State-of-the-art - Pulmonary
Non-cystic fibrosis bronchiectasis

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Summary

Bronchiectasis is characterized by irreversible widening of the medium-sized airways, with inflammation, chronic bacterial infection and destruction of the bronchial walls. Exercise or inspiratory muscle training may improve quality of life and exercise endurance in people with non-cystic fibrosis bronchiectasis. Prolonged-use antibiotics improve clinical response rates, but may not reduce exacerbation rates or lung function. Surgery is often considered for people with extreme damage to one or two lobes of the lung who are at risk for severe infection or bleeding. In this review, the authors will focus on non-cystic fibrosis bronchiectasis, pointing out the differences in management when compared with the cystic fibrosis context, with special emphasis on surgical management.

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Keywords: Bronchiectasis; Fibrosis; Lung; Non-cystic; Transplantation

1. Introduction

Bronchiectasis was described by Laennec [1] in 1962 as an affection of the bronchia, which ‘is always produced by chronic catarrh, or by some other disease attended by long, violent and often repeated fits of coughing’. It is a pathological description of a disease process that has many possible causes. The characteristic features are abnormally dilated, thick-walled bronchi that are inflamed and chronically infected by bacteria. It is a chronic condition, which can be a significant physical problem, causing social morbidity.

Non-cystic fibrosis bronchiectasis (NCFB) can be categorized according to the pathological or radiographic appearance of the airways (Fig. 1):

- **Cylindrical or tubular bronchiectasis** is characterized by dilated airways alone and is sometimes seen as a residual effect of pneumonia.
- **Varicose bronchiectasis** (with an appearance similar to that of varicose veins) is characterized by focal constrictive areas between the dilated airways caused by defects in the bronchial wall.
- **Saccular or cystic bronchiectasis** is characterized by progressive dilatation of the airways, which end in large cysts, saccules or grape-like clusters (this being the most severe form of bronchiectasis) [2].

NCFB is currently diagnosed using high-resolution computed tomography (HR-CT) scanning. The main diagnostic features are an internal diameter of a bronchus wider than its adjacent pulmonary artery, a failure of the bronchi to taper and the visualization of bronchi in the outer 1–2 cm of the lung fields [3].

With the widespread availability of HR-CT, it has been concluded that bronchiectasis remains a common and important cause of respiratory disease. It has been estimated that there are at least 110,000 adults in the USA with this condition [4]. Besides this, there is an overlap with chronic obstructive pulmonary disease (COPD), with a reported incidence of bronchiectasis in COPD of between 29% and 50% [5]. There are also reports [6] of a high prevalence in relatively isolated populations with poor access to health care and high rates of respiratory tract infection during childhood.

2. Etiology

The most common cause of NCFB in the literature is post-infectious. This is not a well-defined entity, but the usual context appears to be one acute infectious episode that is thought to result in bronchiectasis. A possible mechanism for post-infectious NCFB is a significant infection in early childhood which causes structural damage to the developing lung, allowing perpetual bacterial infection. Over time, persistent infection may then result in bronchiectasis.

Muco-ciliary clearance is a key defense mechanism against pulmonary infection. Recently, there has been renewed interest in ciliary defects [7]. The main ciliary disorder is primary ciliary dyskinesia, which combines upper and lower respiratory tract infection with NCFB formation, male infertility and, in approximately 50% of cases, situs inversus.
Patients with humoral immunodeficiency syndromes involving deficiencies of IgG, IgM, and IgA are at risk for recurrent suppurative sinopulmonary infections and NCFB [8]. NCFB is also associated with rheumatoid arthritis (1–3%) [9]. In this context, it has been described as preceding the arthritis, as well as occurring during the course of the disease.

Repeated respiratory tract infections and bronchiectasis have been noted in patients with inflammatory bowel disease, most often in those with chronic ulcerative colitis [10]. Postulated mechanisms include the infiltration of the airway by immune effector cells, such as lymphocytes, enhanced autoimmune activity as part of the underlying disease, and complications of immune-modulating therapies. Bowel resection does not improve the respiratory symptoms and may even worsen the progression of the disease.

Patel et al. [5] found that 50% of patients with COPD had co-existent bronchiectasis, and this was associated with bacterial airway colonization, inflammatory markers and a longer duration of exacerbations. Patients with COPD and NCFB tend to have more dyspnea, worse lung function and a lack of upper airway involvement when compared to other subjects with bronchiectasis [11]. There is also some overlap in the pathology of COPD and NCFB. Both conditions have neutrophils and T-lymphocytes as the predominant inflammatory cell, pulmonary damage caused by protease release and airflow obstruction worsened by lymphoid follicles [12].

Beyond these etiological factors, there are many others that correlate with NCFB, such as extremes of age, malnutrition, socioeconomic disadvantage and α1-antitrypsin deficiency.

3. Pathophysiology and distribution

NCFB is characterized by mild-to-moderate airflow obstruction that generally worsens over time. The most widely known model of the development of bronchiectasis is Cole’s ‘vicious cycle hypothesis’ [13]. This proposes that an environmental insult, often against a background of genetic susceptibility, impairs mucociliary clearance, resulting in persistence of microorganisms in the bronchial tree and microbial colonization. The microbial infection causes chronic inflammation, resulting in tissue damage and impaired mucociliary motility. This then leads to more infection, with a cycle of progressive inflammation, causing lung damage. The current viewpoint requires two factors for the development of this condition: persistent infection and a defect in host defenses.

Although there are no studies of patients in the very early stages of bronchiectasis, findings in patients with proven NCFB give weight to the importance of enhanced cellular and mediator responses: bronchial mucosal biopsies reveal infiltration by neutrophils and T-lymphocytes. An analysis of expectorated sputum shows increased concentrations of elastase and the chemoattractants interleukin-8, tumor necrosis factor-α and prostanoids [2].

The distribution of NCFB may be associated with different pathophysiological processes. Allergic bronchopulmonary aspergillosis is classically associated with central bronchiectasis. NCFB has been described as being localized (i.e. confined to one lobe) or generalized. Most commonly, this condition is generalized, and seems to be usually found in the lower lobes [14]. The involvement of the lower lobes may reflect gravity-dependent retention of infected secretions.

Three types of focal airway obstruction may lead to NCFB. One type is luminal blockage by a foreign body, broncholith or slowly growing tumor that is usually benign.

A second type of obstruction is extrinsic narrowing due to enlarged lymph nodes. One good example is middle lobe syndrome, which involves a small angulated orifice surrounded by a collar of lymph nodes that may enlarge and encroach on the main airway after infection with granulomatous disease-causing organisms, such as mycobacteria or fungi [15].

A third type of obstruction is twisting or displacement of the airways after a lobar resection (i.e. the occasional apical displacement of a lower lobe after surgery for the resection of the upper lobe). Recurrent lobar pneumonia is a distinguishing feature of the first two types of focal NCFB and is important to recognize, since interventional bronchoscopy or surgery may offer palliation and sometimes cure.

4. Symptoms

The symptoms and clinical course of NCFB are variable. Some patients have no symptoms at all or symptoms only during exacerbations, whereas others have them daily.

The classic clinical manifestations of this clinical condition are cough and daily mucopurulent sputum production, often lasting months to years. Blood-streaked sputum or hemoptysis may result from airway damage associated
 Spirometry often shows a limitation of airflow, with a reduced ratio of forced expiratory volume in one second (FEV$_1$) to forced vital capacity (FVC), a normal or slightly reduced FVC, and a reduced FEV$_1$. A reduced FVC may indicate that airways are blocked by mucus, that they collapse with forced exhalation, or that there is pneumonitis in the lung [18].

Diagnosing NCFB on radiological imaging needs further diagnostic work-up to reveal the underlying cause. HR-CT-scans do not contribute towards identifying the etiology and, most importantly, a specific etiological diagnosis frequently leads to a change in management. Other tests may indicate the underlying etiology, including a detailed patient history, biochemical evaluation of a venous blood sample, radiology, pulmonary function tests, sputum investigations and ciliary function tests [19].

5. Diagnosis

Bronchography-proven bronchiectasis shows that chest radiography is normal in only 7.1% of patients. Common findings in this setting include crowding of the bronchi, loss of definition of the bronchovascular markings, oligemia and, in more severe disease, honeycombing, air-fluid levels or fluid-filled nodules (Fig. 2). Therefore, careful examination of chest radiographs is essential [17]. When CT appeared as a diagnostic tool, it replaced bronchography as the gold standard for the diagnosis of NCFB.

Cylindrical malformation appears as ‘tramlines’ or, when imaged in cross-section, as thick-walled circular structures called ‘signet rings’ (Fig. 3). Varicose bronchiectasis has a typical beaded appearance, and saccular or cystic changes appear as a string of cysts, a cluster of grapes, or even as air-fluid levels due to retained secretions.

Currently, HR-CT is the best tool for diagnosing NCFB, clarifying the findings from chest radiography and standard CT, and mapping airway abnormalities that cannot be seen on plain films of the chest.

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6. Management

6.1. Physiotherapy

The treatment aims in adult care are to control the symptoms and thus enhance quality of life, reduce exacerbations and maintain pulmonary function [20]. It is important that treatments are carefully evaluated and, in particular, that treatments routinely used in cystic fibrosis are not simply translated into use in NCFB [21].

The increased production of mucus, together with impairment of the mucociliary system, leads to mucus accumulation, cough and recurrent infections. Patients with NCFB may benefit from interventions to help clear the excessive secretions. Physiotherapy is considered one of standard treatments when dealing with cystic fibrosis, but evidence for its use in the context of non-cystic fibrosis is limited.
6.2. Vaccination

There are no randomized controlled trials determining the effectiveness of influenza vaccination in patients with NCFB. There is limited evidence to support the use of 23-valent pneumococcal vaccination as routine management in adults and children with NCFB [23].

6.3. Airway pharmacotherapy

Most of the agents that have been used attack the physical properties of the mucus. Hyperosmolar inhalation has shown to improve airway clearance in all the major chronic diseases characterized by sputum retention. Hypertonic saline may provide an useful adjunct to physiotherapy [24]. The potential for recombinant human DNase to favorably influence symptoms in NCFB has not been tested in children [25], but it has been well studied in adults and there is no evidence of benefit [26]. The Cochrane database suggests that bromhexine is the only mucolytic so far shown to be benefical in the treatment of NCFB exacerbations [25]. No randomized controlled trials have investigated the role of short- and long-acting bronchodilators in NCFB [27]. Some adults may show a favorable response with the use of anticholinergic drugs, such as ipratropium bromide [28]. Methylxanthines, such as theophylline and aminophylline are not useful in the treatment of NCFB [29]. Current evidence does not support routine use of inhaled corticosteroids in adults with NCFB [30].

6.4. Antimicrobial therapy

Antimicrobial therapy, mostly antibiotics, has been tried systemically and via inhalation. When systemic antibiotics are used, the strategies applied differ greatly. Sometimes they are used as needed or schematically, alternating one or more antibiotics. Overall, chronic antibiotic treatment is currently, not recommended, but there is one exception: macrolide therapy. This class of antibiotic has a non-antibiotic effect on bronchiectatic inflammation. Total bronchoalveolar lavage cell count, sputum volume, interleukin-8 level and neutrophil level all seem to decrease with macrolide use. Patients with frequent exacerbations of NCFB who had been treated with rescue antibiotics showed an improvement in exacerbation frequency, spirometry and sputum microbiology when treated with long-term low-dose azithromycin [31]. This explains the current widespread use of macrolide therapy for bronchiectatic patients.

Inhaled antibiotics have more limited side effects. However, they are more expensive and may be less well tolerated because of bronchospasm. Nebulized tobramycin decreased the number of admissions and days in hospital. Some studies [32] showed a possible positive effect of prolonged (more than four weeks) antibiotic use for NCFB in selected patients. Overall, antibiotics are rarely used in clinical practice for NCFB, but in patients with cystic fibrosis bronchiectasis, treatment with aerosolized anti-pseudomonal antibiotics is recommended [33].

6.5. Acute exacerbations

Antibiotics are recommended for exacerbations that present with acute deterioration (usually over several days) with worsening local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, and hemoptysis) and/or systemic upset (Fig. 4). The drug selected should be active against Haemophilus influenzae and Staphylococcus aureus. For patients with more severe disease, recent antibiotic treatment or cystic fibrosis, an anti-pseudomonal treatment should also be considered [34]. Sputum culture should be performed with sensitivity testing in order to guide further therapy.

Bronchodilator therapy can be added in the case of obstruction or symptoms, as well as steroid therapy, although there are no randomized controlled trials on this. High doses of bromhexine can facilitate sputum expectoration [25].

6.6. Surgery

There are studies [35] reporting lung resection surgery for bronchiectasis in both children and adults, aiming to improve the symptoms. The indications for surgery are listed in Table 1.

The goals of surgical therapy for NCFB are to improve the quality of life for those patients in whom medical treatment has failed and to solve complications, such as empyema, severe or recurrent hemoptysis, and lung abscess [35]. Complete and anatomic resection should be done with preservation of as much lung function as possible in order to avoid cardiorespiratory restriction.

There are important factors to consider in the selection of patients, such as their respiratory function and performance...
status, which must be compatible with the anesthetic risk. In addition, the resection should be performed early in the natural history of the disease because of the risk of the contamination of healthy bronchi [35].

Surgery should be delayed in cases of severe inflammation until adequate control has been achieved. In addition, the preoperative treatment should include reducing airway obstruction and eliminating microorganisms from the lower respiratory tract, therefore consisting of antimicrobial therapy, postural physiotherapy, bronchodilators and corticosteroids.

The presence of multiple or bilateral NCFB is generally considered to be a contraindication to operation [36]. Surgery for bilateral NCFB is considered risky, and hemorrhagic or infectious complication are expected because of the bronchial arterial circulation and septic context. However, some groups [37] have proposed radical operations for bilateral NCFB, although others have reported higher operative mortality [36]. It seems that limited operations should be offered to some patients with diffuse NCFB.

In this context, patients who may benefit from surgery have the following indications: (1) disease that is symptomatic, is unresponsive to medical treatment and can be completely resected; (2) hemoptysis that cannot be controlled or recurs after bronchial artery embolization; and (3) a need for palliative surgery, in which the most involved lobe or segments are resected to improve the symptoms.

In select individuals, limited resections of targeted segments may achieve longstanding symptom improvement. Mazieres et al. [36] observed that a total disappearance or regression of preoperative symptoms occurred in 75% of such patients. In a recent study [38], the authors suggest that surgery for bilateral NCFB can be performed with morbidity and mortality patterns quite similar to those results in localized disease, with a disappearance or regression of preoperative symptoms in 83% of patients.

Eren et al. [39] reported postoperative complications in 11% of patients who underwent complete resection and in 80% of those who underwent incomplete resection. The same authors stated that, beyond incomplete resection, a history of tuberculosis was a risk factor both for postoperative complications and for a worse operative result. The lack of a preoperative bronchoscopic examination and a low FEV1 were risk factors for postoperative complications.

A recent retrospective analysis [40] showed that advanced age (P=0.04) and renal failure (P=0.001) were related to postoperative mortality, and that preoperative renal failure was associated with mortality (P=0.025). The same study reported that, after surgery, 478 (60.5%) patients were asymptomatic, 111 (14.1%) had improved, and 117 (14.8%) showed no improvement or a worsened condition.


Table 1. Indications for surgery in bronchiectasis

<table>
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<th>Failure of medical/conservative therapy</th>
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<td>Recurrent respiratory infections</td>
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<td>Persistent sputum production</td>
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<tr>
<td>Hemoptysis</td>
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<tr>
<td>Chronic cough</td>
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<td>Persistent lung abscess</td>
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Adapted from Pasteur et al. [21].

Prieto et al. [41] reported that, in a series of 119 patients, 73 patients (68%) were asymptomatic after surgery, and 31 (29%) showed significant clinical improvement, whereas only four (3.7%) maintained or worsened their prior symptoms, after a mean follow-up of 4.5 years. The same authors concluded that the best clinical improvement occurred in patients with complete resection of the disease (P=0.008). A study performed in our institution showed no mortality and an overall morbidity of 15.7%, with a mean follow-up of 3.4 years [42].

When suggestive lung regions are not excised, with the aim of sparing as much lung tissue as possible, more postoperative complications occur and a second operation that carries a higher morbidity and mortality might be required to remove the residual diseased tissues [43]. Therefore, during intraoperative examinations, if suggestive areas that could not be determined by radiological examination are present, these parenchymal areas should be resected in order to perform complete resection and to decrease relapse rates [39]. Indirect signs that may be helpful during operation are poor expansion of the involved segments or lobes, the actual palpation of ectatic bronchi, and a lack of anthracotic pigment over the abnormal lung, indicating a lack of function. If there are affected areas in different lobes, multiple-segment resection can be performed in order to protect as much pulmonary function as possible [44].

Technically, surgery for NCFB can be either very easy or extremely difficult. A double-lumen tube should always be used to avoid possible intraoperative contamination of the contralateral lobes. The surgeon may experience some technical difficulties caused by dense adhesions, hyperplastic lymph nodes around the pulmonary artery and its branches, and incomplete fissures. Because the bronchial arteries are usually hypertrophied, special care should be taken with these vessels in order to avoid postoperative bleeding. Besides technical issues, as well as pre-operative pleuropulmonary infection, the incidence of postoperative bronchopleural fistula after lung resection for NCFB is identical with surgery for lung cancer.

Surgery can be performed via thoracotomy or can be video-assisted. A recent study [45] showed that video-assisted thoracoscopic lobectomy in localized NCFB is a safe and more efficient procedure for selected patients, with better recovery.

6.7. Lung transplantation

Lung transplantation is available for end-stage cardiopulmonary disease in children and adults, although there is a lack of literature specifically relating to bronchiectasis. In fact, specific guidelines for the referral of patients with NCFB have not been established. Therefore, parameters similar to those set for cystic fibrosis patients can eventually be applied to patients with NCFB [46].

The indicators of end-stage lung disease in bronchiectasis are listed in Table 2. In general, patients should be considered for transplantation if there is <a 50% probability of survival for two years without transplantation, quality of life is likely to be improved by transplantation, there are no contraindications to transplantation, and patients are fully informed of the risks and benefits of lung transplant and fully committed to proceeding with evaluation and potential
Table 2. Indicators of end-stage lung disease in bronchiectasis

<table>
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<th>Condition</th>
<th>Value</th>
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<tr>
<td>Postbronchodilator FEV&lt;sub&gt;1&lt;/sub&gt;, &lt;30% (especially young females with cystic fibrosis)</td>
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<tr>
<td>Exacerbation of pulmonary disease requiring intensive care unit admission</td>
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<tr>
<td>Increasing frequency of exacerbations requiring intravenous antibiotics</td>
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<tr>
<td>Recurrent hemoptysis not controlled by embolization</td>
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<tr>
<td>Other factors to consider:</td>
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<tr>
<td>Hypercarbia (PaCO&lt;sub&gt;2&lt;/sub&gt; &gt;45 mmHg)</td>
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<tr>
<td>Rapidly progressive decline in lung function</td>
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<tr>
<td>Resting hypoxemia (PaO&lt;sub&gt;2&lt;/sub&gt; &lt;55 mmHg)</td>
<td></td>
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FEV<sub>1</sub>, forced expiratory volume in one second; PaCO<sub>2</sub>, partial pressure of carbon dioxide in arterial blood; PaO<sub>2</sub>, partial pressure of oxygen in arterial blood. Adapted from Hayes and Meyer [46].

listing. Referred patients should have a rigorous evaluation to determine whether they meet criteria for being placed on the waiting list and to identify co-morbidities that can complicate further management.

Because the number of lung transplants performed for patients with NCFB is much smaller than that for patients with cystic fibrosis, few data are available concerning patient selection, choice of procedure and outcomes. Nonetheless, bilateral lung transplantation is widely accepted in this patient population, with the assumption that infection in the contralateral native bronchiectatic lung would threaten single-lung transplantation [47].

The current medical literature includes only one study that has examined lung transplantation for NCFB [48]. This study included 22 patients (12 males, 10 females) with an average age of 43.4 years (range 20–58) years who underwent lung transplantation for this condition over a 13-year period. Bilateral sequential lung transplants were performed in four patients, double-lung transplants with tracheal anastomosis in five, heart–lung transplants in six, and single-lung transplantation in seven. A total of five out of seven patients who underwent a single-lung transplant had minimal sputum production, whereas four out of seven had asymmetrical findings on a CT-scan of the chest. The authors therefore, concluded that a good outcome is possible after single-lung transplantation in selected patients [49]. Survival and lung function after transplantation for NCFB were similar to those after transplantation for cystic fibrosis.

7. Prognosis

Keistinen et al. [50] reviewed the National Hospital Discharge Register in Finland and identified 842 patients with bronchiectasis. During a follow-up period of between 8.0 and 12.9 years, the number of hospitalizations for patients with bronchiectasis varied widely (range 1–51, mean 2.2). Mortality was 28% among patients with bronchiectasis, 20% among asthma patients and 38% among COPD patients.

Onen et al. [49] showed that, in NCFB, factors associated with higher mortality were advanced age, poor functional status, more severe disease based on radiographic findings, and evidence of hypoxemia or hypercapnia.

Bronchiectasis associated with cystic fibrosis carries a worse prognosis than NCFB. Current mortality is difficult to estimate, given the difficulty in identifying the prevalence and the lack of definitive studies. Overall, the prognosis for bronchiectasis varies with the underlying or predisposing condition.

8. Conclusions

The introduction of HR-CT has improved the diagnosis of bronchiectasis, and emphasis should now be placed on the role of treatment and follow-up measures, as well as the influence of concomitant diseases, as the prognosis for these patients is poorer than that for asthmatics.

Medical management has improved in recent years, improving the prognosis of NCFB. However, there are few randomized controlled trials supporting evidence for the management of NCFB, which has to be clearly distinct from that of cystic fibrosis because of the differences in pathophysiology.

With regard to surgical management, it is clear that surgery for NCFB can nowadays be performed with minimal complications and that it improves symptoms and quality of life, mostly in younger patients with localized disease.

References
