

# **Airway Clearance Indications in Bronchiectasis: An Overview**

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## **Author Profile**

Dr. Jane Braverman has experience in laboratory, academic, and technological medicine. She has worked as a medical technologist in basic research at the University of Minnesota and in clinical laboratory medicine at Twin Cities hospitals. After earning her Ph.D., she served as assistant professor in the Department of the History of Medicine at the University of Minnesota. Dr. Braverman, as research analyst/writer for Hill-Rom, has contributed to a variety of research endeavors and developed white papers, case studies, and other supporting materials.

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Bronchiectasis is a pathological process characterized by irreversible dilation and destruction of bronchial walls. The condition may be confined to a single pulmonary lobe or segment, or may involve multiple pulmonary segments or lobes, frequently associated with chronic bronchitis.<sup>1</sup> Because persistent or recurrent airflow limitation is a distinguishing feature, it is classified generically as one of the chronic obstructive pulmonary diseases (COPDs). Bronchiectasis is a consequence of a broad variety of primary disease processes and should not be regarded as a single diagnostic entity. Instead, the condition is best understood as the final common pathway of a series of structural and functional alterations created by specific pathological mechanisms.<sup>2</sup>

The clinical features of the COPDs frequently overlap. Bronchiectasis is distinguished by the intensity of its inflammation.<sup>3,4</sup> As a result, mucociliary clearance is compromised, bronchopulmonary infections occur, and copious secretions pool throughout the bronchial tree. These events characterize a vicious cycle of recurrent inflammation, infection, and permanent pulmonary damage with bronchial dilation, i.e. bronchiectasis.<sup>5,6</sup>

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## 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.<sup>7,8</sup> 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.<sup>9</sup>

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.<sup>10</sup> By the 1970s, fewer than 10% of patients included in follow-up studies died of that cause.<sup>11</sup>

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.<sup>12,13</sup> A 1981 review of 116 British patients followed for 14 years reported that 19% died of bronchiectasis at an average age of 54.<sup>14</sup> 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%.<sup>15</sup>

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.<sup>16,17</sup> 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 dyskinesic 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.<sup>18,19</sup> In Western Europe and the U.S., cystic fibrosis is the leading cause of advanced bronchiectasis.<sup>20</sup> In high resolution computed tomographic assessments of pulmonary involvement of 117 CF patients ranging in age from infancy to adult, 80% demonstrated bronchiectasis.<sup>21</sup> In studies limited to adult patients, 90-100% demonstrate radiographic evidence of bronchiectasis.<sup>22,23</sup>
- 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.<sup>24</sup> The majority of immune-compromised patients with chronic

symptomatic lung disease show radiologic evidence of bronchiectasis.<sup>25</sup>

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

### **Scientific factors**

- High resolution computed tomography (HRCT) has revolutionized the imaging of bronchi, allowing early detection and providing new information.<sup>28</sup> 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.<sup>29</sup>
- Recent studies of mycobacterial diseases, including tuberculosis, suggest that these organisms have both primary and secondary roles in bronchiectasis.<sup>30</sup>
- Genetics advances have stimulated research to discover abnormalities associated with bronchiectasis.<sup>31,32,33</sup>

### **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.<sup>34</sup> Today, causative organisms are most commonly opportunistic and frequently antibiotic-resistant, rather than the generic childhood bacterial or viral infections of the past.<sup>35</sup> Airway obstruction in bronchiectasis occurs as a consequence of mucus plugging associated either with the infectious process or with a defect in mucociliary clearance.<sup>36</sup> 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.<sup>37</sup> In a retrospective study of elderly individuals with the established diagnosis of bronchiectasis, prior infection was the common denominator.<sup>38</sup> However, infection and/or obstruction remain the necessary antecedents of bronchiectasis.<sup>39</sup>

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.<sup>40</sup> For practical purposes, however, morphologic classification is not as relevant as the extent of mucociliary dysfunction.<sup>41</sup>

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.<sup>42</sup> 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.<sup>43</sup>

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.<sup>44,45,46</sup> 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.<sup>47</sup> In effective inflammatory responses, these agents, called proteolytic enzymes, are neutralized by corresponding antiproteolytic agents, preventing damage to adjacent tissues.<sup>48</sup> When inflammation persists, an ongoing chemical reaction ensues, resulting in progressive, irreversible damage to both the bronchial wall and airway cilia.<sup>49</sup> Significant mucus hypersecretion and retention is a consequence of such damage.<sup>50</sup>

### ***Airway obstruction and ciliary dysfunction***

Airway obstruction develops when mucus plugging and infection occur together in association with dysfunctional cilia.<sup>51</sup> 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.<sup>52</sup>

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.<sup>53,54</sup> Ciliary impairment occurs in both localized and diffuse disease. Mucus clearance is moderately to markedly impaired.<sup>55</sup> Studies of the biochemistry of the lung suggest that several factors are involved in causing damage to clearance mechanisms.<sup>56</sup> 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.<sup>57</sup> Further, those bacteria may be chemotactic for leucocytes, preventing the inflammatory reaction from subsiding.<sup>58</sup>

### ***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.<sup>59</sup>

## **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.<sup>60</sup> 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.<sup>61</sup>

### ***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 phalanges of the fingers and toes. This phenomenon is associated with the chronic suppurative 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.<sup>62</sup> 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.<sup>63,64,65</sup>

### ***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.<sup>66</sup> 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.<sup>67</sup>

### ***Mucolytic agents***

Mucolytic agents have little or minimal effect on secretion clearance and are rarely prescribed.<sup>68</sup>

### ***Steroids***

Steroids may be prescribed for exacerbations of bronchiectasis, but their usefulness is unclear.<sup>69</sup>

### ***Bronchodilators***

Bronchodilators are prescribed for selected bronchiectasis patients with concurrent reactive airway disease.<sup>70</sup>

### ***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.<sup>71</sup>

### **Airway clearance therapy**

The central role of retained secretions in initiating and perpetuating the bronchiectatic process is supported by abundant research.<sup>72,73,74,75</sup> 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.<sup>76</sup>

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.<sup>77</sup> 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

<sup>1</sup> Localized bronchiectasis results from a focal insult, such as severe lobar pneumonia, followed by persistent weakened defenses of the injured area. Generalized, or diffuse, bronchiectasis develops in the context of a global disorder predisposing to chronic inflammation. Mysliwiec V, Pina JS. Bronchiectasis: the "other" obstructive lung disease. *Postgrad Med* 1999; 106(17): 123-131.

<sup>2</sup> Hansell DM. Bronchiectasis. *Radiol Clin N Am* 1998; 36(1): 107-128.

<sup>3</sup> 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.

<sup>4</sup> Mysliwiec, et al. *op cite*, (n. 1).

<sup>5</sup> Fahy JV, Schuster A, Ueki I, Boushey HA, Nadal JA. Mucus hypersecretion in bronchiectasis. *Am Rev Respir Dis* 1992; 146: 1430-1433.

<sup>6</sup> 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.

<sup>7</sup> First described in 1819 by Rene Laennec in his treatise introducing his recent invention, the stethoscope, bronchiectasis was defined as a common sequela to a variety of infections of the upper respiratory tract. Clinical features included severe cough, the production of notably offensive, purulent sputum, and major, often life-threatening episodes of hemoptysis. Laennec RTH. *De l'Auscultation Mediate ou Traite du, Diagnostic Des Maladies Des Poumons et du Coeur, Fonde, Principalement sur ce Nouveau Moyen d' Exploration*. Paris, France Brosson et Chaude 1819.

<sup>8</sup> 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 suppurative 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).

<sup>9</sup> 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.

<sup>10</sup> Konietzko NFJ, Carton RW, Leroy EP. Causes of death in patients with bronchiectasis. *Am Rev Respir Dis* 1969; 100: 852-858.

<sup>11</sup> In studies of mortality in bronchiectasis published in 1974 and 1981, the condition was listed as primary cause of death in some 10% of patients. Sanderson JM, Kennedy MCS, Johnson MF, Manley DCE. Bronchiectasis: results of surgical and conservative management. A review of 393 cases. *Thorax* 1974; 29: 407-416; Ellis DA, Thornley PE, Weightman AJ, Walker M, Chalmers J, Crofton JW. Present outlook in bronchiectasis: clinical and social study and review of factors influencing prognosis. *Thorax* 1981; 36: 659-664.

<sup>12</sup> A very high prevalence of bronchiectasis has been reported, for example, among specific ethnic groups including Native Americans, New Zealand Maori, and Western Samoans. It is unclear, however, how much of that disease is due to specific genetic influences or to environmental/socioeconomic factors. Rea HH, Wells AU. Chronic airflow obstruction, acute and chronic bronchitis, and bronchiectasis. In: Ellis M, Friend P (eds): *Investigation and Management of Pulmonary Infections*. Cambridge, Cambridge University Press 1997, pp 553-579.

<sup>13</sup> Kolbe J, Wells AU. Bronchiectasis: a neglected cause of respiratory morbidity and mortality. *Respirology* 1996; 1(4): 221-225.

<sup>14</sup> Ellis, *op cite*, (n.11).

<sup>15</sup> 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).

<sup>16</sup> Hansell, *op cite* (n. 2).

<sup>17</sup> Nicotra MB, Rivera M, Dale AM, Shepherd R, Carter R. Clinical, pathophysiological, and microbiologic characterization of bronchiectasis for an aging cohort. *Chest*; 108 (4): 955-961.

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<sup>19</sup> Ruzal-Shapiro C. Cystic fibrosis: an overview. *Radiol Clin N Am* 1998; 36(1): 143-161.

<sup>20</sup> Bronchiectasis and other bronchial abnormalities. In: Fraser RS, Muller NL, Colman N, Pare PD, (eds), *Diagnosis of Diseases of the Chest*, 4th Ed., (WB Saunders, Philadelphia 1999), p. 2165.

<sup>21</sup> Helbich TH, Heinz-Peer G, et al. Cystic fibrosis: CT assessment of lung involvement in children and adults. *Radiology* 1999; 213(2): 537-544.

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<sup>29</sup> Smith IE, Flower CD. Review article: Imaging in bronchiectasis. *Br J Radiol* 1996; 69: 589-593.

<sup>30</sup> Erasmus JJ, McAdams HP, Farrell MA, Patz EF Jr. Pulmonary nontuberculosis mycobacterial infection: radiologic manifestations. *Radiographics* 1999; 19(6): 1487-1505.

<sup>31</sup> Romano L, Padoan R, Romano C. Disseminated bronchiectasis and cystic fibrosis gene mutations. *Eur Respir J* 1997 10(6): 1380-1391.

<sup>32</sup> Mason AC, Nakielna BE. Newly diagnosed cystic fibrosis in adults: pattern and distribution of bronchiectasis in 12 cases. *Clin Radiol* 1999; 54: 507-512.

<sup>33</sup> Pignatti PF, Bombieri C, Marigo C, Benetazzo M, Luisetti M. Increased incidence of cystic fibrosis gene mutation in adults with disseminated bronchiectasis. *Hum Mol Genet* 1995; 4(4): 635-639.

<sup>34</sup> (n. 30.)

<sup>35</sup> Bacteria frequently associated with bronchiectasis include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, *Mycobacterium avium-intracellulare*, *Mycoplasma pneumoniae*, and *Bordetella* species; viruses include human papillomavirus, latent adenovirus infection, influenza viruses, herpes simplex, and measles viruses; frequently isolated fungi include *Histoplasma capsulatum*, *Pneumocystis carinii*, and *aspergillus*.

<sup>36</sup> Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M. Regulation of mucociliary clearance in health and disease. *Eur Respir J* 1999; 13: 1177-1188.

<sup>37</sup> Nicotra MB, et al, op cite, (n. 17).

<sup>38</sup> Ibid. Seventy-one of 86 patients who were reliable historians cited severe infection prior to developing bronchiectasis. Although all subjects could not be screened meticulously for genetic disease, only five of 38 patients with diffuse bronchiectasis demonstrated primary ciliary dyskinesia and another five had some form of underlying mucous disorder. None had hypogammaglobulinemia or alpha<sub>1</sub>-antitrypsin deficiency.

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<sup>40</sup> In 1950, Reid described three types of bronchiectasis: Fusiform (cylindrical), the most common type, refers to mildly enlarged bronchi that fail to taper distally; varicose, in which bronchial walls appear beaded, because areas of dilation are mixed with areas of constriction; and sacular (cystic) characterized by severe, irreversible ballooning of the bronchi peripherally, with or without air-fluid levels. Reid LM. Reduction in bronchial subdivision in bronchiectasis. *Thorax* 1950; 5: 233-247.

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<sup>42</sup> Currie DC, Saverymattu SH, Needham S, et al. Indium-labeled granulocyte traffic to the respiratory tract of patients with bronchiectasis producing purulent sputum daily. *Thorax* 1990 Jul; 45(7): 541-4.

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<sup>44</sup> Fahy, JV, Schuster A, Ueki I, Boushey HA, Nadel JA. Mucus hypersecretion in bronchiectasis. *Am Rev Respir Dis* 1992; 146: 1430-1433.

<sup>45</sup> Stockley, op cite, (n. 39).

<sup>46</sup> Nicotra MB. Bronchiectasis. *Semin Respir Infect* 1994; 9(1): 31-40.

<sup>47</sup> Cytotoxic agents include proteases, collagenases, elastases, and other biodegrading enzymes.

<sup>48</sup> The balance between proteolytic and antiproteolytic secretions is important in determining the development and extent of airway damage. This is exemplified by alpha<sub>1</sub>-antitrypsin deficiency, in which an

endogenous lack of antiprotease activity is presumably responsible for the development of bronchiectasis as well as emphysema. King MA, Stone JA, Diaz PT, et al. Alpha<sub>1</sub>-antitrypsin deficiency: evaluation of bronchiectasis with CT. *Radiology* 1996; 199: 137-141; Shin MS, Ho KJ. Bronchiectasis in patients with alpha<sub>1</sub>-antitrypsin deficiency: a rare occurrence? *Chest* 1993; 104: 1384-1386.

<sup>49</sup> Bronchiectasis and other bronchial abnormalities. In: Fraser RS, Muller NL, Colman N, Pare PD, (eds), *Diagnosis of Diseases of the Chest*, 4th Ed., (WB Saunders, Philadelphia 1999), p. 2165.

<sup>50</sup> Mysliwiec, op cite, (n.1). Sputum production in bronchiectasis varies in quantity from 20-500 milliliters per day, but the majority of patients 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."

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<sup>52</sup> Houtmeyers, et al. op cite, (n. 36).

<sup>53</sup> 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, Newhouse MT, Newman sp. (eds.) *Aerosols in Medicine. Principles, Diagnosis, Therapy*. (Elsevier, Amsterdam, 1993), pp. 247-260. Abstracted in Houtmeyers, et al, op. cite, (n. 36).

<sup>54</sup> 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.

<sup>55</sup> Svartengren M, Mossberg B, Philipson K, Camner P. Mucociliary clearance in relation to clinical features in patients with bronchiectasis. *Eur J Respir Dis* 1986; 68: 267-278.

<sup>56</sup> For a detailed discussion of the pathophysiology of mucociliary damage in bronchiectasis, see, *inter alia*, Houtmeyers, et al, op cite, (n. 36); Wilson R, Sykes DA, Currie D, Cole PJ. Beat frequency of cilia from sites of purulent infection. *Thorax* 1986; 41: 453-458; Currie DC, Pavia D, Agnew JE, Lopez-Vidriero MT, Diamond PD, Cole PJ, Clarke SW. Impaired tracheobronchial clearance in bronchiectasis. *Thorax* 1987; 42: 126-130.

<sup>57</sup> *Pseudomonas aeruginosa*, *Hemophilus influenzae*, and *Streptococcus pneumoniae* all release factors that slow ciliary beat; H influenza also produces a factor that may disrupt ciliated epithelium. Wilson, R, Roberts D, Cole PJ. Effect of bacterial products on human ciliary function in vitro. *Thorax* 1987; 40: 125-131.

<sup>58</sup> Currie, op cite, (n. 42).

<sup>59</sup> Mazzocco M, Kirilloff L, Owens G, Rogers R. Chest percussion and postural drainage in patients with bronchiectasis. *Chest* 1985; 88: 360-363.

<sup>60</sup> In a 1995 retrospective study of 123 elderly bronchiectasis patients, 54% never smoked and 70% were female. Nicotra, op cite, (n. 17).

<sup>61</sup> Houtmeyers, et al. op. cite, (n. 36 ).

<sup>62</sup> Cole PJ, ed. *Strategies for the Management of Chronic Bronchial Sepsis*. (Oxford: Medicine Publishing Foundation, 1984.)

- <sup>63</sup> Mazzocco MC, Owens GR, Kirilloff LH, Rogers RM. Chest percussion and postural drainage in patients with bronchiectasis. *Chest* 1985; 88 (3): 360-363.
- <sup>64</sup> Stockley RA, Bronchiectasis: new therapeutic approaches based on pathogenesis. *Clin Chest Med* 1987 8(3): 481-494.
- <sup>65</sup> Nicotra, op cite. (n. 17).
- <sup>66</sup> Ibid.
- <sup>67</sup> A recent study of the effect of inhaled dry powder mannitol on mucociliary clearance in bronchiectasis indicates that it may be a useful adjunct to a regimen of airway clearance therapy. Daviskas E, Anderson SD, Eberl S, et al. Inhalation of dry powder mannitol improves clearance of mucus in patients with bronchiectasis. *Am J Respir Crit Care Med*. 1999; 159: 1843-1848.
- <sup>68</sup> 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.
- <sup>69</sup> A recent study evaluating the anti-inflammatory effects of inhaled fluticasone in bronchiectasis demonstrated no significant changes in spirometry, but notable reductions in sputum inflammatory indices. Tsang K, Ho PL, Lam WK, et al. Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. *Am J Respir Crit Care Med* 1998; 158: 723-727.
- <sup>70</sup> 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).
- <sup>71</sup> Frey HR, Russi EW. [Bronchiectasis: current aspects of an old disease]. *Schweiz Med Wochenschr* 1997; 8 (127): 219-230.
- <sup>72</sup> Houtmeyers, et al. op cite, (n. 36).
- <sup>73</sup> Reid LM. The pathology of obstructive and inflammatory airway diseases. *Eur J Respir Dis* 1986; 69 (Suppl 147): 26-37.
- <sup>74</sup> Cole, op cite, (n. 6).
- <sup>75</sup> Warwick WJ. Mechanisms of mucous transport. *Eur J Respir Dis* 1983; (Suppl 127): 162-167.
- <sup>76</sup> Stockley, op cite, (n. 64 ).
- <sup>77</sup> Hardy KA, A review of airway clearance: new techniques, indications, and recommendations. *Respir Care* 1994; 39(5): 440-455.