# PHYSIOPATHOLOGY AND TREATMENT IN NON-CYSTIC BRONCHIECTASIS

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**Abstract**

Non-cystic bronchiectases are an underdiagnosed pathology that is oftentimes classified as idiopathic. Identification of risk factors and determination of an accurate diagnosis are paramount in order to improve patient outcomes. Infectious exacerbations are often incorrectly treated, which leads to the onset of antibiotic resistance and microbial colonization. Determination of the pathogen agent that caused the infectious episode and its subsequent course of treatment must be carried out via specialized paediatric medical facilities or paediatric pneumology departments. Long term monitoring of the pulmonary function and clinical status in these patients is essential, as it reduces adult age mortality.

**Keywords:** non-cystic bronchiectases, child, antibiotics

**Introduction**

Bronchiectases were first described in 1819 by Laenec and before the age of antibiotics they were seen as a high mortality disease due to the associated respiratory failure and complications.

Bronchiectases are defined from an anatomical point of view as irreversible and abnormal dilations of various calibres (particularly medium sized ones) in the bronchial lumens, being located exclusively in a pulmonary lobe/segment, but also diffusely.[1]

The underlying causes of bronchial tree damage includes major pathological modifications, particularly the alteration of the elastic and muscular components in the bronchial wall, secondary to chronic inflammation, and other endogenous and exogenous factors. Concurrently, mucosal edema and ulceration are also described. In its turn, healthy pulmonary tissue exerts contracting forces that deform the bronchia. The possibility of having other associated pulmonary pathologies such as fibroses, foreign bodies or tumoral formations should also be taken into consideration, as they can exert traction forces in certain areas of the parenchyma and contribute to the formation of bronchiectases.

The association with the centripetal and centrifugal forces exercised on the bronchial structure leads to modifications in its calibre, being able to become up to three or four times larger than the sizes deemed normal. Stagnation of bronchial secretions and puss clogs that can form in case of microbial superinfections also contribute to the deformation of structures, maintenance of chronic inflammation and disease progression.[2]

**Contents**

Cough is a very frequent symptom in childhood. Literature data state that a third of children present with intermittent coughing on a monthly basis, and some parents describe it as chronic. To describe this symptom we used a series of terms, including « pre-bronchiectases », so as to highlight the importance of any potential changes that can be detected on the HRCT (fig.1). Persistence of the symptomatology for more than three week evidently requires the commencement of certain investigations in order to establish a diagnosis and prevent complications.[3] The symptoms and indications that are associated with the existence of bronchiectases are chronic productive cough, recurrent respiratory infections, dyspnea, wheezing, fever, weight loss, chest pain, and hemoptysis.

The cause of bronchiectases in children can be extrinsic or, more rarely, intrinsic. The most frequently encountered etiological factors are infectious ones, which cause irreversible anatomical modifications.[4] Pathologies such as severe pneumonia, pulmonary tuberculosis, and Bordetella pertussis infections frequently cause the onset of bronchiectases.[5] The microorganisms involved in infections that favour the occurrence of bronchiectases also include Klebsiella pneumoniae, Staphylococcus aureus, Histoplasma, H. Influenzae, flu adenoviruses and viruses. Immune deficiency states are another factor involved therein. Acquired immune deficiencies and congenital agammaglobulinemia are the most frequently cited factors in medical literature. Kartagener Syndrome, Williams-Campbell, and primary ciliary dyskinesia are associated with the existence of cystic and non-cystic bronchiectases.[1] In comparison with adult patients, the etiological factor in paediatric patients can be determined in over 70% of cases.

The clinical symptomatology is determined by a series of factors such as the child's age, extent to which bronchiectases are extended, and other associated pathologies.

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Identifying the location of anatomical modifications is important as it guides the clinician towards to a potential etiology. Dry cough is associated with the presence of post-tuberculosis bronchiectases located in the upper lobes. Lobe-level bronchiectases in a child with a previously normal chest X-ray can raise the etiological suspicion of a treated abscessed infection, an endobronchial obstruction cause by aspiration of foreign bodies or, more rarely, by the existence of a tumour. Generalized bronchiectases can be the cause of an underdiagnosed asthma in young children, of recurrent aspiration of gastric secretions in severe cases of gastric reflux or in case of congenital gastro-oesophageal anatomic anomalies, gas intoxications, and viral or bacterial bronchopneumonia treated either late or incorrectly.

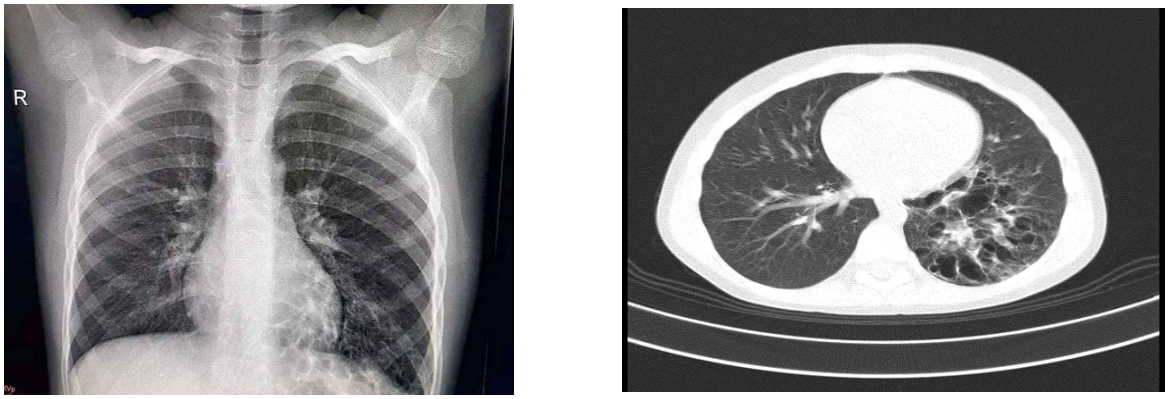


Fig.1 Left basal bronchiectases in a 9 year old child.

In a study published in 2005 and conducted on a sample of 136 patients aged between 3 and 18 years old, *Li AM et al* identify the etiology of bronchiectases confirmed via CT. Thus, they noticed that in 67% of the patients the cause was immune deficiency, foreign body aspiration, and primary ciliary dyskinesia; of the total sample of children, the identification of etiology in 56% of them (77 patients) caused important modifications in terms of medical management of the disease. 26% of the cases were diagnosed with idiopathic bronchiectases. The authors also noticed the existence of an obstructive ventilatory dysfunction in most of the investigated cases, with a mean FEV1 of 71% (15-133% of the forecast). This aspect is relevant because the presence of bronchiectatic modifications on the HRCT was correlated with the decrease in the spirometry parameters. Monitoring these patients is essential for determining a long term bronchodilator treatment.[5]

The results obtained by *Kim HI et al* and published in 2011 are not consistent with Li AM's in terms of frequency of the etiology of bronchiectases cases. Although the study sample was smaller (92 patients), it revealed that obliterative bronchiolitis was the main causal factor for the existence of non-cystic bronchiectases (33%), followed by childhood respiratory infections (tuberculosis, cytomegalovirus), and interstitial pulmonary pathology of various etiologies. Only 14% of the cases were deemed idiopathic. This data is similar with the data in the study described previously in terms of distribution, as bronchiectases are most frequently located in the lower lobes, then in the upper lobes and bilaterally. The results here also confirm the presence of the obstructive syndrome, with a 63% mean FEV1.[6]

In a study published in Thorax in 2004 on a similar patient sample (92 children with an average age of 7.2 years), *Eastham KM et al* identifies the association between bronchiectases and lobar pneumonias as the most frequent etiology (30%), followed by the existence of a congenital or acquired immune deficiency (21%). Idiopathic pathology also describes a significant share of approximately 18% in this study. The data obtained does not support the hypothesis that obliterative bronchiolitis is the main cause of bronchiolitis modifications, as this diagnosis was determined beforehand in just 9% of the children.[7]

In accordance with the results published in 2008 in Pediatric Lung Disease by *Bastardo CM et al*, obstructive ventilatory dysfunction in children with bronchiectases is persistent over time, then stabilizes, and does not respond to specific courses of treatment. Mean levels of FEV1 also fluctuated in this study, ranging between 68-71%.[8] This mandates the careful monitoring of these patients in their adult age in order to identify any potential declines in terms of pulmonary function.

In addition to the evaluation of the pulmonary function via HRCT and X-rays in case of exacerbations, the microbiological testing of sputum for flora and fungi or of bronchial aspirate culture is necessary for sleep quality assessment purposes. Sleep quality is most of the times affected in case of diffuse or localized bronchiectases that cover large pulmonary areas and cause a chronic symptomatology manifested via frequent – and sometimes inefficient – expectoration, at times associated with hypoxia.

Application of the questionnaires known as the Pittsburgh Sleep Quality Index (PSQI) and Paediatric Sleep Questionnaire (PSQ), peripheral oxygen saturation measurement, and sometimes even a polygraph test are necessary for determining an adjuvant treatment.[9]

In accordance with the British Thoracic Society Bronchiectasis (non-CF) Guideline Group (BTS 2010) guidelines, the treatment principles for bronchiectases in both adults and children are based on treating the cause that influences the development of bronchiectases, educating patients and their parents, optimizing the clearance of respiratory tract – physical therapy, exercises, use of mucolytic agents and hyperosmolar solutions, medication for respiratory tropism – anti-inflammatory medicine, bronchodilators, antibiotics, identification of cases with recommended surgical treatment, and optimum complications' management.[10]

Targeted antimicrobial therapy is highly recommended. The microorganisms that were most frequently involved in the etiology of bronchiectases and isolated from sputum collected from patients with superinfected bronchiectases are: Haemophilus influenzae, Streptococcus pneumoniea, Moraxella catarrhalis, Staphylococcus aureus, and Klebsiella pneumoniae.[8,11,12] The isolation of Pseudomonas aeruginosa or the MRSA staphylococcus is associated with a chronic colonization and recurrent infectious exacerbations. *Orriols et al* studied the effects of long term antibiotic therapy (ceftazidime 1000 mg every 12 h or tobramycin 100 mg every 12 h) in aerosols for children with non-cystic bronchiectases (tested negative for the 31 CF mutation, as well as for AF508, G542X, N1303K) colonized with Pseudomonas aeruginosa. The duration and frequency of hospital admissions dropped significantly in comparison with a control group studied. The results thus obtained are encouraging for these patients' outcomes.[13] The British Thoracic Society Bronchiectasis (non-CF) Guideline Group (BTS 2010) guideline also proposes the use of gentamycin (80 mg every 12 hours), colistin (1-2 million every 12 hours), which was substantiated as having favourable effects. First-line medication recommendations for oral therapy in case of infectious exacerbations differ based on the isolated microorganism, noting that the duration of the treatment is of 14 days irrespective of the case (table 1).[10]

Also, the literature cites long term macrolide oral therapy as effective. There were several studies, including that with roxithromycin 4 mg/kg every 12 hours, 12 weeks (*Koh YY et al*), erythromycin 400 mg every 12 hours, 12 months (*Masekela R er al*), azithromycin 30 mg/kg, once a week, 12-24 months (*Valery PC et al*), which highlighted a genuine benefit in reducing the number of hospital admissions and exacerbations.

Table 1. Recommendations for antibiotic therapy in children with superinfected bronchiectases as per the British Thoracic Society Bronchiectasis (non-CF) Guideline Group (BTS 2010) guide.

| Pathogen agent | First-line medication | Second-line medication |
|---|---|---|
| Streptococcus pneumoniae | amoxicillin | clarithromycin |
| Haemophilus influenzae (b-lactamase negative) | amoxicillin | clarithromycin or ceftriaxone |
| Haemophilus influenzae (b-lactamase positive) | co-amoxiclav | clarithromycin or ceftriaxone |
| Moraxella catarrhalis | co-amoxiclav | ciprofloxacin |
| Staphylococcus aureus (MSSA) | flucloxacillin | clarithromycin |
| Pseudomonas aeruginosa | ciprofloxacin | ceftazidime or tazocin or aztreonam or meropenem or combinations |
| Staphylococcus aureus (MRSA) | rifampicin + trimethoprim (oral) | rifampicin + doxycycline |
| | vancomycin or teicoplanin (injectable) | linezolid |

In the result of the research published in 2010 in the Journal of Pediatrics, *Hare KM et al* focused on identifying the microbial etiology of upper and lower respiratory tract infections in children with bronchiectases in comparison with children without this pathology. S. pneumoniae, H. influenza, and M. catarrhalis were the main pathogens that caused infectious episodes, sometimes also being identified in association or even all together. The frequency of these germs in children with bronchiectases is not fully known due to the fact that collection of the biologic products is oftentimes impossible, as the patient is too young to be able to expectorate, while fibrobronchoscopic testing is unavailable in many paediatric medical facilities.[14]

Episodes of bacterial or viral superinfection are responsible for increasing morbidity levels, lung function deterioration, and decrease in terms of quality of life. Literature data indicates that almost half of the infectious episodes are viral, thus the use of antibiotics is most often unsuitable. The relevant inflammatory markers such as C-reactive protein, ESR, procalcitonin, IL 6, and SAA should be dosed before establishing a course of treatment. The association of several markers increases the specificity of the diagnosis. In a study published in 2014, *Kapur N et al*

monitored 69 patients with a 7 years old mean age over a period of approximately 13 months. A total of 77 fully investigated exacerbations were identified during the research. Of these, 48% were of viral etiology, most of them being caused by the rhinovirus (26%) and parainfluenzae (8%). These viral exacerbations were associated with the presence of fever, hypoxia, and hospital admission.[15] The results presented by these authors are very important, as they reiterates the importance of accurate and complete investigation of all infections by the specialized departments in paediatric patients with bronchiectases, so as to determine the correct course of treatment and to avoid antibiotic abuse which could subsequently lead to microbial resistance, secondary candidiasis, and potential food allergies.

**Conclusions**

Most of the studies confirm that even in children there is a significant percentage of patients for whom it is impossible to determine the etiology of bronchiectases. Owing to access to healthcare, the number of non-cystic bronchiectases cases in developed countries is dropping. The correct use of antibiotics and early management of the disease are essential for the long-term reduction of mortality rates.

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