MEDICINE REPORTS

Published: 26 August 2009

Non-cystic fibrosis bronchiectasis: review and recent advances

Galit Livnat and Lea Bentur*

Address: Meyer Children's Hospital, Rambam Medical Center, Haifa 31092, Israel

* Corresponding author: Lea Bentur (l_bentur@rambam.health.gov.il)

F1000 Medicine Reports 2009, **1**:67 (doi:10.3410/M1-67)

Abstract

Bronchiectasis is an abnormal dilatation of bronchi and bronchioles associated with repeated cycles of airway infection and inflammation. This review will focus on non-cystic fibrosis bronchiectasis in children, with regard to etiology, diagnosis, treatment options, and recent advances.

Introduction and context

Although the frequency of childhood bronchiectasis has been reduced in western countries, it remains a common problem in poorer countries and among certain demographic groups (native Alaskan children in the USA, in Pacific Islanders, and in New Zealand Maori). Additionally, non-cystic fibrosis (non-CF) bronchiectasis is now being identified more often by high resolution computed tomography (CT).

Bronchiectasis results when inflammatory and infectious damage to the bronchial and bronchiolar walls leads to a vicious cycle of airway injury [1] and airway and lung parenchyma destruction [2]. Sputum analyses and bronchial mucosal biopsy specimens from bronchiectasis patients have shown increased concentrations of elastase [3], interleukin-8 [4], tumor necrosis factor [5], and prostanoids [6]. Hence, anatomic factors, chronic infection and inflammation, and host defense all play important, yet poorly understood, roles in the development of bronchiectasis [7].

Bronchiectasis is categorized as focal or diffuse. All patients with focal bronchiectasis require bronchoscopy and/or high resolution CT to evaluate the airways, while patients with diffuse bronchiectasis should be assessed for underlying systemic abnormalities. Focal bronchiectasis can be secondary to airway obstruction such as bronchial atresia/malacia/stenosis, vascular ring/sling, following foreign body aspiration, extrinsic compression, airway tumors, necrotizing pneumonia, or congenital parenchymal malformation. The etiologies of diffuse non-CF bronchiectasis are presented in Table 1. Even after thorough evaluation, diagnosis remains idiopathic in the majority of patients. The relative frequency of each etiology varies, but idiopathic, post-infectious, and immune deficiencies are probably the commonest etiologies.

Diagnosis and treatment

Bronchiectasis should be suspected in children who present with chronic productive cough, airway obstruction, and recurrent infections. The diagnosis is made by high-resolution CT scans, which can classify the bronchiectasis as focal or diffuse, cylindrical, varicose, or saccular.

Treatment goals are to reduce the number of exacerbations and improve quality of life. Therapeutic strategies are largely derived from CF. All patients with bronchiectasis should have a microbiological examination (spontaneous/induced sputum or bronchoalveolar lavage) for routine bacterial and non-tuberculosis mycobacteria (NTM). About one-third of patients with non-CF bronchiectasis are chronically colonized with *Pseudomonas aeruginosa*. Patients with *P. aeruginosa* experience an accelerated decline in lung function and more frequent exacerbations [8]. Maintenance therapy with inhaled tobramycin has shown a microbiological benefit in two studies [1,9] but those studies were not powered to detect a clinical benefit. Antimicrobial, anti-inflammatory, airway clearance therapies, and immunization are the mainstays of therapy.

Table 1. Etiologies of non-cystic fibrosis bronchiectasis

Etiology	Examples	Comments
Idiopathic		Should be classified after a thorough evaluation
Post-infection	Post measles, pertussis, adenovirus, tuberculosis	Decreasing frequency in western countries. Non-progressive bronchiectasis
Genetic disease	CF, primary ciliary dyskenesia*, alfa 1 anti-trypsin (AAT) deficiency	Atypical CF has been increasingly recognized. AAT causes bronchiectasis only in adulthood
Aspiration/gastroesophageal reflux	Impaired gag reflex, impaired esophageal motility, esophageal atresia + fistula, convulsions, cleft palate	Barium swallow, pH metry, and swallowing mechanisms should be evaluated
Immune deficiency	Severe combined immune deficiency, Omenn's syndrome, hypogammaglobulinemia, hyper-IgE chronic granulomatous disease, common variable hypogamma*, ataxia telangiectasia, bare lymphocyte syndrome*, DEL1*, Wiskott-Aldrich syndrome, HIV, immunosuppressive treatment [corticosteroids, irradiation, organ and bone marrow transplants, biologic agents (for example, infliximab, etanercept)]	This group has increased due to descriptions of new immune deficiencies and increased iatrogenic immunodeficiency. Refer for immunological evaluation
Collagen vascular disorders	Systemic lupus erythematosus, rheumatoid arthritis	
Inflammatory bowel diseases	Ulcerative colitis, Crohn's disease	
Miscellaneous	Sarcoidosis, Young syndrome, Mounier-Kuhn syndrome, Ehler-Danlos syndrome, Marfan syndrome, yellow nail syndrome	
ABPA	CF, asthma	New treatment options*

*See text for recent advances. AAT, alfa 1 anti-trypsin; ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; DEL-1, developmental endothelial locus-1.

Recent advances

Etiology

Common variable immunodeficiency should be considered, as the age at diagnosis shows two peaks, between 6 and 10 years of age, and in young adulthood [10].

Bare lymphocyte syndrome is an autosomal recessive disorder [11] characterized by the absence of constitutive and inducible expression of major histocompatibility complex class II (MHCII) genes [12,13], which affect all cell types. An additional immune deficiency associated with pulmonary manifestations is that of Del-1 (developmental endothelial locus-1), which is an anti-adhesive factor that interferes with leukocyte-endothelial adhesion dependent on the integrin lymphocyte function-associated antigen-1 (LFA-1). Endothelial Del-1 deficiency increases LFA-1-dependent leukocyte adhesion and transmigration into the lungs, leading to excessive neutrophilic lung inflammation and bronchiectasis [14].

Post-infectious bronchiectasis secondary to NTM may occur in children with CF or HIV infection and in middle-aged Caucasian women without pre-existing conditions [15]. Of interest, in one study 36% of these females carried mutations in the CF transmembrane regulator (*CFTR*) gene [16].

Diagnosis

Primary ciliary diskenesia (PCD) is characterized by bronchiectasis, rhinosinusitis, ear infections, and infertility. Approximately one-half of the patients with PCD have *situs inversus totalis* or heterotaxy [17]. Eight genes have been linked with PCD: two outer dynein arm (ODA) genes, intermediate chain (DNAI1) and heavy chain (DNAH5), have been found to be mutated in approximately 30-38% of affected families [18-21]. Mutations in other ODA genes (*TXNDC3* and *DNAI2*) have been noted in a small fraction (approximately 2%) of PCD patients [22]. Lately, mutations in *ktu*, which is required for the dynein complex assembly, have been described in approximately 12% of PCD patients with defects in both the ODA and inner dynein arm (IDA) [23]. Recently, mutations in radial spoke head protein genes *RSPH9* and *RSPH4A* have been shown to cause central-microtubular-pair abnormalities in seven consanguineous Pakistani families in the UK [24]. Digital high-speed videomicroscopy has been used to detect more subtle abnormalities in ciliary beat pattern and has demonstrated that some of these patterns are associated with specific ultrastructural defects: immotile or limited flickering for ODA defects; low-amplitude stiff beat for isolated IDA defects or radial spoke defects; and circular, whip-like beat for central microtubular defects such as transposition [25]. The nasal nitric oxide method was shown to be a *bona fide* diagnostic test, as in PCD nasal and exhaled nitric oxide values are lower than normal, for reasons that are still unclear [26].

Treatment

There is no evidence base or consensus on the treatment of non-CF bronchiectasis [27]. Anwar *et al.* [28] recently reported the efficacy of long-term, oral, low-dose

azithromycin in non-CF bronchiectasis patients. Beneficial effects were demonstrated on exacerbation frequency, sputum microbiology, FEV1 (forced expiratory volume in 1 second) testing, and sputum volume. This therapy was recommended for the management of difficult-to-control bronchiectasis. The mechanism of action of azithromycin is not fully elucidated, but studies suggest potential immunomodulatory effects. Azithromycin significantly reduces bronchoalveolar lavage neutrophilia and interleukin-8 mRNA [29]. It is also known to have prokinetic effects on the gut and has been associated with lower levels of aspiration markers. The anti-pseudomonal effect of azithromycin may represent an inhibitory effect on quorum sensing (a phenomenon whereby the accumulation of signaling molecules enables a single cell to sense the number of bacteria according to the local density of their population), biofilm formation, production of immunostimulatory exoproducts, and the inflammatory response to this organism [30].

There is an ongoing debate about the efficacy of inhaled corticosteroids in CF and non-CF bronchiectasis [31]. Mucoactive agents such as hypertonic saline 7% are beneficial in patients with CF [32]. Few reports are available on hypertonic saline in non-CF bronchiectasis. Mannitol in a dry powder inhaler has been used as a hyperosmolar stimulus to increase mucociliary clearance in bronchiectatic subjects [33].

Two case reports documented the usefulness of short-term use of dornase alfa in treating PCD [34]. As DNAH5 mutations in PCD patients are nonsense mutations, pharmacogenetic therapies such as PTC124 that are designed to read through premature stop codons may potentially correct the primary defect in these PCD patients.

Allergic bronchopulmonary aspergillosis (ABPA) treatment involves long-term attenuation of the inflammatory and immunological activity with corticosteroids and reduction of the antigen burden from fungal colonization with antifungal agents. High-dose intravenous pulse methylprednisolone was found to be an effective treatment for ABPA in CF with relatively minor side effects [35]. Omalizumab, a humanized monoclonal antibody directed against IgE, has a potential role as adjuvant therapy for CF patients that are corticosteroid-dependent [36].

Prognosis

Lung function usually stabilizes in children with non-CF bronchiectasis [27] if diagnosed early and a consequent long-term treatment plan is followed. Surgery and lung transplantation are rarely required for non-CF bronchiectasis.

Implications for clinical practice

Non-CF bronchiectasis in childhood is still a common cause of childhood morbidity. Identifying and treating the underlying disease is essential to prevent the progression of bronchiectasis. New diagnostic tools such as the nasal nitric oxide test, immunological tests for bare lymphocyte syndrome and DEL-1, and culture for NTM, may aid in specific diagnosis. Therapeutic strategies are largely derived from CF bronchiectasis and include antimicrobial, anti-inflammatory, and airway clearance therapies, and immunization. Pulse steroids and omalizumab may offer a better control for ABPA. Azithromycin, as an immuno-modulator agent, should be considered in patients with severe bronchiectasis. The role of new mucoactive agents should be further explored.

Abbreviations

ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; CFTR, CF transmembrane regulator; CT, computed tomography; Del-1, developmental endothelial locus-1; FEV1, forced expiratory volume in 1 second; IDA, inner dynein arm; LFA-1, lymphocyte function-associated antigen-1; MHCII, major histocompatibility complex class II; NTM, non-tuberculous mycobacteria; ODA, outer dynein arm; PCD, primary ciliary diskenesia.

Competing interests

The authors declare that they have no competing interests.

References

1. Barker AF: **Bronchiectasis.** *N Engl J Med* 2002, **346:**1383-93.
2. Cole PJ: **Inflammation: a two-edged sword - the model of bronchiectasis.** *Eur J Respir Dis Suppl* 1986, **147:**6-15.
3. Tsang KW, Chan K, Ho P, Zheng L, Ooi GC, Ho JC, Lam W: **Sputum elastase in steady-state bronchiectasis.** *Chest* 2000, **117:**420-6.
4. Richman-Eisenstat JB, Jorens PG, Hébert CA, Ueki I, Nadel JA: **Interleukin-8: an important chemoattractant in sputum of patients with chronic inflammatory airway diseases.** *Am J Physiol* 1993, **264:**L413-8.
5. Shum DK, Chan SC, Ip MS: **Neutrophil-mediated degradation of lung proteoglycans: stimulation by tumor necrosis factor-alpha in sputum of patients with bronchiectasis.** *Am J Respir Crit Care Med* 2000, **162:**1925-31.
6. Tamaoki J, Chiyotani A, Kobayashi K, Sakai N, Kanemura T, Takizawa T: **Effect of indomethacin on bronchorrhea in patients with chronic bronchitis, diffuse panbronchiolitis, or bronchiectasis.** *Am Rev Respir Dis* 1992, **145:**548-52.
7. Fuschillo S, De Felice A, Balzano G: **Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms.** *Eur Respir J* 2008, **31:**396-406.
8. Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J: **Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis.** *Chest* 2007, **132:**1565-72.

9. Scheinberg P, Shore E: **A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis.** *Chest* 2005, **127:**1420-6.

10. Urschel S, Kayikci L, Wintergerst U, Notheis G, Jansson A, Belohradsky BH: **Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation.** *J Pediatr* 2009, **154:**888-94.

11. Lisowska-Grospierre B, Fondaneche MC, Rols MP, Griscelli C, Fischer A: **Two complementation groups account for most cases of inherited MHC class II deficiency.** *Hum Mol Genet* 1994, **3:**953-8.

12. Klein C, Lisowska-Grospierre B, LeDeist F, Fischer A, Griscelli C: **Major histocompatibility complex class II deficiency: clinical manifestations, immunologic features, and outcome.** *J Pediatr* 1993, **123:**921-8.

13. Elhasid R, Etzioni A: **Major histocompatibility complex class II deficiency: a clinical review.** *Blood Rev* 1996, **10:**242-8.

14. Choi EY, Chavakis E, Czabanka MA, Langer HF, Fraemohs L, Economopoulou M, Kundu RK, Orlandi A, Zheng YY, Prieto DA, Ballantyne CM, Constant SL, Aird WC, Papayannopoulou T, Gahmberg CG, Udey MC, Vajkoczy P, Quertermous T, Dimmeler S, Weber C, Chavakis T: **Del-1, an endogenous leukocyte-endothelial adhesion inhibitor, limits inflammatory cell recruitment.** *Science* 2008, **322:**1101-4.

F1000 Factor 3.0 *Recommended*
Evaluated by Caroline Owen 05 Jan 2009

15. Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, Brown MR, Chernick M, Steagall WK, Glasgow CG, Lin J, Jolley C, Sorbara L, Raffeld M, Hill S, Avila N, Sachdev V, Barnhart LA, Anderson VL, Claypool R, Hilligoss DM, Garofalo M, Fitzgerald A, Anaya-O'Brien S, Darnell D, DeCastro R, Menning HM, Ricklefs SM, Porcella SF, Olivier KN, *et al.*: **Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome.** *Am J Respir Crit Care Med* 2008, **178:**1066-74.

F1000 Factor 3.0 *Recommended*
Evaluated by Shawn Skerrett 16 Dec 2008

16. Ziedalski TM, Kao PN, Henig NR, Jacobs SS, Ruoss SJ: **Prospective analysis of cystic fibrosis transmembrane regulator mutations in adults with bronchiectasis or pulmonary nontuberculous mycobacterial infection.** *Chest* 2006, **130:**995-1002.

17. Kennedy MP, Noone PG, Leigh MW, Zariwala MA, Minnix SL, Knowles MR, Molina PL: **High-resolution CT of patients with primary ciliary dyskinesia.** *AJR Am J Roentgenol* 2007, **188:**1232-8.

18. Failly M, Saitta A, Muñoz A, Falconnet E, Rossier C, Santamaria F, de Santi MM, Lazor R, DeLozier-Blanchet CD, Bartoloni L, Blouin JL: **DNAI1 mutations explain only 2% of primary ciliary dykinesia.** *Respiration* 2008, **76:**198-204.

19. Guichard C, Harricane MC, Lafitte JJ, Godard P, Zaegel M, Tack V, Lalau G, Bouvagnet P: **Axonemal dynein intermediate-chain gene (DNAI1) mutations result in situs inversus and primary ciliary dyskinesia (Kartagener syndrome).** *Am J Hum Genet* 2001, **68:**1030-5.

20. Hornef N, Olbrich H, Horvath J, Zariwala MA, Fliegauf M, Loges NT, Wildhaber J, Noone PG, Kennedy M, Antonarakis SE, Blouin JL, Bartoloni L, Nüsslein T, Ahrens P, Griese M, Kuhl H, Sudbrak R, Knowles MR, Reinhardt R, Omran H: **DNAH5 mutations are a common cause of primary ciliary dyskinesia with outer dynein arm defects.** *Am J Respir Crit Care Med* 2006, **174:**120-6.

21. Zariwala MA, Leigh MW, Ceppa F, Kennedy MP, Noone PG, Carson JL, Hazucha MJ, Lori A, Horvath J, Olbrich H, Loges NT, Bridoux AM, Pennarun G, Duriez B, Escudier E, Mitchison HM, Chodhari R, Chung EM, Morgan LC, de Iongh RU, Rutland J, Pradal U, Omran H, Amselem S, Knowles MR: **Mutations of DNAI1 in primary ciliary dyskinesia: evidence of founder effect in a common mutation.** *Am J Respir Crit Care Med* 2006, **174:**858-66.

22. Loges NT, Olbrich H, Fenske L, Mussaffi H, Horvath J, Fliegauf M, Kuhl H, Baktai G, Peterffy E, Chodhari R, Chung EM, Rutman A, O'Callaghan C, Blau H, Tiszlavicz L, Voelkel K, Witt M, Zietkiewicz E, Neesen J, Reinhardt R, Mitchison HM, Omran H: **DNAI2 mutations cause primary ciliary dyskinesia with defects in the outer dynein arm.** *Am J Hum Genet* 2008, **83:**547-58.

23. Omran H, Kobayashi D, Olbrich H, Tsukahara T, Loges NT, Hagiwara H, Zhang Q, Leblond G, O'Toole E, Hara C, Mizuno H, Kawano H, Fliegauf M, Yagi T, Koshida S, Miyawaki A, Zentgraf H, Seithe H, Reinhardt R, Watanabe Y, Kamiya R, Mitchell DR, Takeda H: **Ktu/PF13 is required for cytoplasmic pre-assembly of axonemal dyneins.** *Nature* 2008, **456:**611-6.

F1000 Factor 4.9 *Must Read*
Evaluated by Trina Schroer 08 Jan 2009, Greg Pazour 30 Jan 2009, Herbert Steinbeisser 03 Apr 2009

24. Castleman VH, Romio L, Chodhari R, Hirst RA, de Castro SC, Parker KA, Ybot-Gonzalez P, Emes RD, Wilson SW, Wallis C, Johnson CA, Herrera RJ, Rutman A, Dixon M, Shoemark A, Bush A, Hogg C, Gardiner RM, Reish O, Greene ND, O'Callaghan C, Purton S, Chung EM, Mitchison HM: **Mutations in radial spoke head protein genes RSPH9 and RSPH4A cause primary ciliary dyskinesia with central-microtubular-pair abnormalities.** *Am J Hum Genet* 2009, **84:**197-209.

25. Chilvers MA, Rutman A, O'Callaghan C: **Ciliary beat pattern is associated with specific ultrastructural defects in primary ciliary dyskinesia.** *J Allergy Clin Immunol* 2003, **112:**518-24.

26. Narang I, Ersu R, Wilson NM, Bush A: **Nitric oxide in chronic airway inflammation in children: diagnostic use and pathophysiological significance.** *Thorax* 2002, **57:**586-9.

27. Bastardo CM, Sonnappa S, Stanojevic S, Navarro A, Lopez PM, Jaffe A, Bush A: **Non-cystic fibrosis bronchiectasis in childhood: longitudinal growth and lung function.** *Thorax* 2009, **64:**246-51.

28. Anwar GA, Bourke SC, Afolabi G, Middleton P, Ward C, Rutherford RM: **Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis.** *Respir Med* 2008, **102:**1494-6.

F1000 Factor 3.0 *Recommended*
Evaluated by Cori Daines 30 Oct 2008

29. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE: **Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome.** *Am J Respir Crit Care Med* 2006, **174:**566-70.

30. Mertens V, Blondeau K, Pauwels A, Farre R, Vanaudenaerde B, Vos R, Verleden G, Van Raemdonck DE, Dupont LJ, Sifrim D: **Azithromycin reduces gastroesophageal reflux and aspiration in lung transplant recipients.** *Dig Dis Sci* 2009, **54:**972-9.

31. Kapur N, Bell S, Kolbe J, Chang AB: **Inhaled steroids for bronchiectasis.** *Cochrane Database Syst Rev* 2009:CD000996.

32. Wark P, McDonald VM: **Nebulised hypertonic saline for cystic fibrosis.** *Cochrane Database Syst Rev* 2009:CD001506.

33. Ilowite J, Spiegler P, Chawla S: **Bronchiectasis: new findings in the pathogenesis and treatment of this disease.** *Curr Opin Infect Dis* 2008, **21:**163-7.

34. ten Berge M, Brinkhorst G, Kroon AA, de Jongste JC: **DNase treatment in primary ciliary dyskinesia - assessment by nocturnal pulse oximetry.** *Pediatr Pulmonol* 1999, **27:**59-61.

35. Cohen-Cymberknoh M, Blau H, Shoseyov D, Mei-Zahav M, Efrati O, Armoni S, Kerem E: **Intravenous monthly pulse methylprednisolone treatment for ABPA in patients with cystic fibrosis.** *J Cyst Fibros* 2009, **8:**253-7.

36. Zirbes JM, Milla CE: **Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis.** *Pediatr Pulmonol* 2008, **43:**607-10.