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Bronchiectasis a Comprehensive Review

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Abstract: Bronchiectasis is a chronic lung disease, defined pathologically as irreversible dilatation of bronchi. The clinical course of the disease is chronic and progressive and in most cases causes lung damage over many years. There is usually an initial event, which causes impairment of mucociliary clearance of the bronchial tree. The respiratory tract becomes colonized by bacteria that inhibit the ciliary function and promote further lung damage. The hallmark of bronchiectasis is a chronic cough with mucopurulent or purulent sputum, lasting for months to years and may progress to chronic respiratory failure. Diagnosis of bronchiectasis is suspected on the basis of clinical manifestations. In order to confirm the diagnosis and underlying causes, appropriate investigations must be performed. In this comprehensive review we discuss the etiology, pathogenesis, clinical presentation, appropriate investigations and management of bronchiectasis.

Key words: Bronchiectasis, chronic lung disease

Introduction

Bronchiectasis is a chronic lung disease that is characterized by permanent dilatation of the bronchi and fibrosis of the lung (Stockley, 1987; Koh *et al*., 1997; Evans *et al*., 2003). The true incidence of bronchiectasis is difficult to determine as a result of several factors (Stockley, 1987). One of the factors is the under-investigation of the disease in patients with a known cause for chronic sputum production e.g., Smokers (Stockley, 1987). Previously, bronchiectasis was a very common chronic pulmonary problem; however, currently the prevalence of the disease is decreasing (Barker *et al*., 2002; Annest *et al*., 1982; Evans *et al*., 1944; Ochsner, 1975; Kinney, 1947). The decline in the prevalence could be the result of early treatment of mild cases, effective anti-tuberculous therapy and immunization against pertussis and measles (Barker *et al*., 2002; Annest *et al*., 1982). The prevalence of bronchiectasis worldwide is unknown. In the United States, bronchiectasis is still prevalent in certain populations with high rates of childhood respiratory tract infections and poor access to healthcare facilities (Singleton *et al*., 2000). The incidence of bronchiectasis in Saudi Arabia is not well studied. In a study by Al-Mobeireek *et al*. (2000) bronchiectasis was found to represent only 5% of the causes of chronic persistent cough in adult population referred to a pulmonary clinic.

Types of Bronchiectasis and Clinical Presentation

Pathologically, bronchiectasis can be divided into four types (Barker, 2002). The First type, cylindrical bronchiectasis, is characterized by uniform dilatation of bronchi that extends into the lung

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periphery without tapering. The second type is called varicose bronchiectasis and is characterized by irregular and beaded outline of bronchi with alternating areas of constriction and dilatation. The third type is called cystic or saccular bronchiectasis and is the most severe form of the disease. The bronchi dilate forming large cysts, which are usually filled with air and fluid. The fourth type of bronchiectasis is called follicular and is characterized by extensive lymphoid nodules within the bronchial walls. It usually occurs following childhood infections. However, the clinical usefulness of designating bronchiectasis to one of these patterns is questionable and no study to date has shown a clinical, epidemiologic, or pathophysiologic difference between these patterns (Cohen *et al*., 1999).

Bronchiectasis can present as either local disease or a diffuse process involving both lungs (Barker *et al*., 2002). Focal bronchiectasis may be the result of blockage of the bronchial lumen by foreign body, tumour or as a result of extrinsic compression of the bronchi. The middle lobe syndrome is an example of focal bronchiectasis caused by extrinsic compression of the bronchi by enlarged lymph node secondary to mycobacterial or fungal infection (Kwon *et al*., 1995). Diffuse bronchiectasis is usually caused either by congenital disease or in association with systemic diseases (Barker *et al*., 2002; Cohen *et al*., 1999).

Clinically, most patients present with long-standing history of either persistent or intermittent sputum production (Stockley, 1987; Evans *et al*., 2003; Barker *et al*., 2002). Sputum could be mucoid, mucopurulent or viscous (Barker *et al*., 2002). Hemoptysis does occur and may range from minor to life threatening. Other symptoms include constitutional symptoms such as fever, loss of appetite and shortness of breath (Evans *et al*., 2003; Baker *et al*., 2002). Approximately 50% of patients have pleuritic chest pain that may be due to peripheral bronchiectasis or distal pneumonitis (Barker *et al*., 2002). The clinical spectrum of the disease is broad. Some individuals with mild disease are completely asymptomatic between exacerbations. Others have chronic production of large amounts of mucoid sputum that turns into purulent during infective episodes (Stockley, 1987). The most severely affected subjects usually have continuous purulent sputum production and a proportion of those with chronic symptoms will have their disease progressing to chronic respiratory failure and develop cor-pulmonale (Stockley, 1987; Evans *et al*., 2003).

Causes of Bronchiectasis

Although many patients seem to have no associated disease that lead to the development of bronchiectasis, there are many conditions that have been recognized to cause bronchiectasis (Stockley, 1987; Barker *et al*., 2002; Cohen *et al*., 1999). Less than 40% of patients with bronchiectasis will have an obvious cause for their condition and the majority will be classified as idiopathic. Table 1 lists some of these conditions.

Infections

Many infections have been implicated to cause bronchiectasis. Measles, pertussis, adenovirus 21, tuberculosis, aspergillosis and Human Immunodeficiency Virus (HIV) may all lead to permanent airway damage (Stockley, 1987; Barker *et al*., 2002; Johnston *et al*., 1998; Kauffman *et al*., 1995; Chauhan *et al*., 2000; Holmes *et al*., 1992; McGuinness *et al*., 1993; Shiekh *et al*., 1997). Immunizations against measles and pertussis have led to marked reduction in the incidence of bronchiectasis caused by these two infections (Barker *et al*., 2002). Tuberculosis was among the most important causes of Bronchiectasis. Currently, the incidence of bronchiectasis secondary to Mycobarium tuberculosis is declining due to effective antituberculous treatment. Lately, Mycobarium

Table 1: Conditions associated with bronchiectasis

Infections
Pertussis
Measles
Adenovirus 21
Tuberculosis
Aspergillosis
Mycobacterium Apium Complex (MAC)
HIV infection
Immune Dysfunction
Primary and secondary immunoglobulin deficiency
Complement deficiency
Chronic granulomatous disease
Other Inherited Diseases
Cystic fibrosis
α1-antitrypsin deficiency
Williams-Campbell syndrome
Swyer-James syndrome
Mounier-Kuhn syndrome
Clearance defects
Immotile cilia
Kartagener's syndrome
Young's syndrome
Others
Rheumatoid arthritis
Sjogren's syndrome
Ulcerative colitis
Crohn's disease
Yellow nail syndrome
Celiac disease
Toxic chemicals
Herion
Inhaled gastric contents
Foreign body
Pulmonary fibrosis
Absence of bronchial cartilage

Apium-intracellular Complex (MAC) has been recognized to cause bronchiectasis. Allergic bronchpulmonary aspergillosis is associated with airway damage and bronchiectasis. Several factors may lead to this including direct invasion of the airways by the fungus, immune reaction to aspergillus and the action of several mediators including interleukins (Kauffman *et al*., 1995; Chauhan *et al*., 2000).

Immune Dysfunction

Immunodeficiency syndromes such as immunoglobulin deficiency, complement deficiency and chronic granulomatous disease are associated with bronchiectasis (Stockley, 1987) Deficiency of IgG, IgM and IgA put the patient at increased risk of recurrent pulmonary infections that eventually end in bronchiectasis (Rosen *et al*., 1995; Cunningham-Rundles *et al*., 1999). Whether IgG subclass deficiency leads to bronchiectasis in the presence of a near-normal levels of total IgG is still a controversial issue. However, some reports suggest that IgG subclass deficiency may have a role in bronchiectasis development (De Gracia *et al*., 1996; Hill *et al*., 1998).

Cystic Fibrosis

Cystic Fibrosis is well known to cause bronchiectasis as a result of recurrent respiratory tract infections with *Staphylococcus aureus* and mucoid *Pseudomonas aeruginosa* (Davis *et al*., 1996). In

addition, the gene responsible for Cystic Fibrosis (CF), the Cystic Fibrosis Transmembrane Regulator (CFTR), is shown to occur in high frequency in children with idiopathic bronchiectasis (Ninis *et al*., 2003). However, CFTR mutations alone cannot be responsible for bronchiectasis, as the heterozygotes for this gene mutation were not found to be at increased risk of bronchiectasis (Castellan *et al*., 2001). It is suggested that CFTR mutation acts with other factors (genetic, enviroumental) to contribute to bronchiectasis (Ninis *et al*., 2003).

α1-Antitrypsin Deficiency

Bronchiectasis has been reported to occur in α1-antitrypsin deficiency in the absence of emphysema (Longstreth *et al*., 1975; Scott *et al*., 1977; Rodriquez-Cintron *et al*., 1995; Shin *et al*., 1993). However, in a study by Cuvelier *et al*. (2000) the gene frequency of α1- antitrypsin deficiency was not different between patients with bronchiectasis and controls. It has been suggested that bronchiectasis in patients with α1-antitrypsin deficiency is caused by emphysema rather than α1-antitrysin deficiency itself. Shin *et al*. (1993) suggested that the clinical expression of a α1-antitrysin deficiency may cause emphysema alone, emphysema with chronic bronchitis, or emphysema with bronchiectasis. They also suggested that bronchiectasis may occur in those patients before the appearance of emphysema if they are exposed to recurrent respiratory tract infections.

Immotile Cilia Syndrome/Kartagener's Syndrome

Inherited as an autosomal recessive disease, immotile cilia syndrome can lead to bronchiectasis as a result of recurrent pulmonary infections due to retained secretions (Barker, 2002). Approximately 50% of patients with immotile cilia syndrome have Kartagener's syndrome. It consists of sinusitis, bronchiectasis and situs inversus (Le Mauviel, 1991; Bush *et al*., 1998).

Rheumatoid Arthritis

The association between rheumatoid arthritis and bronchiectasis has recently received considerable interest. Walker *et al*. (1967) found that the incidence of bronchiectasis is 3.1% in patients with rheumatoid arthritis compared to 0.3% in patients with osteoarthritis Solanki *et al*. (1992) found that the incidence of bronchiectasis in patients with rheumatoid arthritis was 5.2%.

Bronchiectasis can occur before or after the onset of rheumatoid arthritis (Bamji *et al*., 1985; McMahon *et al*., 1993). It has been suggested that if bronchiectasis occurs before the onset of rheumatoid arthritis, that chronic suppurative infection leads to triggering an immune response to the synovial membrane causing rheumatoid arthritis (McMahon *et al*., 1993). In contrast, those patients who develop bronchiectasis after the onset of rheumatoid arthritis may have increased susceptibility to respiratory infections caused by rheumatoid arthritis itself or its treatment. The recurrent pulmonary infections eventually lead to airway damage and bronchiectasis. This association is still controversial (Vandenbroucke *et al*., 1987; Van Al Bada-kuipers *et al*., 1988). The combination of rheumatoid arthritis and bronchiectasis carries a poor prognosis. In the study conducted by Swinson *et al*. (1997) it was found that patients with rheumatoid arthritis and bronchiectasis have the worse 5-year survival compared to that of either diseases alone.

Inflammatory Bowel Disease

Pulmonary involvement in inflammatory bowel disease is uncommon (Cohen *et al*., 1999). The majority of cases reported have airway disease with bronchiectasis occurring in 25% of cases with pulmonary involvement (Camus *et al*., 1993; Higenbottam *et al*., 1980; Butland *et al*., 1981).

Interestingly, some patients with inflammatory bowel disease develop bronchiectasis after colectomy (Camus *et al*., 1993; Leon *et al*., 1999; Eaton *et al*., 1998). It has been suggested that bronchiectasis in inflammatory bowel disease is due autoimmune process and infection has a minor role in its pathogenesis (Eaton *et al*., 1998). This may explain the occurrence of bronchiectasis post-colectomy as the inflammatory and autoimmune processes shift from the bowel to the lung (Kinnear and Higenebottom, 1983).

Pathogenesis of Bronchiectasis

In spite of the numerous conditions that are associated with bronchiectasis, the underlying cause may be very difficult to identify. Idiopathic bronchiectasis represents about half of the cases (Pasteur *et al*., 2000). The common feature among all the conditions that lead to bronchiectasis is that they either lead to alteration in the pulmonary defense mechanisms or are associated with inflammation (Stockley, 1987). The end result is that the individual becomes susceptible to bacterial colonization and infection. Regardless the initiating event, any damage to the airways that results in loss of the mucociliary transport, renders the airways susceptible to microbial colonization. Infection leads to inflammatory response and progressive lung damage (Evans *et al*., 2003). Neutrophils are thought to play a central role in the pathogenesis of tissue damage that occurs in bronchiectasis (Stockley *et al*., 1984). The progressive nature of bronchiectasis is thought to result from a continuous "vicious circle" of inflammation and tissue damage (Stockley, 1987; Koh *et al*., 1997; Evans *et al*., 2003). Although all patients with bronchiectasis have impaired mucociliary clearance and excess sputum production, not all patients are persistently colonized with bacteria (Stockley, 1987; Koh *et al*., 1997; Evans *et al*., 2003). In the majority, bacterial colonization and presence of markers of inflammation in the sputum are intermittent. However, there are some patients in whom colonization with bacteria and high levels of inflammatory markers in the sputum are persistent (Stockley, 1987; Evans *et al*., 2003). The sputum of these patients contains large amounts of serum proteins, including albumin (Stockley, 1987; Evans *et al*., 2003; Stockley *et al*., 1984). This reflects the degree of airway inflammation that results in increased capillary permeability and exudation of serum proteins into the alveolar space. In addition, it has been found that the sputum of patients with bronchiectasis has high levels of neutrophil products such as elastase and superoxide radicals (Stockley *et al*., 1983). Neutrophil elastase is a serine proteinase that has been implicated in the pathogenesis of bronchiectasis, emphysema and adult respiratory distress syndrome. It leads to mucous gland hyperplasia, increased airway secretion, damage of the ciliated epithelium and acceleration of airway inflammation (Snider *et al*., 1984; Sykes *et al*., 1987; Smallman *et al*., 1984; Chan *et al*., 2003). In a study by Tsang *et al*. (2000), sputum elastase activity correlated with the 24 h sputum volume, the number of bronchiectatic lung lobes. This can explain the worse lung function in patients who have persistently high levels of elastase in their sputum. In addition to promoting tissue damage, there is a strong evidence that neutrophil elastase promotes bacterial colonization (Stockley, 1987; Evans *et al*., 2002). This may be mediated through its destructive effect on IgA, thus allowing bacterial adherence to the lung epithelium (Niederman *et al*., 1986). It also affects the phagocytic and the complement-fixing activity of IgG, thereby reducing its opsonophagocytic function (Fick *et al*., 1984). Endogenous nitric oxide production is involved in the pathogenesis of many respiratory diseases (Tsang *et al*., 2002). When present in excess, it can induce cytotoxic effects on the bronchial epithelium (Beckman *et al*., 1990). It also reacts with superoxide anion to form a highly cytotoxic compound (Beckman *et al*., 1990). Tsang *et al*. (2002) found that the exhaled nitric oxide is reduced in bronchiectatic patients with Pseudomonas aeruginosa infection. This correlated well with the 24 h sputum volume in these patients. The potential mechanisms for the reduction in exhaled nitric oxide in bronchiectasis may include poor nitric oxide diffusion through the diseased tissue, consumption of nitric oxide by reaction with superoxide and the down regulation of nitric oxide synthetase (Tsang *et al*., 2002).

A number of inflammatory mediators are involved in the recruitment and activation of neutrophils in patients with bronchiectasis (Tsang *et al*., 1999; Nakamura *et al*., 1999; Shultz *et al*., 2001). These include interleukin 8 (IL-8), interleukin Iβ (IL-1β), interleukin 10 (IL-10), interleukin 6 (IL-6), tumour necrosis factor α (TNF-α) and leukotriene β4 (LT- β4). Tumour necrosis factor α (TNF-α) leads to the expression of chemo-attractants and IL-8 leads to neutrophil degranulation (Tsang *et al*., 1999; Nakamura *et al*., 1999; Schultz *et al*., 2001; Schleimer *et al*., 1991; Baggiolini *et al*., 1989). The combination of these inflammatory mediators acts synergistically to induce airway inflammation. Airway hyper-responsiveness is frequently seen in patients with bronchiectasis (Bahous *et al*., 1984; Pang *et al*., 1989; Ip *et al*., 1991). It may contribute to the pathogenesis of bronchiectasis by interfering with mucous clearance mechanism of the lung, thus promoting bacterial colonization (Koh *et al*., 1997). The prevalence of airway hyper-responsiveness in bronchiectasis, as measured by reactivity to methacholine, varies between 33-69% (Bahous *et al*., 1984; Pang *et al*., 1989; Ip *et al*., 1991).

Diagnostic Testing

Chest Radiograph

Routine chest radiographs are abnormal in approximately 90% of symptomatic patients with bronchiectasis (Barker, 2002). Findings include hyperinflation, tram tracks, increased linear markings, focal pneumonitis, ring shadows and atelectasis (Nicotra *et al*., 1995).

High-Resolution CT Scan

High-resolution CT (HRCT) of the chest has become the imaging technique of choice in the diagnosis of bronchiectasis (McGuinness *et al*., 1993; Eun *et al*., 1995; Naidich *et al*., 1982; Grenier *et al*., 1986). It helps to detect findings that are not seen on plain chest radiographs as well as clarifying the findings from chest x-rays. Spiral CT scan may show subtle changes because it reduces motion artifacts (Van der Bruggen-Bogaarts *et al*., 1996). Van der Bruggen-Bogaarts et al, compared the role of chest radiography and high-resolution CT Scan in the screening for bronchiectasis (Van der Bruggen-Bogaarts *et al*., 1996). They found that a normal chest radiograph almost always excludes relevant bronchiectasis with a sensitivity of 87.8% and no further investigation is usually necessary. In addition, there was a linear relationship between the severity of bronchiectasis at HRCT and abnormalities seen on chest radiograph. They concluded that HRCT is rarely needed in the presence of a normal chest x-ray.

Pulmonary Function Tests

Pulmonary function studies may be normal in localized and mild bronchiectasis. With more severe and diffuse disease, pulmonary function tests may show obstructive or combined obstructive and restrictive abnormalities (Barker, 2002). Evidence of hyperinflation and reduced carbon monoxide diffusing capacity may also be seen. In addition, between 30-69% of patients with bronchiectasis has evidence of airway hyper responsiveness as evident by histamine or methacholine challenge test (Bahous *et al*., 1984; Pang *et al*., 1989).

Sweat Chloride Test

Cystic fibrosis is usually diagnosed early in life with about 70% of cases diagnosed by the age of one year (Yankaskas *et al*., 2004). However, there are few patients in whom the diagnosis is not made until early adulthood. Those patients usually present with recurrent respiratory symptoms

(Gan *et al*., 1995). The initial test in adult patient presenting with clinical features suggestive of cystic fibrosis is sweat chloride test. Chloride levels <40 mM are considered normal, from 40-60 mM are borderline and levels >60 mM are abnormal (Yankaskas *et al*., 2004; Baumer, 2003). Using the above criteria, more than 90% of patients will have abnormal test (Yankaskas *et al*., 2004). However, a normal sweat chloride test cannot rule out cystic fibrosis and further tests are required such as CFTR mutation analysis (Yankaskas *et al*., 2004; Stewart *et al*., 1995; Wang *et al*., 2002).

Tests for Primary ciliary dyskinesia

Measurement of nitric oxide levels in exhaled breath condensate may be used as a screening test for Primary Ciliary Dyskinesia (PCD) (Bush *et al*., 2002). Levels below 250 ppb are suggestive of PCD, but can occur in other diseases as well (Karadog *et al*., 1999; Balfour-Lynn *et al*., 1996; Nakano *et al*., 2000). Definitive testing for PCD requires measurement of ciliary beat frequency using high-speed digital video photography. This usually requires biopsy taken from nasal or tracheal epithelium. Friedman et al, performed a study to determine the most cost-effective method of biopsy for the diagnosis of PCD (Friedman *et al*., 2000). They concluded that nasal biopsy collected in the outpatient setting is a cost-effective method for diagnosing PCD. Similarly, MacCormick and Coworker found that nasal brushing is a very cost-effective way for the initial investigation of PCD. In view of the large number of genetic mutations causing PCD, genetic testing is not very useful diagnostic tool for PCD (Mac Cormick *et al*., 2002).

Bronchoscopy

There are few published data regarding the airway appearance during fibro-optic bronchoscopy in patients with bronchiectasis. Chang *et al*. (2000) conducted a retrospective study to describe the bronchoscopic airway appearance in children with non-cystic fibrosis bronchiectasis. Five major airway findings were identified: mucosal inflammation, bronchomalacia, obliterative-like lesion, combination of bronchomalacia and obliterative-like lesions and no abnormalities. The most frequent abnormality was mucosal inflammation followed by bronchomalacia occurring in 58.3 and 18.8% of children, respectively. The airway abnormalities present on bronchoscopy correlated with the same lobe abnormality on the high resolution CT scan of the chest.

In patients with localized bronchiectasis, bronchoscopy is usually indicated to exclude the possibility of foreign body or any endobronchial lesion. There are multiple case reports of complete resolution of bronchiectasis after removal of the foreign body via fibro-optic bronchoscopy (Mansour *et al*., 1998; Bertolani *et al*., 1999; Ernst *et al*., 1994). Other diagnostic workup is outlined in Table 2.

Table 2: Diagnostic testing for bronchiectasis

Chest X-ray
HRCT of chest
Complete and differential blood count
Immunoglobulin level (IgG, IgM, IgA, IgE)/ IgG subclasses
Sweet chloride test
Rheumatoid factor
Aspergillus precipitins
Alpha-1 antitrypsin level
Sinus CT Scan
Sputum bacterial, mycobacterial, Fungal culture and sensitivity

Microbiology of Bronchiectasis

In contrast to healthy non-smokers, the lower respiratory tract of patients with bronchiectasis is frequently colonized with Potentially Pathogenic Micro-organisms (PPMs) (Laurenzi *et al*., 1961; Roberts *et al*., 1980). These microorganisms are responsible for the progressive tissue damage that occurs in bronchiectasis. In the study by Angrill and Coworkers, the incidence of bronchial colonization with PPMs was 64% in patients with bronchiectasis (Angrill *et al*., 2002). The most commonly found microorganism was Hemophilus influenza (55%) followed by *Pseudomonas* spp. (26%) and Streptococcus. pneumonia (12%). Thirty percent (30%) of isolates were found to be resistant to antibiotics. Risk factors for bacterial colonization include diagnosis of bronchiectasis before the age of 14 years, FEV1 <80% of predicted value and the presence of varicose or cystic bronchiectasis (Angrill *et al*., 2002).

Not all patients with bronchiectasis who are colonized with Pseudomonas develop infection due to this microorganism. Differentiation between colonization and infection is important because of therapeutic and prognostic implications. It has been found that patients who have chronic lung infection with Pseudomonas aeruginosa develop antibodies induced by the infection. However, these antibodies don't protect against the infection. In contrast, they correlate with poor prognosis (Hoiby, 2001). The antibodies react with different antigens of the Pseudomonas, resulting in antigen-antibody immune complex that leads to chronic inflammation. Caballero *et al*. (2001) studied the role of anti-pseudomonas aeruginosa antibodies in the differentiation between colonization and infection. They found that the presence of antibodies differentiated between the two groups at 75% sensitivity and specificity. Pseudomonas aeruginosa infection correlates with clinical parameters in patients with bronchiectasis. Ho *et al*. (1998) found that isolation of pseudomonas in patients with bronchiectasis was associated with high sputum volume and worse lung function (FEV 1/FVC <60%). Wilson *et al*., (1998) also found that patients infected with *P. aeruginosa* have worse quality of life, greater extent of bronchiectasis and worse lung function. Infection with Burkholderia cepacia is well known in patients with cystic fibrosis, immuno-compromised patients and those requiring mechanical ventilation (Jarvis *et al*., 1987). However, chronic colonization with *B. cepacia* in non-cystic fibrosis individuals has not been described. Ledson *et al*. (1998) reported a case of *B. cepacia* bronchieotasis in a mother of two siblings with cystic fibrosis colonized with *B. cepacia*. The mother did not have evidence of cystic fibrosis or immune-deficiency. The author postulated that chronic colonization with *B. cepacia* resulted from direct transmission of the micro-organism from the siblings to their mother. This resulted in lung damage and bronchiectasis.

Treatment of Bronchiectasis

The life expectancy of patients with bronchiectasis has improved tremendously as a result of advances in therapy (Annest *et al*., 1982). Before the development of surgical resection and antibiotic treatment, the mortality of bronchiectasis was as high as 49% in 3 to 6 years follow up (Roles *et al*., 1993). Even those who survive, they usually have poor quality of life and incapacitating symptoms (Annest *et al*., 1982; Perry *et al*., 1940; Sanderson *et al*., 1974).

Surgery

Surgical resection is considered one of the therapeutic options for the treatment of bronchiectasis (Annest *et al*., 1982; Crutcher *et al*., 1960; Oscher *et al*., 1949). The reported operative mortality rates

are 1-8.6% (Roberts *et al*., 1980; Roles *et al*., 1993; Perry *et al*., 1993; Sanderson *et al*., 1974; Crutcher *et al*., 1960). Operative morbidity ranges between 14 to 53% in different series (Roles *et al*., 1993; Sanderson *et al*., 1974; Oscher *et al*., 1949). In a study conducted in Saudi Arabia to assess the results of surgery for unilateral bronchiectasis, Ashour *et al*. (1996) found no operative mortality and 15% operative morbidity. The number of patients cured by the operation was 72.5% with 27.5% of patients improved. This was similar to the numbers reported by Annest *et al*. (1982). In a systematic review of the studies that compared surgical versus non-surgical treatment of bronchiectasis, the authors could not find any randomized controlled trials addressing this issue (Corless and Warburton, 2000). Therefore, no conclusion could be obtained regarding whether surgical treatment is superior to other non-surgical therapy for patients with bronchiectasis.

Bronchopulmonary Hygiene

Bronchopulmonary hygiene consists of different maneuvers and drugs that aid the patient to remove respiratory secretions. It includes physical therapy such as postural drainage, chest percussion, forced exhalation and controlled cough, in addition to the use of mucolytics, inhaled broncho-dilators and corticosteroids (Barker, 2002).

Trials have found that chest physical therapy improved pulmonary clearance as measured by sputum production and radioisotope clearance (Bateman *et al*., 1981, Sutton *et al*., 1983). However, a recent systematic review of chest physical therapy in patients with bronchiectasis concluded that there is insufficient evidence to support the routine use of chest physiotherapy in patients with bronchiectasis (Jones *et al*., 2000).

Mucolytics are used in patients with bronchiectasis to assist in the bronchpulmonary clearance. Their aim is to make it easy for the patient to clear their sputum. Bromhexine treatment for more than 7 days has been reported to produce some beneficial effect in sputum clearance during acute exacerbation of bronchiectasis (Olivieri *et al*., 1991). The use of aerosolized recombinant human DNase (rhDNase) is approved for patients with cystic fibrosis. Its use in patients with bronchiectasis has been studied in a large randomized controlled trial and has been found to increase the rate of exacerbations as well as accelerate the decline in FEV1 (O`Donnel *et al*., 1998). So, the use of rhDNase is not recommended in bronchiectasis.

The use of Inhaled Bronchodilators and Corticosteroids

Bronchiectasis is usually associated with an obstructive ventilatory defect and during exacerbation; the airflow limitation may even become worse (Cherniak *et al*., 1997). Although many patients with bronchiectasis may also have asthma, in the majority the airflow limitation is poorly reversible (Murphy *et al*., 1984). There are no randomized controlled trials that assessed the effectiveness of short acting β-2 agonists in the treatment of bronchiectasis. Although some trials have shown some benefit, a systematic review concluded that the evidence currently available is insufficient to draw any conclusion regarding the use of short-acting β-2 agonist in bronchiectasis (Franco *et al*., 2002). Tsang *et al*. (1998) studied the use of fluticasone 1000 mc g day^{-1} for four weeks in patients with bronchiectasis. They showed that the use of inhaled corticosteroid was associated with a reduction in the sputum inflammatory markers (IL-1 β, IL-8 and LT-β4) but there was no change in pulmonary function. Elborn *et al*. (1992) studied the effect of six-week treatment with beclomethasone 1500 mc g day^{-1} in patients with bronchiectasis. They found that treatment with inhaled corticosteroid resulted in reduction in sputum volume and improvement of the FEV_1.

Effects of Antibiotics in Bronchiectasis

Antibiotics have been used successfully in the treatment of acute infective exacerbations of bronchiectasis (Evans *et al*., 2003; Chan *et al*., 1996; Pines *et al*., 1967; Lam *et al*., 1986). Short courses of high dose antibiotics result in reduction in sputum volume and purulence as well as clinical improvement of the patient (Evans *et al*., 2003; Pines *et al*., 1967). In contrast to the well established role of short course of antibiotics in the management of bronchiectasis, the role of long-term antibiotic use is less well established (Evans *et al*., 2003).

Antibiotics have several effects on the lung in patients with bronchiectasis. Antibiotics have been shown to reduce the microbial load within the sputum and decrease the level of neutrophil elastase and the degree of protein transudation in the secretions (Evans *et al*., 2003). In a study of 15 patients with bronchiectasis treated with antibiotics for 14 days, Stockley *et al*. (1984) demonstrated a reduction in neutrophil elastase activity and sputum albumin level in 12 of the 15 patients studied. These changes were associated with change of the sputum from purulent to mucoid. Hill *et al*. (1988) studied the effects of prolonged antibiotic treatment (over 4 months) in 10 patients with bronchiectasis who have chronic purulent sputum. Similarly, they demonstrated that antibiotic treatment resulted in significant fall in sputum elastase activity as well as albumin level. In both studies, the level of elastase and albumin increased again after stopping the antibiotic treatment (Stockley *et al*., 1984) (Hill *et al*., 1988). In a non-randomized study, Hill et al demonstrated that patients with purulent sputum needed high dose of antibiotics over longer periods of time to show clinical improvement (Hill *et al*., 1986). Again, after stopping the antibiotic, the purulent sputum retained rapidly in these patients.

Another study by Ip *et al*. (1993) on 12 patients with bronchiectasis treated with two weeks antibiotics for acute exacerbation, the authors were able to demonstrate a fall in sputum Neutrophil Chemotactic Activity (NCA) and Elastase Activity (EA) after one week of treatment. The levels returned back to pre-treatment level after stopping the antibiotics. Another effect of antibiotics in bronchiectatic patients is reducing airway hyper-responsiveness. Kelly *et al*. (1987) studied the effect of 3 weeks treatment with amoxycillin on the degree of airway responsiveness in bronchiectatic patients. They found that treatment with amoxycillin resulted in a decrease in airway hyper-responsiveness. Recently several studies have found that macrolide antibiotics can reduce airway hyper-responsiveness in patients with bronchial asthma and bronchiectasis (Koh *et al*., 1997; Miyatake *et al*., 1991; Shimizu *et al*., 1994). The mechanism of action of macrolides in reducing airway responsiveness is unknown. Two postulated mechanisms have been proposed. The first includes reduction in airway inflammation and the other is related to clearing of sepsis (Koh *et al*., 1997). Macrolides have several anti-inflammatory effects in addition to their anti-microbial action. This was demonstrated in several lung diseases such as bronchial asthma, Diffuse Panbronchiolitis (DPB) and Cystic Fibrosis (CF) (Kaplan *et al*., 1959; Kadota *et al*., 2003; Kudah, 1998; Tredaniel *et al*., 1993; Kudah *et al*., 1998; Wolter *et al*., 2002; Gaylor *et al*., 2002; Baumann *et al*., 2001; Ordonex *et al*., 2001; Salman *et al*., 2003; Equi *et al*., 2002; Schni, 2003; Southern *et al*., 2003; Tagaya *et al*., 2002).

Inhaled antibiotics have been used extensively in patients with cystic fibrosis but to lesser extent in patients with non-cystic fibrosis bronchiectasis. Several studies that examined the effect of inhaled tobramycin solution in patients with bronchiectasis and Pseudomonas colonization conclude that it is effective and safe mode of therapy (Drobnic *et al*., 2005; Couch, 2001; Barker *et al*., 2000; Orriols *et al*., 1999).

Role of Pneumococcal and Influenza Vaccines

Polysaccharide pneumococcal vaccine is recommended for all individuals between the age of 2 and 64 years who have chronic pulmonary disease like bronchiectasis as these groups of patients are at

increased risk of complicated pneumococcal disease (MMWR, 1997). Pneumococcal vaccine efficacy in preventing invasive disease was examined by Whitney *et al*. (2003), where they demonstrated a 32% decrease in the incidence of invasive pneumococcal disease among young adults and a smaller but still significant decrease in the incidence in older adults. The vaccine is also effective in reducing the incidence of pneumococcal pneumonia in individuals over the age of 65 years (Jackson *et al*., 2003).

Both influenza A and B viruses lead to acute respiratory illness with high rate of complications in patients with underlying lung disease such as bronchiectasis. Vaccination of the elderly can reduce the risk of complications or death by 70-85% (Jackson *et al*., 2003). Currently influenza vaccine is recommended for all individuals who suffer from chronic pulmonary disease including bronchiectasis (WHO-Weekly Epidemiological Record, 2002).

Conclusions

Bronchiectasis is still one of the frequently seen chronic lung diseases that can affect the life quality and expectancy of the affected person. Multiple conditions are associated with the development of bronchiectasis, but all require both an infectious insult plus impairment of drainage, airway obstruction and/or a defect in host defense. Many attempts have been made to treat this disease, but none of the treatment options altered the natural course of the disease. Treatment of bronchiectasis is aimed at controlling infection and improving bronchial hygiene. Surgical extirpation of affected areas may be useful in selected patients

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