Review

Bronchiectasis in congenital diseases
Pathogenesis, imaging, diagnostic approach

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SUMMARY. Bronchiectasis is defined as the abnormal, irreversible dilatation of the cartilage-containing airways in the context of repeated cycles of airway infection and inflammation. Many pulmonary syndromes and systemic diseases have been described that have bronchiectasis as an integral feature. Contrary to earlier perceptions that it is an "orphan disease", bronchiectasis appears to be underdiagnosed, especially in childhood, and new disease associations continue to be described. With the advent of high resolution computerized tomography (HRCT) scanning, bronchiectasis has been demonstrated as an important cause of respiratory disease that may predispose to premature mortality. This long-neglected illness should receive more research attention in order to provide better understanding of its aetiology, pathogenesis and multimodality treatment. *Pneumon 2011, 24(3):248-262.*

Key words:
- congenital bronchiectasis,
- cystic fibrosis,
- primary ciliary dyskinesia-Kartagener's syndrome,
- Young's syndrome,
- primary immunodeficiency,
- alpha-1-antitrypsin deficiency,
- Williams-Campbell syndrome,
- Mounier-Kuhn syndrome,
- bronchial atresia,
- intralobar sequestration,
- yellow nail syndrome

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INTRODUCTION

Bronchiectasis is a morphological term used to describe the abnormal, irreversible dilatation of the cartilage-containing conducting airways in the context of repeated cycles of inflammation and infection[1]. It is not a specific disease entity *per se*, but the common end stage of a variety of pathophysiological processes that cause destruction of the bronchial wall and its surrounding supportive tissues[2]. Bronchiectasis accounts for severe pulmonary infections and loss of lung function, results in chronic morbidity, and may contribute to premature mortality[3]. The clinical pattern of bronchiectasis has changed over the past half century, especially in the industrialized countries[4], due to the widespread use of antibiotics, better control of tuberculosis, improvements in sanitation and nutrition, and the introduction of routine early childhood immunization schedules. An increasing proportion of the new generation of patients with bronchiectasis is recognized to be suffering from an underlying disease that predisposes to the development of chronic lung infection[5]. Multiple genetic, anatomical, and systemic causes of bronchiectasis have been identified (Table 1).

TABLE 1. Pathophysiological classification of conditions associated with bronchiectasis

- **Congenital bronchial structural defects**
  Williams-Campbell syndrome, Mounier-Kuhn syndrome, Tracheo-/bronchomalacia, Bronchial atresia, Bronchopulmonary sequestration, Marfan syndrome, Ehlers-Danlos syndrome, Dwarfism
- **Congenital cellular or biochemical defects**
  Cystic fibrosis (CF) and its variants, Alpha-1 antitrypsin (AAT) deficiency
- **Ciliary disorders**
  Primary ciliary dyskinesia (PCD) - Kartagener's syndrome, Young's syndrome
- **Immunodeficiency syndromes**
  Congenital: X-linked agammaglobulinaemia, Selective hypogammaglobulinaemia, Common variable immunodeficiency, Severe combined immunodeficiency, Chronic granulomatous disease, Ataxia-telangiectasia, Bloom syndrome, Natural killer cell deficiency, Bare lymphocyte syndrome, T-cell deficiency, Ectodermal dysplasia, DNA ligase I defect
  Acquired: Human immunodeficiency virus (HIV) infection, Chronic lymphocytic leukemia, Immune modulation (after transplantation), Chemotherapy
- **Postinfectious**
  Bacterial: *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Bordetella pertussis, Klebsiella pneumoniae, Pseudomonas aeruginosa*
  Mycobacterial: *Mycobacterium tuberculosis, Mycobacterium avium complex*
  Viral: Measles, Adenovirus, Influenza
  Fungal: *Aspergillus fumigatus, Coccidioides immitis, Histoplasma capsulatum*
- **Exaggerated immune response**
  Allergic bronchopulmonary aspergillosis, Bronchocentric granulomatosis, Inflammatory bowel disease, Rheumatoid arthritis, Sjögren's syndrome, Relapsing polychondritis, Systemic lupus erythematosus, Ankylosing spondylitis, c-ANCA-positive vasculitis, Primary biliary cirrhosis, Pernicious anaemia, Hashimoto's thyroiditis, After heart-lung, lung, or bone marrow transplantation (bronchiolitis obliterans)
- **Focal mechanical airway obstruction**
  Intrinsic: Slow-growing tumour, aspirated foreign body, broncholith, granulation tissue (stricture)
  Extrinsic: Vascular ring, lymph node encroachment (eg, middle lobe syndrome), post-surgical distortion of bronchial anatomy
- **Inhalational/aspiration injury**
  Toxic gases (ammonia, chlorine), Thermal injury, Overdose (heroin), Gastro-oesophageal reflux disease, Tracheo-oesophageal fistula
- **Obstructive lung diseases**
  Chronic obstructive pulmonary disease (COPD), Asthma, Diffuse panbronchiolitis
- **Idiopathic**
- **Miscellaneous**
  Yellow nail syndrome, Swyer-James-MacLeod syndrome, Coeliac disease, Radiation injury, Eosinophilic lung disease, Amyloidosis, Endometriosis, Klinefelter's syndrome, Congenital dyskeratosis, Usher syndrome
- **Traction bronchiectasis**

PATHOPHYSIOLOGY

Bronchiectasis in the context of congenital diseases may be either due to a gross developmental dysplasia (e.g., flexibility of the proximal airways) or be predisposed to by some inherited defect in mucociliary clearance (MCC), either ultrastructural, as in primary ciliary dyskinesia (PCD), or related to a generalized defect of ion transport, as in cystic fibrosis (CF)[6], or it may result from an underlying deficiency of pulmonary host defenses, as in primary immunodeficiencies (PID). Congenital bronchiectasis, whatever the underlying cause, shares the common denominator of mucus retention and superimposed bacterial colonization[1] (Figure 1). It is not known whether bronchiectasis starts in one section of the respiratory tract and then spreads or if it begins as a generalized process. One report of children with bronchiectasis and chronic rhinosinusitis described the apparent spread of sinus infection to the lungs, resulting in bronchiectasis[9]. The large body of patients with "idiopathic" bronchiectasis represents a poorly understood subtype that may have currently unrecognized immunological dysfunction or

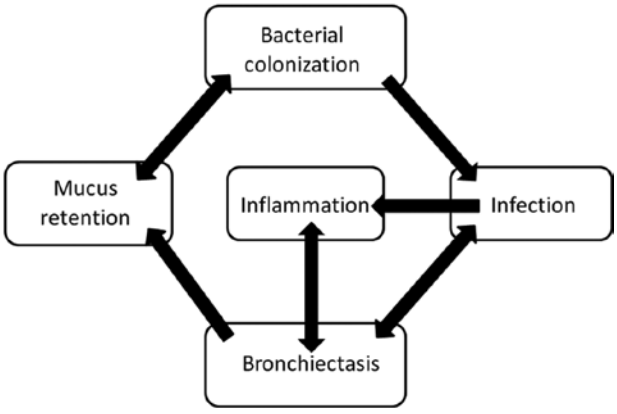

FIGURE 1. Mucus retention and persistent infection sustain the mechanisms of bronchial inflammation and destruction. The toxins released by the bacteria and the immune mediators released by the surrounding inflammatory cells[7] create a vicious cycle of progressive airway wall damage and obstruction, mucus plugging, and increased bacterial proliferation[8].

autoimmune abnormalities. In addition, since functional immunological immaturity usually improves with time, it has been suggested that complete maturation may have been reached by the time bronchiectasis is diagnosed[10].

The lungs of most patients are chronically colonized by potentially pathogenic microorganisms. The range of microbial flora isolated from the sputum of two large series of patients with non-CF bronchiectasis is shown in table 2. Bronchiectasis is characterized by a dynamic turnover of microbial strains[13]. There also appears to be a change in the microbial flora with severity of disease[14]. Colonization with *Pseudomonas aeruginosa* has been associated with more intense inflammatory response[15] and more frequent exacerbations, resulting in accelerated decline in lung function and impaired health-related quality of life[16]. This may be due to the ability of the organism to form biofilms on tissue surfaces, shielding them from the effects of the immune system and antibiotics. The mucoid appearance of *Pseudomonas* in CF bronchiectasis is due to the production of alginate. This bacterium is difficult to eradicate due to the poor penetration of antibiotics into the purulent airway secretions and to the interference in the phagocytic killing process by alginate[17].

TABLE 2. Microbiology of non-cystic fibrosis bronchiectasis

Author, year	Li, 2005[11]	Angrill, 2002[12]
Number and mean age of patients	**n=136, 12.1 years**	**n=42, 58 years**
Potential pathogenic microorganisms		
Haemophilus influenzae	40%	26%
Streptococcus pneumoniae	18%	14%
Pseudomonas aeruginosa	11%	9%
Staphylococcus aureus	7%	NI
Moxarella catarrhalis	2%	5%
Proteus	1%	2%
Klebsiella pneumoniae	1%	NI
Anaerobes	1%	NI
Aspergillus fumigatus	1%	2%

NI: not isolated

GENERAL CLINICAL FEATURES

The clinical features of bronchiectasis, regardless of aetiology, and the usual findings in acute exacerbations are shown in Table 3.

TABLE 3.

General clinical features of bronchiectasis
- chronic cough (occasionally dry)
- copious sputum production
- progressive dyspnoea
- repeated pulmonary infections
- haemoptysis (ranging from blood-streaked sputum to life-threatening haemoptysis)[a]
- chronic sinusitis[b]
- fatigue and weight loss
- digital clubbing and hypertrophic pulmonary osteoarthropathy[c]
- respiratory insufficiency and cor pulmonalec

Findings in acute exacerbations
- increased dyspnoea/cough/sputum production
- fever (>38°C)
- reduced pulmonary function
- malaise/lethargy/decreased exercise tolerance
- radiographic changes consistent with a new inflammatory process
- changes in chest sounds

Auscultation
- early and mid-inspiratory crackles
- diffuse rhonchi and wheezing
- bronchial breath sounds

a: Due to erosive damage of the airway wall and bronchial arterial neovascularization[18]
b: Common in patients with cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome, and diffuse panbronchiolitis
c: Rarely seen now, due to the increased use of antibiotics

IMAGING

Chest computed tomography

Although the initial evaluation is usually based on chest X-ray, this technique is limited by its low sensitivity and specificity. High resolution computed tomography (HRCT) is currently the imaging technique of choice for the assessment of bronchiectasis (Table 4) and has largely eliminated the need for more invasive techniques of the past, such as bronchography. It enables the assessment of bronchial abnormalities to the level of the secondary pulmonary lobule, where the inflammatory process begins[19]. The optimization of paediatric HRCT protocols allows the radiation dose to be kept to a minimum[20]. Early changes on HRCT identify bronchiectasis even before the development of significant symptoms or detectable abnormalities in pulmonary function[21]. Less severe forms of bronchiectasis and misdiagnosed cases of "difficult asthma" have been recognized with the widespread availability of HRCT[22]. Nevertheless, potential pitfalls in HRCT interpretation[23] should be kept in mind, in order for an accurate diagnosis to be achieved.

TABLE 4. High resolution computed tomographic (HRCT) findings in bronchiectasis

Direct signs
- signet ring sign → increased ratio of internal bronchial lumen diameter to the size of its adjacent pulmonary artery
- failure of the bronchi to taper
- visualization of bronchi in the outer 1–2 cm of the lung fields
- tram lines → thickened bronchial walls perpendicular to the radiation beam
- varicose constrictions along airways → varicose bronchiectasis
- ballooned cysts at the end of a bronchus, often with air-fluid levels → cystic bronchiectasis

Indirect signs
- focal areas of air-trapping on expiration → constrictive bronchiolitis
- mucosal wall thickening
- mucous impaction → branching dense tubular structures, coursing parallel to the adjacent artery
- tree-in-bud pattern → bronchiolectasis in the centre of the secondary pulmonary lobule

Additional signs
- lobar consolidation
- crowding of the airways
- enlarged lymph nodes
- focal areas of decreased attenuation and vascularity → destruction of smaller airways and vessels

THE MAIN CONGENITAL DISEASES PREDISPOSING TO BRONCHIECTASIS

1. Cystic fibrosis

CF is initiated by a defect in a single gene located on chromosome 7 that is normally responsible for encoding CF transmembrane conductance regulator (CFTR) protein, which is expressed in the epithelial cells of affected organs and is necessary for the flow of electrolytes and fluid across cell membranes. In the lung, the abnormalities in electrolytes and water transport change the properties of the mucus layer lining the epithelia and the composition of the periciliary fluid layer, ultimately resulting in deficiency in mucociliary clearance (MCC) (Figure 2). The question of whether the viscid secretions are primary or secondary to chronic bacterial infections remains unresolved. In favour of a primary disturbance is the demonstration of mucus obstructing submucosal gland ducts in the airways of neonates with CF, who have not yet developed any evidence of chronic colonization

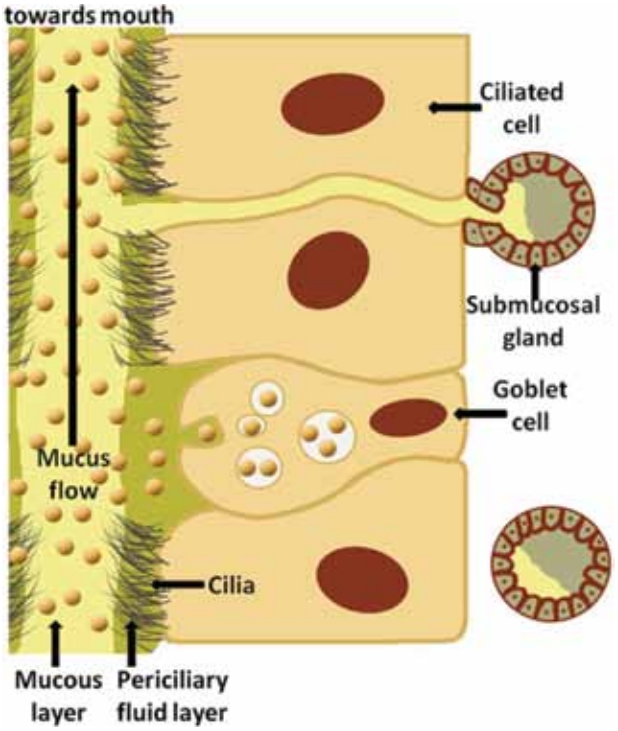

FIGURE 2. Components of the mucociliary clearance apparatus: the cilia, the periciliary fluid layer and the mucous layer. In cystic fibrosis, the respiratory cilia remain intact, but impairment of the quantity and composition of the periciliary fluid and of the hydration of the mucus result in deficient mucociliary clearance.

of the airways. Chronic obstructive airway disease in patients with CF typically progresses from bronchiolitis to bronchitis to diffuse bronchiectasis[24]. Studies have shown that the large airways of minimally symptomatic infants with CF have thicker walls and are more dilated than those of healthy control infants[25], and it has been suggested that their airways increase in size at a greater rate than those of normal children. These findings suggest that the structural airway changes that lead to bronchiectasis begin very early in life, although adult presentation is not unusual[26]. The diagnosis of bronchiectasis in patients with CF is made before age 5 years in about 80%, during adolescence in 10%[27], and during adulthood in 10% of cases[28]. Bronchiectasis is usually diffuse, with upper lobe involvement being almost universal and more severe, and both central and peripheral bronchiectasis being present in approximately two thirds of patients (Figure 3). The best scoring system for quantifying bronchiectasis abnormalities on HRCT of the chest is that of Brody and colleagues[29], which has been shown to be both sensitive to variation in the severity of lung disease and reproducible.

2. Primary ciliary dyskinesia

PCD is a genetic disorder characterized by abnormalities in the structure or function of the cilia and flagella, causing congenital impairment of MCC, sperm motility, and left-right body orientation. The structure of the respiratory cilia is shown on cross-section in Figure 4.

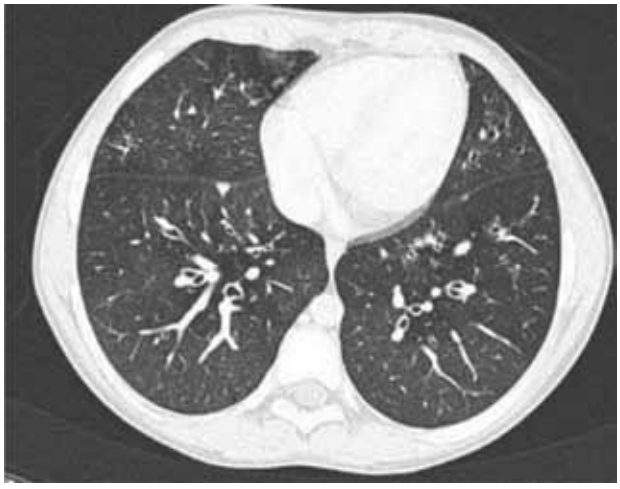

FIGURE 3. High resolution computed tomography (HRCT) scan of the thorax of a 19 year-old patient with cystic fibrosis showing bilateral central and peripheral bronchiectasis with mucus plugging and patchy areas of decreased attenuation.

The triad of situs inversus totalis, bronchiectasis, and either nasal polyps or recurrent sinusitis is known as Kartagener's syndrome[33]. It has an autosomal-recessive inheritance pattern with variable penetrance, although rarely other modes of inheritance, such as X-linked, have been described[34].

The age of presentation ranges from 4 months to 51 years and the manifestations vary with age[35]. In the full-term newborn, neonatal respiratory distress syndrome can be the first sign of PCD, reflecting the importance of functional cilia in clearing lung liquid in the early period after birth[36]. Typically, the infant has a combination of upper and lower airway symptoms. Nasal polyps are found in up to 18% of the patients[37], with chronic secretory otitis media and otosalpingitis requiring repeated courses of antibiotics during childhood and adolescence, but these problems usually improve spontaneously following puberty[37]. The diagnosis is often missed or delayed as many of the symptoms of PCD are common in normal children. Bronchiectasis is a consistent finding in all adults with PCD. In a study of 94 patients, Noone et al.[35] showed that cough was a feature in 100% of patients, while bronchiectasis, sinusitis, otitis media, and situs inversus were observed in 98%, 47%, 92%, and 46%, respectively. Both the number of pulmonary lobes involved and the severity

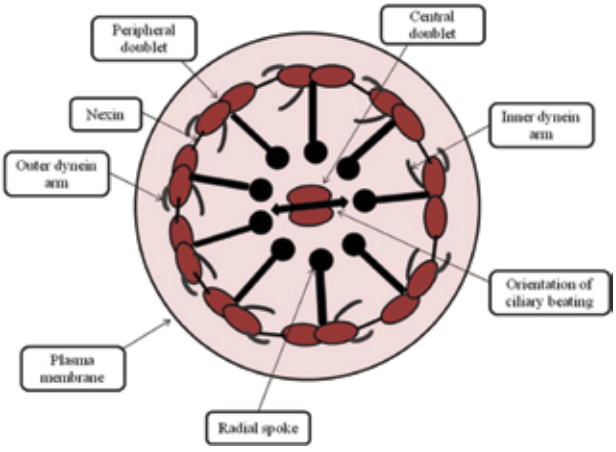

FIGURE 4. Cross-section of a respiratory ciliary axoneme. Respiratory cilia are complex structures that line the upper and lower airways, formed from more than 250 different proteins. The ciliary axoneme is the cytoskeleton of the cilium composed of microtubules[30]. Major structures that attach to the microtubules are the outer and inner dynein arms, which are the force-producing units for ciliary beating and bending. Primary ciliary dyskinesia (PCD) arises primarily from a defect in the dynein arms[31,32].

of bronchiectasis increase as age progresses[38] (Figure 5). Early diagnosis in childhood may enable the administration of appropriate treatment to delay, and possibly even prevent, the occurrence of bronchiectasis[39,40]. An association between PCD and pectus excavatum (9%) has also been identified[41], although a case of situs inversus totalis and pectus excavatum without the clinical phenotype of PCD has been reported[42]. Some patients with PCD have neither situs inversus totalis nor situs solitus, where some internal organs are located in the usual position, but others are in a mirrored position or in duplicate (heterotaxy). A recent review of 337 patients with PCD revealed that 6.3% had heterotaxy, most which had complex congenital heart disease[43]. For this reason patients with PCD should undergo cardiac evaluation, particularly those with heterotaxy, since the incidence of congenital heart disease is reported to be 200-fold higher in PCD than in the general population[43]. However, isolated situs inversus has a prevalence of about one in 10,000 in Scandinavia, and only about 20 to 25% of persons with situs inversus have bronchiectasis. About half of the men with PCD are infertile, which is entirely attributed to the poor motility of the live spermatozoa, although the sperm count is typically normal. Women with PCD correspondingly exhibit subfertility, with fewer than 50% successfully completing pregnancy[44]. The general prognosis of bronchiectasis due to PCD is good, as the rate of decline of lung function is much slower than that in CF.

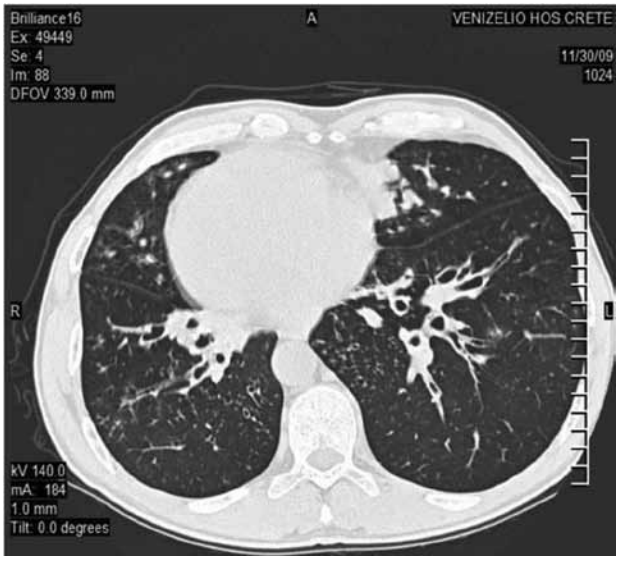

FIGURE 5. High resolution computed tomography (HRCT) scan of the chest of a 28 year-old patient with Kartagener's syndrome showing widespread bilateral bronchiectasis with a predilection for the central and lower lung fields, mucoid impaction and scattered centrilobular nodules along with patchy areas with tree-in-bud pattern. Note the presence of dextrocardia.

Bronchiectasis due to PCD has also been described in the Usher syndrome, an autosomal recessive disease characterised by congenital sensorineural deafness, involvement of the vestibular system and progressive visual loss owing to retinitis pigmentosa. The combined involvement of three sensory systems could be explained by the shared origin of photoreceptors and the auditory and vestibular hair cells from ciliated progenitor cells[45].

3. Young's syndrome (idiopathic obstructive azoospermia)

Young's syndrome, first described by a urologist named Donald Young in 1970[46], consists of a combination of bronchiectasis, chronic rhinosinusitis and infertility despite normal spermatogenesis, due to congenital vas deferens obstruction. The cause and pathogenesis of the syndrome are not known, nor has it been definitively established to be a hereditary disease. The combination of clinical manifestations suggests a common defect of the ciliated columnar epithelium at the various different sites. Although Young's syndrome has been proposed to be a variant of PCD, the respiratory cilia appear for the most part to have normal ultrastructure and beat pattern. There may, however, be some overlap between Young's syndrome and PCD, as unique variants of the syndrome have been described characterized by obstructive azoospermia associated with situs inversus totalis and slight defects of the cilia of the nasal mucosa[47,48]. Based on the abnormal rheological properties of mucus, it cannot be excluded as a *forme fruste* of CF[49], with milder clinical manifestations and normal sweat electrolyte concentration (Table 5). On the other hand, one possible aetiology of the syndrome is considered to be mercury exposure during childhood ("pink disease"), since a history of mercury intoxication (from teething powders and vermifuges which were formerly used) was elicited in some patients who later developed the syndrome. The subsequent observation of its reduction in incidence following the removal of such preparations from general availability led to the postulation of Hendry et al.[50] that this was the reason for the declining prevalence of Young's syndrome. The disease is probably overlooked and underreported because most patients have only mild respiratory disease that improves after adolescence, although severe progressive cases have also been reported. Physicians should keep the syndrome in mind when considering

TABLE 5. Differential diagnosis of syndromes consisting of bronchiectasis-sinusitis-male infertility

	Cystic fibrosis	Primary ciliary dyskinesia	Young's syndrome
Occurrence	Familial		Sporadic
Situs inversus	(-)	(+) / (-)	(-)
Sweat chloride	Elevated	Normal	
Seminal fluid	Azoospermia	Immotile sperms	Azoospermia
Cilia	Impaired function due to viscous mucus	Abnormal ultrastructure or beating	Primary or secondary dysfunction (?)
Vas deferens	Absent	Palpable	
Prominence of bronchiectasis	Upper lobes	Middle lobe and lingula	

male patients with sinopulmonary infections associated with infertility. In a study by Handelsman and associates[51] in Australia, the estimated prevalence of the syndrome among infertile men is comparable to that of Klinefelter's syndrome and higher than that of CF or PCD. In addition, Young's syndrome should always be included in the differential diagnosis of bronchiectasis. A study from the United Kingdom[52] found a prevalence of 3.3% of Young's syndrome among 150 adult patients with bronchiectasis.

4. Primary immune deficiencies

The PIDs comprise a heterogeneous group of genetic disorders that affect the development and maturation of innate or adaptive (humoral and cellular) immunity. The respiratory tract is profoundly affected by humoral immunodeficiency[53]. Humoral immunodeficiencies can vary from a complete failure of B-cell development to a decreased ability to produce some classes or subclasses of immunoglobulin, or a diminished ability to make an antigen-specific antibody response. Almost all of the original descriptions of primary B-cell deficiencies were in children, but the propensity for infection may not be so obvious in childhood, becoming apparent in adolescence or adulthood. Over the last decade, therefore, people aged 18 years and above constitute an increasing percentage of those identified to have PID. A recent retrospective analysis of children with a history of respiratory symptoms referred to a tertiary centre between 1996 and 2002 showed that as many as 9.6% had non-CF bronchiectasis, of which 21% had a form of immunodeficiency[5]. In a study that reviewed the aetiology of non-CF bronchiectasis in 136 paediatric patients monitored at 2 tertiary care institutions, PID was identified as the underlying cause in 46 subjects (33.8%)[11]. Regarding innate immunity, defects of neutrophil adhesion, respiratory burst, and chemotaxis rarely lead to bronchiectasis[52]. Most of the clinical investigation on the aetiological relationship between bronchiectasis and PID has focussed on patients with X-linked agammaglobulinaemia[54] and common variable immunodeficiency[55], these being the most common of the primary antibody deficiencies (Table 1).

The clinical significance of selective IgG subclass deficiency should be carefully evaluated, as testing has not been standardized and there are distinct difficulties in the accurate measurement of the levels, their "normal" ranges are variable and the levels increase with age[56]. In addition it is known that some individuals who are completely healthy have one or more missing IgG subclasses. Analysis of specific antibody production is more informative than measurement of the IgG subclasses[57]. A challenge with a provocative B-cell antigen, such as the pneumococcal vaccine or tetanus toxoid, might reveal a reduced specific antibody response, suggesting that the subclass deficiency is playing a role.

5. Alpha-1-antitrypsin deficiency

Deficiency of α1-antitrypsin (AAT), beyond being the only established genetic risk factor for chronic obstructive pulmonary disease (COPD), may also be associated with bronchiectasis, neonatal jaundice, juvenile hepatitis, cirrhosis, hepatocellular carcinoma and, much less frequently, vasculitis and panniculitis. The development of bronchiectasis, rather than emphysema, in adult life (Figure 6) is less common but has been documented in a few case reports. Only a few studies have assessed the association between AAT deficiency and bronchiectasis or bronchial wall thickening. In Eriksson's original study, bronchiectasis was reported in two of 23 patients[58]. In a

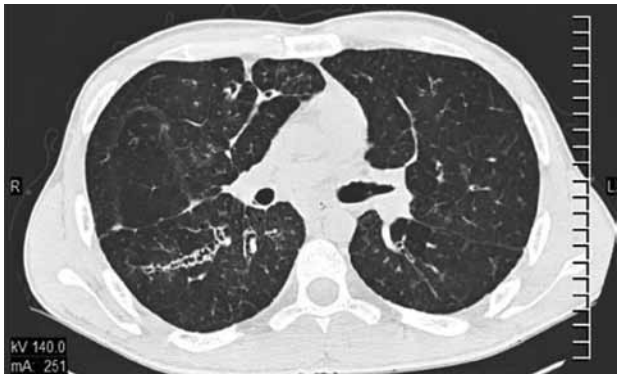

FIGURE 6. High resolution computed tomography (HRCT) scan of the chest of a 27 year-old patient with α1-antitrypsin deficiency showing varicose bronchiectasis accompanied by incipient emphysema, mainly in the right lung.

series of 17 patients with panlobular emphysema due to AAT deficiency, bronchial wall thickening and/or dilatation was observed in 7 and it was suggested that the deficiency "may directly affect the airways in addition to the lung parenchyma".[59] King et al[60] found evidence of multilobar bronchiectasis on CT scan in 6 of 14 patients with AAT deficiency, and the bronchiectasis was more common in the lobes with higher emphysema scores. A recent study[61] about airways disease in AAT-deficient subjects revealed that 70 of 74 subjects had radiological evidence of bronchiectasis and 20 (27%) were classified as having clinically significant bronchiectasis. On average, the airway lesions affected more than three lobes and the distribution mirrored that of emphysema, with significantly more airway disease in the lower lobes. This concordance may indicate that there is a regional interaction between the inflammatory processes considered to be causative of each condition. On the other hand, another study[62] showed that patients with bronchiectasis but without emphysema did not have AAT phenotype distribution and gene frequencies different from those of control subjects, in contrast to patients with both bronchiectasis and emphysema, suggesting that the bronchiectasis may be a consequence of emphysema rather than of AAT deficiency *per se*. Shin and Ho[63] suggested that the sequential clinical expression of AAT deficiency may be emphysema alone, emphysema with chronic bronchitis, and emphysema with chronic bronchitis and bronchiectasis. The occurrence of bronchiectasis in patients with emphysema is thought to be usually secondary to matrix destruction and pressure loss. Bronchiectasis may, however, appear in AAT-deficient patients who are exposed to repeated pulmonary infections, even before the development of emphysema[63]. It may be that some of the proteases released from phagocytes are more liable to cause bronchial wall damage if unopposed by antiproteases, and all these findings indicate the need for further characterization of airway disease to be included in future therapeutic strategies for AAT deficiency. A case-control study could be conducted to compare the prevalence of CT-diagnosed bronchiectasis in emphysema patients with and without AAT deficiency.

6. Williams-Campbell syndrome

In 1960, Williams and Campbell described 5 children with recurrent pulmonary infections, bronchographic findings of thin-walled bronchiectasis with the airway diameter fluctuating with respiration, and main histological findings of extensive cartilage deficiency in the subsegmental bronchial tree, from the fourth-generation to sixth- or eighth-generation bronchi[64]. Later, the name Williams-Campbell syndrome was given to the constellation of airway collapse, bronchiectasis, and bronchial cartilage deficiency. Since these initial reports, several further clinical and histopathological descriptions of the syndrome have been published, including cases with unilateral lung involvement[65] or with proximal airway involvement[66], but it is a rare form of congenital bronchiectasis. The cause of the cartilage deficiency is uncertain and there are no observable cartilage deficits other than in the bronchi. Its occurrence in siblings and the very early onset of symptoms suggest a congenital aetiology, although the disorder may also present sporadically. Occasionally, it is associated with other congenital abnormalities (congenital heart disease, bronchial isomerism, situs inversus), and there have been recent descriptions of the condition in adults, probably in an acquired form, following adenovirus, measles or pertussis infection[67]. The highly compliant bronchi render the cough mechanism inefficient for successful mucous drainage, as they collapse during forced expiration[68]. The lung distal to the bronchiectasis is often emphysematous. The clinical course of the syndrome is variable, and children have been described who rapidly progressed to respiratory failure and death while others survived into adulthood with recurrent infections and varying degrees of respiratory limitation. Documentation of long-term follow-up in patients with the Williams-Campbell syndrome is limited.

7. Mounier-Kuhn syndrome (tracheobronchomegaly)

Tracheobronchomegaly, first described by Mounier-

Kuhn in 1932[69], is characterized by marked dilatation of the tracheobronchial tree involving the trachea and main bronchi, but it may extend from the larynx to the periphery of the lungs, with recurrent lower respiratory tract infections[70]. A review of the world literature up to 2006 revealed less than 100 cases. The identification of some patients with minimal or no symptoms suggests that the incidence of the syndrome may be greater than suspected. The syndrome has been described predominantly in males, usually in their third and fourth decades of life, although cases have been reported at ages ranging from 18 months[71] to 76 years. A familial form has been described with possible recessive inheritance and acquired forms have been reported as a complication of pulmonary fibrosis in adults and of mechanical ventilation in preterm neonates. Secondary tracheobronchomegaly has also been described in association with the Ehlers-Danlos syndrome, the Kenny-Caffey syndrome[72], rheumatoid arthritis[73], ataxia-telangiectasia, ankylosing spondylitis[74] and cutis laxa, but the majority of cases appear to be sporadic. The aetiology is uncertain, but a congenital defect or atrophy of the smooth muscle and elastic connective tissue of the trachea and main bronchi have been reported in autopsy studies. As a result, mucosal herniations through the cartilaginous rings are developed, leading to saccular tracheal diverticulosis (most commonly originating from the right posterolateral wall), with retention of secretions and resultant chronic pulmonary suppuration, true bronchiectasis, and non-specific fibrosis. More specific manifestations are the development of steroid-unresponsive stridor and the occurrence of respiratory distress during feeding. Pulmonary function tests show an increase in the dead space and tidal volume. The diagnosis of tracheobronchomegaly should be considered in patients with recurrent pneumonia and chronic sputum production, and as a cause of chronic respiratory failure in young adults. A careful observation of the central airways on the chest X-ray of these patients is obligatory.

Congenital tracheomalacia refers to diffuse or localized weakness of the tracheal wall and may be part of a generalized chondrodystrophy. The affected portion is mainly intrathoracic, with accentuated obstruction during expiration. The condition occurs in primary (intrinsic abnormality of the tracheal wall) or secondary (extrinsic compression) forms, although either can be congenital, and occasionally other forms of tracheal dysplasia, such as tracheoesophageal fistula, may also be observed. Histopathological examination shows an increase in the ratio of muscle to cartilage. Tracheomalacia impairs the clearance of mucus and is associated with recurrent pneumonia. The disorder may persist into adult life and is often referred to interchangeably with the Mounier-Kuhn syndrome.

8. Bronchial atresia

Bronchial atresia is a rare congenital dysplasia characterized by a focal, juxtahilar interruption of the normal continuity of a segmental bronchus (the apicoposterior segmental bronchus of the left upper lobe being most commonly involved), which becomes sealed off from the proximal airway to which it remains connected by fibrous, vestigial strands[75]. More than 100 cases have been reported in the English language literature since 1953, when bronchial atresia was first described[76]. The bronchial tree proximal to the atresia is patent and the bronchi distal to the atresia maintain a branching pattern[77], but become filled with inspissated mucus not removable by ciliary action and become progressively dilated, forming a bronchocoele. Infections and scarring may ensue, with the presentation of associated symptoms. The alveoli supplied by the atretic bronchus are ventilated through collateral pathways by a check-valve type mechanism, resulting in trapping of air around the bronchocoele. The diagnosis is usually incidental, as a transradiant left upper zone on imaging draws attention to the anomaly, usually during the second or third decade of life. When diagnosed in young children, the clinical presentation may be more severe, including cases of respiratory distress[78]. Sometimes, bronchial atresia may resemble a "cavitary lesion" with the depiction of an air-fluid level in the region of bronchocoele[79] due to liquefaction of the impacted mucous as a result of an infection (Figure 7).

9. Intralobar sequestration

Intralobar sequestration (ILS) refers to a mass of non-functioning pulmonary tissue contiguous with adjacent normal lung parenchyma that does not communicate normally with the tracheobronchial tree[80]. The vast majority of lesions are situated in the posterior basal segment, approximately 2/3 being on the left and 1/3 on the right. ILS derives its arterial supply from the descending thoracic aorta or one of its branches via the inferior pulmonary ligament. In a number of cases, ILS is clearly congenital in origin, but in the majority it is acquired secondary to chronic bronchial obstruction and chronic infection[81]. The chief histopathological features are chronic inflammation, cystic change, and fibrosis. The cysts resemble dilated bronchi and are filled with mucus or, when infection is

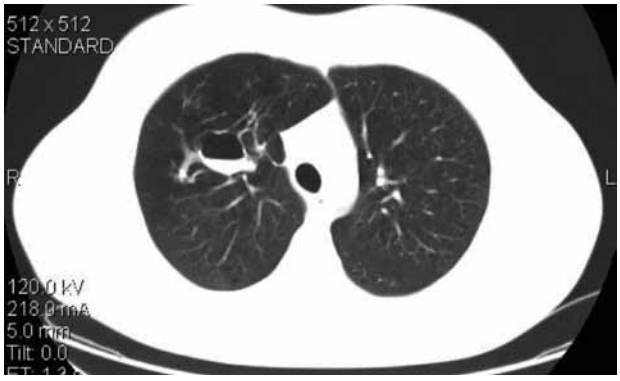

FIGURE 7. High resolution computed tomography (HRCT) scan of the chest of a 26 year-old patient with bronchial atresia showing a thin-walled cavity with an air-fluid level in it, instead of the typical bronchocele, in association with the typical findings of distal oligaemia and hyperlucency of the lung. (Reproduced from reference 79).

present, with pus. Symptoms (fever, cough, and sometimes haemoptysis) typically begin in the first or second decades of life, but may also arise in the middle-aged and elderly[82]. ILS should be suspected in young adults with nonresolving or recurrent lower lobe pneumonia[83]. Bronchiectasis may also occur within an ILS that contains disorganized, dilated and deformed bronchi[84]. The abnormal bronchi may communicate with normal surrounding lung tissue if the sequestration becomes complicated by infection and ruptures.

10. Yellow nail syndrome

Yellow nail syndrome is a rare entity first described in 1964 by Samman and White[85], and it is characterized by the triad of chronic lymphoedema, thickened, dystrophic yellow finger nails without clubbing and intractable pleural effusions. Individual manifestations of the syndrome can appear at different times and with variable severity, and the diagnosis can be established if two of the manifestations are present. Recently, it has been proposed that the frequent association of rhinosinusitis and bronchiectasis with the syndrome may warrant their recognition as integral features of the disease. The median age of diagnosis is 40 years, but it has been recognized as early as birth and as late as the seventh decade. The aetiology remains obscure; some authors have classified it as a hereditary disorder, transmitted in an autosomal-dominant fashion, while others have linked it to a variety of underlying diseases including connective tissue disease, malignancy, immunodeficiency states and endocrine disorders, or to an adverse drug reaction[86]. The pathophysiology of the syndrome remains unclear, but various anatomical and/or functional abnormalities of lymphatics have been proposed as the underlying cause, and recently microvasculopathy with protein leakage has been suggested to be more likely[87]. The occurrence of bronchiectasis is also difficult to explain, but is attributable to the impaired lymphatic drainage in the bronchi, which are normally supplied by a rich network of lymphatics. Various types of immunodeficiency described in earlier case reports that could account for bronchiectasis were not manifest in the population of a recent study at a tertiary referral medical centre[88]. The possibility of PCD as a cause for bronchiectasis in the yellow nail syndrome has been investigated and refuted[89].

DIAGNOSIS

The diagnosis of bronchiectasis is based on the detailed history, clinical features, and radiological demonstration of bronchiectatic airways. Ascertaining the aetiology of bronchiectasis provides many clinical benefits (Table 6) and the correct diagnosis permits the discontinuation of unnecessary and potentially dangerous medications, such as high-dose inhaled corticosteroids given for chronic cough attributed to "difficult to control asthma"[90]. Unfortunately, the symptoms of bronchiectasis can be very vague and, on many occasions, they do not point to the underlying aetiology. It was often regarded in the past as a condition in which extensive investigation is unlikely to yield treatable causes, but recent studies have produced results to change this concept. Pasteur et al[52], for example, in a cohort of patients with bronchiectasis identified a cause in 47% of cases. Li et al[11] in a study of 136 patients found a specific aetiology in 101 patients (74%), and, more

TABLE 6. Benefits of ascertaining the aetiology of bronchiectasis

1. Modification of treatment strategy
2. More accurate assessment of the benefits of forms of treatment that may vary in their efficacy in different groups
3. Identification of specific therapeutic regimen required (e.g., nutritional, Ig replacement, alpha-1-antitrypsin augmentation therapy, artificial fertilization)
4. Vigilance about specific extrapulmonary manifestations (pancreatic insufficiency, infertility, congenital heart disease, hearing loss, emphysema)
5. Prognosis assessment
6. Genetic counseling

important, in 77 of these patients the diagnoses led to significant changes in the management. Table 7 shows the diagnostic algorithm for the initial assessment of a patient with bronchiectasis.

The diagnostic role of imaging studies

A confident diagnosis of Williams-Campbell syndrome can be made on volumetric HRCT, which shows the characteristic distribution of bronchiectasis (bilateral and symmetrical in the subsegmental bronchi)[98], and CT bronchoscopy shows absence of the cartilage ring impressions in the bronchial wall[68].

Regarding the Mounier-Kuhn Syndrome, HRCT allows the precise airway measurement. In adults, the limits are 3cm for the transverse diameter of the trachea, and 2.4cm and 2.3cm for the transverse diameters of the right and left main bronchi, respectively[99]. The dilated bronchi typically have thin walls[100]. Dynamic CT scan shows

TABLE 7. Diagnostic algorithm for initial assessment of a patient with bronchiectasis

Detailed history
- Age at onset of symptoms
- Family history (affected siblings)

Clinical features
- Associated with bronchiectasis (sputum volume and constituents, frequency of exacerbations, digital clubbing, haemoptysis, adventitious breath sounds)
- Associated abnormalities (pancreatic insufficiency, infertility, congenital heart disease, pectus excavatum, lymphoedema)

Preliminary laboratory examination
- Complete blood cell count
- Erythrocyte sedimentation rate, C-reactive protein
- Quantitative assessment of serum immunoglobulins
- Pulmonary function tests
- Sputum culture (routine bacteria, mycobacteria, fungi)[a]

Imaging
- Chest X-ray
- High resolution computed tomography (HRCT) scan of the chest
- Imaging of the sinuses

Otorhinolaryngological evaluation

Screening for underlying cause
- Sweat chloride concentration
- Exhaled nNO/assessment of ciliary clearance with an aerosolized, isotopic tracer (99Tc)[91]
- Quantitation of IgG subclasses
- Serum α1-antitrypsin level[b]
- Sperm motility in males of appropriate age
- Specific IgE and precipitins (IgG) to Aspergillus
- Oesophageal pH monitoring

Specific examinations based on initial results and referral to specialized centre
- If suspected cystic fibrosis (CF) → Genetic testing for a CFTR mutation
- If suspected primary ciliary dyskinesia (PCD) → Analysis of ciliary ultrastructure (transmission electron microscopy) and function (high-speed video microscopy)[92,c]; genetic testing for DNAI1 and DNAH5 mutations[93]
- If suspected primary immunodeficiency (PID) → Immunization with a specific provocative antigen for analysis of specific antibody production, lymphocyte and neutrophil function studies
- If suspected alpha-1-antitrypsin deficiency (AATD) → Assessment of the genotype (PCR on dried blood-spot specimen) and phenotype (speed of migration of AAT on gel electrophoresis) of AAT

a: Sputum cultures showing mucoid *Pseudomonas aeruginosa, Staphylococcus aureus* or *Burkholderia cepacia* suggest CF as the underlying cause of bronchiectasis[94-96].

b: Testing has been recommended for all patients with bronchiectasis without evident aetiology[97].

c: Patients should be free of an acute upper respiratory tract infection for 4–6 weeks.

pronounced ballooning of the trachea and main bronchi on inspiration and collapse on expiration[100]. Similarly, the diagnosis of tracheobronchomalacia is suggested when a decrease of greater than 50% in the cross-sectional area of the central airway lumen is observed on dynamic CT expiratory imaging.

In bronchial atresia, volumetric HRCT affords excellent visualization of the mucoid impaction and segmental overinflation and hypovascularity, even in cases where the atresia affects non-typical segments of the lung[101]. These findings are considered pathognomonic for bronchial atresia by most authors[102,103], and help to differentiate between bronchial atresia and congenital lobar emphysema (absence of focal opacity) and bronchogenic cyst (absence of hyperinflation). Similar findings can sometimes be identified in other serious disorders, such as lung cancer or bronchial adenoma, which must be excluded by bronchoscopy that can also demonstrate the patency of the central bronchi in doubtful cases[72]. ILS appears on CT scanning as a complex mass with focal areas of lucency or irregular cystic spaces with or without fluid[104]. Less common findings include nodules, multiple dilated vessels, mucoid impaction, and foci of calcification. The lung adjacent to ILS frequently shows focal areas of emphysema and air trapping. Magnetic resonance (MR) angiography can also accurately map the aberrant vascular supply and optimally differentiate the cystic, solid, haemorrhagic, and mucous components of the mass, without the use of contrast material[105,106].

Although there is still controversy about whether the pattern of bronchiectasis distribution seen in the different diseases is sufficiently characteristic to suggest a specific diagnosis[107], characteristic locations have been described in bronchiectasis of specific aetiology (Table 8). Additional helpful features are the presence of bilateral, rather than unilateral, disease and the symmetry or asymmetry of the distribution. In spite of this a study by Lee et al[108] showed that the distribution of bronchiectasis overlapped greatly among the various causes, with the result that experienced chest radiologists could accurately diagnose the cause of bronchiectasis purely on HRCT appearances in only 45% of the cases, with a low level of agreement between them. In addition, HRCT performed very late into the disease process, when a spilling-over effect of the underlying disease may have occurred, may not permit correlation of the distribution of abnormalities with specific aetiology. The low percentage of confidence in specific HRCT diagnosis is also attributed to the wide range of abnormalities seen in any given condition. For milder or alternative forms of endobronchial infection (protracted bacterial bronchitis, chronic suppurative lung disease)[109], fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) has proved to be more sensitive than HRCT scan in detecting airway pathology, at least in small children, and should be considered complementary to HRCT in the diagnosis and staging of recurrent endobronchial infection[110]. For these reasons, the diagnosis of the various different causes of bronchiectasis cannot be reliably made on the basis of the HRCT appearance alone and the HRCT findings need to be interpreted in the specific clinical context, but using this approach the radiologist remains an integral partner in the diagnostic procedure.

TABLE 8. Presumptive distribution of congenital bronchiectasis

Location	Disease
Focal	• Congenital bronchial atresia (apical-posterior segment of left upper lobe) • Intralobar sequestration (posterior basal segment)
Diffuse	
Upper lung fields	• Cystic fibrosis
Central lung fields (also lower lobes in case of repeated infections)	• Primary ciliary dyskinesia • Young's syndrome • Mounier-Kuhn syndrome
Lower lung fields	• Hypogammaglobulinemia • Alpha-1-antitrypsin deficiency • Idiopathic

ΒΙΒΛΙΟΓΡΑΦΙΑ

1. Barker AF. Bronchiectasis. N Engl J Med 2002;346(18):1383-93
2. King P, Holdsworth S, Freezer N, Holmes P. Bronchiectasis. Int Med J 2006;36:729-37.
3. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Gallagher M, Holmes PW. Outcome in adult bronchiectasis. COPD 2005;2:27-34.
4. Karadag B, Karakoc F, Ersu R, Kut A, Bakac S, Dagli E. Non-cystic-fibrosis bronchiectasis in children: A persisting problem in developing countries. Respiration 2005;72:233-8.
5. Eastham KM, Fall AJ, Mitchell L, Spencer DA. The need to redefine non-cystic fibrosis bronchiectasis in childhood. Thorax 2004;59:324-7
6. Sturm R. Age-dependence and intersubject variability of tracheobronchial particle clearance. Pneumon 2011;24:77-85
7. Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. Eur Respir J 2008;31:396-406

8. Morrissey BM. Pathogenesis of bronchiectasis. Clin Chest Med 2007;28:289-96
9. King P. Bronchiectasis and chronic rhinosinusitis. Respir Med CME 2008;1:284-5
10. Fall A, Spencer D. Paediatric bronchiectasis in Europe: what now and where next? Paediatr Respir Rev 2006;7:268-74
11. Li AM, Sonnappa S, Lex C, et al. Non-CF bronchiectasis: does knowing the aetiology lead to changes in management? Eur Respir J 2005;26:8-14
12. J Angrill, C Agustí, R de Celis, et al. Bacterial colonization in patients with bronchiectasis: Microbiological pattern and risk factors. Thorax 2002; 57:15-9
13. Klingman KL, Pye A, Murphy TF, Hill SL. Dynamics of respiratory tract colonization by Branhamella catarrhalis in bronchiectasis. Am J Respir Crit Care Med 1995;152:1072-8
14. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Microbiologic follow-up study in adult bronchiectasis. Respir Med 2007;101:1633-8
15. Λουκίδης Σ. Ο ρόλος του συμπυκνώματος του εκπνεόμενου αέρα στην αξιολόγηση της φλεγμονής των αεραγωγών. Πνεύμων 2004;17:39-44
16. Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest 2007;132:1565-72
17. Karampela I, Dimopoulos G. Immunomodulatory actions of antibiotics. Pneumon 2008;21:33-44
18. Νικολούζος Σ, Σταματελόπουλος Α. Διαγνωστική και θεραπευτική προσέγγιση στη μαζική αιμόπτυση. Πνεύμων 2006;19:192-201
19. Pappas K, Pentheroudaki A, Ferdoutsis E, Meletis G, Patsourakis G, Bachlitzanakis N. Primary bronchiolar disorders: diagnosis and treatment. Pneumon 2010;23:64-79
20. Rossi UG, Owens CM. The radiology of chronic lung disease in children. Arch Dis Child 2005;90:601-7
21. Hansell DM. Bronchiectasis. Radiol Clin North Am 1998;36:107-28
22. Gupta S, Siddiqui S, Haldar P, et al. Qualitative analysis of high resolution computed tomography scans in severe asthma. Chest 2009;136:1521-8
23. Agarwal R. Bronchiectasis in acute pneumonia … Pseudobronchiectasis. Chest 2007;132:2054-5
24. Gershman AJ, Mehta AC, Infeld M, Budev MM. Cystic fibrosis in adults: an overview for the internist. Cleve Clin J Med 2006;73:1065-74
25. British Thoracic Society Working Group on Home Oxygen Services: Clinical component for the home oxygen service in England and Wales, 2004; www.brit-thoracic.org.uk/ public_content.asp
26. Ιγγλέζος Ηλ. Αναπνευστικά προβλήματα στον ενήλικα με κυστική ίνωση. Πνεύμων 2003;16:23-5
27. Fitzpatrick SB, Rosenstein BJ, Langbaum TS. Diagnosis of cystic fibrosis during adolescence. J Adolesc Health Care 1986;7:38-43
28. Fraser RS, Colman N, Müller NL, Paré PD. Disease of the airways. In: Fraser RS, Colman N, Müller NL, Paré PD (eds), Synopsis of Diseases of the Chest, 1st ed, Elsevier Saunders, Philadelphia;2005, pp 627-713
29. Brody AS, Klein JS, Molina PL, Quan J, Bean JA, Wilmott RW. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. J Pediatr 2004;145:32-8
30. Satir P, Christensen ST. Overview of structure and function of mammalian cilia. Annu Rev Physiol 2007;69:14.1-14.24
31. Bush A, Chodhari R, Collins N, et al. Primary ciliary dyskinesia: current state of the art. Arch Dis Child. 2007;92:1136-40
32. Geremek M, Witt M. Primary ciliary dyskinesia: genes, candidate genes and chromosomal regions. J Appl Genet 2004;45:347-61
33. Kartagener M, Stucki P. Bronchiectasis with situs inversus. Arch Pediatr 1962;79:193-207
34. Narayan D, Krishnan SN, Upender M, et al. Unusual inheritance of primary ciliary dyskinesia (Kartagener's syndrome). J Med Genet 1994;31:493-6
35. Noone PG, Leigh MW, Sannuti A, et al. Primary ciliary dyskinesia: diagnostic and phenotypic features. Am J Respir Crit Care Med 2004;169:459-67
36. Hünseler C, Lange L, Kribs A, Vierzig A, Roth B. Primary ciliary dyskinesia causing neonatal respiratory distress. Klin Padiatr 2009;221:440-3
37. Leigh MW, Zariwala MA, Knowles MR. Primary ciliary dyskinesia: improving the diagnostic approach. Curr Opin Pediatr 2009;21:320-5
38. Kennedy MP, Noone PG, Leight MW, et al. High-resolution CT of patients with primary ciliary dyskinesia. AJR Am J Roentgenol 2007;188:1232-8
39. Coren ME, Meeks M, Morrison I, Buchdahl RM, Bush A. Primary ciliary dyskinesia: age at diagnosis and symptom history. Acta Paediatr 2002;91:667-9
40. Ellerman A, Bisgaard H. Longitudinal study of lung function in a cohort of primary ciliary dyskinesia. Eur Respir J 1997;10:2376-9
41. Mead J, Sly P, Le Souef P, Hibbert M, Phelan P. Rib cage mobility in pectus excavatum. Am Rev Respir Dis 1985;132:1223-8
42. Eroglu A, Kurkcuoglu IC, Karaoglanoglu N, Ikbal M. Pectus excavatum and situs inversus totalis: a new combination or a coincidence? Genet Couns 2004;15:227-8
43. Kennedy MP, Omran H, Leigh MW, et al. Congenital heart disease and other heterotaxic defects in a large cohort of patients with primary ciliary dyskinesia. Circulation 2007;115:2814-21
44. Afzelius BA, Mossberg B, Bergström SE. Immotile-cilia syndrome (primary ciliary dyskinesia) including Kartagener syndrome. In: Scriver, CR, Beaudet, AL, Sly, WS, Vale, D (eds), The Metabolic and Molecular Bases of Inherited Disease, 8th ed, McGraw Hill, New York;2001, pp 4817–27
45. Bonneau D, Raymond F, Kremer C, Klossek JM, Kaplan J, Patte F. Usher syndrome type I associated with bronchiectasis and immotile nasal cilia in two brothers. J Med Genet 1993;30:253-4
46. Young D. Surgical treatment of male infertility. J Reprod Fertil 1970;23:541-2
47. Shiraishi K, Ono N, Eguchi S, Mohri J, Kamiryo Y, Takihara H. Young's syndrome associated with situs inversus totalis. Arch

Androl 2004;50:169-72
48. Ichioka K, Kohei N, Okubo K, Nishiyama H, Terai A. Obstructive azoospermia associated with chronic sinopulmonary infection and situs inversus totalis. Urology 2006;68:204.e5-7
49. Friedman KJ, Teichtahl H, De Kretser DM, et al. Screening Young syndrome patients for CFTR mutations. Am J Respir Crit Care Med 1995;152(4 Pt 1):1353-7
50. Hendry WF, A'Hern RP, Cole PJ. Was Young's syndrome caused by exposure to mercury in childhood? Br Med J 1993;307:1579-82
51. Handelsman DJ, Conway AJ, Boylan LM, Turtle JR. Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections. N Engl J Med 1984;310:3-9
52. Pasteur MC, Helliwell SM, Houghton SJ, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 2000;162(4 Pt 1):1277-84
53. Zeimpekoglou K. The role of B-lymphocytes in lung disease. Pneumon 2008; 21:196–9
54. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 2006;85:193-202
55. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 1999;92:34-48
56. Hill SL, Mitchell JL, Burnett D, Stockley RA. IgG subclasses in the serum and sputum from patients with bronchiectasis. Thorax 1998;53:463-8
57. Maguire GA, Kumararatne DS, Joyce HJ. Are there any clinical indications for measuring IgG subclasses? Ann Clin Biochem 2002;39(Pt 4):374-7
58. Eriksson S. Studies in alpha-1 antitrypsin deficiency. Acta Med Scand 1965;177:1-85
59. Guest PJ. Hansell DM. High resolution computed tomography (HRCT) in emphysema associated with alpha-1-antitrypsin deficiency. Clin Radiol 1992;45:260-6
60. King MA, Stone JA, Diaz PT, Mueller CF, Becker WJ, Gadek JE. Alpha 1-antitrypsin deficiency: evaluation of bronchiectasis with CT. Radiology 1996;199:137-41
61. Parr DG, Guest PG, Reynolds JH, Dowson LJ, Stockley RA. Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med 2007;176:1215-21
62. Cuvelier A, Muir JF, Hellot MF, et al. Distribution of alpha(1)-antitrypsin alleles in patients with bronchiectasis. Chest 2000;117:415-9
63. Shin MS, Ho KJ. Bronchiectasis in patients with alpha 1-antitrypsin deficiency. A rare occurrence? Chest 1993;104:1384-6
64. Williams H, Campbell P. Generalized bronchiectasis associated with deficiency of cartilage in the bronchial tree. Arch Dis Child 1960;35:182-91
65. Shankar G, Kothari P, Sarda D, Kulkarni B, Kalgutkar A. Pneumonectomy in a child with congenital bronchiectasis: A case report and review of literature. Ann Thorac Med 2006;1:81-3
66. Palmer SM Jr, Layish DT, Kussin PS, Oury T, Davis RD, Tapson VF. Lung Transplantation for Williams-Campbell Syndrome. Chest 1998;113;534-7
67. McAdams HP, Erasmus J. Chest case of the day: Williams-Campbell syndrome. AJR Am J Roentgenol 1995;165:190-1
68. George J, Jain R, Tariq SM. CT bronchoscopy in the diagnosis of Williams-Campbell syndrome. Respirology 2006;11:117-9
69. Mounier-Kuhn P. Dilatation de la trachee: constatations radiographiques et bronchoscopiques. [Tracheal diatation: radiography and bronchoscopy findings]. Lyon Med 1932;150:106-9
70. Marques A, Filix M, Barata F, et al. Mounier-Kuhn syndrome: a rare etiology of recurrent respiratory tract infections. Rev Port Pneumol 2007;13:721-7
71. Hubbard M, Masters IB, Chang AB. Rapidly progressing case of Mounier-Kuhn Syndrome in early childhood. Pediatr Pulmonol 2003;36:353-6
72. Sane AC, Effmann EL, Brown SD. Tracheobronchiomegaly: the Mounier-Kuhn syndrome in a patient with the Kenny-Caffey syndrome. Chest 1992;102:618–9
73. Celenk C, Celenk P, Selçuk MB, Ozyazici B, Kuru O. Tracheomegaly in association with rheumatoid arthritis. Eur Radiol 2000;10:1792-4
74. Padley S, Varma N, Flower CD. Tracheobronchomegaly in association with ankylosing spondylitis. Clin Radiol 1991;43:139-41
75. Ward S, Morcos SK. Congenital bronchial atresia: presentation of three cases and a pictorial review. Clin Radiol 1999;54:144-8
76. Ramsey BH, Byron FX. Mucocele, congenital bronchiectasis and bronchogenic cyst. J Thorac Surg 1953;26:21-30
77. Pedicelli G, Ciarpaglini LL, De Santis M, Leonetti C. Congenital bronchial atresia (CBA): a critical review of CBA as a disease entity and presentation of a case series. Radiol Med 2005;110:544-53
78. Morikawa N, Kuroda T, Honna T, et al. Congenital bronchial atresia in infants and children. J Pediatr Surg 2005;40:1822-6
79. Psathakis K, Eleftheriou D, Boulas P, Mermigkis C, Tsintiris K. Congenital bronchial atresia presenting as a cavitary lesion on chest radiography: a case report. Cases J 2009;2:17
80. Cooke CR. Bronchopulmonary sequestration. Respir Care 2006;51:661-4
81. Stoker JT, Malczak HT. A study of pulmonary ligament arteries: relationship to intralobar sequestration. Chest 1984;86:611-5
82. Petersen G, Martin U, Singhal A, Criner GJ. Intralobar sequestration in the middle-aged and elderly adult: recognition and radiographic evaluation. J Thorac Cardiovasc Surg 2003;126:2086-90
83. Spartalis E, Lachanas E, Pavlopoulos D, Michail O, Karakatsani A, Tomos P. Two cases of broncho-pulmonary foregut malformations. Pneumon 2009;22:182–5
84. Bolman RM, Wolfe WC. Bronchiectasis and bronchopulmonary sequestration. Surg Clin North Am 1980;60:867-81
85. Samman PD, White WF. The "yellow nail" syndrome. Br J Dermatol 1964; 76:153-7
86. Hoque SR, Mansour S, Mortimer PS. Yellow nail syndrome: not a genetic disorder? Eleven new cases and a review of the literature. Br J Dermatol 2007;156:1230-4
87. D'Alessandro A, Muzi G, Monaco A, Filiberto S, Barboni A, Abbritti G. Yellow nail syndrome: does protein leakage play a role? Eur Respir J 2001;17:149-52

88. Maldonado F, Tazelaar HD, Wang CW, Ryu JH. Yellow nail syndrome: analysis of 41 consecutive patients. Chest 2008;134:375-81
89. Miro AM, Vasudevan V, Shah H. Ciliary motility in two patients with yellow nail syndrome and recurrent sinopulmonary infections. Am Rev Respir Dis 1990;142:890-1
90. Shields MD, Bush A, Everard ML, McKenzie S, Primhak R. BTS guidelines: Recommendations for the assessment and management of cough in children. Thorax 2008;63 Suppl 3:iii1-iii15
91. De Boeck K, Proesmans M, Mortelmans L, Van Billoen B, Willems T, Jorissen M. Mucociliary transport using 99mTc-albumin colloid: a reliable screening test for primary ciliary dyskinesia. Thorax 2005;60:414-7
92. Rosen MJ. Chronic cough due to bronchiectasis: ACCP evidence-based clinical practice guidelines. Chest 2006;129:122S-31S
93. Morillas HN, Zariwala M, Knowles MR. Genetic causes of bronchiectasis: primary ciliary dyskinesia. Respiration 2007;74:252-63
94. Li Z, Kosorok MR, Farrell PM, et al. Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children with cystic fibrosis. JAMA 2005;293:581-8
95. Shah P, Mawdsley S, Nash K, Cullinan P, Cole PJ, Wilson R. Determinants of chronic infection with Staphylococcus aureus in patients with bronchiectasis. Eur Respir J 1999;14:1340-4
96. Nick JA, Rodman DM. Manifestations of cystic fibrosis diagnosed in adulthood. Curr Opin Pulm Med 2005;11:513-8
97. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med 2003;168:818-900
98. Hartman TE, Primack SL, Lee KS, Swensen SJ, Müller NL. CT of bronchial and bronchiolar diseases. Radiographics 1994;14:991-1003
99. Fortuna FP, Irion K, Wink C, Boemo JL. Mounier Kuhn syndrome. J Bras Pneumol 2006;32:180-3
100. Newell JDJ, Chan ED, Martin RJ. Imaging of airway disease. In: Lynch DA, Newell JDJ, Lee JS (eds), Imaging of Diffuse Lung Disease, 1 ed, B.C. Deeker Inc, Hamilton;2000, pp 171-97
101. Beigelman C, Howarth NR, Chartrand-Lefebvre C, Grenier P. Congenital anomalies of tracheobronchial branching patterns: spiral CT aspects in adults. Eur Radiol 1998;8:79-85
102. Matsushima H, Takayanagi N, Satoh M, et al. Congenital bronchial atresia: radiologic findings in nine patients. J Comput Assist Tomogr 2002;26:860-4
103. Mata JM, Caceres J, Lucaya J, Garcia-Conesa JA. CT of congenital malformations of the lung. RadioGraphics 1990;10:651-74
104. Ahmed M, Jacobi V, Vogl TJ. Multislice CT and CT angiography for non-invasive evaluation of bronchopulmonary sequestration. Eur Radiol 2004;14:2141-3
105. Deguchi E, Furukawa T, Ono S, Aoi S, Kimura O, Iwai N. Intralobar pulmonary sequestration diagnosed by MR angiography. Pediatr Surg Int 2005;21:576-7
106. Berrocal T, Madrid C, Novo S, Gutiérrez J, Arjonilla A, Gómez-León N. Congenital anomalies of the tracheobronchial tree, lung, and mediastinum: embryology, radiology, and pathology. Radiographics 2004;24:e17
107. Reiff DB, Wells AU, Carr DH, Cole PJ, Hansell DM. CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. AJR Am J Roentgenol 1995;165:261-7
108. Lee PH, Carr DH, Rubens MB, Cole P, Hansell DM. Accuracy of CT in predicting the cause of bronchiectasis. Clin Radiol 1995;50:839-41
109. Chang AB, Redding GJ, Everard ML. Chronic wet cough: Protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol 2008;43:519-31
110. Douros K, Alexopoulou E, Nicopoulou A, et al. Bronchoscopic and High-Resolution CT Scan Findings in Children With Chronic Wet Cough. Chest 2011;140:317-23