

Rare and orphan lung diseases

Introduction



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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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

- Lymphangiomyomatosis 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
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Table 1 – The main rare lung diseases.

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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 cavitory 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. lymphangiomyomatosis, 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 (ANCA):

- 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 cavitory, or consolidation (the filling of alveolar tissue with liquid). ANCA are mainly cytoplasmic with anti-proteinase 3 specificity.
- Microscopic polyangiitis often manifests in the lung by producing alveolar haemorrhage. ANCA 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.

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.

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 polychondritis 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 lymphangiomyomatosis (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.

Further reading



General

- Ayme S, Kole A, Groft S. Empowerment of patients: lessons from the rare diseases. *Lancet* 2008; 371: 2048–2051.
- Buckley BM. Clinical trials of orphan medicines. *Lancet* 2008; 371: 2051–2055.
- Clarke JTR, Giugliani R, Sunder-Plassmann G, *et al.* Impact of measures to enhance the value of observational surveys in rare diseases: the Fabry Outcome Survey (FOS). *Value Health* 2011; 14: 862–866.
- Cordier JF. Rare and orphan lung diseases. *Breathe* 2005; 2: 147–154.
- Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54.
- Desser AS, Gyrd-Hansen D, Olsen JA, *et al.* Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. *BMJ* 2010; 341: c4715.
- Garg NJ. Global health: neglected diseases and access to medicines. *Infect Dis Clin North Am* 2011; 25: 639–651.
- Hotez PJ, Fenwick A, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. *Lancet* 2009; 373: 1570–1575.
- Ingelfinger JR, Drazen JM. Patient organizations and research on rare diseases. *N Engl J Med* 2011; 364: 1670–1671.
- Llera VA, Roldan EJA. Postmarketing trials for rare diseases. *Science* 2012; 337: 154.
- Luisetti M, Balfour-Lynn IM, Johnson SR, *et al.* Perspectives for improving the evaluation and access of therapies for rare lung diseases in Europe. *Respir Med* 2012; 106: 759–768.
- Rath A, Olry A, Dhombres F, *et al.* Representation of rare diseases in health information systems: the orphanet approach to serve a wide range of end users. *Hum Mutat* 2012; 33: 803–805.
- Simoens S, Cassiman D, Dooms M, *et al.* Orphan drugs for rare diseases. Is it time to revisit their special market access status? *Drugs* 2012; 72: 1437–1443.

Specific diseases

- Hoepfer MM, Humbert M, eds. Pulmonary Hypertension. *Eur Respir Monogr* 2012; 57.
- Johnson SR, Cordier JF, Lazor R, *et al.* European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. *Eur Respir J* 2010; 35: 14–26.
- Lazor R, Etienne-Mastroianni B, Khouatra C, *et al.* Progressive diffuse pulmonary Langerhans cell histiocytosis improved by cladribine chemotherapy. *Thorax* 2009; 64: 274–275.
- Lorillon G, Bergeron A, Detoumignies L, *et al.* Cladribine is effective against cystic pulmonary Langerhans cell histiocytosis. *Am J Respir Crit Care Med* 2012; 186: 930–932.
- Nelson D, Specks U. Granulomatosis with polyangiitis. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 1–14.
- Lazor R. Alveolar haemorrhage syndromes. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 15–31.
- Cottin V. Idiopathic eosinophilic pneumonias. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 118–139.
- Guillevin L, Dunogue B, Pagnoux C. Churg–Strauss syndrome. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 140–151.
- Bonella F, Theegarten D, Guzman J, *et al.* Alveolar lipoproteinosis syndromes. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 171–186.
- Ryu JH, Maldonado F, Tomassetti S. Idiopathic tracheopathies. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 187–200.
- Lucas JSA, Walker WT, Kuehni CE, *et al.* Primary ciliary dyskinesia. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 201–217.
- Bobbio A, Trisolini R, Damotte D, *et al.* Thoracic endometriosis and catamenial pneumothorax. In: Cordier JF, ed. Orphan Lung Diseases. *Eur Respir Monogr* 2011; 54; pp. 265–281.