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A review on non-cystic fibrosis bronchiectasis in children

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Prevalence and aetiology

Bronchiectasis is characterised by chronic persistent abnormal dilatation of bronchi and bronchioles leading to chronic cough and sputum hyper-secretion. It is more prevalent in developing countries where severe early childhood infections are common. Although once considered of fading relevance to the developed world, non-cystic fibrosis (non-CF) bronchiectasis is now being diagnosed with increasing frequency around the world. The increased diagnosis could be partly due to the widespread use of high-resolution chest CT (HRCT) scanning which is convenient and very sensitive in diagnosing bronchiectasis. According to a retrospective study by Edwards et al,[1] prevalence of non-CF bronchiectasis was estimated to be 1 in 6,000 children in New Zealand, being more prevalent in Pacific Island and Maori children than in European children. In United States, the estimated prevalence of non-CF bronchiectasis was 4.2/100,000 in 18-34 years old and 272/100,000 in >75 years old.[2] There is no local prevalence data on bronchiectasis in Hong Kong; however, a study on the burden of lung disease in Hong Kong[3] has revealed that the overall crude mortality rate of bronchiectasis was 2.7/100,000, ranking fifth as a cause of respiratory mortality. The hospitalisation rate for bronchiectasis in children of 5-14 years old is 1.3/100,000, much lower than the overall hospitalisation rate of 21.9/100,000.

Establishing the cause of bronchiectasis is important in guiding future management. Cohorts of children and adults with non-CF bronchiectasis had been characterised and causes of bronchiectasis studied. However, in up to 38-53% of bronchiectasis cases no cause could be found even with extensive clinical, laboratory and pathologic testing.[1,4-6] A review of 136 children with non-CF bronchiectasis concluded that in 77 (56%) of these children, the identification of a cause led to a specific change in management.[4] Table 1 is a list of possible underlying causes for non-CF bronchiectasis.

Karadag et al[5] reviewed the medical record of 111 children with non-CF bronchiectasis retrospectively. In 62.2% of these patients an underlying aetiology was identified. Post-infectious bronchiectasis was the most common underlying cause (29.7%). Immunodeficiencies were the second most common underlying causes (15%), followed by primary ciliary dyskinesia (6%), asthma (4%), foreign body aspirations

Table 1. Conditions associated with non-CF bronchiectasis

Idiopathic
Post-infectious
Mycobacterium tuberculosis
Viruses
Bacteria
Allergic Broncho-pulmonary Aspergillosis
Immunonodeficiency
Primary
Hypogammaglobulinemia
Secondary
Primary ciliary dyskinesia
Alpha 1-antitrypsin deficiency
Gastro-esophageal reflux (GERD)
Foreign body inhalation
Rheumatoid arthritis
Systemic lupus erythematosus
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Young's syndrome

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(4%) and esophageal atresia/tracheoesophageal fistula (3%).

Pasteur et al[6] reviewed 150 adult patients with bronchiectasis in Papworth Hospital, Cambridge and determined the causative factors in these patients. No cause could be established in 80 patients (53%). The common causes identified include early childhood pneumonia (44 patients, 29%), followed by immune defects (12 patients, 8%), allergic broncho-pulmonary aspergillosis (11 patients, 7%). Other causes include gastroesophageal reflux disease, ciliary dysfunction, rheumatoid arthritis, and Young's syndrome.

Pathophysiology

Bronchiectasis is an anatomic distortion of the airway characterised by irreversible dilatation of the bronchi and bronchioles caused by progressive damage to the structural components of the airway wall (smooth muscle and elastic matrix). This leads to increased mucus secretion and impaired mucociliary transport, resulting in mucus accumulation and bacterial colonisation. Repeated inflammation and infection will further increase mucus secretion and impair mucociliary clearance, which predispose to further infection and form the vicious cycle of airway damage which finally leads to bronchiectasis. Regardless of the underlying cause, bronchiectasis is the end result of repeated airway injury secondary to inflammatory and infectious damage to the bronchial and bronchiolar walls.

Clinical features

The hallmark symptom of bronchiectasis is a chronic productive cough. The sputum could be mucoid, mucopurulent or thick viscous. However, young children may not be able to expectorate sputum which is usually swallowed. Haemoptysis is more commonly reported in adults than in children. With generalised and advanced disease, dyspnoea, chest pain, fever and fatigue could be present. In a review of children with non-CF bronchiectasis, cough was the primary presenting symptom (96.9%), followed by sputum production (80.6%), dyspnoea (49%) and wheeze (46.9%).[5] Abnormal auscultatory signs include localised or diffused coarse crackles and less commonly wheeze. In the presence of wheeze, children should be assessed for coexistence of asthma which occurs in approximately a third of the children with bronchiectasis. Digital clubbing is found in 3-51% of patients of bronchiectasis and is more common in patients with moderate to severe bronchiectasis.[5] Failure to thrive is unusual in children with bronchiectasis and may be seen in advanced disease or with specific causes like immunodeficiency or severe gastroesophageal reflux.

Laboratory investigations

Chest X-ray abnormalities are found in most bronchiectatic patients.[7] The X-ray findings are usually nonspecific and include focal pneumonitis, scattered irregular opacities, linear or plate-like atelectasis. More specific signs include ring-like shadows (when airways are seen end on) and tram lines (when airways are perpendicular to the X-ray beam).

HRCT has now become the gold standard for diagnosing bronchiectasis. Typical HRCT findings include dilation of an airway lumen to at least 1.5 times the size of its associated nearby artery and lack of tapering of airway lumen towards the periphery.[7] Signet ring sign is seen when a dilated and thickened bronchiole, sectioned perpendicularly, is juxtaposed against its accompanying pulmonary artery. Focal constrictions along the airways are seen in varicose bronchiectasis while ballooned cysts, saccules or grape-like clusters at the end of a bronchus can be seen in cystic or saccular bronchiectasis. There can also be nonspecific findings including consolidation or infiltration of a lobe with dilatation of the airways, thickening of the bronchial walls and mucous plugging etc. Bronchography was previously used to diagnose bronchiectasis but has been replaced by HRCT.

Bronchoscopy is not indicated routinely for the diagnosis of bronchiectasis. However, bronchoscopy is useful in localised bronchiectasis when an obstructing lesion is likely to be the cause of bronchiectasis.

Pulmonary function tests usually show a limitation of airflow, with a reduced ratio of forced expiratory volume in one second (FEV1) to forced vital capacity

(FVC), normal to slightly reduced FVC, and reduced FEV1. Karadag et al[5] and Edwards et al[1] showed that the mean FEV1 were 63% and 69% predicted and FVC were 67 and 69% predicted in two groups of bronchiectatic children respectively. Bronchial hyperreactivity is prominent in bronchiectasis and can be demonstrated in 30 to 69 percent of patients with bronchiectasis.[7]

Sputum cultures should be done in all patients with bronchiectasis during their first visit, at annual intervals and during exacerbations. In a review of paediatric non-CF bronchiectatic patients, Hemophilus influenzae and Streptococcus pneumoniae were the most frequently isolated organisms (38.5% and 23% respectively).[5] The other isolated organisms include Staphylococcus aureus (16.9%), Pseudomonas aeruginosa (10.8%), Moraxella catarrhalis (6.2%) and Klebsiella pneumoniae (4.6%). Sputum for mycobacterial culture and tuberculin skin test should also be done during first visit for bronchiectasis.

After the diagnosis of bronchiectasis, a work up for the underlying cause of bronchiectasis should be done, starting with a detailed history and physical examination. The specific work up in individual patients should be guided by the history and physical examination findings. Primary investigations that should be done on all patients with bronchiectasis include measurement of complete blood count with differential count, liver and renal function tests, sputum cultures, and immunoglobulin levels (IgG, IgA, IgM). Secondary investigations should base on clinical suspicion after assessing the history, physical examination and primary investigation results. If immunodeficiency is suspected, further serological tests including IgG subclasses, complement levels, neutrophil function tests, specific antibody responses to tetanus, H. influenzae type b and Streptococcus pneumoniae, antigen/mitogen stimulation tests, and HIV screening test can be done. A sweat test should be done on all bronchiectatic patients in populations where cystic fibrosis is common. Other tests include alpha 1-antitrypsin level to exclude alpha-1-antitrypsin deficiency, 24 hour oesophageal pH monitoring and barium fluoroscopy for gastroesophageal reflux and swallowing problem, and nasal ciliary study for primary ciliary diskinesia.

Treatments

The goals of treatment for bronchiectasis are to improve quality of life and to reduce exacerbations. If an underlying aetiology is identified, it should be treated accordingly. Examples include immunoglobulin replacement therapy for immunoglobulin deficiency and steroid treatment for allergic broncho-pulmonary aspergillosis. Antibiotics, airway clearance therapy, anti-inflammatory and bronchodilator therapy are the general treatments for bronchiectasis patients.

Antimicrobial therapy

Acute exacerbations

Antimicrobial therapies should be prescribed during acute exacerbations. However, it could be difficult to define exacerbations because many patients have chronic symptoms of cough, sputum production and dyspnoea. Exacerbation is usually diagnosed when patient has increased sputum production, increased purulence of sputum, worsening of chest signs of dyspnoea, or new radiological infiltrations.

Antibiotics prescribed should be aimed at the specific pathogens that caused the exacerbations. If culture results are not available, the choice of antibiotics would be based on knowledge of the most likely pathogens from past sputum culture results and local prevalence rates. Amoxicillin/clavulanic acid can be used to treat the common pathogens including Hemophilus influenzae, Streptococcus pneumoniae and Staphylococcus aureus and quinolones can be used in the presence of Pseudomonas infections.[8] Although the optimal duration of therapy is unknown, it is usually advisable to give a longer course of antibiotics of at least 10 days to 2 weeks. Mild to moderate exacerbations can be treated with oral antibiotics while intravenous antibiotics need to be used for severe exacerbations.

Prophylactic antibiotics in the prevention of exacerbations

Use of long term maintenance antibiotics in bronchiectasis patients has been controversial. Long-term antibiotic therapy can decrease bacterial load and hence decrease the inflammation of the bronchial tree. This may interrupt the 'vicious cycle' of infection

and inflammation and progressive airway damage. Apart from the antibmicrobial effects, macrolides have the additional advantage of anti-inflammatory effect. Koh et al[9] studied the effect of 12 weeks treatment of roxithromycin in children with bronchiectasis. They found that roxithromycin decreased the degree of airway responsiveness. However it was not clear whether the decreased airway responsiveness paralleled clinical improvement. In another study on effects of clarithromycin on inflammatory parameters and clinical conditions in children with bronchiectasis, Yalcin et al[10] found out there is laboratory improvement of reduced lung inflammation in the group treated with clarithromycin. Again no corresponding clinical improvement could be demonstrated.

Evans et al reviewed nine randomised trial (378 participants) on use of long term antibiotics in non-CF bronchiectasis.[11] There was a significant treatment effect following meta-analysis for clinical response rates but no significant difference for exacerbations, sputum score, lung function and mortality. It is not possible to conclude on the issue of inducing antibiotic resistance as many studies did not give data on antibiotic resistance. The authors concluded that because of the possible positive effect for prolonged antibiotics, this can be used in selected patients but close monitoring of the effects and side effects of antibiotics should be ensured.

Broncho-pulmonary hygiene therapy

Broncho-pulmonary physical therapy has been considered the standard therapy for bronchiectasis and has been practiced for years. Most children should be performing chest physiotherapy once to twice daily and more frequently during exacerbations but compliance is often an issue. The traditional chest physical therapy methods include active cycle of breathing, chest clapping and postural drainage. Newer devices like oral oscillatory positive expiratory pressure devices can maintain the patency of the airway during expiration and allow better drainage of secretions. The use of inflatable vests or mechanical vibrators has also replaced the traditional chest clapping in some patients. Despite being the mainstay of therapy for bronchiectasis for many years, this labour intensive therapy was not well studied in clinical trials. A Cochrane review found only 7 small trials on chest physical therapy and the trials were not generally of good quality.[12] The authors concluded that there is not enough evidence to support or refute the use of bronchial hygiene physical therapy in patients with bronchiectasis.

Mucolytics

Aerosolized recombinant human DNase

Different mucolytics have been used to help mobilise the viscous secretions and mucus plugging in bronchiectasis. DNA is a major degradation product of neutrophils and bacteria that contributes to viscous secretions. Recombinant human DNase breaks down the DNA and may make the sputum less viscid and therefore easier to expectorate. In cystic fibrosis, aerosolized recombinant human DNase has been shown to improve lung function and decrease exacerbations.[13,14] However, study in non-CF bronchiectasis patients showed very different results. A large multicenter, double-blind, randomised, placebo-controlled study on use of aerosolized recombinant human DNase in 349 adult patients with idiopathic bronchiectasis showed that pulmonary exacerbations were more frequent and FEV1 decline was greater in patients who received rhDNase compared with patients receiving placebo during a 24-week trial.[15] The results strongly suggest that rhDNase should not be used in idiopathic bronchiectasis. The authors postulated that patients with idiopathic bronchiectasis had more disease in their lower lobes, compared with those with cystic fibrosis who had disease predominantly in upper lobes, which could lead to more pooling of secretions and adverse results.

Bromhexine

One randomised trial[16] involving 88 patients studied the effectiveness of bromhexine in the treatment of bronchiectasis. Bromhexine and Ceftazidine were compared with placebo and Ceftazidine during acute exacerbations. Bromhexine group had easier expectoration of sputum and cough score was also significantly reduced. Further well designed randomised studies are required to confirm these findings. A Cochrane review concluded that although

high doses of bromhexine coupled with antibiotics may help with sputum production and clearance, there is not enough evidence to evaluate the routine use of mucolytics for bronchiectasis.[17]

Inhaled steroids

Neutrophilic airway inflammation is a dominant feature in patients with bronchiectasis. Inhaled steroids are effective anti-inflammatory treatment for diseases characterised with airway inflammation and had been studied in adult bronchiectasis patients. A systematic review showed that huge doses (2 gm per day of budesonide equivalent) of inhaled steroid of less than 6 months duration were associated with improved FEV1, FVC, and sputum volume but did not affect exacerbation rates.[18] When only placebo-controlled studies were included, there was no significant difference in all outcomes examined. The single study on long term outcomes showed no significant effect of inhaled steroids in any of the outcomes.[19] However, at a subgroup analysis, the authors report a significant improvement in the amount of sputum volume/day in the subgroup of patients with sputum volume <30 ml/day, exacerbation frequency ≤2/year, and sputum purulence score >5. There was no paediatric study. The conclusion of the systematic review[18] was that there is insufficient evidence to recommend the routine use of inhaled steroids in patients with stable state bronchiectasis. A therapeutic trial may be justified in adults with difficult to control symptoms but this has to be balanced with adverse events especially if high doses are used. No recommendation can be made for children as there was no study. There has been no study on use of oral steroids in patients with bronchiectasis.

Bronchodilators

Many patients with bronchiectasis show signs of airflow obstruction and bronchial hyper-responsiveness, and therefore received bronchodilator therapy. Hassan et al[20] studied acute reversibility of airway obstruction to fenoterol and ipratropium in 24 bronchiectasis patients. Eleven patients (45.8%) responded to one or both bronchodilators significantly with >15% improvement in FEV1. It is advisable to perform bronchodilator response studies on bronchiectasis patients to determine whether they are likely to benefit from bronchodilator therapy. However, there is no randomised controlled trial on use of short acting and long acting beta-2-agonists in bronchiectasis.[21,22] Randomised controlled trials should be conducted to investigate the role of bronchodilators in bronchiectasis in the future.

Inhaled hyperosmolar agents

Increased mucus secretion and mucus retention is a prominent feature of bronchiectasis. Increasing airway hydration and optimising the viscoelastic and surface properties of mucus can lead to improvement in mucus clearance. This has been the role of hyperosmolar agents, including mannitol and hypertonic saline.

Hypertonic saline

Nebulized hypertonic saline is a traditional treatment for sputum retention. The possible mechanism of action is through inducing liquid influx from epithelium into mucus, altering its rheology to allow more rapid clearance by cilia. Hypertonic saline has not been specifically tested in bronchiectasis, but improves clearance in other conditions and in chronic bronchitis.[23] In cystic fibrosis patients, hypertonic saline treatment led to greater improvement in FEV1, fewer pulmonary exacerbations, accelerated mucus clearance and improved lung function when compared with normal saline treatment.[24-26] However, these findings cannot be generalised to non-CF bronchiectasis as illustrated by the different effects of rhDNase on cystic fibrosis and non-CF bronchiectasis patients. As there is no study of hypertonic saline on non-CF bronchiectasis, no recommendation can be made and more research is needed.

Mannitol

Mannitol is an osmotic agent that is poorly absorbed from the respiratory epithelium. As an osmotic agent, mannitol creates a driving force for water efflux into the airway lumen and therefore improves mucus transport. In a Cochrane review,[23] two small studies involving 28 patients met the inclusion criteria. The authors concluded that dry powder mannitol has been shown to improve tracheobronchial clearance in bronchiectasis, as well as cystic fibrosis, asthmatics

and normal subjects. This review found some evidence that mannitol may help but more studies are required to demonstrate its impact on clinical outcome following sustained use.

Surgery

Surgical therapy is rarely recommended for bronchectasis due to generalised disease. Surgical resection may be considered in patients with focal disease, uncontrolled hemoptysis, and disease not responsive to medical management. End-stage bronchiectasis has been successfully treated with lung transplantation.[27]

Conclusion

Non-CF bronchiectasis is a common and serious respiratory disease both in developing and developed countries. All patients with bronchectasis should be evaluated for potential underlying causes. Early diagnosis and treatment can decrease the long term morbidity and mortality associated with bronchiectasis. Because there are few studies of therapies for children with non-CF bronchiectasis, patients must be evaluated and treated on an individual basis. Antibiotics should be prescribed for acute exacerbations. Broncho-pulmonary hygiene therapy is probably beneficial but requires further studies. Patients with more severe disease may also benefit from one or more of the therapeutic options summarised above.

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