History and Epidemiology

Before the advent of antibiotics and the widespread practice of immunizing against childhood diseases, bronchiectasis was a common condition, and the prognosis was generally poor. A report published in 1940 based on follow-up of 400 individuals with bronchiectasis states that bronchiectasis was the primary or secondary cause in 92% of the mortality. Seventy percent of fatalities occurred before the age of 40.

Beginning in the mid 1950s, however, immunization campaigns and effective antimicrobial agents caused a sharp reduction in the incidence of childhood infections. The prognosis for bronchiectasis improved, and its prevalence declined. A 1969 study reported 50% of bronchiectasis patients died of their disease, but at an average age of 55. By the 1970s, fewer than 10% of patients included in follow-up studies died of that cause.

Recently however, bronchiectasis has reemerged as a serious health risk; especially in less developed countries, and among population subgroups where preventive and therapeutic interventions are poorly distributed. A 1981 review of 116 British patients followed for 14 years reported that 19% died of bronchiectasis at an average age of 54. In Finland, a nation with exemplary healthcare services, a 1997 study of 842 individuals aged 35-74 with bronchiectasis reported significant morbidity and a mortality rate of 13%.

Evidence reported in the recent literature indicates that currently, bronchiectasis is frequently underrecognized and underdiagnosed. Moreover, until recently, understanding of the etiology and pathogenesis of bronchiectasis has been inadequate. In the past few years, however, epidemiological and scientific aspects have prompted renewed interest in the study of bronchiectasis:

Epidemiological factors

- Bronchiectasis is now recognized as a major manifestation of disease progression in cystic fibrosis (CF), ciliary dyskinetic syndromes, and some immune deficiency syndromes. The increased survival of such patients in response to therapeutic advances is associated with a sharp increase in clinically significant bronchiectasis. In Western Europe and the U.S., cystic fibrosis is the leading cause of advanced bronchiectasis. In high resolution computed tomographic assessments of pulmonary involvement of 117 CF patients ranging in age from infancy to adult, 80% demonstrated bronchiectasis. In studies limited to adult patients, 90-100% demonstrate radiographic evidence of bronchiectasis.

- As a concomitant of the HIV epidemic, there have been dramatic rises in the incidence of opportunistic infections, including Pneumocystis carinii and pulmonary tuberculosis. In affected individuals, bronchiectasis may develop rapidly. The majority of immune-compromised patients with chronic...
symptomatic lung disease show radiologic evidence of bronchiectasis.25

• Bronchiectasis is recognized as an important complication of heart, lung, and bone marrow transplantation related to recurrent infection and graft versus host disease.26, 27

Scientific factors
• High resolution computed tomography (HRCT) has revolutionized the imaging of bronchi, allowing early detection and providing new information.28 It is now possible to detect bronchiectasis early. Recognition of associated clinical manifestations add to understanding of associations between clinical features and structural abnormalities in the airways is progressing.29

• Recent studies of mycobacterial diseases, including tuberculosis, suggest that these organisms have both primary and secondary roles in bronchiectasis.30

• Genetics advances have stimulated research to discover abnormalities associated with bronchiectasis.31,32,33

Etiology
Bronchiectasis is a destructive, self-perpetuating process initiated by a broad spectrum of clinical diseases and conditions. In general, infection and obstruction are the underlying causes leading to the development of dilated i.e. bronchiectatic airways.34 Today, causative organisms are most commonly opportunistic and frequently antibiotic-resistant, rather than the generic childhood bacterial or viral infections of the past.35 Airway obstruction in bronchiectasis occurs as a consequence of mucus plugging associated either with the infectious process or with a defect in mucociliary clearance.36 The list of clinical conditions predisposing to infection or obstruction is impressive, and includes hilar adenopathy, aspirated foreign bodies, congenital tracheobronchial, vascular, or lymphatic anomalies and tumors. Previously, certain genetic abnormalities were presumed significant factors in bronchiectasis. However, recent research suggests that although a complex array of factors, including genetic disease, may increase susceptibility to bronchiectasis, the condition is fundamentally the result of structural damage caused by prior bacterial or viral bronchial infection.37 In a retrospective study of elderly individuals with the established diagnosis of bronchiectasis, prior infection was the common denominator.38 However, infection and/or obstruction remain the necessary antecedents of bronchiectasis.39

In summary, causative factors are:
• postinfective bronchial damage (bacterial, viral, fungal, protozoan)
• mechanical bronchial obstruction (foreign body, tumor, lymph node mass)
• congenital structural abnormalities (bronchial wall abnormalities, etc.)
• immune deficiency (hypogammaglobulinemia, HIV, malignancy)
• immunological hyperresponse (allergic bronchopulmonary aspergillosis, post-organ transplant rejection)
• mucociliary clearance defects (cystic fibrosis, primary and secondary ciliary dyskinesia, Young’s syndrome)
• granulomata and fibrosis (tuberculosis, sarcoidosis, etc.)

Pathology/Pathogenesis
The pathology of bronchiectasis covers a broad spectrum. The primary feature of the condition, marked dilation of the airways in affected regions of the lung, is visible on gross inspection. Three specific patterns of airway dilation are recognized; cylindrical, varicose, and saccular.40 For practical purposes, however, morphologic classification is not as relevant as the extent of mucociliary dysfunction.41

In the pathogenic sequence recognized in bronchiectasis, bronchial dilation, inflammation, and weakening cause airway distortion and scarring, altering both the structure and function of the mucociliary apparatus. Secretion clearance is impaired. Bronchial inflammation, characterized by neutrophil infiltration, results in increased protease activity, which in turn leads to more mucus hypersecretion and further airway destruction. In addition, the toxic byproducts of inflammation precipitate rheological changes in airway mucus, and it becomes thick and tenacious.42 Typically, affected passages are filled with large quantities of frequently purulent mucus. Microscopic examination of bronchial tissues demonstrate severe damage to squamous epithelia, cilia, and associated structures.43

Three major mechanisms contribute to the destruction of bronchial tissue: infection, airway obstruction, and peribronchial fibrosis.

Infection and inflammation
Inflammation, usually initiated by infection, is recognized as the critical factor in the pathogenesis of bronchiectasis.44,45,46 In healthy individuals, a brief, controlled inflammatory response is generally successful in protecting against microorganisms that have entered the upper and lower respiratory tract. In compromised hosts, inflammatory defense mechanisms fail to eliminate such organisms, which then colonize the respiratory tract. In response, inflammation is intensified and becomes
chronic. Powerful chemoattractants continue to recruit inflammatory cells including neutrophils and macrophages to the site of infection, releasing increasing quantities of cytotoxic agents. In effective inflammatory responses, these agents, called proteolytic enzymes, are neutralized by corresponding antiproteolytic agents, preventing damage to adjacent tissues. When inflammation persists, an ongoing chemical reaction ensues, resulting in progressive, irreversible damage to both the bronchial wall and airway cilia. Significant mucus hypersecretion and retention is a consequence of such damage.

**Airway obstruction and ciliary dysfunction**

Airway obstruction develops when mucus plugging and infection occur together in association with dysfunctional cilia. In healthy individuals, airway secretions are cleared by several mechanisms, including the mucociliary escalator, cough, peristalsis, two-phase gas-liquid flow and alveolar clearance. Cilia lining the conducting airways move mucus cephalad into the central airways so that it can be swallowed or expectorated. The efficiency of this complex mechanism is influenced by several factors, including the structure, number, movement, and coordination of the cilia present in the airways as well as the amount, composition, and rheological properties of mucus.

In bronchiectasis, a generalized impairment of mucociliary clearance is present, either as a component of a pre-existing condition such as primary ciliary dyskinesia, or as a result of chronic inflammation. Ciliary impairment occurs in both localized and diffuse disease. Mucus clearance is moderately to markedly impaired. Studies of the biochemistry of the lung suggest that several factors are involved in causing damage to clearance mechanisms. It is well known that excess neutrophil elastase and other toxic byproducts of the inflammatory process disrupt both the structure and function of airway cilia. In addition, certain colonized microorganisms release substances that damage host cilia and reduce their motility. Further, those bacteria may be chemotactic for leucocytes, preventing the inflammatory reaction from subsiding.

**Peribronchial fibrosis**

Simultaneously, there is lysis of elastic tissue in the bronchial walls, and thickening and fibrosis occur. Multiple abscesses may develop in these peribronchial areas, contributing to excess tracheobronchial secretions, impaired mucociliary clearance and chronic infection.

**Clinical features**

Clinical findings in individuals with bronchiectasis are characteristic, but not specific. Typically, bronchiectasis follows a relapsing, remitting course. In contrast to patients with classical COPD, bronchiectasis is not related to tobacco smoking. In contrast to studies of older patients with chronic bronchitis, in which the majority are male, two-thirds of older bronchiectasis patients are female. As a result of complications associated with chronic infection, most bronchiectasis patients are underweight. Typical bronchiectasis patients exhibit symptoms including:

**Mucus hypersecretion**

Clinically active bronchiectasis is characterized by the production and expectoration of large quantities of sputum. The volume of mucus hypersecretion is in proportional to the extent of inflammatory damage to both the secretory apparatus and the mucociliary clearance system.

**Cough**

Patients with bronchiectasis typically produce more than 100 ml of mucus daily; some more than 500 ml. The effort to expectorate this mucus may result in persistent, sometimes convulsive coughing episodes. Cough may be ineffective both because impaired mucociliary apparatus fail to mobilize secretions to the central airways and because changes in the rheological properties of mucus make it difficult to shear from tracheal walls.

**Hemoptysis**

Significant hemoptysis is a feature of advanced bronchiectasis. In response to severe inflammatory changes in the bronchial wall, the blood supply is increased and the vessels may rupture.

**Rales**

There may be few auscultatory findings, or pronounced rales, rhonchi, and wheezing.

**Digital clubbing**

Frequently, bronchiectasis patients exhibit bulbous swelling of the terminal phylanges of the fingers and toes. This phenomenon is associated with the chronic supplicative process and sometimes with arterial hypoxia.

**Respiratory insufficiency and congestive heart failure**

Progressive respiratory insufficiency, congestive heart failure, and sepsis are the most common causes of
pulmonary-related death in patients with advanced bronchiectasis.

**Pulmonary function tests (PFTs)**

No specific pattern of pulmonary malfunction is evident in bronchiectasis, but individual pulmonary function scores may reflect combinations of obstructive and restrictive pathology. In localized disease, functional impairment is rare. In patients with significant atelectasis, pulmonary function test (PFT) results indicate restrictive disease, including reduced vital capacity (VC), functional residual capacity (FRC), and total lung capacity (TLC). In diffuse disease, PFTs are similar to those found in other COPDs.

**Treatment**

Bronchiectasis is a serious, debilitating, and increasingly prevalent disease. New descriptive data and improved diagnostic techniques permit early recognition and accurate diagnosis. Likewise, research has improved understanding of the etiology and pathophysiology of the condition, permitting timely, effective therapeutic interventions. Previously, bronchiectasis was viewed as an advanced stage in the natural progression of a variety of diseases and conditions. Currently, however, data on the pathophysiology of bronchiectasis suggests that certain diseases and conditions, such as uncontrolled infection, cystic fibrosis, ciliary dyskinesia, and immunological defects, are viewed more accurately as risk factors rather than as of specific causes. The common denominator that unifies diseases and conditions associated with bronchiectasis is their ability to increase susceptibility to the classic vicious cycle of pulmonary infection.

Patients with risk factors predisposing them to the development of bronchiectasis require preventative strategies. In patients presenting with clinical evidence of bronchiectasis, underlying pathologies must be identified to prevent disease progression. Although the etiology of bronchiectasis is complex and varied, the components of treatment are well established. Appropriate physical and pharmacologic interventions must be implemented to control infection and disease progression, relieve bronchial obstruction, and improve ventilation and gas exchange.

**Antibiotics**

Effective use of antibiotics, usually for acute exacerbations, successfully prevents disease progression both by eliminating or reducing bacteria populations and by decreasing harmful enzymes associated with the inflammatory response. Not all patients respond to antibiotics alone. Patients may be infected or colonized with antibiotic-resistant organisms, or have significant defects of the mucociliary apparatus, exuberant inflammation, or advanced disease which confound antibiotic treatment. Effectiveness of antibiotic therapy is further limited by increases in the variety and resistance of nosocomial organisms in populations of immune-compromised patients.

**Mucociliary stimulants**

A variety of pharmaceutical agents have been prescribed as adjunct therapies to enhance mucociliary clearance. Among them, dry powder mannitol may be beneficial.

**Mucolytic agents**

Mucolytic agents have little or minimal effect on secretion clearance and are rarely prescribed.

**Steroids**

Steroids may be prescribed for exacerbations of bronchiectasis, but their usefulness is unclear.

**Bronchodilators**

Bronchodilators are prescribed for selected bronchiectasis patients with concurrent reactive airway disease.

**Surgery**

Although surgical resection is a controversial therapeutic intervention, it may be performed to treat localized symptomatic bronchiectasis. In younger patients with severe, generalized disease and respiratory failure, bilateral lung transplantation is an option.

**Airway clearance therapy**

The central role of retained secretions in initiating and perpetuating the bronchiectatic process is supported by abundant research. Mucus hypersecretion is both the cause and the effect of the destructive events characterizing bronchiectasis. Uncleared secretions nurture organisms that trigger the vicious cycle of pulmonary infection, support chronic inflammation, and retain high concentrations of these cytotoxic byproducts. Also, mucus is the medium transporting the chemicals that damage ciliary apparatus and other components of the lung defense system. Excess mucus not only facilitates destruction of clearance mechanisms; certain rheological alterations make the mucus tenacious. Retained secretions further promote and exacerbate bronchiectasis by obstructing airways and interfering with ventilation and gas exchange.

Today, with new understanding of the etiology and pathogenesis of bronchiectasis, treatment must focus upon prevention or early intervention. With current knowledge of diseases and conditions that increase the risk of developing bronchiectasis, as well as awareness of dangers associated with excessive use of antibiotics, a new approach to therapy is indicated. Because bronchiectasis is a consequence of a well-defined cascade of pathological events, it is imperative...
to prevent patients’ initiation into the vicious cycle. If the infectious cycle is already established, therapy should be designed to limit disease progression.9

With the implementation of aggressive, effective airway clearance therapy, pathogenic microorganisms and inflammatory byproducts are removed. Such therapy mobilizes retained secretions, augments mucociliary transport, and enhances clearance of thick mucus.77 Because bacterial colonization and irreversible damage from mucus plugging occurs most frequently in the peripheral airways, it is important to utilize a modality that treats all regions of the lungs and reliably mobilizes mucus from small as well as large airways.

References
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3 As diagnostic entities, COPD per se may be regarded as a progressive disease resistant to treatment, asthma as a progressive condition which can be managed with therapy including anti-inflammatory agents, and bronchiectasis as a condition characterized by an inflammatory "vicious circle" which may be managed by aggressive interventions. Keistinen T, Saynajakangas O, Tuuponen T, Kivela SL. Bronchiectasis: an orphan disease with a poorly understood prognosis. Eur Respir J. 1997; 10: 3787-2787.

4 Mysliwiec, et al. op cite, (n. 1).


6 Cole (1986) proposed a “vicious circle” hypothesis with the following elements to describe the pathophysiological events that define bronchiectasis: "An initial insult to the tissue, usually a pneumonitis, must occur. The resulting damage to the respiratory tract compromises mucociliary-clearance mechanisms and allows propagation of microbes that are not eliminated by the normal inflammatory response. The poor clearance of the microorganisms, therefore, and their longer stay in the damaged area, allow them to gain a foothold with resultant colonization. These resident organisms then provoke an increased inflammatory response in the area of the bronchus. This response itself is damaging, through delivery of destructive enzymes by inflammatory cells. Increased destruction leads to further damage, and the situation is perpetuated. In addition, the microorganisms themselves may be the cause of damage to the clearance mechanisms, by disrupting normal ciliary function necessary to clear the lumen of debris and secretions. Cole PJ. Inflammation: a two-edged sword—the model of bronchiectasis. Eur J Respir Dis 1986; 16 (suppl 147): 6-15.

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8 Sir William Osler, the preeminent medical educator of his day, suggested that bronchiectasis was a result of bronchial wall inflammation and bronchial obstruction resulting from secretion retention. Osler recognized that conditions including suppurrative pneumonias of childhood, chronic tuberculosis, and the aspiration of foreign bodies were common antecedents of bronchiectasis. Osler W. The Principles and Practice of Medicine. New York, NY, Appleton 1892 (Special Edition: Birmingham, AL, The Classics of Medicine Library. 1978, pp 495-497).

9 Among patients who died during the study period 1926-1938, bronchiectasis was listed as the primary cause of death in 78%, and as a primary or secondary cause in 92%. Methodological and demographic factors notwithstanding, the figures are impressive. Perry KMA, King DS, Bronchiectasis: a study of prognosis based on follow-up of 400 patients. Am Rev Tuberc 1940; 41: 531-548.


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14 Ellis, op cite, (n.11).

15 In an effort to assess the long-term prognosis for bronchiectasis patients, investigators reviewed the Finnish National Hospital Discharge Register to search for patients aged 35-74 newly diagnosed with bronchiectasis between 1982-1986. Each of the 842 patients identified was then matched by age and sex with a COPD patient and an asthmatic patient. Bronchiectasis proved to be the main cause of death in 13% of those in that group, and, relative to the bronchiectasis patients, the risk of death was greater for the COPD patients and lower for the asthmatics. Keistinen, op cite, (n. 3).
This is exemplified by alpha1-antitrypsin deficiency, in which an important in determining the development and extent of airway damage.

The balance between proteolytic and antiproteolytic secretions is not be screened meticulously for genetic disease, only five of 38 patients infected prior to developing bronchiectasis. Although all subjects could produce at least 100 ml. A minority of patients whose bronchiectasis is confined to the upper lobes, such as that due to Mycobacterium tuberculosis, do not pool secretions, resulting in so-called “dry bronchiectasis.”

Research suggests that, in a subgroup of patients, generalized impairment of mucociliary transport is a major factor in their eventual development of bronchiectasis. This subgroup includes patients with congenital defects as well as patients acquiring widespread damage to their mucociliary systems early in life, possibly due to infections. In fact, for most bronchiectatic patients, local damage to the respiratory tract epithelium or bronchial wall along with a local clearance defect (e.g. due to infection) might be the cause of mucociliary transport defect. Camner P, Mossberg B. Airway clearance mucus and mucociliary transport. In: Moren F, Dolovich MB, Newman sp. (eds.) Aerosols in Medicine. Principles, Diagnosis, Therapy. (Elsevier, Amsterdam, 1993), pp. 247-260. Abstracted in Houtmeyers, et al, op. cite, (n. 36).

In the study of Wills et al., sputum from patients with bronchiectasis was transported slowly, at a mean rate of 15% of that of control mucus on the mucus-depleted bovine trachea. Results suggest a serious defect in the ciliary transportability of sputum unrelated to the presence of infection, as neither the presence of purulence or Pseudomonas aeruginosa in the mucus influenced transportability. This study indicated that mucus retention is not simply due to a larger quantity of normal mucus being produced, as sputum was transported more slowly than an equal quantity of control mucus. Wills PJ, Garcia-Suarez MJ, Rutman A, Wilson R, Cole PJ. The ciliary transportability of sputum is slow on the mucus-depleted bovine trachea. Am J Respir Crit Care Med 1995; 151: 1255-1258.

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65 Nicotra, op cite. (n. 17).

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68 There is little data to support the usefulness of currently available mucolytic agents in the treatment of bronchiectasis. N-Acetylcysteine may cause bronchospasm. The value of iodinated glycerol, though widely used, is unproven. However, preliminary results suggest that the recently available human deoxyribonuclease holds promise. Ibid.


70 Although the use of bronchodilators may be an attractive option in the treatment of bronchiectasis, in many cases the airway obstruction is not reversible. In the presence of bronchospasm, the use of inhaled beta-adrenergic agonists may be of value in those patients who demonstrate a clear response. Nicotra, op cite, (n.17).


72 Houtmeyers, et al. op cite, (n. 36).


74 Cole, op cite, (n. 6).


76 Stockley, op cite, (n. 64).