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Does the Etiology of Bronchiectasis Change Over the Years, One Central Experience

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Abstract

Introduction: Bronchiectasis is the abnormal enlargement of one or more bronchial walls, destroying elastic and muscle structures. It is still a big problem in developing countries, although the incidence in developed countries is decreasing.

Objective: We aimed to evaluate sociodemographic and clinical characteristics, bronchiectasis localizations, pulmonary function tests (PFT) and etiologic factors of bronchiectasis patients who applied to our clinic.

Methods: In our study, 158 cases diagnosed by bronchiectasis and followed up in our clinic were evaluated retrospectively.

Results: 86 of the cases (54,4%) were male. The mean age was 16,03 ± 5,2 (2-25) years. The age of diagnosis was 10,4 ± 4,8 (0-18) years, while the onset of symptoms was 6,07 ± 5,4 (1-17) years. The most common complaints were cough (85,4%), sputum (75,5%), shortness of breath (46,1%) and recurrent wheezing (43%). 81 cases (58,3%) have been diagnosed by pneumonia at more than once previously. The most frequent pathologies in the etiology, the first was immunodeficiencies (47 patients (29,9%)), the second was primary ciliary dyskinesia (30 patients (19,1%). The other etiologies were sequelae pneumonia(13 cases (8,3%)) and Bronchiolitis obliterans (8 patient (5,1%)).

Conclusion: Bronchiectasis is being very important for pediatricians especially. Previous studies were showed the infections have an important place in bronchiectasis etiology in our country as in developing countries. Our study shows that the invention of new tests and increases in society scans are leading to an increase in immunodeficiency and primary ciliary dyskinesia in the etiology of bronchiectasis.

Keywords: Bronchiectasis, Immunodeficiency, Primary Ciliary Dyskinesia, Orphan desiase, Children

Introduction

Bronchiectasis is an abnormal and permanent expansion of more than one bronchial wall resulting from damage to the elasticity of muscle structures. While the incidence in developed countries is decreasing, it is still a big problem in developing countries.[1]

The condition was first identified by Rene Laennec in 1819.[2] Although cystic fibrosis (CF) is the most common cause of bronchiectasis in developed countries, many conditions apart from cystic fibrosis (non-CF) may also be responsible, including previous infections, congenital anomalies, primary immunodeficiencies, acquired immunodeficiencies, ciliary anomalies, mechanical causes, aspiration syndromes secondary to gastroesophageal reflux (GER) or tracheoesophageal fistula (TOF), and toxic gas inhalation.[3] Due to recent developments in antibiotic therapy, vaccination programs, improved socioeconomic status, and effective treatment of pneumonia, the incidence of bronchiectasis secondary to infection have substantially reduced, with the disease now confined to people with an underlying systemic disease in developed countries.[4] A decrease in the incidence of infection-associated bronchiectasis has led to a relative increase in the proportion of other factors contributing to the etiology of bronchiectasis.[5]

In the present study, we aim to evaluate the sociodemographic and clinical characteristics, bronchiectasis localizations, pulmonary function tests (PFT) results, and etiologic factors of the bronchiectasis patients who applied to our clinic.

Methods

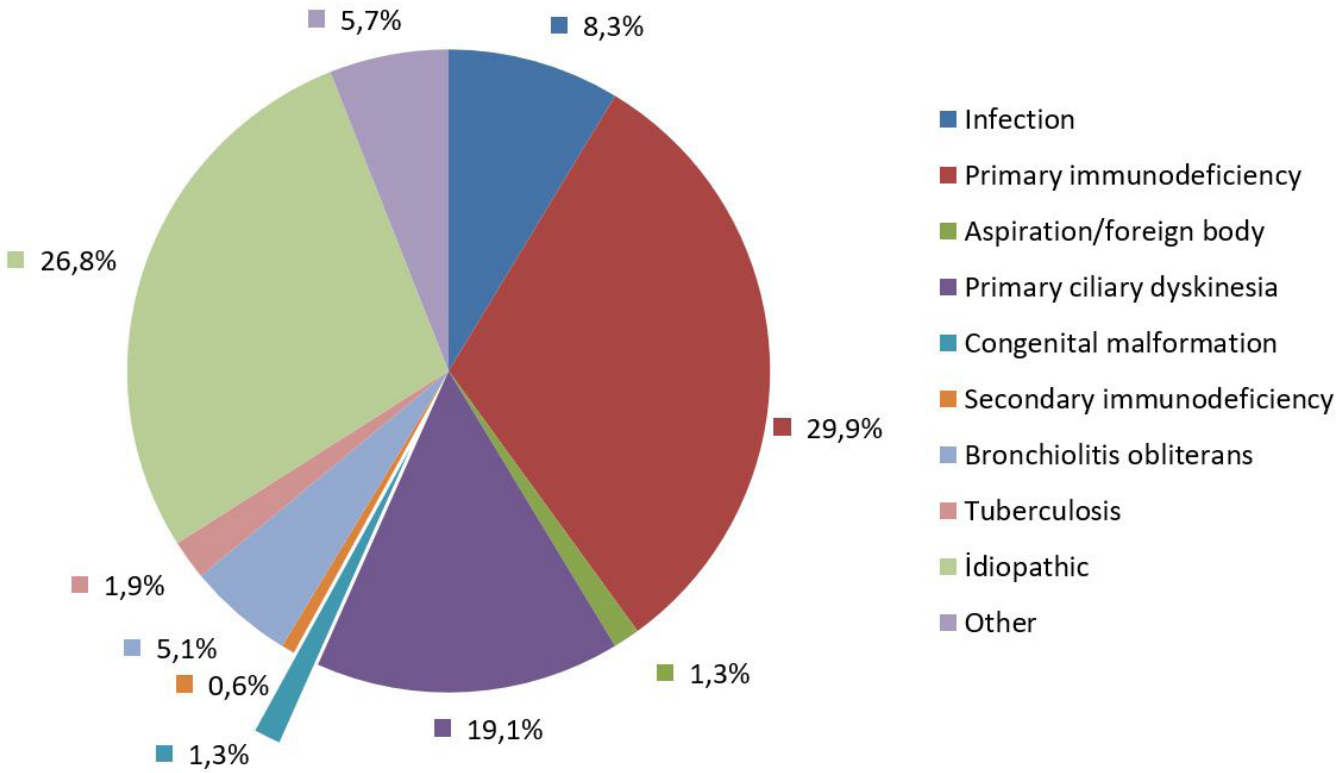
Our study retrospectively evaluates 158 patients who've been diagnosed with bronchiectasis using high-resolution computerized tomography (HRCT) between 2008-2018 in the Pediatric Pulmonology Department of Necmettin Erbakan University Meram Faculty of Medicine. All of the following tests were performed on all patients who had been diagnosed with bronchiectasis in any part of the lung using HRCT. Those with cystic fibrosis, which is diagnosed through clinical findings, sweat tests, and genetic analyses, have been excluded from the study. The medical records taken for all 158 patients included physical examination findings, anthropometric measurements, smoking history, symptoms, chest x-rays, and chest computerized tomography (CT) studies from the initial diagnosis, sputum cultures, flexible bronchoscopy findings, immunoglobulin titers (IGA, IGM, IGG, IGE), forced vital capacity (FVC), forced expiratory volume-per-second (FEV1) and mid-expiratory flow rates in children older than 6 years of age who were able to complete a respiratory function test, bronchoalveolar lavage (BAL) and culture, advanced immunological tests including lymphocyte subsets, nitroblue tetrazolium (NBT) blood test, complement levels, antibody titers, esophagus-stomach-duodenum (ESD) x-rays, pH meters, nasal nitric oxide (NO) levels, video microscopy, transmission electron microscopy, and barium swallow test as necessary. The norm values for immunoglobulin were determined with respect to Aksu et al's study.[6] The pulmonary function test was performed according to American Thoracic Society standards. The FEV1, FVC, and FEF25-75 measurements are expressed in liters and referenced to a healthy population as a percentage of the predicted value. The surgical (lobectomy) and medical treatment methods applied to the patients were reviewed. Primary ciliary dyskinesia diagnosis 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 high-speed video microscopy) and/or a genetic mutation recognized to cause primary ciliary dyskinesia in most patients. Immunodeficiency diagnoses were based on immunoglobulin titers, NBT blood tests, and advanced immunological tests, including lymphocyte subgroup analysis, complement levels, and antibody titers. Tuberculosis was diagnosed with respect to clinical signs, symptoms, chest x-rays, chest CT studies, and microbiological analyses including ARB staining, PCR, and culture methods. Structural anomalies were evaluated using chest x-rays, chest computerized tomography studies, flexible bronchoscopy findings, and ESD x-rays. The same tests were applied to all patients involved in the study. Other patients who had no possible triggers in their history or as a result of our investigations were considered idiopathic. Parental consent was received from each of the patients involved in the study. This study was approved by the Necmettin Erbakan University Institutional Ethics Committee (Approval No. 2019/2176).

We used the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses. Continuous variables are presented as mean ± standard deviations (SD) for normally distributed variables and as medians (min-max) for non-normally distributed variables. Fisher Chi-Square and independent samples t-tests were used for inter-group comparisons. A $p < 0.05$ is considered statistically significant.

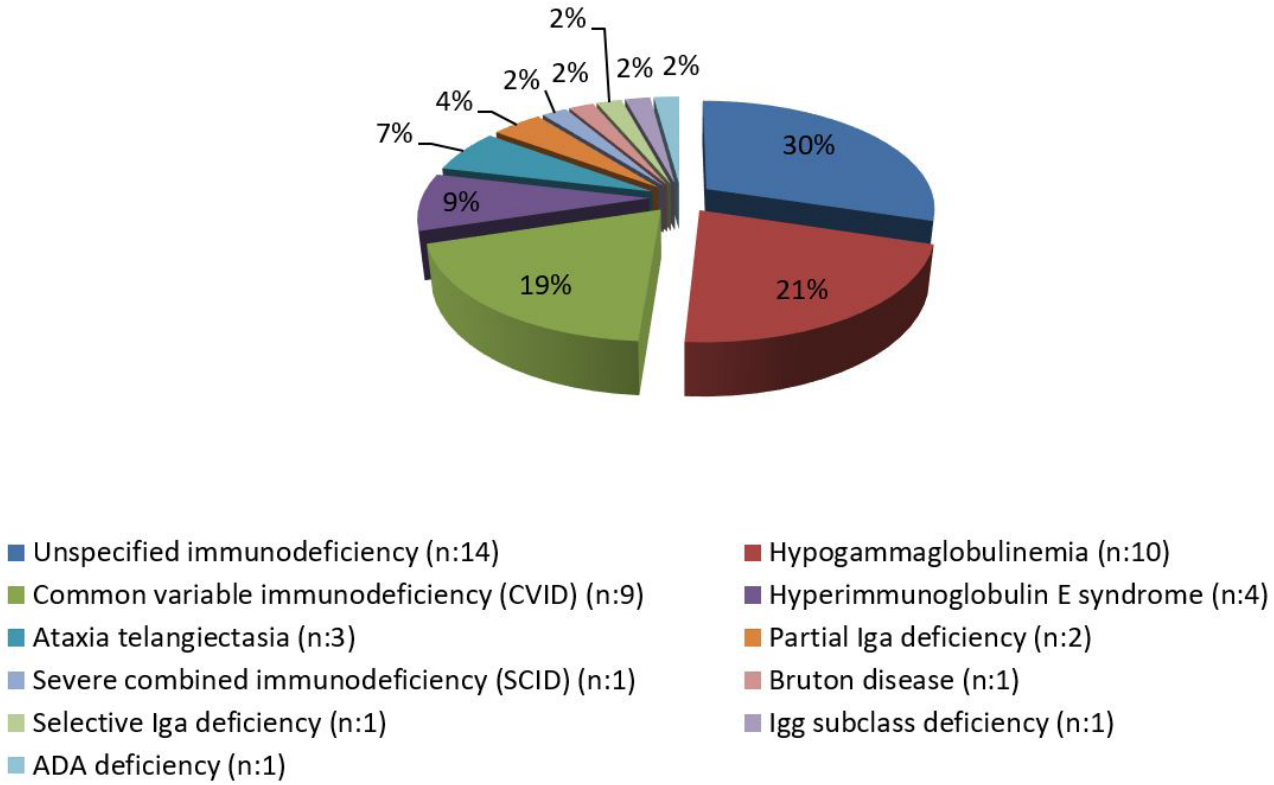
Results

158 patients were evaluated for non-cystic fibrosis bronchiectasis. 86 of the cases (54.4%) are male. The mean age is 16.03 ± 5.2 (2-25) years. The average age of diagnosis is 10.4 ± 4.8 (range = 0-18) years, while the average onset of symptoms is 6.07 ± 5.4 (range = 1-17) years.

The most frequent pathology in the etiology is immunodeficiencies (47 patients [29.9%]) and primary ciliary dyskinesia (30 patients [19.1%]) in the second etiology of bronchiectasis, other etiologies were sequelae pneumonia (13 cases [8.3%]) and bronchiolitis obliterans (8 patients [5.1%]). We were unable to identify the etiology of bronchiectasis for 42 patients (26.8%, see *Figures 1 & 2*). Among the patients with a consanguineous family history, immunodeficiencies were the first etiology of bronchiectasis (22 patients [33.3%]) and primary ciliary dyskinesia (8 patients [12.1%]) was the second. 15 other patients also had a consanguineous family history, but their bronchiectasis etiology could not be determined (22%).



Graphic- 1: Etiology of Non-CF Bronchiectasis With our Study



Graphic-2: Primary Immune Deficiency Disorders in Bronchiectasis Patients (n=47)

The most common complaints are prolonged cough (85.4%), sputum (75.5%), shortness of breath (46.1%), and recurrent wheezing (43%). 81 cases (58.3%) had previously been diagnosed with pneumonia more than once (see *Table 1*). 74 patients (48.3%) have consanguinity in their family history.

	n	%
Prolonged Cough	129	85,4
Sputum	115	75,5
Dyspnea	67	46,1
Recurrent Wheezing	63	43
Fever	19	13
Weight Loss	11	7,5
Hemoptysis	5	3,4

Table 1: Symptoms of patients at admission

Symptoms were similar within the groups, patients with primary ciliary dyskinesia had a higher frequency of a consanguineous family history, sibling/family history of bronchiectasis, history of asthma, and clubbing in the physical examination compared to the other groups. The most common pathogens that developed in sputum cultures were P. aeruginosa (12 patients [33.3%]) and S. pneumoniae (12 patients [33.3%]). P. aeruginosa was the most commonly grown pathogen in the sputum culture of immunodeficient patients (5 patients [13.8%]).

Respiratory function tests were performed on 66 patients. Pulmonary function tests were evaluated primarily on the first visit. Regular PFT was performed during the follow-up checks with the last PFT values being re-evaluated. According to the PFT results taken during the first visit, the mean FVC was 81.2 ± 25.4%, mean FEV1 was 77.2 ± 26.5%, mean FEV1/FVC was 90.1 ± 13.6%, mean FEF25-75 was 71.1 ± 38.6% (see Table 2). The patients who had a PFT evaluation in their last check-up were divided into two groups according to the follow-up period. For those under 7 years since last check up, the mean FVC was 78.6 ± 17.1%, mean FEV1 was 72.2 ± 21.8%, mean FEV1/FVC was 88.3 ± 13.1%, mean FEF25-75 was 62.3 ± 33.1%. For those over 7 years since last check-up, the mean FVC was 72 ± 18.9%, mean FEV1 was 64.9 ± 26.6%, mean FEV1/FVC was 85.8 ± 16.6%, mean FEF25-75 was 52.2 ± 34.8%. No statistically significant difference was found within the follow-up groups.

	Brower KS et al. (2014)		Doğru D et al. (2005)		Bahçeci S et al. (2016)		Satırer O et al (2018)		**Our Study (2020)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Infection	174	19	33	16,1	29	26,4	6	3,2	13	8,3
Primary immunodeficiency	158	17	11	5,4	13	11,8	28	15	47	29,9
Aspiration/foreign body	91	10	7	3,4	7	6,4	-		2	1,3
Primary ciliary dyskinesia	66	7	24	11,8	29	26,4	96	51,3	30	19,1
Congenital malformation	34	4	1	0,5	2	1,8	-		2	1,3
Secondary immunodeficiency	29	3	0	0	2	1,8	-		1	0,6
Asthma	16	2	24	11,8	2	1,8	-		0	0
Bronchiolitis obliterans	12	1	0	0	9	8,2	-		8	5,1
Tuberculosis	-		-		-		11	5,9	3	1,9
İdiopathic	308	34	100	49	17	15,4	42	22,5	42	26,8
Other	0	0	4	2	0	0	4	2,1	9	5,7

Table 2: Comparison of Studies About Etiology of Non-CF Bronchiectasis With our Study

All patients in our study were re-evaluated annually using the newest techniques. Only one patient was determined to have cystic fibrosis after many years compared to her first examination. At the initial examination of this patient investigating the etiology of bronchiectasis, the sweat test was 44mEQ / L and the 38 mutation analyses known to cause cystic fibrosis were seen to be completely normal. CT examination revealed bronchiectasis localized on the left lower lobe. This patient was accepted as having non-cystic fibrosis bronchiectasis, and a lobectomy was performed. Two cystic fibrosis gene mutations were detected upon reexamining this patient at the age of 25, at which point she was diagnosed with cystic fibrosis.

In the patient evaluations using High-Resolution Computerized Tomography (HRCT), the most common location of bronchiectasis was in the bilateral lungs (86 patients [62.8%]). It was observed primarily in the left lower lobe (82 patients [54%]), the right lower lobe (59 patients [39%]), or the right middle lobe (52 patients [34%]).

25 patients (16.7%) in our study had undergone an operation before applying to our center and receiving a diagnosis. While 23 of them were being monitored at an external center due to a chronic cough, they had been operated on for unknown reasons.

Discussions

Bronchiectasis is still a big problem for developing countries.[7, 8] While bronchiectasis was less known in past years, the feasibility of diagnosis (such as high-resolution computed tomography) and follow-up have increased in recent years. It has been described as an "orphan disease."[9, 10] Our study has established the etiologic diagnosis of bronchiectasis in 116 of 158 patients (73.4%). A further increase in diagnosis and follow-up possibilities will help reveal the etiology of bronchiectasis and increase early diagnosis and treatment possibilities. This can lead to significant improvements in the morbidity and mortality of bronchiectasis.

Wheezing was very frequent in our study. Also, we found in our study that bronchiectasis and asthma coexistence were common. We saw this association upon looking again at previous studies.[11] Some authors have included asthma in the etiology of bronchiectasis.[12] We believe this condition in bronchiectasis patients to be caused by the occurrence of bronchial hyperreactivity and to primarily be a result of bronchiectasis, not the presence of asthma. However, few studies are found to have addressed this, so further molecular and pathological research is needed.

Prolonged cough is the most common clinical presentation in patients with bronchiectasis. In a study of 136 patients in 2005 by Li et al.,[13] recurrent pulmonary infections were the most common cause of clinical presentation at a rate of 77%. Chronic cough was reported in 35% of patients, recurrent wheezing in 10%, and persistent rhinitis, otitis media, weight loss, and exercise intolerance in less than 5%.[13] In another study conducted on 187 patients in 2018, prolonged cough was the most common reason for admission (94%). In addition, 70.5% reported sputum production and 65% reported dyspnea.[14] Our study showed similar findings and has demonstrated prolonged cough to be responsible for 85.4% of clinical presentations.

Another remarkable finding in our study was the high rate of consanguineous marriage in patients' family histories. According to the data from the Turkish Statistical Institute's 2006 report, the rate of consanguineous marriage in Turkey is high (21.2%), especially in Konya (25.7%). The consanguineous marriage rate in our study was 48.3%. In addition, 46.8% of the patients with immunodeficiencies and 26.6% with primary ciliary dyskinesia also had consanguineous marriage in their family history. We think such a high consanguineous marriage frequency in the etiology of bronchiectasis to play an important role in the rise of diseases such as primary immunodeficiency and primary ciliary dyskinesia.

Our study showed the left lower lobe (54%), right lower lobe (39%), and right middle lobe (34%) to be the most commonly involved lung lobes within the group of the patients who had bilateral involvement (62.8 %). Our results resemble those in the literature.[15] Previous literature reports have indicated the involvement of the left lower lobe and lingula to be the most common involvement of bronchiectasis, followed by the right lower lobe and right middle lobe involvement. In contrast, CF bronchiectasis involves the lower lobes less frequently, which may be associated with impaired mucociliary clearance.[16-19]

Like other studies, the most common pathogens growing in sputum culture in our study were P. aeruginosa and S. pneumoniae. [20] The distributions of both pathogens by age were homogeneous and statistically insignificant. P. aeruginosa frequently grew in immunocompromised patients (n = 7). Among the immunodeficiency etiologies, P. aeruginosa growth was statistically insignificant. Among the etiologies of bronchiectasis, the growth of S. pneumoniae was also statistically insignificant. Satirer et al.'s study[14] had similar sputum culture pathogens and distributions. Care should be taken in terms of the growth and colonization of P. aeruginosa in patients with immunodeficiencies.

In the previous studies, the most common etiologic cause was pulmonary infection and tuberculosis.[19] As can be seen in the meta-analysis study conducted by McCallum and Binks[21], while infectious etiologies were at the forefront in previous studies, immunodeficiencies and PCD come to the fore as we approach today. Our study is an example of current studies. In 2005, various studies were performed in the field of bronchiectasis in Turkey. For example, Doğru et al's study[15] found the first etiology as infections. In the same year, Karadağ et al.'s study[5] had similar results. However, the development of techniques used in the last 10 years has changed the etiological factors. As a result, 13 years after Doğru et al.'s study, another study conducted in the same center by Satirer et al.[14] showed the most common cause of bronchiectasis to be primary ciliary dyskinesia and the second to be immunodeficiencies. In fact, new methods developed over the years in developing countries such as Turkey have made new diagnoses in the etiology of bronchiectasis become more detectable. In our study, immunodeficiencies and primary ciliary dyskinesia were found as first-line causes. This also resembles the studies done by Brower et al.,[3] and Satırer et al.,[14] and Eralp et al.,[22] etiological factors had changed in their studies just like in ours (see *Table 2*). These results show advanced facilities to be used in our clinic and patients to have been monitored well.

In our study, the age of symptom onset was found to be very early (M = 6.07 years). However, a pronounced delay occurred from onset to diagnosis (M = 4.3 years). A similar delay in diagnosis was found in Eastham et al.'s[9] study. They based this delay on the false diagnosis of "cough-variant asthma" in patients with only cough complaints, which McKenzie[23] had highlighted previously. Our results also support these assertions.

In accordance with the literature, patients with immunodeficiencies most commonly had humoral immunodeficiency (n = 15 [31%]) followed by combined immunodeficiency (n = 10 [21%]) and cellular immunodeficiency (n = 3 [7%]). Hypogammaglobulinemia was the most common humoral deficiency subtype, affecting 10 (21%) patients.[24]

Accurate identification of the etiology of bronchiectasis plays a key role in successfully treating this disease.[25, 26] In addition to treating the underlying disease, treatment is also required to preserve lung function and suppress the inflammation-infection cycle present in patients with recurrent sinus and lung infections.[4] Antibiotics, nasal oxygen therapy, chest physiotherapy, bronchodilators, mucolytics, and inhaled steroids can be used to treat the disease. Surgery should be considered in patients with localized bronchiectasis who have a history of recurrent infection caused by resistant microorganisms despite appropriate treatment.[10] In our study, 25 (16.7%) patients had been operated on. 23 of them had undergone surgery in another center prior to our first evaluation. This result was much lower than what Wilson et al.[27] reported (47%) in the 1980s. This shows our clinic to detect the etiology of bronchiectasis with better and higher percentages, and therefore antibiotics were able to be used more effectively. Although chest physiotherapy is very important in this disease in terms of excreting secretions and protecting the lungs, our patients had low rates of administration.

Conclusion

Bronchiectasis is particularly important to pediatricians in developing countries. In previous studies, infections had an important role in the etiology of bronchiectasis. However, recent studies including ours suggest that immunodeficiency and primary ciliary dyskinesia may be the major etiologic causes of bronchiectasis as a result of newly developed tests and increased screening. In light of this result, we think the etiology of bronchiectasis will be determined by finding different methods for patients diagnosed with the infection or for patients whose etiology our study was unable to determine. One should keep in mind that infections are not a diagnosis but a finding in the etiology of bronchiectasis. Laboratory and clinical re-evaluations of these patients in terms of bronchiectasis etiology at certain intervals is important. Also, we believe reviewing the results of patients with bronchiectasis who have no underlying cause and trying to determine the etiology to be important because genetic and other diagnostic methods are developing rapidly in today's medicine.

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Author Disclosure Statement

No competing financial interests exist. This study was conducted in Necmettin Erbakan University Meram Medical Faculty Hospital Pediatric Chest Diseases Clinic.

Conflict of Interest

There is no conflict of interest between the authors.

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