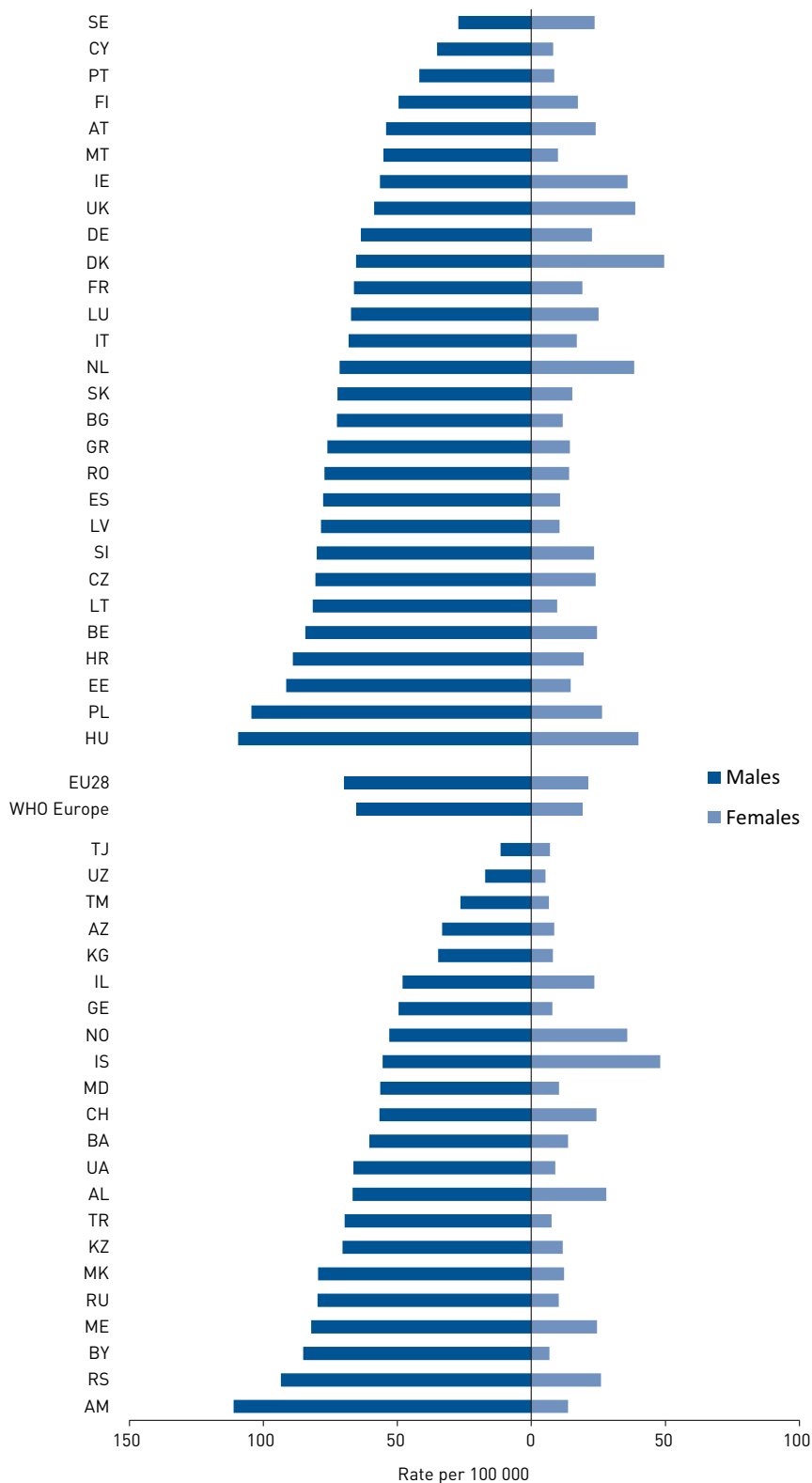
Figure 2 – Age-standardised incidence of lung cancer by sex, 2008. Data from Ferlay *et al*., GLOBOCAN 2008 v2.0, 2010.

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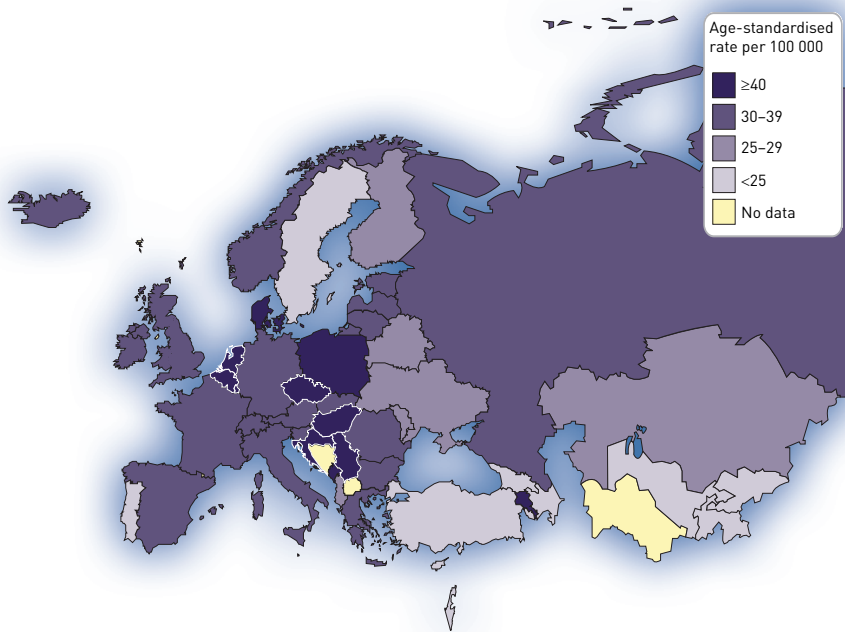
Figure 3 – Mortality rate for lung cancer. Data from the World Health Organization World and Europe Detailed Mortality Databases, November 2011 update.

A commonly used index of the burden of a disease is the loss of disability-adjusted life-years (DALYs). This is a term developed by the WHO and the World Bank to measure the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. Due to its high prevalence and mortality, lung cancer causes the highest losses of DALYs of all the cancers: in Europe, lung cancer accounts for approximately 3.2 million DALYs lost annually.

Causes

Table 1 summarises the risk factors for lung cancer. Smoking is by far the most important cause, accounting for 90% of cases in men and 80% in women. Tobacco smoke contains more than 7000 chemicals, at least 70 of which are known to cause cancer in humans or animals (see chapters 8 and 9). People who smoke are 15–30 times more likely to be diagnosed with lung cancer or die from it than those who do not smoke, and the risk increases with the quantity and duration of smoking. Chronic obstructive pulmonary disease (COPD) is also a risk factor for lung cancer and patients with airflow limitation are more likely to develop lung cancer than those with normal airway function, independent of smoking status. Asbestos exposure is another important risk factor,

Risk factors for lung cancer		
Smoking	COPD	Asbestos
Radon	Chromium	Arsenic
Beryllium	Diesel exhaust	Pulmonary fibrosis
Head/neck/oesophageal cancer	Genetic susceptibility	Lymphoma or breast cancer treated with thoracic radiotherapy
Family history of lung cancer	Air pollution	Coal smoke, indoor emissions from other fuels

Table 1 – Lung cancer risk factors. COPD: chronic obstructive pulmonary disease.

with lung cancer developing in 20–25% of heavily exposed asbestos workers (see chapters 7 and 24). Asbestos is particularly found in insulation, pipe lagging and brake pads. Exposure to radon, chromium, arsenic and beryllium are further risk factors, and recently, diesel exhaust was added to the list. Other factors that may predispose to lung cancer include pulmonary fibrosis and a medical history of cancer of the head and neck or oesophagus. Genetic susceptibility plays a contributory role in the development of lung cancer, especially in those who develop the disease at a younger age and those who are nonsmokers. A family history of lung cancer has been implicated in conferring a higher risk. Smokers who have previously had lymphoma or breast cancer treated with thoracic radiotherapy also appear to be at increased risk.

Prevention
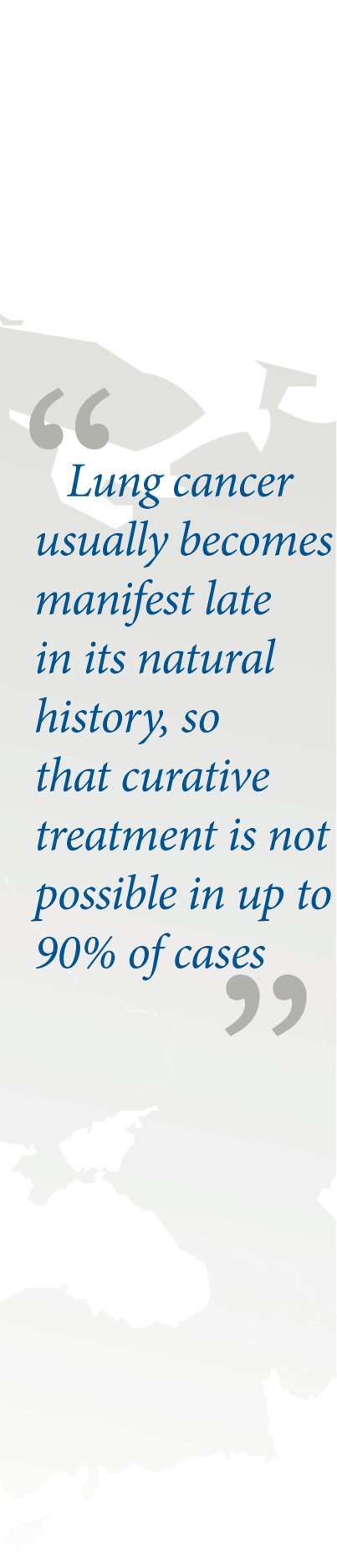
It is widely accepted that smoking is the leading cause of lung cancer and smoking cessation remains the most effective method of reducing its incidence. Although attempts to reduce smoking rates have been relatively successful in the Western world, there is a lag of 20 years or so between reducing smoking and reducing the incidence of lung cancer. Despite the recent reduction in smoking rates seen in some countries (particularly in men), further education on the harmful effects of smoking as well as smoking-cessation programmes are urgently required and efforts need to be intensified (see chapter 8). It is recognised that exposure to environmental tobacco smoke is also associated with lung cancer risk (see chapter 9). Therefore, uniform policies on the banning of smoking in public places are required and their implementation needs to be assured in all countries.

Asbestos is a known carcinogen and its combination with cigarette smoking confers a greater than 40 times increased risk of lung cancer. Despite this, a worldwide ban on asbestos use is not in force and is urgently required (see chapter 7).

Management

Treatment options are determined by the histological cell type, the stage of cancer at diagnosis, patient performance status and the patient's wishes. Socioeconomic

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deprivation, depression, comorbidities and late diagnosis all result in lung cancer being difficult to treat. Treatments include surgery, chemotherapy and radiotherapy.

Over the past 10 years, surgical techniques have trended towards minimal invasiveness. This offers comparable or sometimes better results in terms of patient outcome than the classical, more invasive procedures. Video-assisted thoracic surgery (VATS) is a form of keyhole surgery on the lung; its use in the management of patients with lung cancer was initially met with much scepticism. However, VATS-guided excisions and lobectomies have become established in the management of patients with early-stage lung cancer. VATS has an important role in patients with significant comorbidities and borderline pulmonary function, since recovery is usually quicker than after thoracotomy. Consequently, more patients with lung cancer are able to have operations. In addition, in order to improve the prognosis, adjuvant (post-operative) or neo-adjuvant (pre-operative) chemotherapy and/or radiotherapy may be useful (this is known as multimodal therapy).

Significant advances have also been made in chemotherapy. It is now recognised that patients with different subtypes of lung cancer respond differently to treatments and it is possible to tailor treatment according to the tumour subtype. For example, patients with advanced adenocarcinoma of the lung will benefit from pemetrexed plus platinum, while those with squamous cell carcinoma of the lung will benefit from gemcitabine plus platinum.

Recent advances in understanding the biology of lung cancer have resulted in newer targeted therapies, such as the tyrosine kinase inhibitors (erlotinib or gefitinib), which are known to be particularly beneficial in patients with advanced lung cancers that harbour a mutation in the epidermal growth factor receptor. Oral tyrosine kinase inhibitors are now licensed for the first-line treatment of patients with advanced lung cancer. In genetically selected patients with advanced lung cancer, these oral agents have been shown to be superior to conventional chemotherapy. In 2012, the European Medicines Agency approved the oral agent crizotinib for patients with advanced lung cancer and this may be preferred to standard chemotherapy when the lung cancer is shown to have an EML4-ALK fusion gene.

Radiotherapy techniques for lung cancer are also continuing to evolve. Modern radiotherapy employs techniques to spare surrounding tissues from the damage-enabling higher radiation doses applied to the cancer. The advent of

> *Lung cancer usually becomes manifest late in its natural history, so that curative treatment is not possible in up to 90% of cases*

stereotactic radiotherapy has allowed patients with poor lung function, who previously may not have received treatment, to receive radiotherapy.

Interventional bronchoscopic techniques are useful in the palliative care of patients with cancers that obstruct major airways.

Prognosis

Lung cancer survival rates are a measure of the proportion of people who remain alive with lung cancer after a certain amount of time. Survival rates for lung cancer vary depending on the subtype of cancer and at what stage the illness is diagnosed. The 1-year relative survival for lung cancer in the USA increased from 35% in 1975–1979 to 43% in 2003–2006, largely due to advances in surgical techniques and chemoradiotherapy. However, the prognosis also depends upon the histological type: for example, small cell lung cancer usually has a worse prognosis than nonsmall cell lung cancer.

The TNM (Tumour, Nodes, Metastases) system, which was updated for nonsmall cell lung cancer in 2010, is used by health professionals as a common way of staging cancer. In individual patients, the TNM system is used in decisions about treatment and prognosis. It is also used on a population basis to inform and assess treatment guidelines, cancer research and planning. The individual T, N and M scores are based, respectively, on the size and situation of the primary tumour (T1–T4), the extent of lymph node involvement (N0–N4), and recognition of the presence of metastases (M0 or M1). These scores are combined to give a stage (I–IV) for the cancer, with higher stages associated with shorter survival (table 2).

Treatment of lung cancer: current needs
- Lung cancer patients should be investigated and treated as outpatients whenever possible. This should reduce the financial burden of the disease and decrease the psychological impact of the disease on patients and families.
- Staging of lung cancer is critical to determine the prognosis and treatment options. Novel staging techniques (positron emission tomography (PET) scans, endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS)) should increasingly be made available in cancer centres as they will offer quick and accurate outpatient diagnosis and staging of the disease. Hospital admissions will be reduced and shorter time intervals from presentation until treatment decision will be achieved.
- Targeted therapy: advances in tailoring chemotherapy to the type of lung cancer must be matched by the availability of diagnostic services for lung cancer phenotyping and genotyping.
- The availability of lung-sparing radiotherapy techniques should increase in treatment centres throughout Europe. Intensity modulation radiation therapy (IMRT), gamma knife and image-guided radiation therapy are all high-precision modalities that allow tracking of respiratory movement during treatment, sparing of healthy lung tissue and reduced risk of radiation-induced lung toxicity.

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Stage	T	N	M	5-year survival %
Ia	T1a	N0	M0	50
	T1b	N0	M0	
Ib	T2a	N0	M0	43
IIa	T1a	N1	M0	36
	T1b	N1	M0	
	T2a	N1	M0	
	T2b	N0	M0	
IIb	T2b	N1	M0	25
	T3	N0	M0	
IIIa	T1	N2	M0	19
	T2	N2	M0	
	T3	N2	M0	
	T3	N1	M0	
	T4	N0	M0	
	T4	N1	M0	
IIIb	T4	N2	M0	7
	T1	N3	M0	
	T2	N3	M0	
	T3	N3	M0	
	T4	N3	M0	
IV	T Any	N Any	M1a or 1b	2

Table 2 – The new TNM (Tumour, Node, Metastases) classification in nonsmall cell lung cancer with corresponding 5-year survival rates per stage. Ta and Tb refer respectively to larger and smaller primary tumours and M1a and M1b respectively to intrathoracic and distant metastases. Modified from International Union against Cancer, 2010 and see also details in Detterbeck *et al.*, 2009.

The 5-year survival rate for patients with lung cancer of all stages combined remains poor, at only 12.6%. Figure 4 shows the age-adjusted 5-year relative survival, reported in 2008, of patients diagnosed in 2000–2002 in various European countries. Detailed comparisons between countries suggest that some differences (for example, the low survival rate in the UK) may be explained in part by presentation with more advanced disease due to poor population awareness and consequent late access to healthcare, but an effect of differences in diagnostic and therapeutic activity cannot be excluded.

Future developments

- A further reduction in smoking prevalence in all groups may be achieved by government campaigns with the longer-term goal of reducing lung cancer incidence.

The advent of low-dose helical computed tomography has revolutionised the landscape of lung cancer screening
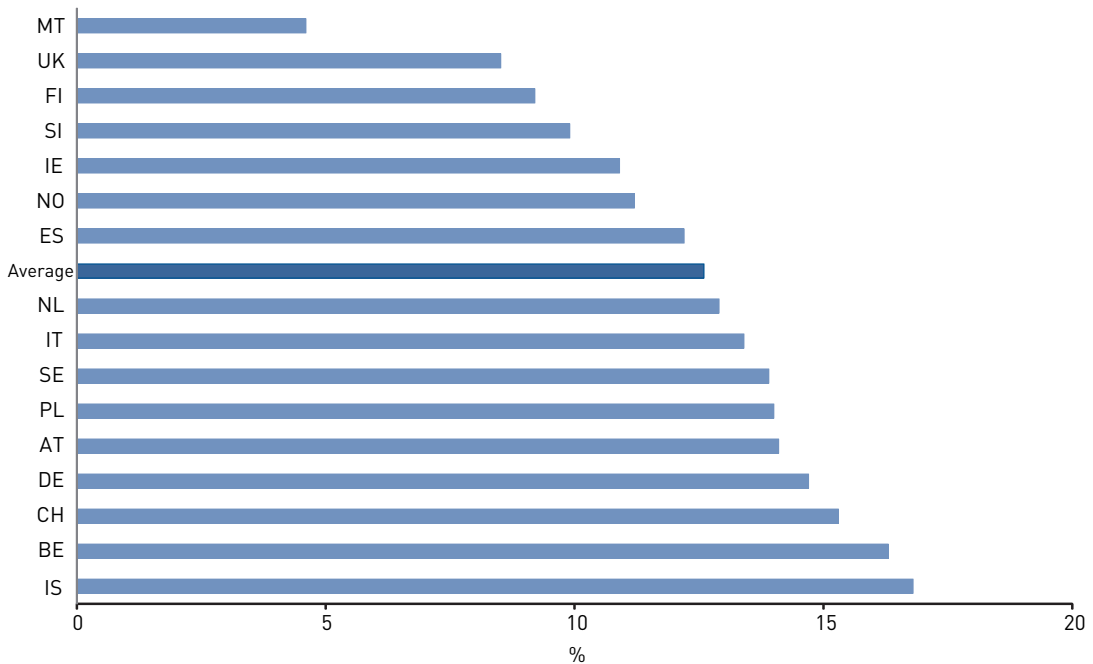
Figure 4 – Age-adjusted 5-year survival from lung cancer in selected European countries among patients diagnosed 2000–2002 relative to that of the general population. Survival for the UK has been derived from estimates for England, Scotland, Wales and Northern Ireland and the average independently calculated. Data from EUROCARE-4 study (www.eurocare.it).

However, this will require intensification and further funding of smoking-cessation programmes.

- Genetic profiling of lung cancer may become routinely available or be encompassed in clinical trials, and will enable therapy to be personalised using targeted agents according to the genetic profile of the tumour.
- Standardised and universal data collection for patients with lung cancer across Europe must be a priority.
- Positron emission tomography-computed tomography (PET-CT), endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) will play a prominent role in diagnosing and staging lung cancer.
- Lung-sparing radiotherapy techniques will become more widely available.
- The clinical effectiveness and cost-effectiveness of lung cancer screening with low-dose computed tomography (CT) will be clarified, as will patient selection.
- There will be a focus on quality of life of patients with advanced lung cancer as well as survival.
- Patients will have improved access to palliative care resources.

Research needs

In patients with advanced nonsmall cell lung cancer, drugs against newer molecular targets (*e.g.* Ros1) are currently being evaluated in early-phase clinical trials. It is a priority that these agents are then tested in later-phase trials so that any benefits discovered can be translated into better patient outcomes as soon as possible.

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Refining radiotherapy techniques also holds considerable promise, while there is ongoing work in the area of biomarkers for the early diagnosis of lung cancer. Novel staging tools (for example, newer PET ligands and magnetic resonance imaging (MRI)) may improve the accuracy of lung cancer staging, thereby leading to more appropriate treatment for patients.

Lung cancer screening is another promising research field. Since the majority of lung cancer patients present late in the natural history of the disease, the concept of screening high-risk asymptomatic people to detect early-stage (curable) disease is attractive. The advent of low-dose helical CT has revolutionised the landscape of lung cancer screening and has made this a possibility. In 2011, the National Lung Screening Trial (NLST) in the USA demonstrated that screening with the use of low-dose CT reduces mortality from lung cancer by 20%. The challenge is now to determine whether results from this trial can be reproduced in trials in Europe and whether the intervention is cost-effective. Currently, there is optimism about screening with low-dose CT scanning, with results awaited from ongoing lung cancer screening trials in western Europe (NELSON and the UK Lung Cancer Screening (UKLS) trial). Further research is required on identifying high-risk patient groups using phenotypic or genetic characteristics or biomarkers. Finally, studies of pre-malignant lesions may offer insight into cancer formation and provide targets for preventing the development of lung cancer.

There is a great need to establish well-organised and reliable lung cancer databases with a uniform design and standardised collection of (and ready access to) epidemiological data across Europe. This would allow trends to be identified, and prompt investigation at a public health level to clarify the reasons for differences in survival between countries. In addition, reporting of the disease and its impact on patients would be improved.

Lung cancer in never-smokers is of particular interest, and these patients comprise a growing proportion of adults with lung cancer in economically developed countries. It is important to identify epidemiological, clinical and molecular patterns of this disease and, in particular, the relevant risk factors. A uniform database of patients with lung cancer would be an important step forward in achieving these goals.

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Acute respiratory distress syndrome

Key points

- Acute respiratory distress syndrome is triggered by injury to the alveolar–capillary barrier from any of a variety of causes, resulting in fluid accumulation and acute respiratory failure.
- A significant proportion of all patients admitted to intensive care units are suffering from acute respiratory distress syndrome.
- The mortality of acute respiratory distress syndrome is high, at between one-quarter and one-half of patients.
- In the absence of effective pharmacological therapies, mechanical ventilation using small tidal volumes remains the keystone of acute respiratory distress syndrome management.

Acute respiratory distress syndrome (ARDS) is an acute severe lung disease commonly encountered in intensive care units (ICU). It can be caused by several triggers, including pneumonia or trauma. It is characterised by widespread injury of the alveolar–capillary membrane, resulting in protein-rich noncardiogenic pulmonary oedema (fluid accumulation in the lungs) and acute respiratory failure (ARF). ARDS results in severe hypoxaemia, which is refractory to oxygen treatment and requires assisted ventilation. It shares some of the features of infant respiratory distress syndrome (IRDS), which results from insufficient production of surfactant that normally lines the alveoli and reduces the surface tension of the alveolar lining fluid, preventing the collapse of the airspace. In contrast to ARDS, IRDS can be treated successfully using surfactant. ARF, a term sometimes used synonymously with ARDS, is far broader and comprises respiratory failure resulting from many other conditions: for example, chronic obstructive pulmonary disease (COPD). The term 'acute lung injury' (ALI) was previously used to characterise a milder form of ARDS, but it is no longer recommended for use.

Definition and diagnosis

ARDS was first described in 1967 in patients with refractory cyanosis due to respiratory failure that necessitated mechanical ventilation. However, the criteria for defining the syndrome were not generally

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> *Despite a variety of triggers, the resulting acute respiratory distress syndrome, in its later stages, shows a uniform clinical and pathological pattern*

agreed until the American–European Consensus Conference (AECC) in 1994. This definition specified an acute onset, refractory hypoxaemia and radiographic evidence of bilateral pulmonary shadowing due to increased permeability of the alveolar–capillary membrane, with the exclusion of left ventricular failure as the cause (table 1). A cardiogenic cause of pulmonary oedema was to be excluded by pulmonary artery catheterisation showing a pulmonary artery occlusion pressure (PAOP) of less than 18 mmHg or by clinical evidence of left atrial hypertension as a sign of left heart failure. The severity of the condition was defined by the ratio of the arterial oxygen tension ($P_{a}O_2$ measured in mmHg) to the inspiratory oxygen fraction ($F_{I}O_2$; where room air is 0.21 and pure oxygen is 1.0).

This definition was superseded by the Berlin definition of 2012, which refined the AECC criteria. The onset of ARDS is now fixed as being within 7 days of an insult or of new or worsening respiratory symptoms. While bilateral radiographic 'opacities' are still necessary, other causes, such as effusions, nodules, and partial or complete collapse of a lobe or lung should be excluded. The exclusion of cardiac failure or fluid overload is stressed but the methods of exclusion now emphasise echocardiography, which can replace pulmonary artery catheterisation, mirroring actual clinical practice. For a clearer definition, a minimum positive end-expiratory pressure (PEEP) has been introduced and the name ALI has been omitted and replaced by grading of ARDS as mild ($P_{a}O_2$/$F_{I}O_2$ of more than 200 mmHg but not more than 300 mmHg), moderate ($P_{a}O_2$/$F_{I}O_2$ of more than 100 mmHg but not more than 200 mmHg) or severe ($P_{a}O_2$/$F_{I}O_2$ of not more than 100 mmHg).

Pathogenesis

ARDS can be initiated by various distinct conditions that lead to a common pathophysiological pathway. The triggering events are grouped into two classes: direct 'pulmonary' and indirect 'extrapulmonary' conditions. The direct causes include various conditions that injure the lung parenchyma, including pneumonia, pulmonary contusion due to trauma, aspiration and inhalation, or ingestion of toxic agents (table 2). The most frequent indirect insult is sepsis syndrome (a common and highly lethal cause of ARDS), but this group also includes acute pancreatitis, overdose of certain drugs (opiates or thiazides), disseminated intravascular coagulation, and multiple blood product transfusions (hypertransfusion). Despite the variety of triggers, the resulting ARDS, in its later stages, shows a uniform clinical

AECC definition 1994	Berlin definition 2012
Acute onset	Onset within 1 week of a known clinical insult or new or worsening respiratory symptoms
Bilateral infiltrates observed on frontal chest radiograph	Bilateral opacities – not fully explained by effusions, lobar/lung collapse or nodules
PAOP less than 18 mmHg (if measured) or no clinical evidence of increased left atrial pressure	Respiratory failure not fully explained by cardiac failure or fluid overload. Objective assessment (*e.g.* echocardiography) required to exclude hydrostatic oedema if no risk factor present
ALI: $P_{a}O_2/F_{I}O_2$ <300 mmHg	All grades with a PEEP or CPAP of ≥5 cmH$_2$O
ARDS: $P_{a}O_2/F_{I}O_2$ <200 mmHg	Mild ARDS: 200 mmHg<$P_{a}O_2/F_{I}O_2$≤300 mmHg
	Moderate ARDS: 100 mmHg<$P_{a}O_2/F_{I}O_2$≤200 mmHg
	Severe ARDS: $P_{a}O_2/F_{I}O_2$≤100 mmHg
No risk factor included	If no risk factor present, need to objectively rule out hydrostatic oedema

Table 1 – Comparison of the American–European Consensus Conference (AECC) and Berlin definitions of acute respiratory distress syndrome (ARDS). PAOP: pulmonary artery occlusion pressure; ALI: acute lung injury; $P_{a}O_2$: arterial oxygen tension; $F_{I}O_2$: inspiratory oxygen fraction; PEEP: positive end-expiratory pressure; CPAP: continuous positive airway pressure.

and pathological pattern, even though the pathophysiological routes and mechanisms may differ depending on the event that injures the lungs.

The acute phase of ARDS is characterised by injury to the alveolar–capillary barrier, with disruption leading to increased permeability ('leakiness'). Leukocytes accumulate in the pulmonary capillaries and invade the airspaces. The consequences include inflammatory vasoconstriction (in contrast to inflammation-induced vasodilatation in the systemic circulation), reduced compliance (greater 'stiffness') of the lungs and atelectasis (collapse of alveoli rendering them airless) due to loss of the surfactant that lines and normally stabilises alveoli, reducing surface tension of the alveolar lining fluid. The consequent respiratory failure is aggravated by severe ventilation/perfusion mismatching, with some perfused alveoli no longer receiving any ventilation ('shunt'), while others are ventilated but not perfused ('dead space').

Histopathologically, three phases are recognised during the evolution of ARDS: 1) an exudative early phase which results from diffuse alveolar damage and endothelial injury; 2) a proliferative phase which ensues about 7–14 days after the injury, incorporating repair of the damaged alveolar structure and re-establishment of the barrier function, together with proliferation of fibroblasts; 3) a fibrotic phase with chronic inflammation and fibrosis of the alveoli, which follows in some patients.

Direct (pulmonary) injury	Indirect (extrapulmonary) injury
Pneumonia (bacterial, viral, fungal)	Severe sepsis
Gastric aspiration	Shock
(Near-) Drowning	Multiple transfusion (including TRALI)
Severe thoracic trauma/pulmonary contusion	Severe non-thoracic trauma
Reperfusion pulmonary oedema (*e.g.* after lung transplantation)	Pancreatitis
Fat embolism	Disseminated intravascular coagulation
Smoke and toxic gas inhalation	Drug overdose (*i.e.* opiates, paraldehyde)
Paraquat	

Table 2 – Main triggers of acute respiratory distress syndrome (ARDS). TRALI: transfusion-related acute lung injury.

Incidence and outcome

Reports of the incidence of ARDS in its different grades of severity vary, to some extent due to the lack of precision in the earlier AECC definition. Incidence estimates range 10–58 cases per 100 000 people, depending on geographical location and on the reporting system used. Using data from a prospective multicentre European cohort study that included 6522 patients treated in ICU, the proportion with ALI and ARDS averaged 7.1% of all patients admitted to critical care. This rose to 12.5% when only patients treated for more than 24 hours in ICU were included. Another study reported that patients with ALI represented 4.5% of all those receiving ventilation at the time of admission to intensive care.

In a recent database analysis from a single ICU treating both surgical and medical patients, a decrease in the prevalence of ARDS was reported: when comparing the periods January 1993–February 1996 and January 2006–April 2009, the authors found a prevalence of 2.5% in the first period and 1.7% in the second period. While the length of stay of survivors in the ICU decreased significantly in the second period, from an average of 17 to 13 days, no significant change in mortality was reported. The mortality rates of 52% and 46% in the first and second periods, respectively, are comparable to the actual mortality seen in routine clinical intensive care. However, studies from ARDSnet, an American network that focuses on ARDS, report a decreasing mortality rate over time. In a study reported in 2000, the network found a significantly lower mortality (31% compared with 39.8%) where a 'protective ventilation' (*i.e.* small tidal volume) approach was used compared with conventional mechanical ventilation. In more recent studies, mortality rates close to 20% have been reported. The latter results, however, probably represent the mortality rates of selected patients included in trials, whereas general surveys or databank analyses of mortality in unselected patients range between 27–45%, or even up to 70%, depending on the severity of disease and comorbidity. The most common cause of death is multi-organ failure, and this has not changed over time. The first 7–10 days seem to be the most relevant for determining the ultimate prognosis of ARDS patients. Within this timespan, about 50% of patients are either successfully weaned from the ventilator or have succumbed to the disease. Young patients with ARDS following trauma seem to fare best, with lung function recovering over 6–12 months. Mild abnormalities of respiratory function (obstructive or restrictive spirometric abnormalities or impaired diffusing capacity) may persist in a proportion

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of patients. Advanced age, pre-existing comorbidities, septic shock and additional organ failure appear to increase mortality.

Overall, the mortality of patients suffering from ARDS remains unacceptably high despite our extensive knowledge of the pathophysiology of the lung injury and the various multicentre studies of treatment reported to date.

Treatment options

Mechanical ventilation

Mechanical ventilation is a major component of the treatment of ARDS as it keeps the patient alive and ensures gas exchange despite compromised and injured lungs. Historically, the therapeutic goal was to achieve almost normal blood gas levels, even if this meant using very high tidal volumes during mechanical ventilation. However, mechanical ventilation itself also has the potential to injure the lungs, as implied by the term 'ventilator-induced lung injury'. The optimal strategy of ventilation is therefore under constant review. In a landmark study by ARDSnet, a strategy of 'protective ventilation' using a low tidal volume (6 mL per kg predicted bodyweight) compared with a traditional high tidal volume (12 mL per kg predicted bodyweight) was successful in significantly reducing mortality from 39.8% to 31%. However, since this trial was reported more than 10 years ago, no further change in ventilation strategy has been shown in a multicentre trial to result in lower mortality. Different strategies in the amount of PEEP applied have shown no clear-cut effects on survival. It remains to be determined whether strategies of ultra-protective ventilation (tidal volumes less than 6 mL per kg predicted bodyweight) or high-frequency oscillation ventilation (HFOV) may prove advantageous. This is important, as overdistension of the lung by excessive tidal volumes may be responsible for both inducing and perpetuating lung injury.

Fluid management

The optimal strategy for supplying fluids to the patient with ARDS remains a controversial management issue. Fluid restriction may benefit gas exchange by reducing alveolar oedema, but this must be weighed against the concept that more liberal fluid management improves cardiac output, protects renal function and increases the delivery of oxygen to vital organs. The ARDSnet studies reported a shorter period of ventilation and better oxygenation, but no increase in survival, using a complex algorithm that aimed simultaneously to protect renal function and to secure circulatory function, while employing a policy of restrictive fluid management.

> " *Within the first 7–10 days, about 50% of patients are either successfully weaned from the ventilator or have succumbed to the disease* "

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These goals may remain difficult to achieve, since, for example, in the early phase of the sepsis syndrome (which may lead to ARDS) a more liberal fluid strategy has proved successful in reducing mortality.

Pharmacological treatment

So far, no pharmacological therapy has been successful in improving the survival of patients with ARDS. Despite numerous strategies appearing to be successful in experimental studies and smaller trials, none has been shown to be successful in multicentre trials. Given the unacceptably high mortality and prevalence of ARDS among critically ill patients, there is an urgent need for a successful pharmacological treatment strategy.

The lung offers the unique possibility of treatment *via* both the vascular bed (intravascular injection) and *via* the airways (inhalational approach). Again, several apparently highly successful strategies in experimental studies and smaller clinical trials have not resulted in improved survival of real-world treated patients. Inhalation of gaseous nitric oxide, which was predicted to redirect the blood flow from injured to better ventilated areas of the lung, has been unsuccessful in general ARDS patients and remains only a last-resort option. Supplying surfactant, which, in healthy lungs, maintains the patency of the alveoli and which is destroyed by lung injury, is successful in IRDS but has not improved survival in adults. Despite these frustrating results, treatment of injured lungs *via* the airways remains a valuable potential approach in further research efforts.

Extracorporeal lung support strategies

The technique of extracorporeal membrane oxygenation (ECMO) allows complete artificial oxygenation of, and removal of carbon dioxide from, the blood by use of a membrane-oxygenator, a pump and two large-bore cannulae. The techniques have been refined in recent years and three different approaches now allow: 1) carbon dioxide removal driven by blood pressure without a pump (extracorporeal lung assist); 2) a step-up solution using the same technique with a pump; and 3) full ECMO. Experience from the most recent influenza epidemic demonstrated successful ECMO treatment of younger patients in specialised centres. The large CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory failure) trial for the first time showed a survival benefit when treating patients with severe ARDS in a specialised centre using ECMO compared with standard treatment. Due to inherent design limitations, however, the results of this trial have not been accepted unequivocally, but, at least in experienced centres, ECMO therapy may be considered as a valuable treatment option in severe cases. As to the other two above options for extracorporeal lung support, data showing their effectiveness are available but results from larger trials concerning survival, for example, are lacking.

Other supportive measures

Further supportive measures have been evaluated for the treatment of ARDS patients. One option is turning the patient on his stomach while he is being ventilated (prone position). This has attracted considerable interest but has not produced unequivocal results in large trials. It seems to be an option for severely ill patients when they are treated for prolonged periods. In experienced centres, it is a valuable option for maintaining oxygenation. Nutritional approaches have shown promising results in several studies but recent trials have not reproduced the favourable results.

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Future developments

As there are no effective pharmacological therapies available, the need for translational research in ARDS is obvious. Research strategies are necessary to understand and manipulate the molecular mechanisms that lead to loss of alveolar–capillary barrier function and oedema formation. Furthermore, newer aims include strategies to repair and regenerate the injured barrier, including new cell-therapeutic approaches. Controlling epigenetic mechanisms and new inhalational approaches, including advanced aerosol techniques and nano-particles, are also attractive prospects.

Clinical research should include strategies to improve the treatment of ARDS patients in relation to ventilatory techniques, extracorporeal devices, and supportive measures. However, such studies need to be carried out on a multicentre basis in order to have the necessary statistical power for adequate evaluation of survival benefit.

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Pulmonary vascular disease

Key points

- Pulmonary embolism is common, difficult to diagnose and potentially very serious, with a fatality rate of 7–11%.
- Several factors predisposing to pulmonary embolism are recognised and prophylactic treatment should be implemented more widely in those at risk.
- Pulmonary hypertension may result from any of a range of causes or may be idiopathic. Although pharmacological treatment has improved, some forms still have a very poor prognosis.
- Awareness of pulmonary hypertension needs to increase and its pathogenesis requires further research.

Pulmonary vascular diseases such as pulmonary embolism (PE) and pulmonary hypertension (PH) and their effects on right heart function contribute markedly to the global burden of chronic respiratory disease. The burden of pulmonary vascular diseases (figures 1 and 2) is certainly underestimated and merits greater attention from the medical community. Better characterisation and management of patients is needed in order to improve disease outcomes.

Pulmonary embolism

Introduction
PE is a common condition that results in the occlusion of the pulmonary arteries by thrombotic material originating from a deep vein thrombosis. It can cause acute life-threatening, but potentially reversible, right heart failure. Nonthrombotic PE (resulting from fat, tumour, amniotic fluid, air, *etc*.) will not be discussed in this chapter.

Epidemiology
European incidence estimates of PE range from 6–20 cases per 10 000 inhabitants per year.

Causes/pathogenesis
PE and deep vein thrombosis are each clinical presentations of venous thromboembolic disease and share the same predisposing factors. PE is usually a consequence of a thrombosis in the veins of the legs or pelvis. Predisposing factors include age, previous venous thromboembolic disease, active malignancy, neurological disease that impairs mobility, medical and surgical events causing prolonged bed rest (such as heart or acute respiratory failure), trauma

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> " *About 70% of patients with pulmonary embolism have a lower-limb deep vein thrombosis* "
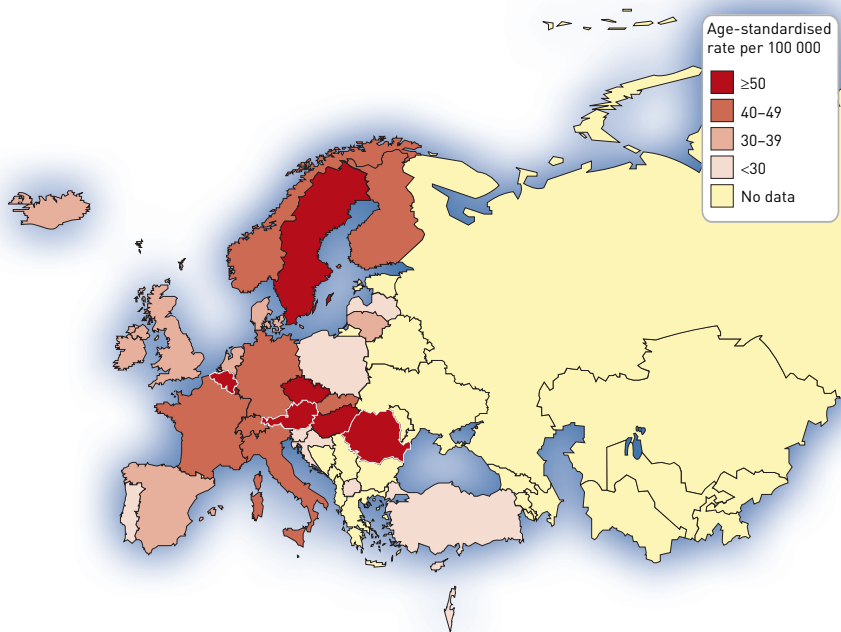
Figure 1 – Hospital admission rate for pulmonary vascular disease. Data from World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update.

and orthopaedic surgery, congenital or acquired thrombophilia, hormone replacement therapy and oral contraceptive therapy (table 1).

Clinical manifestations and consequences

PE is often difficult to diagnose, and may be missed because of its nonspecific presenting features. Patients may be asymptomatic or present with various signs and symptoms (breathlessness, chest pain, haemoptysis, cough, fever, tachycardia (rapid heart rate), tachypnoea (rapid breathing)). Syncope (fainting), hypotension and shock are signs of severity, indicating reduced haemodynamic reserve. Signs of deep vein thrombosis of the lower or upper limbs may be present.

Diagnosis

When considered in isolation, clinical signs, symptoms and routine tests, such as electrocardiograms, arterial blood gases and chest radiography, do not allow acute
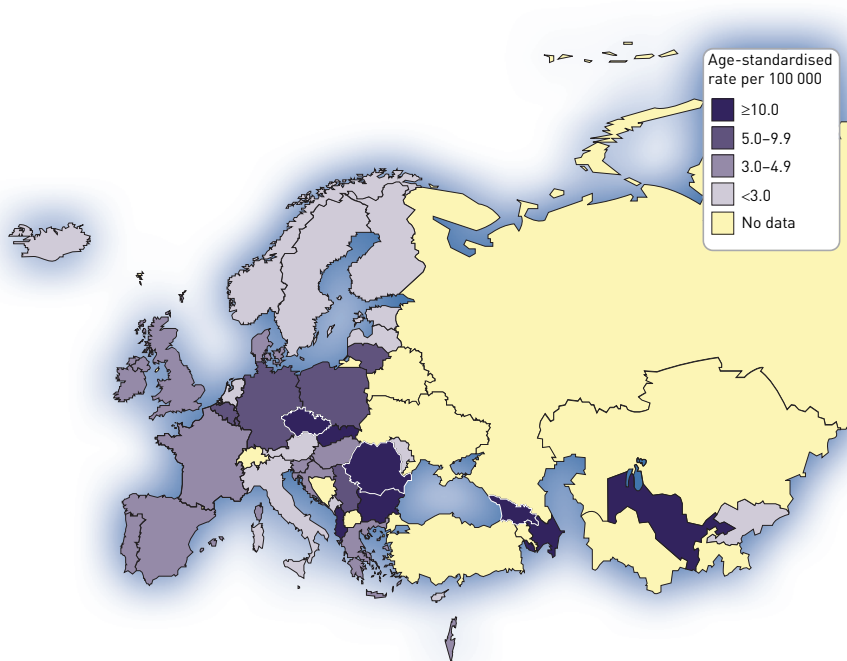
Figure 2 – Mortality rate for pulmonary vascular disease. Data from World Health Organization World and Europe Mortality Databases, November 2011 update.

PE to be definitively confirmed or excluded, although they do influence the index of suspicion. Despite the limited sensitivity and specificity of individual symptoms, signs and common tests, the combination of these variables, along with clinical judgement or use of a prediction rule, makes it possible to categorise patients with suspected PE in terms of increasing likelihood of PE. A low blood concentration of the fibrin degradation product D-dimer safely excludes PE in patients with a low or moderate clinical probability. Imaging of the proximal deep leg and pelvic veins by ultrasonography may identify a deep vein thrombosis (about 70% of patients with PE have a lower-limb deep vein thrombosis). A normal perfusion lung scan is reliable for excluding PE, while a high-probability ventilation/perfusion lung scan may confirm PE. The value of CT angiography for decision-making in suspected PE has been revolutionised by recent technological improvements and invasive pulmonary angiography is now rarely needed (figure 3). The performance of ventilation/perfusion scanning is poor when there is underlying chronic lung disease; CT angiography is superior in that context. In a patient with suspected PE who is in a critical condition (cardiogenic shock or hypotension), bedside echocardiography is particularly helpful in emergency management decisions (figure 4). In such patients, the absence of echocardiographic signs of right ventricular overload or dysfunction practically excludes PE as the cause of haemodynamic compromise.

Predisposing factor	Patient-related	Setting-related
Strong predisposing factors (risk increased >10-fold)		
Fracture (hip or leg)		✔
Hip or knee replacement		✔
Major general surgery		✔
Major trauma		✔
Spinal cord injury		✔
Moderate predisposing factors (risk increased 2–9-fold)		
Arthroscopic knee surgery		✔
Central venous lines		✔
Chemotherapy		✔
Chronic heart or respiratory failure	✔	
Hormone replacement therapy	✔	
Malignancy	✔	
Oral contraceptive therapy	✔	
Paralytic stroke	✔	
Pregnancy/postpartum		✔
Previous VTE	✔	
Thrombophilia	✔	
Weak predisposing factors (risk increased <2-fold)		
Bed rest >3 days		✔
Immobility due to sitting (*e.g.* prolonged car or air travel)		✔
Increasing age	✔	
Laparoscopic surgery (*e.g.* cholecystectomy)		✔
Obesity	✔	
Pregnancy/antepartum	✔	
Varicose veins	✔	

Table 1 – Predisposing factors for venous thromboembolism (VTE). Reproduced and modified from ANDERSON and SPENCER, 2003, with permission from the publisher.

Prevention

Antithrombotic prophylaxis with low-molecular weight heparin significantly reduces the risk of venous thromboembolic diseases in patients who are at risk. After an acute PE, long-term anticoagulation with anti-vitamin K drugs is necessary. The duration of treatment depends on the clinical circumstances and history of previous thromboembolic disease. In some patients at high risk of recurrent embolism it may be necessary to introduce an inferior vena cava filter.

Management

Initial management includes anticoagulation (unfractionated heparin, low molecular weight heparin or fondaparinux), which should be initiated without delay in patients with confirmed PE and in those with a high or intermediate clinical probability of PE, while

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> *It is still widely believed that pulmonary hypertension is a rare condition; this is true for pulmonary arterial hypertension but the global burden as a whole is currently unknown*

Suspected non-high-risk PE
i.e. without shock or hypotension

Assess clinical probability of PE
Implicit or prediction rule

Low/intermediate clinical probability or 'PE unlikely'

High clinical probability or 'PE likely'

D-dimer

Negative
No treatment

Positive
Multidetector CT

Multidetector CT

No PE
No treatment

PE
Treatment

No PE
No treatment
or investigate further

PE
Treatment

Figure 3 – Proposed diagnostic algorithm for patients with suspected non-high-risk pulmonary embolism (PE) (*i.e.* without shock or hypotension). CT: computed tomography. Reproduced and modified from Torbicki *et al.*, 2008, with permission from the publisher.

Suspected high-risk PE
i.e. with shock or hypotension

CT immediately available

No   Yes

Echocardiography
RV overload

No   Yes

CT available and
patient stablised

CT

No other tests available
or patient unstable

Positive

Negative

Search for other causes
Thrombolysis/embolectomy not justified

PE-specific treatment justified
Consider thrombolysis or embolectomy

Search for other causes
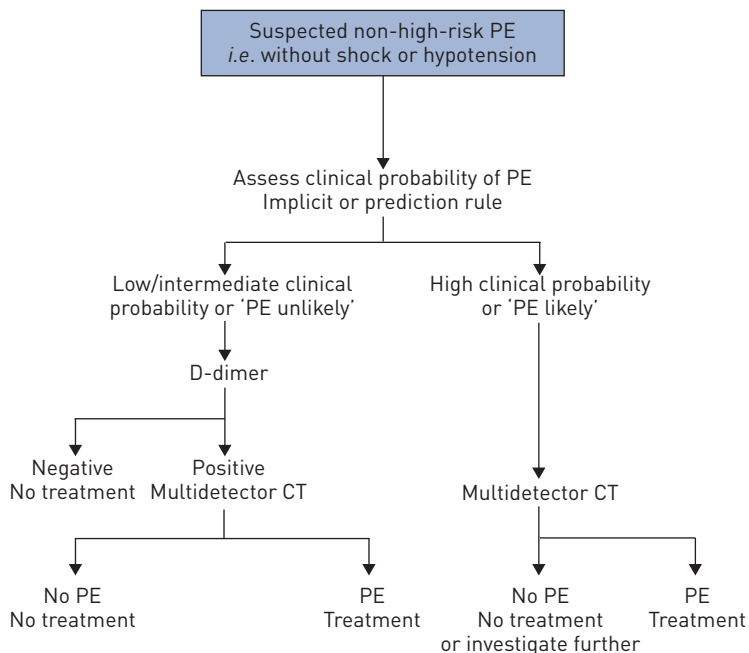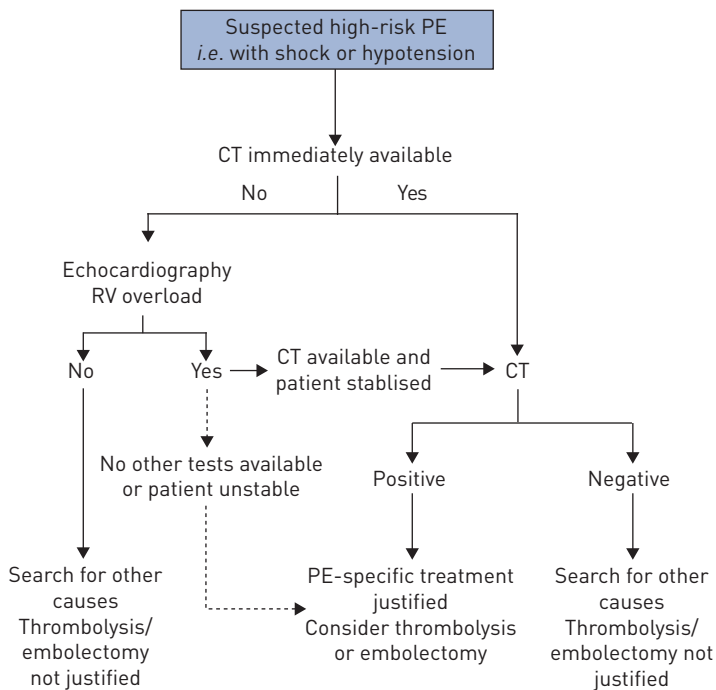Thrombolysis/embolectomy not justified

Figure 4 – Proposed diagnostic algorithm for patients with suspected high-risk pulmonary embolism (PE) (*i.e.* presenting with shock or hypotension). CT: computed tomography; RV: right ventricular. Reproduced and modified from Torbicki *et al.*, 2008, with permission from the publisher.

the results of the diagnostic tests are awaited. Supplementary oxygen should be given to hypoxaemic patients. Systemic hypotension or shock should be managed aggressively to prevent progression of right ventricular failure and death. Thrombolytic therapy is the first-line treatment in patients with high-risk PE presenting with cardiogenic shock and/or persistent hypotension. Surgical pulmonary embolectomy is a valuable therapeutic option in patients in whom thrombolysis is absolutely contraindicated or has failed.

Prognosis

The fatality rate of acute PE is 7–11%. Recurrent episodes are much more likely in individuals who have had a previous PE than after an initial deep vein thrombosis alone (about 60% after PE *versus* 20% after deep vein thrombosis). A small proportion (0.1–4%) of patients will develop chronic thromboembolic PH (CTEPH) after acute PE, even after subclinical PE.

Future developments

Oral anticoagulants that require neither laboratory monitoring nor dose adjustment are currently in development. Preventive methods should also be implemented more widely.

Research needs

Better diagnostic methods are still required and the optimal duration of anticoagulation therapy needs to be clarified. The mechanisms of CTEPH are poorly understood and should be identified.

Pulmonary hypertension

Introduction

PH is defined as an increase in mean pulmonary arterial pressure (mean PAP) to at least 25 mmHg at rest as assessed by right heart catheterisation. PH is categorised according to measurements of pulmonary capillary wedge pressure (PCWP) as pre-capillary (PCWP at or below 15 mmHg) or post-capillary (PCWP more than 15 mmHg). It is classified into five groups according to pathological, pathophysiological and therapeutic characteristics (table 2). The underlying mechanisms, diagnostic approaches, and prognostic and therapeutic implications are completely different in the different clinical groups.

Epidemiology

It is still widely believed that PH is a rare condition; this is true for pulmonary arterial hypertension (PAH) (group 1) but the global burden of PH as a whole is currently unknown. Worldwide, its two most common causes are PH complicating the course of left heart disease (group 2) and PH complicating the course of chronic respiratory disease and/or hypoxia (group 3). CTEPH (group 4) complicates the course of 0.1–4% of patients with acute PE. Better awareness of this complication may result in an increase in detected cases. The burden of PH is certainly underestimated, both in developing and developed countries, and further well-designed studies are essential if we are to better understand and manage the disease in populations exposed to various risk factors.

Approximately half of patients with group 1 PH (PAH) have an associated disease (connective tissue diseases such as systemic sclerosis, congenital heart disease,

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1   PAH

    1.1   Idiopathic PAH

    1.2   Heritable

        1.2.1   BMPR2

        1.2.2   ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)

        1.2.3   Unknown

    1.3   Drug- and toxin-induced

    1.4   Associated with (APAH)

        1.4.1   Connective tissue diseases

        1.4.2   HIV infection

        1.4.3   Portal hypertension

        1.4.4   Congenital heart disease

        1.4.5   Schistosomiasis

        1.4.6   Chronic haemolytic anaemia

    1.5   Persistent pulmonary hypertension of the newborn

1'   Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2   PH due to left heart diseases

    2.1   Systolic dysfunction

    2.2   Diastolic dysfunction

    2.3   Valvular disease

3   PH due to lung diseases and/or hypoxia

    3.1   Chronic obstructive pulmonary disease

    3.2   Interstitial lung disease

    3.3   Other pulmonary diseases with mixed restrictive and obstructive pattern

    3.4   Sleep-disordered breathing

    3.5   Alveolar hypoventilation disorders

    3.6   Chronic exposure to high altitude

    3.7   Developmental abnormalities

4   Chronic thromboembolic pulmonary hypertension

5   PH with unclear and/or multifactorial mechanisms

    5.1   Haematological disorders: myeloproliferative disorders, splenectomy

    5.2   Systemic disorders, sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis

    5.3   Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

    5.4   Others: tumoral bstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Table 2 – Clinical classification of pulmonary hypertension. PAH: pulmonary arterial hypertension; BMPR2: bone morphogenetic protein receptor, type II; ALK1: activin receptor-like kinase 1 gene; APAH: associated pulmonary arterial hypertension. Reproduced and modified from Simonneau *et al.*, 2009, with permission from the publisher.

portal hypertension and HIV infection), while the other half include idiopathic, heritable and appetite suppressant drug- (anorexigen-) induced PAH. The prevalence of PAH in Europe ranges between 1.5–5.2 cases per 100 000 people, with a predominance in women (female:male ratio 2:1). PAH can develop at any age (the mean age at diagnosis is 50 years). In some developing countries such as Brazil, prevalent diseases like schistosomiasis are associated with a high risk of PAH.

Causes/pathogenesis

PAH results from chronic remodelling of the small pulmonary arteries leading to progressive vascular obstruction. CTEPH results from obstruction of the pulmonary vascular bed by nonresolving thromboemboli. PH due to heart disease is a consequence of chronically elevated post-capillary pressure. PH due to chronic lung diseases and/or hypoxaemia is due to persistent hypoxic pulmonary vasoconstriction and remodelling as well as loss of lung vessels due to underlying pulmonary emphysema or fibrosis.

Clinical manifestations and consequences

PH causes breathlessness, fatigue, reduced exercise capacity, chest pain, haemoptysis and hoarseness (left recurrent laryngeal nerve palsy). In the modern management era, PH is still a progressive and fatal disease, which often presents with signs of right heart failure, such as lower limb oedema, ascites, hypotension, presyncope and syncope.

Diagnosis

PAH is notoriously difficult to recognise clinically. In the early stages of disease, patients are generally asymptomatic or mildly symptomatic. Indeed, initial symptoms are often rather unspectacular, and may lead patients, relatives and physicians to assume that they are simply unfit. Later, the symptoms are often attributed to a more common cardiorespiratory disease. As a result, there is commonly a substantial delay of 2 or more years before diagnosis and initiation of PAH treatment.

Clinical signs, symptoms and routine tests, such as electrocardiogram, arterial blood gases, chest radiography and pulmonary function, do not allow the physician to exclude or confirm PH. Doppler echocardiography is used to evaluate the right heart chambers and to estimate PAP. When PH is suspected, invasive right heart catheterisation is mandatory to confirm PH, define whether it is pre- or post-capillary and evaluate its severity.

Because of the progressive and nonspecific nature of PH symptoms, early PH detection is still a challenge. The implementation of screening programmes targeting high-risk patient groups should help to identify patients earlier. Recent screening programmes (based on Doppler echocardiography followed by right heart catheterisation if PH is suspected) have demonstrated that early diagnosis of PH is possible in patients with predisposing conditions, such as HIV infection, systemic sclerosis and sickle cell disease. Such screening programmes allow diagnosis of patients with markedly lower PAP, compared with those diagnosed in routine clinical practice. Similarly, after an acute episode of PE, persistent symptoms, as well as perfusion scan defects or elevation of PAP, may enable early detection of CTEPH.

Prevention

There is no known method of preventing PAH; however, in patients at risk, early diagnosis allows earlier treatment. Appropriate treatment of chronic heart disease

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may prevent the development of post-capillary PH. Chronic respiratory disease and hypoxaemia should be treated with long-term oxygen therapy or assisted ventilation in order to prevent PH. Treatment and follow-up of acute PE is recommended to limit the risk of CTEPH.

Management

Basic therapies include oral anticoagulation, diuretics and oxygen, if needed. PAH can be treated with drugs such as prostacyclin derivatives, endothelin receptor antagonists and type 5 phosphodiesterase inhibitors. Severe PAH is a well-recognised indication for lung transplantation. CTEPH can be cured with surgical pulmonary endarterectomy in eligible patients. PH due to chronic left heart disease and PH due to chronic lung disease and/or hypoxia should not be treated with PAH drugs. Treatment of the underlying heart or lung condition is recommended to prevent or treat PH complicating left heart or respiratory disease.

Prognosis

The natural history of PAH was described in the USA in the 1980s, when a cohort of patients with idiopathic/familial PAH were described and followed for up to 5 years. The study confirmed that PAH had a dismal prognosis, with a median survival of 2.8 years. Recent years have witnessed the approval of three classes of drugs for PAH and survival analyses have been performed in US and European registries. In a mixed cohort of incident and prevalent French PAH patients, 1-, 2-, and 3-year survival rates were 87%, 76%, and 67%, respectively. Better survival was observed in congenital heart disease when compared to idiopathic, familial and anorexigen-associated PAH or connective tissue diseases. In patients with idiopathic, familial and anorexigen-induced PAH, mortality is most closely associated with male sex, right ventricular haemodynamic function and exercise limitation. Thus, PAH remains a progressive, fatal disease even in the modern era of management. CTEPH can sometimes be cured by surgical pulmonary endarterectomy; however, in inoperable patients or if significant PH persists after surgery, the prognosis remains poor. PH due to chronic heart or lung disease usually reflects the severity of the underlying cardiopulmonary condition and this impacts adversely on the patient's prognosis.

Future developments

There is no cure for PAH and novel therapies are required. Prevention measures or early intervention in patients at risk of PH are needed.

"
Pulmonary arterial hypertension is notoriously difficult to recognise clinically
"

Research needs

A simple noninvasive PH diagnostic method is eagerly required. Better awareness of PH is essential for earlier diagnosis and management. The exact pathogenesis of PAH and CTEPH need further study in order for new preventative and/or curative tools to be developed for these severe conditions.

Further reading

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Interstitial lung diseases

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 unkown 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

Table 1 – Classification of interstitial lung diseases (ILDs). IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; CTDs: connective tissue diseases.
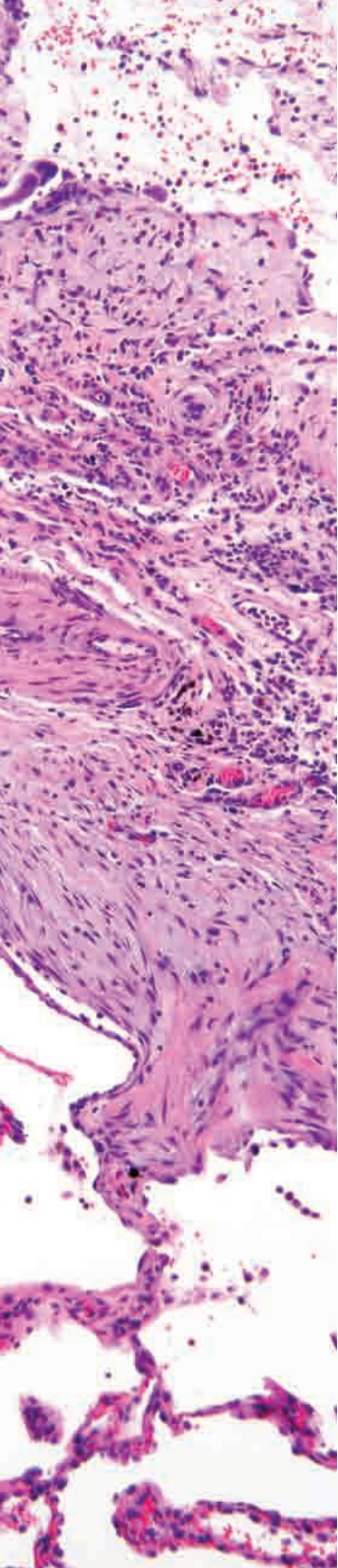
Comparative studies of frequency, incidence and prevalence

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

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	Flanders (Belgium) (1992–1996)		Germany (1995)	Italy (1997–1999)	Spain/RENIA (1998–2000)	Spain/SEPAR (2000–2001)	Greece (2004)	
	Prevalent cases	Incident cases	Incident cases	Prevalent cases	Incident cases	Incident cases	Prevalent cases	Incident cases
Subjects n	362	264	234	1138	744	511	967	254
Unknown aetiology								
Sarcoidosis	112 (31)	69 (26)	83 (35)	344 (30)	87 (12)	76 (15)	330 (34)	60 (23)
IPF/IIP	62 (17)	50 (19)	76 (32)	417 (37)	287 (39)	215 (42)	234 (24)	66 (25)
COP/BOOP	10 (2.3)	9 (3.4)	16 (6.8)	57 (5.0)	38 (5.1)	53 (10)	51 (5.3)	18 (7.0)
(C)EP	9 (2.2)	7 (2.7)		27 (2.3)			21 (2.2)	7 (2.7)
CTD	27 (7.5)	19 (7.2)	5 (2.1)		69 (9.3)	51 (19)	120 (12)	30 (12)
Vasculitis#	5 (1.4)	4 (1.5)	2 (0.8)	25 (2.2)			14 (1.5)	6 (2.3)
EG/HX	13 (3.6)	7 (2.7)		73 (7.2)	6 (0.8)	15 (3)	37 (3.8)	7 (2.7)
Exogenous aetiology								
EAA	47 (13)	32 (12)	25 (11)	50 (4.3)	38 (5.1)	34 (7)	25 (2.6)	7 (2.7)
Drug¶	12 (3.3)	12 (5)	6 (2.6)	21 (1.8)		21 (4)	17 (1.8)	4 (1.5)
Pneumoconiosis+	19 (5.0)	18 (6.8)	6 (2.6)		55 (7.4)		20 (2.0)	8 (3.1)
Variable aetiology								
Nonspecific fibrosis	33 (9.1)	27 (10)	12 (5.1)		69 (9.3)		82 (8.5)	40 (15)
Others	13 (3.8)	10 (3.8)		124 (11)	76 (10)	9 (2)	15 (1.5)	6 (2.3)

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; BOOP: 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.

	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,

> *More than 300 drugs are recognised as causing respiratory disease, particularly interstitial lung disease*

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.

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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.
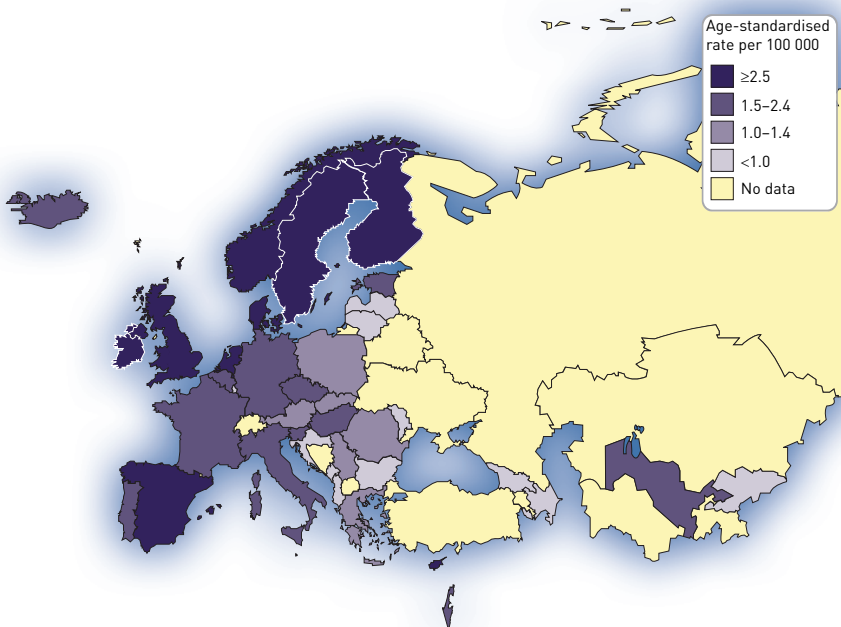

Figure 1 – Mortality rate of interstitial lung diseases. Data from the World Health Organization World and Europe Mortality Database, November 2011 update.

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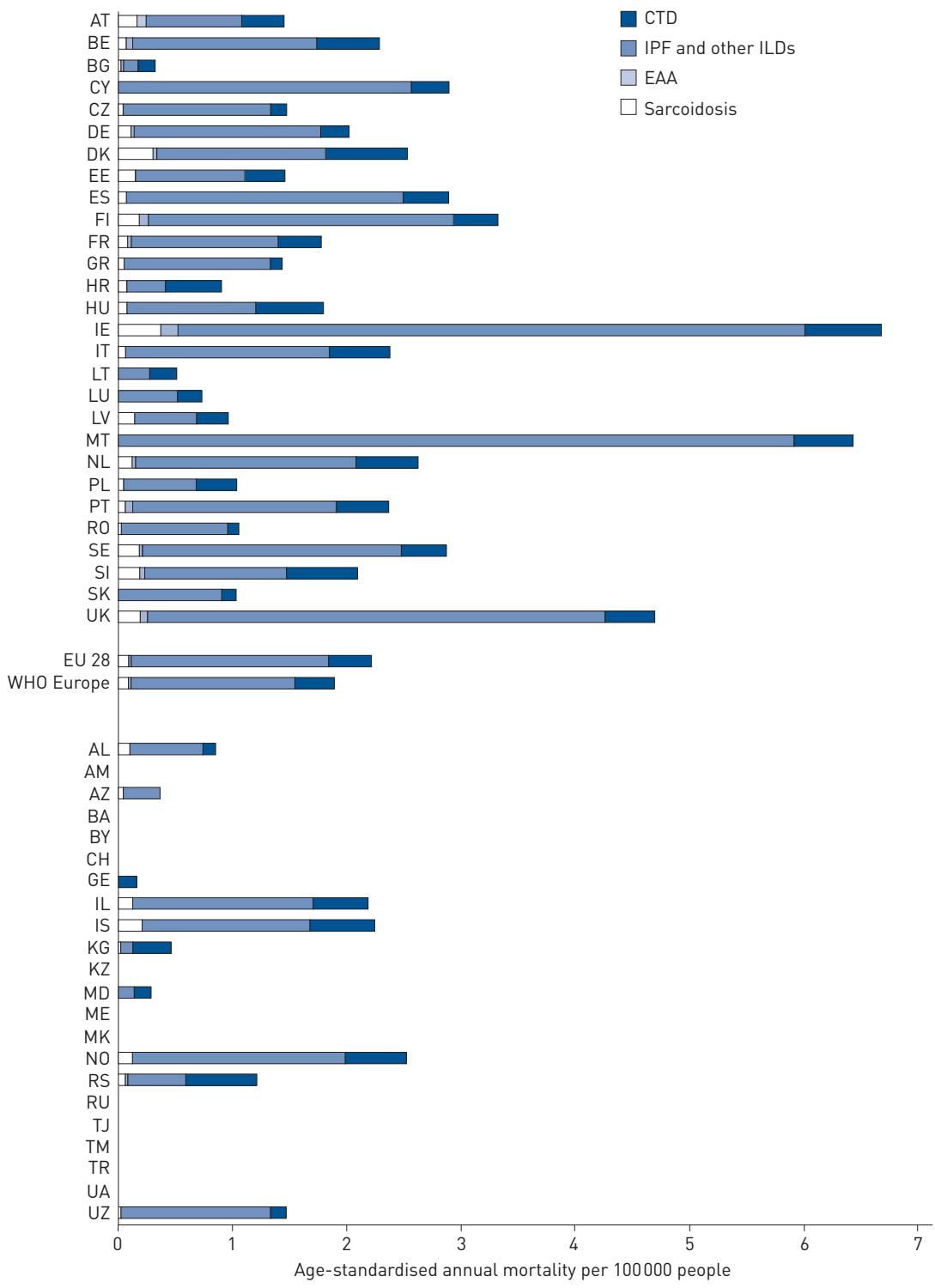MEDICINE IN EUROPE

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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.

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.

> *Powerful strategies are becoming available to increase the resolution of gene mapping even in complex diseases such as interstitial lung diseases*

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 unkown 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%.

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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
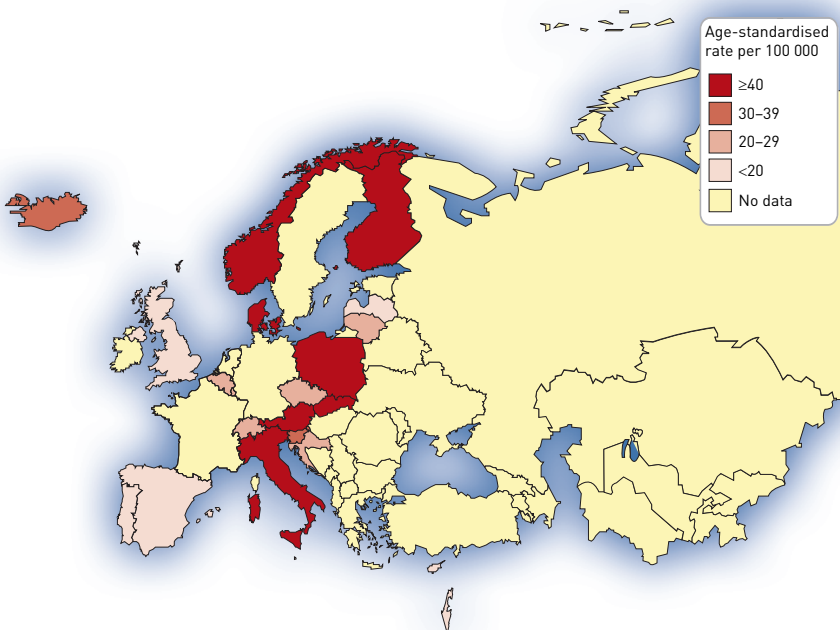

Figure 3 – Hospital admission rate of interstitial lung disease. Data from World Health Organization Hospital Morbidity Database, October 2011 update.

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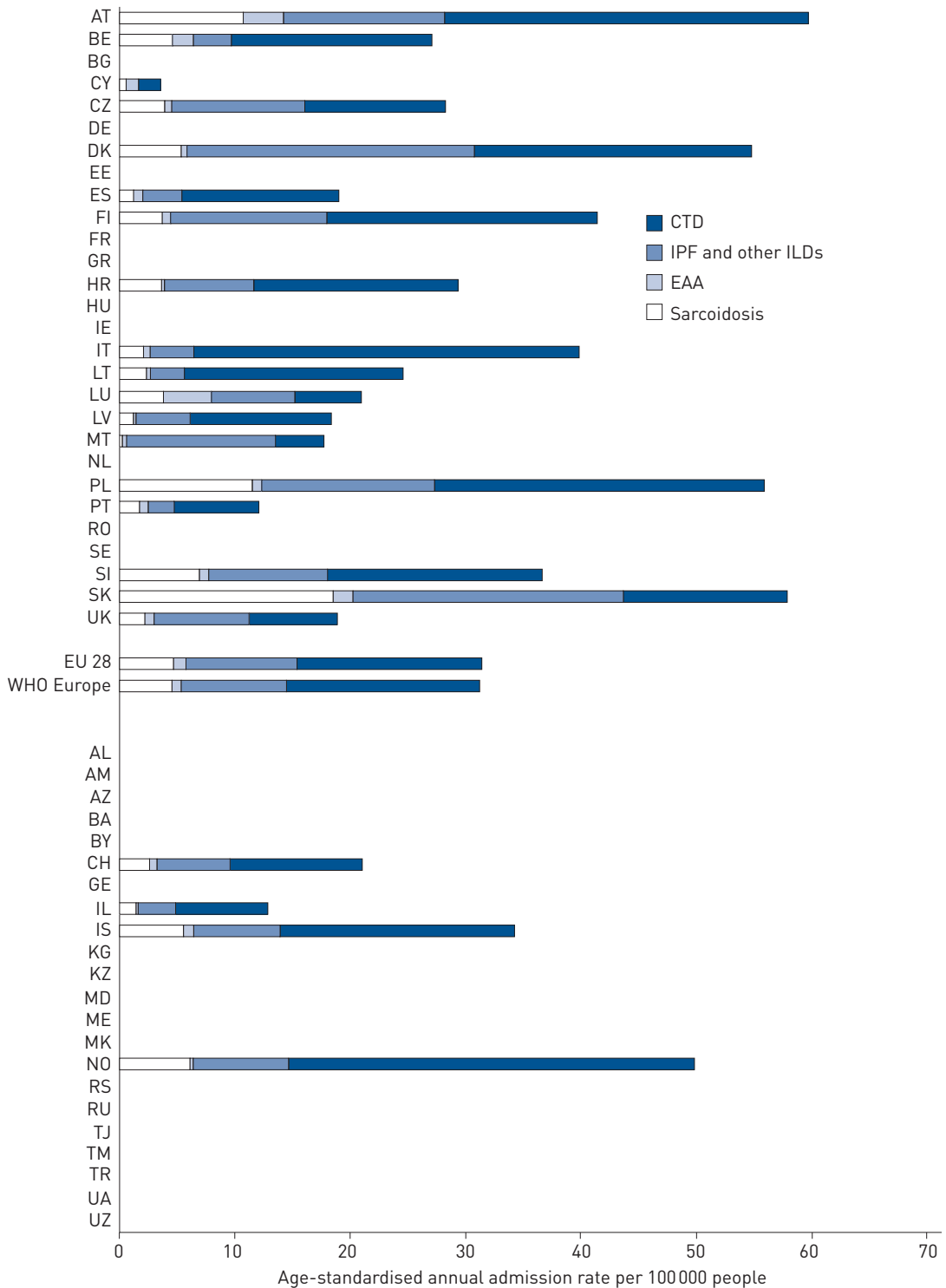MEDICINE IN EUROPE

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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.

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.

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Further reading

Reviews on classification, diagnosis and treatment of ILD

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Sleep breathing disorders

Key points

- Obstructive sleep apnoea syndrome (OSAS) is a major public health problem across Europe.
- Obesity is a major risk factor for OSAS but a significant minority of affected individuals are nonobese.
- The main treatment for OSAS is continuous positive airway pressure – a highly effective and economical intervention.
- Untreated OSAS greatly increases the risk of accidents due to sleepiness.
- Obesity hypoventilation syndrome is an increasing public health issue.

The term 'sleep disordered breathing' encompasses a range of conditions characterised by abnormal breathing during sleep; in many cases this is associated with narrowing or obstruction of the upper airway (pharynx). The disordered breathing ranges from intermittent, partial obstruction of the airway without sleep disturbance (snoring) to, at the other end of the spectrum, frequent apnoeas associated with repetitive hypoxaemia and arousals leading to sleep disruption and daytime sleepiness. The term 'obstructive sleep apnoea' (OSA) refers to intermittent obstruction of the airway, irrespective of the presence of daytime symptoms. If symptoms result, the condition is called obstructive sleep apnoea syndrome (OSAS), also known as obstructive sleep apnoea/hypopnoea syndrome (OSAHS).

Sleep disordered breathing also includes: 1) central sleep apnoea (CSA), in which periodic cessation of breathing occurs without obstruction of the airway and which, in adults, is seen mainly in heart failure; and 2) obesity hypoventilation syndrome (OHS) in which breathing is reduced throughout sleep, with or without accompanying narrowing or obstruction of the upper airway.

Sleep disordered breathing is very common in Europe but no statistics are collected routinely on the associated morbidity or mortality.

This chapter will focus primarily on OSAS, which is a major public health problem in most developed countries.

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> *In few other conditions is a simple treatment so effective and cost-efficient as continuous positive airway pressure in obstructive sleep apnoea syndrome*

Epidemiology

OSAS is common, underdiagnosed and eminently treatable. In developed countries, it is reported to affect between 3–7% of middle-aged men and 2–5% of women. It is diagnosed on the basis of symptoms (usually daytime sleepiness) plus objective evidence of disordered breathing during sleep. The condition is characterised by frequent obstruction of the upper airway during sleep, resulting in repetitive breathing pauses accompanied by oxygen desaturation (reduced oxygen in the blood) and arousal from sleep. The sleep disruption results in daytime sleepiness and, in the long term, it can lead to cognitive impairment and cardiovascular morbidity. The clinical presentation of, and diagnostic criteria for, sleep disordered breathing are different for adult and paediatric cases. The prevalence of OSAS is higher in certain groups, particularly in the obese, and in various medical conditions, for instance Down syndrome. Many epidemiological studies have focused simply on the prevalence of obstructive breathing pauses at night (OSA) without taking the daytime consequences into account. This has introduced a degree of confusion into the epidemiological literature and contributed to the fluidity of the terminology.

The definition of OSAS

OSAS is characterised by episodes of upper airway occlusion: these are termed apnoeas if the airway is completely occluded and hypopnoeas if the occlusion is partial. An obstructive apnoea is defined pragmatically as the cessation of airflow despite continued breathing efforts for at least 10 s. At their termination, apnoeas/hypopnoeas are often, but not always, associated with a change in the electroencephalographic (EEG) signal indicative of arousal and with a drop in blood oxygen saturation. In most instances, such brief arousals are not accompanied by complete awakening and the patient is usually unaware of them. The definition of hypopnoea is rather variable, depending on the type of equipment used to measure breathing, but the core of the definition, as adopted by the American Academy of Sleep Medicine (AASM), is a 30–50% reduction in thoraco-abdominal movement from the preceding stable baseline for at least 10 s. The current (2012) AASM guidelines add an accompanying 3% desaturation or an arousal. However, in some centres, older definitions of hypopnoea are still in use.

An AASM task force in 1999 defined the severity of OSAS on the basis of two separate components: daytime sleepiness and the degree of breathing disturbance measured by overnight monitoring. The commonly used method of assessing sleepiness is discussed further below. The severity of sleep-related obstructive breathing events is assessed using the apnoea/hypopnoea index (AHI) and is graded as mild (5–15 events per h of sleep), moderate (15–30 events per h of sleep) or severe (more than 30 events per h of sleep). Although a good general working classification, this does not take into account age- or sex-related variations. There are very few normative data on either sleepiness or AHI in the healthy population.

The pathophysiology of OSAS

The pharynx is the site of upper airway obstruction during sleep in OSAS. In general, any pathological change or normal variant that narrows the upper airway when awake will predispose the individual to obstructive apnoea or hypopnoea when asleep. Obesity is the single most common predisposing factor, but patients with OSAS may have other contributory factors that narrow the upper airway, such as a large tongue, enlarged tonsils, increased total soft tissue in the pharynx or a retropositioned mandible (receding jaw) (figure 1).

During inspiration, the air pressure in the pharynx is below atmospheric pressure, and the size of the pharyngeal lumen depends on the balance between the narrowing force that results from this suction pressure and the dilating force generated by the small muscles attached to the upper airway, which contract with each inspiration and normally stabilise the
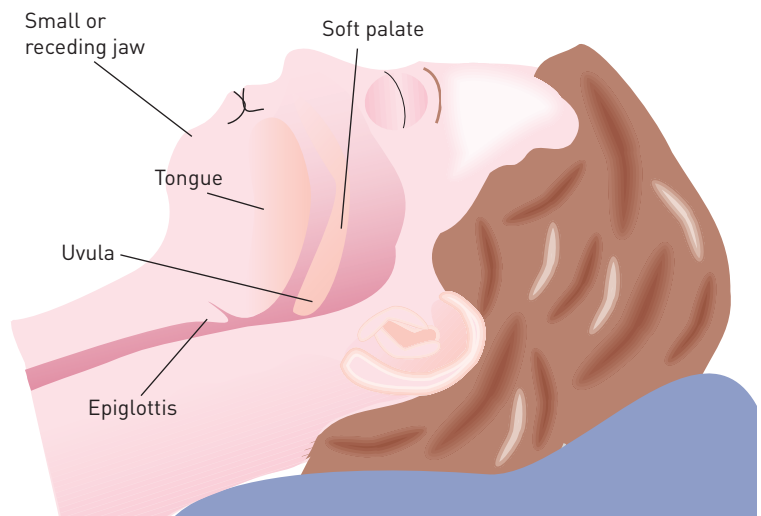

Figure 1 – Cross-section of the back of the pharyngeal area, showing the mechanism of obstruction of the upper airway (in red) during sleep.

floppy walls of the pharynx. At sleep onset, there is a reduction in pharyngeal luminal area and a reduction in upper airway muscle activity, both of which are exaggerated in OSAS. Surface mucosal factors may also influence airway patency, especially in subjects with mucosal inflammation from repetitive trauma and resultant loss of sensation.

Each apnoea or hypopnoea is terminated by an arousal, which is accompanied by a surge in heart rate and blood pressure. In many individuals, the increased blood pressure persists by day, with its attendant risk of developing cardiovascular disease and stroke.

Risk factors for OSAS

The prevalence of OSAS increases with age and reaches a plateau after 60 years of age. However, recent cross-sectional data on more than 5000 subjects have shown significant proportions of people ≥ 70 years of age continuing to present with symptomatic disease.

An association between obesity and OSAS has been noted in many studies, with moderate or severe obesity (body mass index (BMI) > 30 kg·m^{-2}) in 60–90% of patients with OSAS. Central obesity, characterised by a high waist-to-hip ratio or large neck circumference, correlates better with OSAS than BMI, even in people with a normal BMI.

OSAS is more common in men than women. This has been attributed to differences in anatomical and functional properties of the upper airway, differences in craniofacial morphology and fat deposition, and different ventilatory responses to arousal from sleep. However, health professionals need to be particularly alert to the possibility of OSAS in women, as male bed partners may be less aware of the symptoms of obstructive breathing during sleep. The disease prevalence is higher in post-menopausal women and hormone replacement therapy is associated with a lower prevalence; the prevalence of OSAS increases during pregnancy, particularly in the third trimester.

First-degree relatives of patients with OSAS have an increased risk of developing the disorder. The genetic determinants of craniofacial features, obesity and regional fat distribution are also relevant. Congenital conditions affecting craniofacial development, such as Marfan syndrome, Down syndrome and the Pierre Robin sequence, predispose to OSAS, as do acromegaly and hypothyroidism.

Smoking is associated with a higher prevalence of snoring and OSAS, and alcohol can increase upper airway collapsibility leading to apnoeas.

Muscle-relaxant medication (sedative hypnotic drugs, opiates), sleep deprivation and supine posture can all exacerbate OSAS, although the degree to which sleep disordered breathing is worsened in the individual may depend on the predominant pathological mechanism in the individual patient and his or her intrinsic physiological responses.

Reduced nasal patency, due to congestion or anatomical defects, as well as respiratory allergy are also potential contributors.

Clinical manifestations and consequences

The symptoms of OSAS can be classified as those manifesting during sleep and those present during wakefulness (table 1). The most common complaint is excessive daytime sleepiness (EDS). However, EDS is not present in all patients with OSA and

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During sleep	While awake
Loud snoring/snorting	Daytime sleepiness
Witnessed apnoeas by bed partner	Non-restorative sleep
Awakening with choking	Lack of concentration
Nocturnal restlessness	Cognitive deficits
Vivid, strange or threatening dreams	Changes in mood
Gastro-oesophageal reflux	Morning headaches
Insomnia with frequent awakenings	Dry mouth
Nocturia (urination at night)	Impotence or decreased libido
Hypersalivation, teeth grinding	
Diaphoresis (sweating)	

Table 1 – Symptoms of obstructive sleep apnoea syndrome. Adapted from RIHA, 2010, with permission from the publisher.

> *Obstructive sleep apnoea syndrome is common, under-diagnosed and eminently treatable*

consideration should be given to other causes of diurnal sleepiness, such as shift work, medication and alternative diagnoses – periodic limb movement disorder and narcolepsy, for example.

Nocturnal symptoms of OSAS are generally reported by a bed partner. The most common are snoring (which is almost always a feature), snorting, choking attacks terminating a snore, and witnessed apnoeas. Apnoeic episodes are reported by about 75% of bed partners.

A number of clinical features are associated with OSAS (table 2), but the predictive value of any single one for diagnosis is limited and not all will co-exist in the same patient. History and clinical examination alone (including blood pressure and BMI) can predict the presence of OSAS in only 50% of patients attending a sleep disorders clinic: definitive diagnosis requires overnight investigation.

Obesity (particularly central, BMI >30 kg·m^{-2})
Large neck circumference (>40 cm)
Small mandible, small maxilla
Retrognathia (back-set jaw)
Dental malocclusion, overbite
Reduced nasal patency
High and narrow hard palate
Elongated and low-lying uvula
Enlarged tonsils and adenoids
Macroglossia (large tongue)

Table 2 – Clinical features of obstructive sleep apnoea syndrome. BMI: body mass index. Adapted from RIHA, 2010, with permission from the publisher.

Recording and measuring sleep and breathing during the night

Previously, the most widely used method for the diagnosis of OSAS was detailed overnight polysomnography (PSG), but simpler diagnostic investigations are increasingly being used and these often take place in the patient's home rather than in hospital. PSG remains the gold standard by which most newer developments in the measurement of breathing during sleep are assessed. PSG simultaneously monitors:

- nasal and/or oral airflow
- thoraco-abdominal movement
- snoring
- electroencephalogram (EEG)
- electro-oculogram (EOG)
- electromyogram (EMG)
- oxygen saturation

Video recording of any abnormal movements may help identify other disorders. For accurate interpretation, manual scoring of the PSG recording is necessary, using guidelines for the interpretation of the EEG (sleep trace) and for the scoring of respiratory and other events.

Simplified recording systems are increasingly used (respiratory PSG or polygraphy). These measure airflow, respiratory effort, oxygen saturation and heart rate, but not EEG. Their advantages are greater capacity of service, lower cost and better portability and convenience to patients, who can set up the equipment in their own homes. Overnight oximetry is sometimes used as a screening test for identifying patients with OSAS but there are significant limitations to using oximetry alone.

Assessing daytime sleepiness

Sleepiness is difficult to define objectively and a wide variety of behavioural, performance-related, electrophysiological and questionnaire-based tests have been used. The most widely used and best validated and pragmatic scale for assessing daytime sleepiness is the Epworth Sleepiness Scale (ESS). This asks the subject to grade the likelihood of falling asleep in each of eight everyday situations (each scored from 0 to 3). An ESS score of greater than 11 out of 24 generally indicates abnormal daytime sleepiness, irrespective of age. However, as with any subjective measurement, the ESS can be prone to misinterpretation by the patient and, of course, a high score may be due to causes other than OSAS.

Consequences

OSAS is an independent risk factor for hypertension and is associated with an increased risk of cardiovascular disease, abnormal glucose metabolism, depression and sleepiness-related accidents.

OSAS is not generally recognised as a specific cause of death and therefore is not routinely reported on death certificates. However, a number of databases are being created to document OSAS – in France and Denmark, for instance. The association with cardiovascular, cerebrovascular and metabolic disorders implies that OSAS contributes to increased morbidity and mortality in the general population.

Untreated OSAS increases the rate of road traffic accidents and work-related and domestic accidents. A recent meta-analysis has shown that most medical conditions

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confer an increased risk of a driving accident (between 1.2–2-fold compared to the healthy population). By contrast, OSAS was associated with a large increase in risk of a motor vehicle accident, with a relative risk of 3.7; this was second only to age and sex as a general risk factor.

Undiagnosed OSAS results in higher medical costs than those incurred by age-and sex-matched healthy individuals and the more severe the disease, the greater the medical cost. Even a single road accident due to sleepiness caused by OSAS can incur considerable health costs.

There has been no comprehensive evaluation of the financial burden of OSAS across Europe. However, reports from several countries have evaluated healthcare consumption, cost-effectiveness/utility of treatment and treatment costs. These are summarised in the further reading list. Table 3 illustrates the comparative cost-effectiveness of treating OSAS compared to 'doing nothing' across four different countries.

Prevention

As previously discussed in this chapter, a number of risk factors can predispose to, or exacerbate, OSAS. Targets for primary prevention are already integrated into many public health strategies, including campaigns focused on obesity, smoking and excessive alcohol consumption.

Prior to diagnosis, OSAS is associated with a large number of medical complaints and with annual healthcare costs per person of 50–100% more than those for the general population. In adults, these excess costs are attributable to cardiovascular disease, digestive problems and metabolic disease, while in children they are mainly due to ear, nose and throat (ENT) and respiratory conditions. Therefore, primary care physicians as well as physicians in a variety of specialties need to be aware of OSAS and sleep disordered breathing in order for the problem to be diagnosed and treated as promptly

	UK	Canada	Spain	Canada
Cost-effectiveness[#]	£1400	US$3354	€7861	>US$9792
AHI of patients events·h^{-1}	>30	>15	41.3±14.6	67.6±24.3
ESS of patients[¶]	12		13.8±5.8	

Table 3 – Cost-effectiveness studies for continuous positive airway pressure treatment of obstructive sleep apnoea syndrome. Parameters are given as mean values ± standard deviation. AHI: apnoea/hypopnoea index; ESS: Epworth Sleepiness Scale. [#]: cost per quality-adjusted life year; [¶]: out of 24. Reproduced and modified from MWENGE and RODENSTEIN (in MCNICHOLAS and BONSIGNORE, 2010).

as possible. Secondary prevention therefore includes screening patients with the above conditions for symptoms potentially related to OSAS.

Management

Once OSAS is diagnosed, its treatment is relatively straightforward. Lifestyle measures, such as weight loss, alcohol consumption and smoking should be addressed. However, the commonest and most rapidly effective treatment for moderate-to-severe OSAS is with nocturnal continuous positive airway pressure (CPAP) (figure 2). This is usually delivered through the upper airway using a mask over the nose, or the nose and mouth, attached by a hose to an air compressor that generates a flow of air at positive pressure throughout the breathing cycle, of sufficient magnitude to keep the upper airway open and prevent it from collapsing. CPAP thereby acts as a pneumatic splint for the upper airway. Unfortunately, CPAP does not permanently restore or correct the problems leading to upper airway obstruction; it therefore needs to be applied throughout each night for maximum effect. If well tolerated and used consistently, CPAP has been shown to reverse or ameliorate the somnolence, cognitive deficit, reduced health status, hypertension and metabolic disturbances associated with OSAS.

In snoring or mild OSAS, an alternative therapy may be used: the mandibular repositioning device (MRD) (figure 3). This device may also be useful in patients who cannot or will not tolerate or adhere to CPAP. Although less reliably effective than CPAP, MRDs can be used as adjuncts to CPAP therapy. They should always be constructed by a trained professional.

Other potential treatments include: tonsillectomy, where appropriate and especially in children; upper airway surgery in exceptional cases where significant craniofacial abnormalities are present; and bariatric surgery for those in whom severe obesity is the primary contributor to OSAS. Stimulation of the hypoglossal nerve through implanted

Figure 2 – Continuous positive airway pressure equipment. ©iStockphoto David Cannings-Bushell.

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Figure 3 – A mandibular advancement device. Reproduced from Tsuiki *et al.*, 2010.

electrodes is increasingly being trialled in patients with OSAS who fail to respond to more conventional modes of therapy, though this treatment remains very much under development. No effective pharmacological therapies are currently available.

As with other forms of long-term treatment, adherence requires application of the specific treatment by trained personnel and long-term follow-up.

In few other chronic medical conditions is a simple treatment so rapidly effective and cost-efficient as CPAP in OSAS.

Prognosis

Once recognised and treated appropriately, the available data suggest that the prognosis for OSAS is very good and reverts to that of the non-OSAS population, particularly in terms of cardiovascular mortality and morbidity. However, because patients with significant sleepiness need symptomatic treatment with CPAP, it is not ethically acceptable to undertake long-term randomised, placebo-controlled trials in the optimal population to determine its effect on cardiovascular morbidity and mortality; rather, the evidence has to be obtained more indirectly from case-controlled or cohort studies with all of their inherent biases.

Obesity hypoventilation syndrome

OHS is increasingly recognised as a significant public health issue, particularly in the context of the obesity epidemic that is occurring in many countries. However, its prevalence in Europe is unknown.

"*Waiting lists for assessment and treatment of obstructive sleep apnoea syndrome are a serious problem for both patients and medical staff – facilities need to expand*"
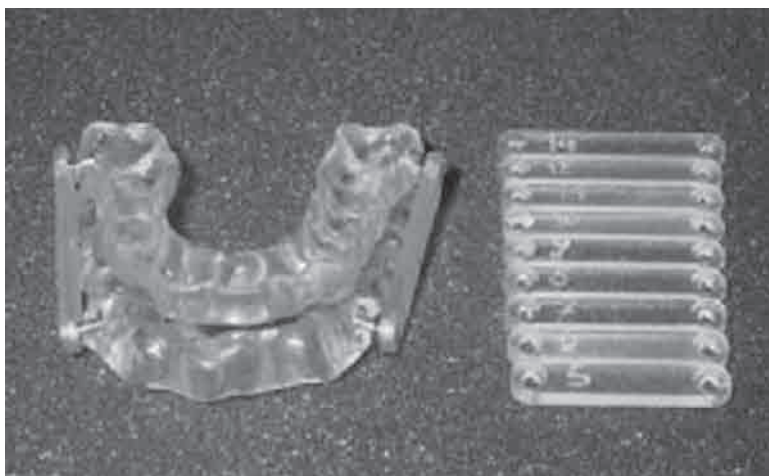
OHS is defined as the combination of obesity (BMI > 30 kg·m^{-2}), hypercapnic (type II) respiratory failure (arterial carbon dioxide partial pressure greater than 45 mmHg or 6.5 kPa) and sleep disordered breathing when all other causes of type II respiratory failure have been excluded. This is unlike uncomplicated OSAS, in which the awake arterial carbon dioxide level is normal. The pathophysiology of OHS is complex, resulting from the interaction between OSA, decreased ventilatory drive and reduced compliance of the chest and abdominal walls caused by obesity.

The problem is under-recognised, with the corollary that the severe respiratory and cardio-metabolic consequences are not being adequately treated, which increases health-related costs and the risk of hospitalisation and death. There are very few well-conducted trials in the area, but the best treatment in terms of reducing mortality is noninvasive ventilation (NIV), which, like CPAP, is delivered *via* a face mask. Unlike CPAP, which provides almost constant pressure throughout the respiratory cycle, NIV provides higher inspiratory pressures than expiratory pressures, in order to assist ventilation; frequently, additional oxygen is also required.

Weight loss is an effective treatment for OHS but is often difficult to achieve without additional intervention such as bariatric surgery.

The limited evidence available suggests that early recognition, intervention and treatment saves lives and limits complications and costs to both the patient and society, but that this is occurring in a minority of instances, both in primary and secondary care settings.

Future developments and research needs

There needs to be a continued effort to better define specific populations with OSAS and to learn which of these populations will respond most favourably to the various forms of treatment available.

Future developments should include devoting more resources to targeted prevention and raising awareness of OSAS. Individuals who are sleepy, who snore and, particularly, those who experience sleepiness while driving, should be encouraged to seek medical advice. Secondary prevention needs to be expanded by improved screening of those presenting with suggestive symptoms and those with associated cardio-metabolic comorbidities. And finally, tertiary prevention, *i.e.* the treatment of patients with OSAS, involves expanding facilities to provide timely investigation and treatment of the large number of patients currently undiagnosed or untreated. As the prevalence of OSAS within the community is considerable, and, in many countries, is being further exacerbated by the current obesity epidemic, the resources needed are large and require commitment by national governments.

National health and transport authorities need to recognise the common and potentially severe effects on driving (both privately and commercially) of sleepiness due to OSAS – a phenomenon that puts both the individual and the general public at risk. The problem needs to be formally recognised by appropriate legislation, which is sorely lacking in many European countries.

In most European countries, waiting lists for assessment and treatment of OSAS are a serious problem for both patients and medical staff – facilities need to be expanded. High-priority research needs in OSAS include the following:

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- Epidemiological studies of the prevalence of OSAS and OHS across Europe
- Assessment of the impact of OSAS and its severity on mortality, cardiovascular disease and type II diabetes mellitus.
- Analyses of the cost-effectiveness of various management strategies for OSAS patients according to disease severity, including long-term outcomes.
- Comparative cost–benefit analyses of different OSAS treatments (CPAP *versus* MRD *versus* surgery) stratified according to patient characteristics, disease characteristics and comorbidities, and including long-term outcomes, *e.g.* severe OSAS in patients with Down syndrome and elderly patients with mild disease.
- Investigation of: treatment adherence strategies for the various treatment modalities available; financial considerations in implementing treatment; and the role of specialised sleep services in the assessment and management of OSAS, *e.g.* should OSAS remain a secondary/tertiary care problem or be devolved into primary care with referral of only difficult cases?

A number of studies are in progress addressing OSAS in the ageing population and in children. It is important to recognise that some populations, such as the elderly, the very young, the intellectually disabled and those with particular morbidities, may have different treatment needs and responses to treatment.

Although not successful to date, the search for a pharmacological treatment for OSAS that can be used together with current treatment modalities for OSAS should be encouraged.

Further effort is needed to simplify diagnostic approaches while maintaining accuracy, including increasing the use of polygraphy and using new technologies, such as telemedicine, to diagnose and monitor patients. Since publication of the first edition of this book in 2003, these needs have not been adequately addressed and have not been met by the requisite public health and research funding. Funding should also be directed towards greater public awareness of the common risk factors for OSAS such as obesity and relevant craniofacial variants. Orthodontic treatments instituted in early life might come to play a more important role in prevention.

Longitudinal cohort studies of OSAS are few and should be instituted as the significance of this disorder in children and young adults is increasingly recognised.

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Occupational lung diseases

Introduction

Key points

- Systematic under-reporting and difficulties in attributing causation both contribute to underappreciation of the burden of occupational respiratory diseases.
- Work-related exposures are estimated to account for about 15% of all adult asthma cases.
- Both the accumulation of toxic dust in the lungs and immunological sensitisation to inhaled occupational agents can cause interstitial lung disease.
- Despite asbestos use being phased out, mesothelioma rates are forecast to continue rising owing to the long latency of the disease.
- The emergence of novel occupational causes of respiratory disease in recent years emphasises the need for continuing vigilance.

Occupational diseases are often thought to be uniquely and specifically related to factors in the work environment; examples of such diseases are the pneumoconioses. However, in addition to other factors (usually related to lifestyle), occupational exposures also contribute to the development or worsening of common respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma and lung cancer.

Information about the occurrence of occupational respiratory diseases and their contribution to morbidity and mortality in the general population is provided by different sources of varying quality. Some European countries do not register occupational diseases and in these countries, information about the burden of such diseases is completely absent. In others, registration is limited to cases where compensation is awarded, which have to fulfil specific administrative or legal criteria as well as strict medical criteria; this leads to biased information and underestimation of the real prevalence. Under-reporting of occupational disease is most likely to occur in older patients who are no longer at work but whose condition may well be due to their previous job. In addition, there may be no incentive to report occupational diseases, and insufficient awareness among physicians may also contribute.

In some countries, schemes have been developed for the voluntary reporting of occupational respiratory diseases by respiratory and occupational physicians. The best known of these schemes is the SWORD

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> *"Where occupational standards are not adequately enforced, the risk of silicosis is still significant"*

(Surveillance of Work Related and Occupational Respiratory Disease) system initiated in the UK in 1989. While such voluntary reporting schemes have drawbacks, they nevertheless enable us to estimate the contribution of work to the occurrence of respiratory disease and to identify priorities for prevention.

For diseases with multiple causes, such as asthma, COPD and lung cancer, reliable information on the contribution of occupational exposures is provided by well-designed epidemiological studies. One complication is that occupational asthma is not directly measured (diagnosed) in general population studies, and attributable risks have to be calculated using often quite crude information about exposure and the phenotype of asthma. Based on such epidemiological analyses, it has been shown that the population-attributable fraction of occupational factors in mortality and morbidity from respiratory diseases is far from negligible: for asthma and COPD, respectively, it varies between 2–15% and 15–20%, resulting in a considerable number of cases in the European Union (EU), even if this is often difficult to substantiate and document in individual subjects. A similarly high contribution is expected for lung cancer.

This chapter provides a brief overview of the major categories of respiratory diseases and, where possible, will indicate the role and contribution of occupational exposures to their occurrence. Little quantitative information will be presented, but this summary should identify the main areas in which efforts are required for the prevention, diagnosis, management and compensation of occupationally induced respiratory diseases in Europe. The chapter will also address management and prevention.

Acute inhalation injuries

In the home

Acute inhalation accidents may occur at home during domestic work; for example, when mixing bleach with acids or ammonia or when using leather impregnation sprays. Respiratory complications are also a major cause of mortality in patients admitted for burn injuries, which affect 0.2–2.9 per 10 000 inhabitants annually in Europe.

In the workplace

The inhalation of certain agents can cause acute injury to the respiratory tract of varying severity. Occasional exposure to high levels of metal fumes or organic dusts

contaminated with microorganisms and endotoxins may lead to metal fume fever and organic dust toxic syndrome, respectively. These inhalation fevers are the clinical expressions of a relatively benign and transient, though nonetheless unacceptable, condition of intense pulmonary inflammation. Such reactions occur commonly in agricultural work. Swedish and Finnish surveys indicate that about one in 10 farmers has experienced an acute febrile attack resulting from organic dust exposure. The possible long-term effects among affected subjects are poorly understood.

More severe injury to the tracheobronchial tree and lung parenchyma may result from the inhalation of toxic gases, vapours or complex mixtures of compounds released from explosions, fires, leaks or spills from industrial installations, transport accidents and military or terrorist operations. Such inhalation incidents can have massive dimensions and affect entire communities.

Toxic tracheobronchitis or pneumonitis with pulmonary oedema can be fatal; in survivors, these conditions may lead to long-term structural or functional effects, including irritant-induced asthma (reactive airways dysfunction syndrome (RADS)). Firefighters and emergency personnel are at particularly high risk, as are those working in confined areas.

The exact incidence of acute inhalational injuries at work is not known. The SWORD scheme registered an annual incidence rate of 5 per million in men and 1 per million in women. Although serious inhalation incidents are not very frequent compared to other injuries at work, they need to be prevented with appropriate administrative and technical measures. At a local level, there must be disaster plans and adequate facilities for the management of individual and collective inhalation injuries.

Occupational infections

Most respiratory infections are 'community acquired'. Sometimes, however, they may be directly related to specific occupations. Common viral or, more rarely, bacterial infections may affect those working in crowded environments, schools, hospitals and other communities.

Bacteria

Tuberculosis (TB) is a well-recognised risk in health workers. However, other categories of workers may also be at risk, such as prison guards or social workers involved with immigrants or asylum seekers originating from areas with a high TB prevalence.

Zoonoses (infectious diseases transmitted from animals), such as pneumonia caused by *Chlamydia psittaci* (ornithosis) or *Coxiella burnetii* (Q-fever), affect agricultural workers and those in other jobs involving direct or indirect contact with animals.

In outbreaks of *Legionella pneumonia*, such as those associated with cooling towers, fountains and whirlpools, or cruise ships, maintenance or other attending personnel are at risk of contracting the infection. Epidemiological evidence also exists that metal-exposed workers, such as welders, are at increased risk of infectious pneumonia and it has therefore been argued that these workers should receive pneumococcal vaccination.

The dissemination of anthrax and other microorganisms by terrorists is a definite threat to various categories of workers, such as postal workers, maintenance workers, law-enforcement personnel and health workers.

In addition, emerging infections pose a particular threat to hospital workers and their families, as shown by the outbreak of the severe acute respiratory syndrome (SARS). Another issue of recent years has been the emergence of drug-resistant microorganisms. Historically, this was mainly considered to be a risk to hospital personnel, but the high use of antibacterials in livestock production among pig and veal farmers has broadened the population at risk to workers in this sector, and even the general public.

Fungi

Although fungi (*e.g. Stachybotrys*) and their mycotoxins may be implicated in building-related illnesses caused by flooding or other types of water damage, the role of fungal contamination in causing such occupational respiratory diseases is not clearly established. Nevertheless, in immune-compromised subjects (due to steroid treatment, organ transplantation, or other causes) the risk of acquiring invasive fungal infections caused by ubiquitous fungi, such as *Aspergillus*, is real, but the quantitative relationship between exposure load (*e.g.* in some work environments) and the risk of becoming infected is still unknown. Further study of this relationship is required and there is a need to develop health-based standards of fungal and microbial exposures for the indoor and outdoor environment.

Sick building syndrome

This common syndrome refers to the occurrence, in a large proportion of the workforce, of nonspecific work-related respiratory and other complaints among occupants of sealed air-conditioned buildings. It is not established to what extent microorganisms and biological contaminants, together with indoor climate factors and volatile organic compounds, as well as psychosocial factors, are responsible for outbreaks of the syndrome.

Asthma

In modern society, occupational asthma is the most frequently occurring work-related respiratory disease. Occupational asthma is defined as a form of asthma that is generally caused by immunological sensitisation to a (specific) agent inhaled at work. A large – and growing – number of causative agents have been identified. These occupational 'asthmogens' may be macromolecules of biological origin, metallic

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agents or synthetic chemicals. Examples are listed in chapter 7. Inhaled irritants can also cause asthma without specific sensitisation, either after a single acute inhalation accident (RADS) or through repeated or chronic exposure to excessive levels, for example during cleaning work. In the latter case, the presentation of occupational asthma may resemble that of allergen-induced occupational asthma because the worker may have been able to work for some time without experiencing respiratory symptoms (*i.e.* there has been a symptom-free latency period). 'Asthma-like' disorders without evidence of sensitisation are also found in workers exposed to (endotoxin-contaminated) vegetable dusts (*e.g.* byssinosis in cotton workers, asthma-like syndrome in swine confinement workers).

In addition to asthma that is caused, more or less clearly, by work, many asthmatics also experience a worsening of their asthma caused by their working circumstances – so-called 'work-aggravated asthma'. It has been estimated that one in seven severe asthma exacerbations is associated with work-related exposures.

Occupational asthma often has a poor prognosis, even when exposure has ceased, and it leads to considerable socioeconomic consequences, even in countries that have adequate provision for compensating workers with occupational diseases.

The population-attributable risk of work-related exposure has been estimated to be approximately 17% of all adult asthma cases, equivalent to an incidence of new-onset occupational asthma of 250–300 cases per 1 million people per year. According to occupational disease registries and voluntary reporting schemes in various European countries, the annual incidence of occupational asthma has been estimated to be 2–5 cases per 100 000 working individuals. Thus, occupational factors play an important role not only in causing specific occupational asthma but also in favouring the development of asthma in adults. Given the high frequency of asthma in the population, occupation represents a potentially important area of prevention. The costs of occupational asthma to society are high, and in most countries the economic burden falls on the state and the individual, not, or hardly ever, on the employer. The incentive for preventive action by employers is therefore weak.

COPD

Although the dominant cause of COPD is cigarette smoking, occupational exposure to mineral dusts, organic dusts and irritant gases or vapours contributes significantly to the incidence and severity of chronic airways disease, including

COPD. The most common respiratory manifestation of exposure to dusts or fumes is a chronic cough productive of sputum (chronic bronchitis). This may or may not be associated with airflow limitation, as determined by a decrease in forced expiratory volume in 1 second (FEV1). Several longitudinal studies have shown that exposure to coal dust is associated with a loss of respiratory function, even in the absence of pneumoconiosis. The average loss of function can be comparable to the changes attributable to smoking, with some individuals suffering substantial and clinically significant impairment. In addition to underground mining, workers in other occupations with exposure to mineral dusts (such as building work) or fumes (such as welding) may be at risk of occupationally induced COPD, although the epidemiological evidence is generally less strong for these categories of workers. It is also underappreciated that exposure to agricultural dusts (such as grain dust, vegetable fibres or animal feed) is a significant cause of chronic airway disease and accelerated decline in lung function. Thus, the prevalence of chronic bronchitis in farmers, particularly swine confinement farmers, is high, even among nonsmokers.

In general, population-based studies have supported the findings of workplace-based studies, particularly with regard to dusty jobs or jobs involving mixed exposure to dusts and gases. The population-attributable fraction of occupational factors to the burden of COPD morbidity has been estimated to range from 15–20% and may reach 40% among nonsmokers. In Europe, it was estimated that a total of 39 300 deaths from COPD in 2000 were a result of work-related exposures to dusts and fumes.

Interstitial lung diseases

Interstitial lung diseases (ILDs) have been more closely associated with an occupational aetiology than any other category of respiratory disease. Classic examples of occupational diseases are the pneumoconioses caused by crystalline silica (silicosis), asbestos (asbestosis) and coal dust (coal worker's pneumoconiosis). Figure 1 shows the mortality rate of pneumoconiosis in Europe. There are also less common pneumoconioses caused by nonfibrous silicates (such as talc, kaolin or mica) or other minerals.

Although individual susceptibility plays a role in mineral pneumoconioses, they are generally considered to be caused by the progressive accumulation of toxic dust in the lungs. In contrast, individual susceptibility and/or immunological sensitisation play a more dominant role in the pathogenesis of ILDs such as extrinsic allergic alveolitis (hypersensitivity pneumonitis) (EAA), chronic beryllium disease (berylliosis) or hard metal/cobalt-related lung disease.

The possibility of an occupational aetiology should always be considered in the differential diagnosis of ILDs, particularly for conditions such as sarcoidosis and idiopathic pulmonary fibrosis, because 'occult' exogenous causes are easily missed if a thorough occupational and environmental history is not taken. There are epidemiological reasons to believe that occupational and environmental factors may be involved in these conditions.

Mineral pneumoconiosis

In 2000 in Europe, it was estimated that a total of 7200 cases of pneumoconiosis were related to occupational exposures to asbestos, silica and coal dust.
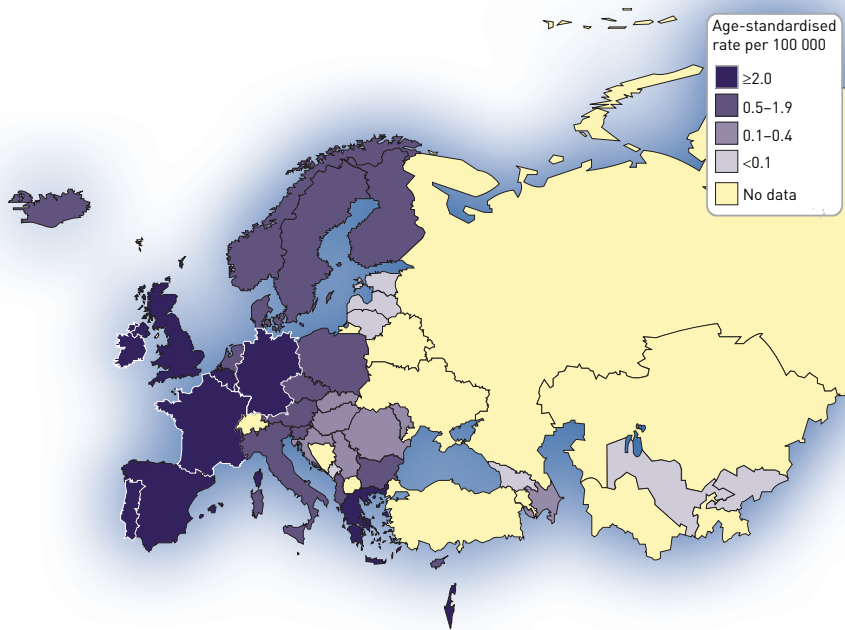
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Figure 1 – Mortality rate for pneumoconiosis. Data from the World Health Organization World and Europe Mortality Databases, November 2011 update.

Silicosis

Silicosis should be a disease of the past, and it has indeed become relatively uncommon in industrialised countries thanks to dust control in the workplace. However, hazardous exposures to free crystalline silica (quartz or cristobalite) may still occur in the following areas: mining, tunnel drilling or stone quarrying; processing stone or sand; building and demolition; foundries; pottery or ceramic manufacture; the abrasive use of sand (sandblasting); the manipulation of calcined diatomaceous earth; as well as other, sometimes unexpected, settings. A tragic recent example was seen in Turkey, where hundreds of young workers contracted silicosis as a result of sandblasting denim jeans.

Small workshops represent a particular risk and in countries where occupational standards are not adequately enforced, the risk of silicosis is still significant. The construction industry also requires specific attention because there are indications that silicosis has re-emerged in this industry since the introduction of mechanical hand tools, which have resulted in high dust and silica exposures.

It is important to appreciate that silicosis is also associated with other conditions such as COPD, TB, lung cancer and systemic sclerosis.

Coal worker's pneumoconiosis

In many European countries, thousands of coal miners have developed more or less advanced degrees of coal worker's

pneumoconiosis. In some countries, this disease is labelled and registered in official statistics as (anthraco)silicosis. Although substantial silica exposure may occur in underground mines, coal worker's pneumoconiosis differs from silicosis. Incidence has declined in recent decades and complicated coal worker's pneumoconiosis (or progressive massive fibrosis) should become a rarity, at least in western European countries.

Asbestosis
Asbestosis (pulmonary fibrosis caused by asbestos) has become uncommon. It is generally found in patients who were heavily exposed to asbestos in the past – during the manufacture of asbestos-cement products, friction materials or fireproof textiles, or when using asbestos for heat insulation or fire protection purposes in construction, heating systems, power stations, furnaces, shipyards and railroads, *etc*. The incidence of asbestosis will continue to decrease in countries in which asbestos use has been forbidden. Nevertheless, the risk of asbestosis will remain for those engaged in asbestos removal and waste handling, as well as in developing countries where the use of asbestos is still allowed and is poorly regulated.

Future aims
A realistic target for labour and health authorities should be to aim for a decrease in the incidence of silicosis, coal worker's pneumoconiosis and asbestosis, until their complete disappearance in all European countries. This should be achievable by appropriate occupational legislation, rigorous enforcement of dust-control measures and adequate medical surveillance.

Berylliosis, hard metal lung disease and other metal-related disorders

Berylliosis
Lung disease caused by sensitisation to beryllium (*i.e.* chronic beryllium disease, or berylliosis) is clinically and pathologically similar to sarcoidosis. Exposure to beryllium is not frequent, but this light metal is increasingly used in modern technology. In a series of 84 patients with suspected sarcoidosis from Germany and Israel, a diagnosis of chronic beryllium disease was made in 34 subjects.

Hard metal lung disease
Hard metal lung disease is caused in susceptible individuals by a reaction to cobalt, which is a constituent of hard metal. In its most typical presentation, the disease is characterised by giant cell interstitial pneumonia. Interestingly, the same disease occurred among Belgian diamond polishers after the introduction of polishing disks made of diamond–cobalt. Hard metal lung disease is uncommon, but cases have been described in small workshops where hard metal or diamond–cobalt tools are manufactured or sharpened. Cobalt is also a possible cause of occupational asthma, which may coexist with interstitial lung disease.

Other metal-related disorders
Many other metals have been associated with interstitial lung disease, which sometimes masquerades as sarcoidosis. However, the epidemiology of these rare conditions is rather poorly understood.

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More effort should be made at a European level to recognise, register and prevent these conditions.

Extrinsic allergic alveolitis (see chapter 22)

Occupational causes of EAA are quite diverse. The more common aetiological agents are organic dusts, originating from microorganisms (farmer's lung, humidifier lung) or from birds (pigeon breeder's lung, bird fancier's lung). However, it should be considered that there is potential for EAA in all environments in which bio-aerosols may be inhaled. These include mushroom farms, composting installations, wood processing, vegetable stores and machining shops (through the use of machining fluids). Some chemicals, most notably isocyanates, may also cause the condition.

Occupational EAA has been most frequently studied in farmers, and is caused by sensitisation to (thermophilic) microorganisms that grow in hay or other organic substrates. The frequency of farmer's lung varies considerably geographically, depending on climate and farming practices, and the causative antigens also differ between regions. It is most frequent in the cold, humid climates of northern Europe or in mountainous areas, such as the Doubs in France. Reported prevalence figures vary between 10 and 200 cases per 100 000 inhabitants, and 4 to 170 per 1000 farmers, depending on area and diagnostic criteria. Yearly incidences have been estimated to be 2–6 cases per 1000 farmers in Sweden and 5 per 1000 farmers in Finland in the 1980s. These figures may be underestimates because of diagnostic problems and the use of hospital data.

Outbreaks of EAA have also been described among workers exposed to metal working (or machining) fluids, *e.g.* in the manufacture of car engines. The exact causative agent cannot always be identified but mycobacteria have been implicated.

Other occupational ILDs

In the 1990s, outbreaks of ILD caused by synthetic agents demonstrated that novel causes of occupational disease can still emerge. The most spectacular outbreak was Ardystil syndrome, a severe form of organising pneumonia in textile workers that was caused by aerosolised paints. Another outbreak was caused by the inhalation of nylon microfibres in nylon flock workers. These outbreaks should serve as reminders that workers should never be exposed to aerosolised compounds unless appropriate inhalation testing has shown that this can be done safely.

Prevention is particularly relevant to the new 'nano-materials' (including carbon nanotubes, insoluble metallic agents, polymers or composites) that are being increasingly produced for various applications. Although no overt pulmonary or other disease has hitherto been attributed convincingly to occupational (or other) exposure to engineered nano-materials, many properties of these materials (including their intended chemical activity), as well as some experimental studies *in vitro* and in laboratory animals, are a cause of justified concern for human health in case of exposure. This is an important responsibility for occupational legislation at a European level.

Lung cancer

Numerous epidemiological studies have investigated the role of occupational exposures in causing lung cancer (other than mesothelioma) and, despite the many difficulties of such studies, several occupational agents and jobs have been identified as definite or probable causes. A large number of potential occupational agents are known to be human lung carcinogens (see chapter 7, table 7). Depending on the agent, as well as on methodological aspects, additive or multiplicative modes of interaction have been shown to operate with cigarette smoking. Established carcinogenic processes relevant to the lung include coke production and coal gasification (possibly related to polycyclic aromatic hydrocarbons), iron and steel founding, paint manufacture and painting. Occupational exposure to diesel exhaust and environmental tobacco smoke are also causes of lung cancer, although the magnitude of risk is smaller than that found for the established carcinogenic agents. However, to take diesel exposure as an example, the population at risk of exposure within the workforce is large, leading to a potentially high burden of disease.

The contribution of occupation to the causation of lung cancer has been shown to be considerably larger than for most other common cancers. The most frequently quoted estimate is 15% in men and 5% in women, although higher population-attributable risks have been reported (24% overall, 29% in men and 5% in women) for the contribution of occupational exposure. In all studies, occupational asbestos exposure is considered the most influential factor. A prospective cohort study in the Netherlands estimated that 12% of cases of lung cancer in men were attributable to lifetime occupational asbestos exposure, after adjustment for smoking and diet. The total burden of lung cancer cases attributable to work-related exposure to respiratory carcinogens in Europe has been estimated to be 32 400 cases per year.

In spite of such high estimates of the quantitative contribution of occupational factors in the aetiology of lung cancer, it is a common feature of all compensation agencies or notification systems that very few lung cancers of occupational origin are reported. There are several reasons for such under-reporting: occupational lung cancer almost always occurs among (former) smokers; the clinical presentation of occupational lung cancer is generally similar to that of non-occupational lung cancer; therapeutic options do not differ between occupational and non-occupational lung cancer; causal inferences have to be based on estimated probabilities that the disease is work related in an individual patient. However, the notion of occupationally induced lung cancer is important in terms of prevention, and European efforts to detect and reduce occupational carcinogenic exposures must continue.

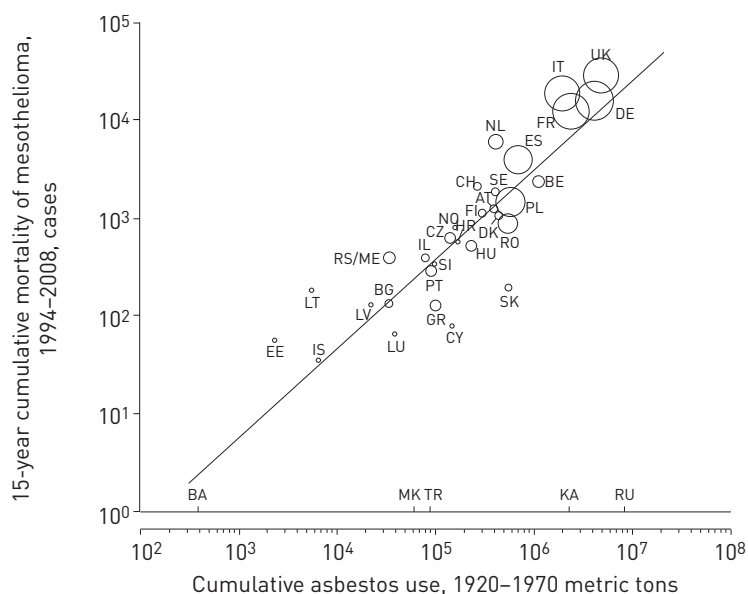Further information on lung cancer can be found in chapter 19.

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Figure 2 – Relationship between the 15-year cumulative mortality (male + female) of mesothelioma (1994–2008) and the cumulative use of asbestos (1920–1970) weighted by the size of national populations in 36 countries with data for both mesothelioma and asbestos use. Asbestos use for countries without mesothelioma frequency data is indicated along the x-axis. Reproduced and modified from Park *et al.*, 2011, with permission from the publisher.

Pleural disease

Occupational pleural disorders almost exclusively concern those who have had exposure to asbestos fibres (and perhaps also refractory ceramic fibres).

Nonmalignant pleural disorders, such as localised pleural plaques, are a relatively frequent occurrence, even in those who have had light exposure to asbestos. Pleural plaques are considered as biomarkers of past exposure to asbestos. It is generally accepted that the mere presence of asbestos-induced pleural plaques does not usually lead to symptoms or impairment and that such plaques are not precursors of a malignant evolution. In contrast, pleurisy and diffuse pleural thickening are more serious manifestations of pleural disease that may result from relatively high cumulative exposure to asbestos. All of these nonmalignant pleural disorders may be seen in isolation or they may accompany asbestosis or malignant asbestos-induced disease.

Malignant mesothelioma is a pleural (or pericardial or peritoneal) tumour which is typically caused by asbestos exposure, either occupationally or environmentally. The majority of mesothelioma cases (>90%) are asbestos related and occupational exposure is the major contributor to its
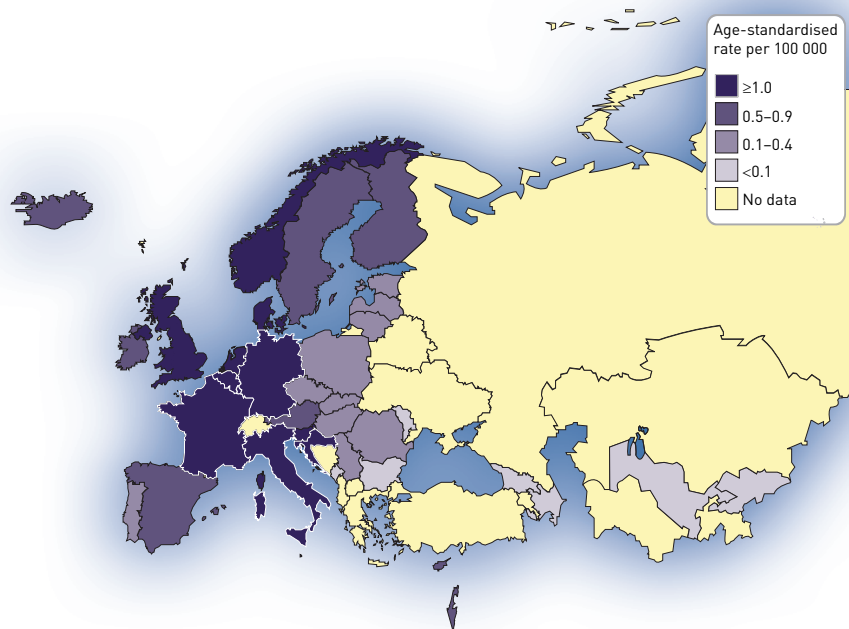
Figure 3 – Mortality rate for mesothelioma. Data from the World Health Organization World and Europe Mortality Databases, November 2011 update.

occurrence, though environmental sources have been identified in some countries. The latency period between exposure and the clinical manifestation of mesothelioma is usually ⩾ 30 years, and the tumour may occur even after brief or low exposure. It has been predicted that the increase in the occurrence of malignant mesothelioma, which has paralleled the industrial use of the material, will continue until approximately 2020 in most European countries, killing about 250 000 people between 1995 and 2029. According to this prediction, one in 150 men born between 1945 and 1950 will die of this 'rare' tumour, for which no effective cure is presently available.

Mesothelioma mortality rates vary considerably between countries and it has been shown that these rates correlate strongly with the amount of asbestos imported into a country (figure 2). In Europe, mortality rates vary more than 10-fold between countries (figure 3), and it is likely that this variation reflects the differences in asbestos use post-second world war, although the low rates seen in some countries might also be associated with diagnostic issues.

Prevention

Occupational diseases are, in principle, more amenable to prevention than diseases that are caused by genetic factors, lifestyle or the general environment. It is easier to intervene in workplace conditions, and there are legal and technical frameworks in the EU and its member states specifically for the work environment. For major hazards, there are occupational exposure standards that define the level under which no major health risks are expected. At the European level, these standards are proposed by the Scientific Committee on Occupational Exposure Limits (SCOEL). For carcinogens, so-called derived maximum exposure levels are usually obtained. These describe the exposure level below which the likelihood of disease is less than a certain level, usually

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a lifetime excess risk of 1 in 250 (acceptable risk) or 1 in 25 000 (negligible risk). However, not all standards are up to date and the standard-setting process at the EU level is slow. Some EU member countries also have their own active standard-setting processes.

Conclusion

Occupational exposure is a potential cause of almost all respiratory diseases. The contribution of the work environment to the development and aggravation of disease is often under-recognised and certainly under-reported. Efforts should be made at a European level to increase the recognition of occupational respiratory diseases amongst the medical profession, expand knowledge about the epidemiology of these diseases through adequate registration systems, and improve their prevention by setting exposure standards and reducing the exposure of the working population.

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Key points

- Orphan diseases are those that are not widely researched: they need not be rare. Likewise, not all rare diseases are orphans.
- Rare lung diseases may involve the lung only or multiple organs.
- Patients' associations are often a lifeline for people with rare lung diseases, providing a sense of community and advocating for better treatment.
- Governments have provided incentives for pharmaceutical companies to develop treatments for rare and orphan diseases; however, drug prices are often high.
- Doctors lack experience of many rare lung diseases, but all respiratory physicians should ensure they have some clinical and scientific knowledge of the field and are open-minded about diagnosis.

The terms 'orphan diseases' and 'rare diseases' are not synonymous.

Orphan diseases

Orphan diseases are those which are not widely researched, where specific treatment is not available, and which may only be of limited interest to scientists and doctors. Consequently, patients feel abandoned and 'orphaned' in the world of healthcare. Orphan diseases may be either common or rare.

The more common orphan diseases are exemplified by the so-called neglected infectious diseases, which are endemic to areas ravaged by poverty in Africa, Asia and the Americas. These disorders affect 1 billion people worldwide and can cause disfigurement, lifelong disabilities and morbidity, and eventually lead to the death of 1 million people annually. The neglected tropical infectious diseases comprise lymphatic filariasis, African trypanosomiasis, schistosomiasis, trachoma, onchocerciasis, leishmaniasis, Chagas disease, *etc*. Coexistence with AIDS or malaria is common. Access to drugs is limited by financial cost. However, in recent years, several pharmaceutical companies have donated drugs to treat neglected tropical disorders (*e.g.* albendazole for lymphatic filariasis).

The orphan lung diseases comprise many disorders and are described in more detail in the recent Orphan Lung Diseases issue of the *European Respiratory Monograph*.

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" *A rare disease is defined as one that affects fewer than one person in 2000 in Europe – there are about 6000 such disorders* "

Rare diseases

Rare diseases are defined numerically – they are diseases that affect fewer than one person in 2000 in Europe. There are about 6000 such disorders, including well-characterised diseases as well as syndromes and anomalies (table 1). Most (about 80%) are of genetic origin. Many rare diseases are also orphan diseases; however, some rare diseases have received significant attention, leading to comprehensive research and ensuing treatments such that they may no longer be considered orphan (a good

Vasculitides	
	Granulomatosis with polyangiitis (Wegener's)
	Microscopic polyangiitis
	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)
	Behçet's disease
	Takayasu's arteritis
Autoimmune diseases	
	Anti-basement membrane syndrome
	Pulmonary alveolar proteinosis
Disorders of genetic origin	
	Lymphangioleiomyomatosis associated with tuberous sclerosis
	Multiple cystic lung disease in Birt–Hogg–Dubé syndrome
	Primary ciliary dyskinesia
Other idiopathic disorders (lung limited)	
	Idiopathic eosinophilic pneumonias
	Tracheobronchopathia osteochondroplastica
	Tracheobronchomegaly (Mounier–Kuhn syndrome)
	Idiopathic bronchiolitis
Other rare diseases	
	Thoracic endometriosis
	Langerhans' cell histiocytosis

Table 1 – The main rare lung diseases.

example is idiopathic pulmonary arterial hypertension: see chapter 21).

This chapter does not include neoplastic disorders (those causing benign or malignant tumours). However, rare chest tumours or unusual manifestations of malignancies may need to be considered in differential diagnosis (*e.g.* pulmonary artery sarcoma, metastatic cavitary nodules).

Specific diseases

There are no reliable epidemiological data for most rare respiratory diseases. Lung involvement in rare diseases may occur in various contexts: 1) rare disease limited to the lung (*e.g.* idiopathic alveolar proteinosis); 2) the lung involvement of a rare systemic disease (*e.g.* granulomatosis with polyangiitis (Wegener's)); 3) a rare lung disease that may be either sporadic or inherited and possibly associated with multi-organ manifestations (*e.g.* lymphangioleiomyomatosis, sporadic or associated with tuberous sclerosis complex); and 4) an iatrogenic lung disease caused by treatment of a rare condition.

Vasculitides of the lung

Inflammation of the small blood vessels of the lung (pulmonary vasculitis) occurs as part of systemic disorders characterised by widespread inflammation of the vessels in several organs and associated with the presence of antineutrophil cytoplasmic autoantibodies (ANCAs):

- Granulomatosis with polyangiitis particularly involves the upper respiratory tract, the lungs and the kidneys. Typical pulmonary features include radiographically visible multiple nodules, which are often cavitary, or consolidation (the filling of alveolar tissue with liquid). ANCAs are mainly cytoplasmic with anti-proteinase 3 specificity.
- Microscopic polyangiitis often manifests in the lung by producing alveolar haemorrhage. ANCAs are mainly perinuclear with anti-myeloperoxidase specificity. Necrotising glomerulonephritis is usually associated (pulmonary–renal syndrome).
- Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) is particularly characterised by severe asthma and a raised blood eosinophil count, together with eosinophilic pneumonia and, often, myocardial involvement resulting in heart failure.

The cornerstones of treatment of these vasculitides are corticosteroids, immunosuppressive drugs, and the monoclonal antibody rituximab.

> " *Accelerated approval of drugs after poorly powered trials necessitates that high-quality post-marketing (phase IV) observational studies are carried out* "

Inflammation of the larger blood vessels (large-vessel vasculitis) may also include pulmonary involvement:

- Behçet's disease, characterised by recurrent oral and genital ulcers with relapsing uveitis, may be associated with pulmonary artery aneurysms, the risk of rupture and pulmonary artery thrombosis.
- Takayasu's arteritis is a chronic inflammation of the aorta and its branches, and less commonly of the pulmonary arteries.

Alveolar haemorrhage syndromes

The main manifestations of diffuse alveolar haemorrhage are haemoptysis (coughing up blood), diffuse alveolar opacities on imaging and rapidly increasing anaemia. Bronchoalveolar lavage retrieving bloody fluid is the key to diagnosis. Associated glomerulonephritis is present in small-vessel vasculitis with alveolar haemorrhage, and in the anti-basement membrane (Goodpasture's) syndrome. Other causes of alveolar haemorrhage syndrome are numerous and include infectious diseases such as leptospirosis.

Bronchiolitis

Inflammation and fibrosis of the small airways result in airflow obstruction. Causes include inhalation of toxins, gases and dusts, lung transplantation, graft-*versus*-host disease and inflammatory intestinal disorders. Bronchiolitis may develop in patients with rheumatoid arthritis and in patients with inflammatory interstitial diseases. It may also be idiopathic. Airflow obstruction and characteristic high-resolution computed tomography (HRCT) features (centrilobular micronodules, 'tree-in-bud' pattern, mosaic pattern) are the main diagnostic signs.

Idiopathic eosinophilic pneumonias

Idiopathic chronic eosinophilic pneumonia manifests as dyspnoea, patchy/diffuse alveolar opacities on imaging and high blood eosinophil count. It may also be associated with asthma. The response to corticosteroids is dramatic but relapses are very common. Idiopathic chronic eosinophilic pneumonia may also be drug-induced or occur in association with diseases caused by parasitic (worm) infestation.

Acute eosinophilic pneumonia results in an adult respiratory distress-like syndrome with alveolar eosinophilia contrasting with the initial absence of blood eosinophilia. It improves with or without corticosteroids. Recent commencement of smoking frequently precedes its development.

Pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis is characterised by deposition of surfactant-like material in the alveoli, and is an autoimmune condition associated with autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF). Alveolar opacities and ground-glass attenuation with a so-called 'crazy paving' pattern on HRCT are characteristic of the disorder. Bronchoalveolar lavage retrieving milky fluid allows diagnosis. Whole-lung lavage is the standard treatment, but inhaled exogenous GM-CSF has become an efficient therapy for this condition.

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Idiopathic tracheopathies

The key tools for diagnosis of tracheal disorders are HRCT and endoscopy.

Tracheobronchopathia osteochondroplastica is characterised by osseous submucosal nodules projecting into the tracheal lumen. It manifests as chronic cough and usually has a benign clinical course.

Tracheobronchomegaly (Mounier–Kuhn syndrome) is associated with chronic cough and recurrent respiratory infections.

Both relapsing polychrondritis and granulomatosis with polyangiitis may involve the trachea and eventually result in severe stenosis (narrowing) of the trachea.

Primary ciliary dyskinesia

Primary ciliary dyskinesia is an autosomal recessive disease with abnormalities of the cilia of airway epithelial cells. It results in impaired mucociliary clearance, with ensuing chronic recurring sinopulmonary infections, further diffuse bronchiectasis and, eventually, chronic respiratory failure.

Thoracic endometriosis and catamenial pneumothorax

Endometriosis in women sometimes affects the respiratory system and may cause pneumothorax (air between the lung and chest wall) around the time of menstruation (catamenial pneumothorax). It has been suggested that as many as one-third of pneumothoraces in young women referred for surgery may be due to this condition.

Multiple cystic lung diseases

These conditions often give rise to pneumothorax, which is the most common presenting manifestation. Extensive lung cysts may result in airflow obstruction and chronic respiratory failure.

Sporadic lymphangioleiomyomatosis (LAM) is a disorder occurring in young women. It may be associated with tuberous sclerosis complex, a disorder of genetic origin (*TSC1* and *TSC2* genes) with frequent skin and neurological manifestations, in addition to pulmonary features. Associated angiomyolipoma(s) are common. Guidelines for the diagnosis and management of LAM have been published by an ERS Task Force.

Pulmonary Langerhans' cell histiocytosis develops in smokers, with HRCT showing diffuse nodules which may cavitate, giving rise to cysts. Improvement has been reported with cladribin.

The Birt–Hogg–Dubé syndrome, which is related to mutations of the *FLCN* gene, is characterised by a family history of pneumothorax, cutaneous lesions, and a strongly increased risk of kidney cancer.

Other causes of multiple lung cysts include congenital cystic disorders, cavitating metastases of malignancies (especially sarcomas), pulmonary infection by *Pneumocystis jiroveci* or *Staphylococcus*, and lymphoid interstitial pneumonia.

Diagnosis and support

Although significant advances have occurred in the past two decades, patients with rare diseases still complain that the appropriate diagnosis was not made and/or was only confirmed after months or even years. Given the large number of rare diseases, most primary care practitioners have little if any experience of them. Furthermore, some patients feel that their respiratory specialist also has limited knowledge of their disease (for example, difficult-to-manage asthma which turns out to be a feature of eosinophilic granulomatosis with polyangiitis). Improved knowledge of the main features of rare diseases is a real ethical duty for all respiratory physicians. Elementary and more comprehensive information can be obtained from a number of sources, including the major pulmonary textbooks, respiratory journals and websites. Notably, the *European Respiratory Monograph* has recently published issues devoted to Orphan Lung Diseases and to Pulmonary Hypertension. The major website for both patients and doctors is Orphanet (www.orpha.net), which provides validated information about hundreds of rare disorders, including those that mainly or occasionally involve the lungs.

Patients' associations have been of major importance in providing support to people suffering from rare pulmonary diseases. They often result from the initiative of an affected patient or the parents of an affected child. Such associations are an indispensable interface between patients and doctors; their translation and explanation of medical information into lay terms is particularly helpful, and they are also able to answer questions that the patient may not wish to ask their doctor. Patients' associations also provide psychological support, and are particularly helpful in helping to break the solitude of isolated patients. Some patients' associations have succeeded in funding major research projects. Eurordis, a European coalition of rare disease associations, plays an important role in federating the national associations.

Therapy

Given the small numbers of patients with each condition, therapeutic research is often limited. Some of the drugs that are widely used for other indications have been developed to treat rare respiratory diseases (*e.g.* the drugs used for the systemic vasculitides). However, some drugs may have an indication limited to only one disease. For this reason, the US Orphan Drug Act (1983) and a similar European regulation (1999) approved 'orphan drugs' for clinical use. Incentives for orphan drug development in particular include a period of exclusivity following marketing authorisation. While the 'orphan' designation raises the price that healthcare organisations have to pay, the cost of research and development per patient may be very high. Some drugs also have an extended use for non-orphan indications and a few of them may even attain blockbuster status. There is a clear need for

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a comprehensive analysis of the most effective incentive strategy for research and development of orphan drugs for rare diseases. Furthermore, clinical trials in rare diseases are often difficult because few patients may be included. Accelerated approval of drugs after poorly powered trials thus necessitates that high-quality post-marketing (phase IV) observational studies are carried out to more firmly establish their efficacy and safety.

The cost of treatment for some rare diseases is very high. Studies that have examined the societal acceptance of such expensive treatments have shown that criteria such as the severity of disease and the efficacy of treatment are rated highly, and that disease severity is more important than its rarity.

Future developments

The European Union Committee of Experts on Rare Diseases (EUCERD) has established recommendations for the criteria of centres of expertise for rare diseases in member states, their mission and scope, and the criteria of their designation. Major principles include the following: healthcare pathways for patients should be organised; patients may be treated as near as appropriately possible to their home through the use of information and communication technologies (*e.g.* telemedicine). Emphasis has been placed upon the development of European reference networks (with respect for the national competences and rules of member states), as well as registries and databases, and the necessity of a multidisciplinary approach.

The history of rare and orphan diseases has followed a course from curiosity to solicitude and eventually to science. Curiosity and keeping an open mind is the first step for considering the possibility of a rare lung disease in a patient with an unusual or atypical presentation. Solicitude, which is the right of any patient, should be emphasised because of patients' feelings that they are 'orphaned' in the world of healthcare. Finally, improved clinical and basic science knowledge as well as research in the field of rare pulmonary diseases should become an ethical duty for all respiratory physicians.

"*Improved clinical and basic science knowledge as well as research in the field should become an ethical duty for all respiratory physicians*"

Further reading

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