Primary Immunodeficiency Disorders in Children with Non-Cystic Fibrosis Bronchiectasis

Deniz Çağdaş[1], Melis Pehlivantürk Kızılkan[2], Anar Tagiyev[2], Nagehan Emiralioğlu[3], Aslınur Keleş[4], Ebru Yalçın[3], Deniz Doğru[3], Uğur Özçelik[3], Nural Kiper[3], İlhan Tezcan[1]

[1] Hacettepe University Medical School, Department of Pediatric Immunology

[2] Hacettepe University Medical School, Department of Pediatrics

[3] Hacettepe University Medical School, Department of Pediatric Pulmonology

[4] Hacettepe University Medical School

The authors declared that they have no conflict of interest.

Note: Nural Kiper and İlhan Tezcan share the last authorship

Corresponding Author:

Deniz Cagdas, MD, PhD

Professor of Pediatrics

Hacettepe University Medical School

Department of Pediatrics

Division of Pediatric Immunology

e-mail : cagdasdeniza@yahoo.com /deniz.ayvaz@hacettepe.edu.tr

Tel: +903122305 1172

Fax: +903123244990

Abstract:

Introduction: Primary Immunodeficiency diseases(PID) are common in patients with non-cystic fibrosis bronchiectasis(NCFB). Our objective was to determine ratio/types of PID in NCFB.

Patients: Seventy NCFB patients followed up in a two-year period were enrolled.

Results: Median age was 14 years (min.-max., 6-30). Patients had their first pulmonary infection at a median age of 6 months(min.-max., 0.5-84), were diagnosed with bronchiectasis at about 9 years(114 months)(min.-max., 2-276)). Male/female ratio was 39/31; parental consanguinity, 38.6%. PID, primary ciliary dyskinesis (PCD), bronchiolitis obliterans, rheumatic/autoimmune diseases, severe congenital heart disease and tuberculosis were evaluated as the most common causes of NCFB. About 40% of patients (n=16) had bronchial hyperreactivity(BH) and asthma. Twenty-nine patients(41.4%) had a PID, and nearly all (n=28) had primary antibody deficiency, including patients with combined T and B cell deficiency.

PID and non-PID groups did not differ according to gender, parental consanguinity, age at first pneumonia, age of onset of chronic pulmonary symptoms, bronchiectasis, presence of gastroesophageal reflux disease(GERD), bronchial hyperreactivity(BH) and asthma ($p>0.05$). Admission to immunology clinic was about 3 years later in PID compared with non-PID group($p<0.001$). Five patients got molecular diagnosis, X-linked agammaglobulinemia(n=2), LRBA deficiency(n=1), RASGRP1 deficiency(n=1), MHC Class II deficiency(n=1). They were given monthly IVIG and HSCT was performed for three patients.

Conclusion: PID accounted for about 40% of NCFB. Early diagnosis/appropriate treatment have impact on clinical course of a PID patient. Thus, follow-up in also immunology clinics should be a routine for patients who experience pneumonia in the first year of their lives and those with NCFB. Most patients with NCFB (84.28%) had their first pulmonary infection within the first year of their lives.

Key Words: Non-cystic fibrosis bronchiectasis, primary immunodeficiency, bronchiectasis, respiratory infections

Introduction:

Bronchiectasis is a chronic pulmonary disease of the conducting airways. It produces persistent productive cough, recurrent respiratory infectious exacerbations, and irreversible bronchial dilatation in children and adults. Two different types of bronchiectasis are defined according to the pattern of the lesion, diffuse and focal [1]. Focal bronchiectasis is usually associated with bronchial obstruction, such as aspiration of foreign body, that leads to infection [2]. Diffuse bronchiectasis is more often found in association with underlying disorders such as cystic fibrosis (CF), primary immunodeficiencies (PID), primary ciliary dyskinesia (PCD), and recurrent aspiration syndromes [3].

Bronchiectasis is often a consequence and a complication of recurrent, uncontrolled respiratory infections and inflammation. In many studies, acute, severe or recurrent pneumonia is the most common cause [4, 5]. Subsequent acute or chronic damage in the conducting airways results in a significant physical and social morbidity [6]. The diagnosis depends on radiological imaging of the typical changes in addition to clinical findings. Chest X-ray is sometimes insufficient to make the clinicians reach the diagnosis. Thus, a high-resolution computed tomography (HRCT) scan is the gold standard diagnostic procedure.

Nowadays, with early immunization and the widespread use of antibiotics in childhood, acute post-infectious damage is likely to be less relevant [7]. However, especially in the countries which the consanguineous marriages are relatively frequent, chronic damage due to hereditary diseases of respiratory system, such as cystic fibrosis, PID and PCD are common cause of bronchiectasis [8].

PIDs are among the frequent causes of non-cystic fibrosis bronchiectasis (NCFB) [9]. Bronchiectasis is seen as a common long-term complication especially in patients with primary antibody deficiency (PAD) [10, 11]. With a detailed history, physical examination and laboratory

analysis, it is not difficult to detect the underlying immunological etiology. Our objective was to identify the ratio of underlying PID in patients with NCFB, and also evaluate the characteristic clinical, microbiological or radiological features in patients with and without PID.

Patients:

In a two year period, 87 patients who were diagnosed with NCFB in pediatric chest disease department and referred to pediatric immunology department were retrospectively evaluated. Seventy patients come to the control visits in each department routinely. However, 17 out of 87 were lost follow-up.

Patients' clinical parameters such as age, gender, parental consanguinity, age at diagnosis, age at onset of infections were recorded from the files. The diagnosis of bronchiectasis was confirmed with a HRCT scan in each of the patients. Cystic fibrosis was excluded in the patient cohort via sweat chloride test and in some of them by mutation analysis in chest disease departments [12]. After exclusion of CF, patients underwent investigations for the common etiologies of bronchiectasis which included nasal nitric oxide (NO) test (n=64), gastroesophageal reflux scintigraphy (n=64), pulmonary function tests with spirometry (n=58) and flexible bronchoscopic evaluation (n=65).

Diagnosis of PCD was based on presentation of the characteristic clinical phenotype, nasal NO results, the presence of ciliary ultrastructural defects (visualized by electron microscopy), and the presence of abnormal ciliary function (as determined by video microscopy).

Bronchiolitis obliterans (BO) was defined as the presence of mosaic pattern in chest X-ray in addition to the history of respiratory symptoms which developed after a severe pulmonary infection, and the findings of obstructive airway disease which does not respond to bronchodilator therapy in respiratory function test.

Evaluation for possible immunodeficiencies included complete and differential blood counts, serum immunoglobulin levels in all, and lymphocyte subgroups (n=37), serum complement hemolytic activity (CH50) (n=39), nitroblue tetrazolium test (NBT) (n=50) and pneumococcal antibody response (n=26). European Society of Immunodeficiency and Pan-American Group for Immunodeficiency (ESID and PAGID) criteria was used for the diagnosis of PID [13]. Selective IgA and selective IgM deficiency are diagnosed according to the ESID criteria [14]. Secondary hypogammaglobulinemia is excluded by history, absence of renal, gastrointestinal and cutaneous protein loss, and other drug or disease related causes [15]. Urinary analysis for proteinuria was done, total protein and albumin values were measured in all the patients with hypogammaglobulinemia. After exclusion of the secondary causes some of the patients may be classified as idiopathic primary hypogammaglobulinemia (IPH), undefined/unclassified hypogammaglobulinemia [16, 17].

Sputum (n=64) and bronchoalveolar lavage (BAL) (n=65) results of the patients were also recorded to determine the microbiological etiology. The final diagnosis of the patients with NCFB were recorded after the follow-up period. All patients with NCFB were grouped according to having PID or not according to their final diagnosis (PID and non-PID).

The study is approved by the Institutional Review Board.

Statistical analysis: SPSS 13.0 was used for the statistical analysis. One-way ANNOVA analysis was used for analysis of more than two groups. Pearson's correlation coefficient was used to evaluate correlation of two variables.

Results:

Characteristics of Patients with NCFB: The mean age was 14.23±4.72 (median; 14 (6-30)) years. Out of 70 patients, 39 (55.7%) were male, 31 (44.3%) were female. Parental consanguinity ratio was 38.6%. The patients had their first pneumonia at a median age of 6 months (0.5-84). Most

patients (84.28%) had their first pulmonary infection within the first year of their lives. The median age of onset of chronic pulmonary symptoms (chronic cough, growling etc.) was about two years (24 months (0.5-276)). The median age at diagnosis of bronchiectasis was about 3 years (114 months (2-276)).

Out of 70 NCFB patients, 46 (60%) experiences other infections, such as tonsillopharyngitis, sinusitis, otitis media. Bronchial hyperreactivity was shown in 26 (37.14%) out of 58 patients by pulmonary function test. Gastroesophageal reflux disease (GERD) was shown in 12 (18.46%) out of 65 patients by scintigraphy. Lipid laden macrophages were detected in BAL in 18 (30.5%) out of 65 patients who were evaluated by bronchoscopy. The congenital heart disease found in one of the NCFB patients was ventricular septal defect and high venosum ASD. The patient had also pulmonary hypertension. Totally 18.6% (n=13) of NCFB patients, 31.7% of non-PID, had the diagnosis of PCD, and among them 2 patients (15.4%) had Kartagener's syndrome.

The NCFB patients are grouped as PID (n=29, 41.4%), and non-PID (n=41, 58.6%). One (complement deficiency) out of all PID group were associating with hypogammaglobulinemia (common variable immunodeficiency, combined immunodeficiency, agammaglobulinemia, etc. (Table 1)). Bronchial hyperreactivity and asthma (n=16, 39%), PCD (n=13, 31.7%), GERD (n=9, 21.9%), and BO (n=3, 7.3%) associate with non-PID (Table 1). Other associated diseases are rheumatic/autoimmune diseases (n=2, 4.9%), tuberculosis (n=2, 4.9%), and severe congenital heart disease (n=1, 2.4%) (Table 1).

The groups did not differ according to gender, the age at first pneumonia episode, age of onset of chronic pulmonary symptoms, parental consanguinity, presence of BH and asthma, GERD, and frequency of infections (Table 2). Also, the age of diagnosis of bronchiectasis did not differ between groups (108 months (2-224) in non-PID, and 132 (12-276) in PID) (p=0.223). The admission to immunology clinic in PID was 13 years (6-20), however it is 16 years (10-30) in non-

PID (p<0.001) (Table 2). Totally five patients underwent left-sided lobectomy, two was in PID, other two was in the group of unidentified causes of non-PID, one was PCD. The two PID patients who underwent lobectomy were diagnosed with combined immunodeficiency (CID) and common variable immunodeficiency (CVID). The patient with CVID developed amyloidosis and died of a severe pneumonia and respiratory failure [18]. Genetic tests were not performed routinely to the NCFB patients. However in the follow-up, five patients got molecular diagnosis; X-linked agammaglobulinemia (BTK defect)(n=2), LRBA deficiency(n=1), RASGRP1 deficiency(n=1) [19], MHC Class II deficiency(n=1). They were given monthly IVIG, and HSCT was performed in three patients (with RASGRP1 deficiency, MHC Class II deficiency, and LRBA deficiency). All tranplanted patients are alive and well.

Microbiology: The sputum microbiology was positive in 55% (33) out of 60 patients (*Hemophilus influenza (H. influenza)* in 25 (75,75%), *Streptococcus pneumonia (S. pneumonia)* in 14 (42.4%), *Candida albicans (C. albicans)* in two (6%), group A beta hemolytic streptococcus (GAS) in two (6%), *Pseudomonas aeruginosa (P. aeruginosa)* in two (6%) patients), multiple agents (*H. influenza, S. pneumonia, Moraxella catarrhalis (M. catarrhalis), Hemophilus parahemolyticus (H. parahemolyticus),* GAS*, C. albicans, P. aeruginosa)* in 11 (33.3%) patients.

BAL microbiology was positive in 56.9% (n=37) (*H. influenza* in 59.46% (n=22), *S. pneumonia* in 21.62% (n=8), *H. haemolyticus, Hemophilus agnus (H. agnus), H. hemolyticus, Hemophilus aphrophilus (H. aphrophilus), Hemophilus segnis (H. segnis), H. parainfluenza, M. catarrhalis, P. aeruginosa, Stenotrophomonas maltophilia (S. maltophilia)* were each isolated in 1 (2.7%) patients, multiple agents (*H. influenza, S. pneumonia, S. maltophilia) i*n 4 (13.5%) of the patients.

The non-PID and PID group did not differ according to the ratio of sputum culture positivity (p=0.59). Increased ratio of positive BAL culture was recorded in younger patients than older ones (p=0.019). Nine patients (34.6%) in PID, 22 patients (66.7%) in non-PID had positive BAL culture,

the difference was statistically significant (p=0.014). The results of microbiological analyses in groups are given in Table 3.

Radiology: According to HRCT results, most affected areas were recorded to be right middle and left lower lobe. Diffuse involvement was seen in 41.43% (n=29) of the patients, diffuse right lung involvement in 15.71% (n=11), diffuse left lung involvement in 7.14% (n=5), isolated left lower lobe involvement in 17.14% (n=12) of the patients, isolated right lower lobe involvement in 2.8% (n=2), left or right upper lobe involvement in 5.7% (n=4) patients. The involvement in PID and non-PID groups is given in Table 3. There was no statistical difference (p>0.05).

Discussion:

Bronchiectasis is still one of the most common causes of childhood morbidity and mortality [20-22]. Main causes are infections, immunodeficiencies, congenital and genetic disorders, aspirations [23]. Pulmonary infections account for 7-20.6% of bronchiectasis cases [24, 25].

Underlying etiology is not identified in 14.2-37% of children [24, 25], and in 35-50% of adults with bronchiectasis [26, 27]. Undiagnosed PID may be partly responsible for the development of unidentified bronchiectasis. The overall prevalence of brochiectasis in CVID is found as 34% [28] and 62.3% [29] in different series. The diagnosis of PID is generally made at the irreversible state when the disease progressed into the end-stage respiratory disease/failure [30]. Physicians usually believe that the PID presents in childhood, and neglect PID especially in adulthood. The median age on admission to immunology clinic was about 3 years later (p<0.001) in PID group. One of the several reasons of this delay may be due to the later admission of PID patients to the primary physician due to the insidious symptoms and other systemic problems. PID could vary greatly in clinical course, and the presentation of patients are not only with infectious diseases, but with allergy, autoimmunity, inflammation, lymphoproliferation/malignancies. With the increase in awareness and the definition of new PID disorders, PID are becoming one of the

most common causes of NCFB. Complete blood count and determination of serum immunoglobulin levels were suggested as the baseline immunological tests in guidelines [31]. Immunodeficiencies account for 10-34% of the childhood bronchiectasis [32, 33], and among them, antibody deficiencies were common disorders leading to NCFB [34, 35]. In our study, PID accounts for about 40% of NCFB, and about 90% was primary antibody deficiency (Table 1). CVID (27.6%) was the most common PID. This high ratio of PID may be due to the routine follow-up of patients in an immunology clinic. Detailed evaluation with not only the suggested baseline tests, but other tests during the follow-up period, such as lymphocyte subset analysis, CH50 and NBT tests were performed to some of the patients. In the study of Reisi et al, PIDs associated with bronchiectasis were CVID, XLA, HIGM and Hyperimmunoglobulin E syndrome[29]. The ratio of bronchiectasis was found to be 62.3% in CVID, and 43% in XLA patients.

In our study, about 40% of NCFB patients had BH and asthma, and about 1/5 had GERD. Although GERD, asthma and BH, were common in non-PID group, each of them is evaluated as associations, rather than a cause. Bronchiectasis could result in BH, as it leads to airway obstruction, increased bronchial secretions and consequently to increased incidence of pulmonary infections. On the other hand, BH could exacerbate the symptoms of bronchiectasis [36]. BH and asthma may associate with PID [29, 37]. In our series this ratio is about 40%, nearly the same as the ratio in all NCFB patients. Asthma and BH may also associate with PCD, BO and GERD. The presence of BH and asthma and the presence of recurrent infections did not differ in groups in our study. These data show that bronchiectasis should be evaluated as a multifactorial disease. Infections, BH and asthma, PID and PCD may be present in the same patient, and it is not easy to determine accurately the most important reason of bronchiectasis. So, the treatment should be individualized.

Non-typeable *H. influenza* and *S. pneumonia* are the main bacterial pathogens in children with bronchiectasis and predominates in all age groups [38, 39]. BAL culture results in NCFB showed that most common pathogens are *H. influenza* (47%), *S. pneumonia* and *M. catarrhalis* [40]. Data about microbiological agents in NCFB patients with PID is scarce. In a retrospective study, PID ratio was 8.6%, and in half, *H. influenzae, S. aureus, S. pneumoniae and C. parapsilosis* were isolated [41]. In our study, the most frequently isolated microorganisms were *H. influenza* and *S. pneumonia* both in sputum and BAL. The ratio of microorganism isolation in BAL culture was significantly increased in young and non-PID patients ($p<0.05$), possibly due to frequent use of antibacterial agents in chronic cases.

Although bronchiectasis tend to appear in upper lobes in CF, it generally locate to the basal segments of lower lobes in children with NCFB [42]. Patients with hypogammaglobulinemia was demonstrated to have lower/middle lobe and lingular segment bronchiectasis [43]. In our study, most affected areas were right middle and left lower lobe in all NCFB patients. Lower, especially left lower lobe and diffuse involvement were seen mostly in PID group.

In our study, underlying etiology is not identified in about 1/3 of NCFB patients. PID, PCD, BO, rheumatic and autoimmune diseases and tuberculosis were evaluated as causes. Asthma and BH were evaluated as associations.

An important finding is that most patients (84.28%) had their first pulmonary infection within the first year of their lives. As far as we know, this study is the first study which compares the PID and non-PID NCFB. Patients with PID would highly benefit from an early diagnosis and appropriate treatment [44, 45]. Earlier immunoglobulin replacement therapy and antibacterial prophylaxis will decrease the infectious episodes, preventing the progress of bronchiectasis in patients with primary antibody deficiency. Thus, follow-up in also immunology clinics should be

a routine for NCFB patients, and also for patients who experience pneumonia in the first year of their lives.

Authors declare that they have no conflict of interest

Table 1. Classification of PID and non-PID causes of NCFB

PID Group (n= 29 (41.4%))		**Non-PID Group** (n= 41 (58.6%))	
CVID	9 (30.9%)	Unidentified	13 (31.7%)
Combined immunodeficiency	6 (20.6%)	Asthma and bronchial hyperreactivity	16 (39%)
Selective IgA deficiency	4 (13.8%)	Primary ciliary dyskinesia	13 (31.7%)
IPH	3 (10.3%)	Gastroesophageal reflux	9 (21.9%)
Selective IgM deficiency	3 (10.3%)	Brochiolitis obliterans	3 (7.3%)
XLA	2 (6.9%)	Rheumatic/Autoimmune disease	2 (4.9%)
Hyperimmunoglobulin M Syndrome	1 (3.4%)	Tuberculosis	2 (4.9%)
Complement deficiency	1 (3.4%)	Congenital heart disease	1 (2.4%)

CVID, common variable immunodeficiency; XLA, X-linked agammaglobulinemia; Ig, immunoglobulin; idiopathic primary hypogammaglobulinemia, IPH.

Table 2. Characteristics of patients with PID and non-PID

	Non-CF Bronchiectasis		
Characteristics	**PID (n=29)**	**Non-PID (n=41)**	**p**
Gender (M/F)	19/10	20/21	0.16
Parental consanguinity	44.8%	34.1%	0.17
Age at first pneumonia*	9.1±13.9 / 6 (0-72)	9.4±13.7 / 6 (0-84)	0.83
Age at onset of chronic pulmonary symptoms *	43.6±53.7 / 24 (0-276)	31.8±35.9 / 18 (0-120)	0.23
Age at diagnosis of bronchiectasis*	139±64.3 / 132 (12-276)	124.4±62.9 / 108 (2-224)	0.22
Age at referral to Immunology department (year)	16.8±5.1 / 16 (10-30)	12.4±3.4 / 13 (6-20)	**<0.001**
Gastroesophageal reflux	4 (14.8%)	9 (24.3%)	0.69
Bronchial hyperreactivity and asthma	10 (38.5%)	16 (50%)	0.93
Frequent infections	16 (55.2%)	24 (58.5%)	0.61
Isolation of microorganism in sputum	13 (44.8%)	21 (51.2%)	0.59
Isolation of microorganism in BAL	9 (34.6%)	22 (66.7%)	**<0.014**
Lobectomy	2 (6.9%)	3 (7.3%)	0.53

* months.
Median (min.-max.) and mean (±standard deviation) ages are given in the table

Table 3. Comparison of the microbiological agents and radiological involvement in PID and Non-PID Groups

		PID	Non-PID
Microbiological agents	**Sputum**	*H. influenza, S. pneumonia, P. aeruginosa, K. pneumoniae, C. albicans*	*H. influenza, S. pneumonia, P. aeruginosa, M. catarralis, C.albicans*
	BAL	*H. influenza, S. pneumonia*	*H. influenza, S. pneumonia, P. aeruginosa, M. catarralis, H. parainfluenza, H. parahemolyticus*
Radiological involvement (HRCT)		Diffuse, left lower, bilateral lower lobes, right middle and right lower lobe, left total	Diffuse, left lower, right lower, bilateral lower lobes, right upper, and right middle lobes

References:

1. Ryu, J.H. and S.J. Swensen. *Cystic and cavitary lung diseases: focal and diffuse*. in *Mayo Clinic Proceedings*. 2003. Elsevier.
2. Barker, A.F. and B. Ejjr, *Bronchiectasis: update of an orphan disease 1, 2.* Am Rev Respir Dis, 1988. **137**: p. 969.
3. Sayedi, S.J., et al., *The etiology of bronchiectasis in Iran.* International Journal of Pediatrics, 2016. **4**(12): p. 4051-4056.
4. Singleton, R.J., et al., *Indigenous children from three countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis.* Pediatr Pulmonol, 2014. **49**(2): p. 129-200.
5. Eastham, K., et al., *The need to redefine non-cystic fibrosis bronchiectasis in childhood.* Thorax, 2004. **59**(4): p. 324-327.
6. Redding, G.J., *Bronchiectasis in children.* Pediatric Clinics of North America, 2009. **56**(1): p. 157-171.
7. Dagli, E., *Non cystic fibrosis bronchiectasis.* Paediatric respiratory reviews, 2000. **1**(1): p. 64-70.
8. Yazdani, R., et al., *Infectious and Noninfectious Pulmonary Complications in Patients With Primary Immunodeficiency Disorders.* J Investig Allergol Clin Immunol, 2017. **27**(4): p. 213-224.
9. Hong, J., Knutsen, AP., *Pulmonary disease in primary immunodeficiency disorders.* Pediatric Allergy Immunology and Pulmonology, 2013. **26**(2): p. 57-69.
10. Hermaszewski, R. and A. Webster, *Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications.* QJM: An International Journal of Medicine, 1993. **86**(1): p. 31-42.
11. Cunningham-Rundles, C. and C. Bodian, *Common variable immunodeficiency: clinical and immunological features of 248 patients.* Clinical Immunology, 1999. **92**(1): p. 34-48.
12. Farrell, P.M., et al., *Diagnosis of Cystic Fibrosis. Consensus Guidelines from the Cystic Fibrosis Foundation.* J Pediatr, 2017. **181s**: p. S4-S15 e1.
13. Conley, M., L. Notarangelo, and A. Etzioni, *representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Diagnostic criteria for primary immunodeficiencies.* Clin Immunol, 1999. **93**(3): p. 190-197.
14. *Diagnosis criteria*. [cited 2019 April 14th]; ESID].
15. Patel, S.Y., J. Carbone, and S. Jolles, *The Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management.* Frontiers in immunology, 2019. **10**.
16. Keles, S., et al., *Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: 'similarities and differences'.* Pediatric Allergy and Immunology, 2010. **21**(5): p. 843-851.
17. Kutukculer, N. and N. Gulez, *The outcome of patients with unclassified hypogammaglobulinemia in early childhood.* Pediatric Allergy and Immunology, 2009. **20**(7): p. 693-698.
18. Esenboga, S., et al., *CVID Associated with Systemic Amyloidosis.* Case Reports Immunol, 2015. **2015**: p. 870179.
19. Salzer, E., et al., *RASGRP1 deficiency causes immunodeficiency with impaired cytoskeletal dynamics.* Nat Immunol, 2016. **17**(12): p. 1352-1360.
20. Bilton, D., *Update on non-cystic fibrosis bronchiectasis.* Curr Opin Pulm Med, 2008. **14**(6): p. 595-9.
21. Lim, C. and D.G. Kim, *Bronchiectasis.* Tuberc Respir Dis (Seoul), 2012. **73**(5): p. 249-57.
22. Dočekal, D., et al., *Bronchiectasis: the consequence of late diagnosis in chronic respiratory symptoms.* Journal of tropical pediatrics, 2005. **51**(6): p. 362-365.
23. Boren, E.J., S.S. Teuber, and M.E. Gershwin, *A review of non-cystic fibrosis pediatric bronchiectasis.* Clinical reviews in allergy & immunology, 2008. **34**(2): p. 260-273.

24. Brower, K.S., M.T. Del Vecchio, and S.C. Aronoff, *The etiologies of non-CF bronchiectasis in childhood: a systematic review of 989 subjects.* BMC pediatrics, 2014. **14**(1): p. 299.
25. Kim, H.-Y., et al., *Bronchiectasis in children: 10-year experience at a single institution.* Allergy, asthma & immunology research, 2011. **3**(1): p. 39-45.
26. Pasteur, M.C., et al., *An investigation into causative factors in patients with bronchiectasis.* Am J Respir Crit Care Med, 2000. **162**(4 Pt 1): p. 1277-84.
27. Dimakou, K., et al., *Non CF-bronchiectasis: Aetiologic approach, clinical, radiological microbiological and functional profile in 277 patients.* Respir Med, 2016. **116**: p. 1-7.
28. Ramzi, N., et al., *Bronchiectasis in common variable immunodeficiency: A systematic review and meta-analysis.* Pediatric Pulmonology, 2019.
29. Reisi, M., et al., *Evaluation of pulmonary complications in patients with primary immunodeficiency disorders.* Eur Ann Allergy Clin Immunol, 2017. **49**(3): p. 122-128.
30. Jesenak, M., et al., *Pulmonary manifestations of primary immunodeficiency disorders in children.* Front Pediatr, 2014. **2**: p. 77.
31. Chang, A.B., et al., *Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines.* Med J Aust, 2015. **202**(1): p. 21-3.
32. Li, A.M., et al., *Non-CF bronchiectasis: does knowing the aetiology lead to changes in management?* Eur Respir J, 2005. **26**(1): p. 8-14.
33. Bouyahia, O., et al., *Etiology and outcome of bronchiectasis in children: a study of 41 patients.* Tunis Med, 2008. **86**(11): p. 996-9.
34. Brower, K.S., M.T. Del Vecchio, and S.C. Aronoff, *The etiologies of non-CF bronchiectasis in childhood: a systematic review of 989 subjects.* BMC Pediatr, 2014. **14**(1): p. 299.
35. Conley, M.E., L.D. Notarangelo, and A. Etzioni, *Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies).* Clin Immunol, 1999. **93**(3): p. 190-7.
36. Truong, T., *The overlap of bronchiectasis and immunodeficiency with asthma.* Immunol Allergy Clin North Am, 2013. **33**(1): p. 61-78.
37. Agondi, R., et al., *Allergic asthma in patients with common variable immunodeficiency.* Allergy, 2010. **65**(4): p. 510-515.
38. Grimwood, K., *Airway microbiology and host defences in paediatric non-CF bronchiectasis.* Paediatr Respir Rev, 2011. **12**(2): p. 111-8.
39. Byrnes, C., *Non cystic fibrosis bronchiectasis.* Paediatr Respir Rev, 2006. **7 Suppl 1**: p. S255-7.
40. Kapur, N., et al., *Lower airway microbiology and cellularity in children with newly diagnosed non-CF bronchiectasis.* Pediatr Pulmonol, 2012. **47**(3): p. 300-7.
41. Kim, H.Y., et al., *Bronchiectasis in children: 10-year experience at a single institution.* Allergy Asthma Immunol Res, 2011. **3**(1): p. 39-45.
42. Dagli, E., *Non cystic fibrosis bronchiectasis.* Paediatr Respir Rev, 2000. **1**(1): p. 64-70.
43. Curtin, J.J., et al., *Bronchiectasis in hypogammaglobulinaemia--a computed tomography assessment.* Clin Radiol, 1991. **44**(2): p. 82-4.
44. Soler-Palacin, P., et al., *Primary immunodeficiency diseases in lung disease: warning signs, diagnosis and management.* Respir Res, 2018. **19**(1): p. 219.
45. Nowas, S., *Pulmonary Manifestations of Primary Immunodeficiency Disorders.* Immunol Allergy Clin North Am, 2015. **35**(4): p. 753-66.