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## REVIEW ARTICLE

# Bronchiectasis

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**Abstract:**

*Bronchiectasis is characterized by dilatation of bronchi, airflow limitation and chronic infection/inflammation.Patients with bronchiectasis have chronic cough and sputum production, and bacterial infections develop in them that result in the loss of lung function.The diagnosis of bronchiectasis is made by high-resolution CT scans. Patients with bronchiectasis may have predisposing congenital disease, immune disorders, or inflammatory disease. The treatment of bronchiectasis is multimodality, and includes therapy with antibiotics, antiinflammatory agents, and airway clearance. Resectional surgery and lung transplantation are rarely required. In this comprehensive review, the etiology, pathogenesis, clinical presentation, appropriate investigations and management of bronchiectasis have been discussed.*

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**Introduction:**

Bronchiectasis is a condition where destruction and damage of bronchioles lead to chronic airflow obstruction and typically copious expectoration. It is characterized by permanent dilation of bronchi and bronchioles caused by destruction of the muscle and elastic tissue, resulting from or associated with chronic necrotizing infection[1] . This was first described by Laennec in 1819 and identified tuberculosis and pertussis as the most likely causes[2] .

Today's most common cause in developing countries is the post infectious route. The development of antibiotic treatments and vaccines has resulted in a continuous decrease in the number of cases of bronchiectasis with post infectious causes in industrial countries[3] . Currently, congenital causes of bronchiectasis are seen more observed than postinfectious causes.In Europe, bronchiectasis is common in patients with cystic fibrosis (CF) [4] .This article aims to provide a comprehensive discussion about the etiology, pathogenesis, clinical presentation, appropriate investigations and management of bronchiectasis.

**Prevalence:**

Because high-resolution computed tomography (HRCT) scanning is more commonly used nowadays, bronchiectasis is diagnosed earlier and

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at earlier stages. This has resulted in a seeming increase in the prevalence of bronchiectasis.[3]

Very few data on prevalence are currently available.In the United States, the rate was reported to be as high as 52/100 000 .[5]

One in 1,800 UK hospital admissions is a result of bronchiectasis as the primary condition, and bronchiectasis patients occupy around one in every 1,000 hospital bed days.[6]Data from UK primary care suggests an incidence of 1/1000 or higher in older age groups.[7]

**Pathogenesis of bronchiectasis:**

The common feature among all the conditions that lead to bronchiectasis, is that they either lead to alteration in the pulmonary defense mechanisms, or are associated with inflammation.[8] The end result, is that the individual becomes susceptible to bacterial colonization and infection. Regardless of the initiating event, any damage to the airways that results in loss of the mucociliary transport, renders the airways susceptible to microbial colonization. Infection leads to inflammatory response and progressive lung damage.[9] Neutrophils are thought to play a central role in the pathogenesis of tissue damage that occurs in bronchiectasis.[10] The progressive nature of bronchiectasis is thought to result from a continuous "vicious circle" of inflammation and tissue damage.[11]

**Pathological types of bronchiectasis:**

Pathologically, bronchiectasis can be divided into four types.[12] The first type, cylindrical bronchiectasis, is characterized by uniform dilatation of bronchi, that extends into the lung periphery, without tapering. The second type is called varicose bronchiectasis and is characterized by irregular and beaded outline of bronchi, with alternating areas of constriction and dilatation. The third type is called cystic or saccular bronchiectasis and is the most severe form of the disease. The bronchi dilate, forming large cysts, which are usually filled with air and fluid. The fourth type of bronchiectasis is called follicular and is characterized by extensive lymphoid nodules within the bronchial walls. It usually occurs following childhood infections.[13]

**Etiology:**

Up to 50% of cases of bronchiectasis are idiopathic, with no identified underlying cause. This aetiology may have better outcomes than bronchiectasis that is associated with COPD or rheumatoid arthritis. There are some known causes of bronchiectasis (see box 1) and several conditions have been associated with bronchiectasis without a clear understanding of the aetiology.[14]

**Infections**

Many infections have been implicated to cause bronchiectasis. Measles, pertussis, adenovirus 21, tuberculosis, aspergillosis and human immunodeficiency virus (HIV), may all lead to permanent airway damage.[16] Immunizations against measles and pertussis have led to marked reduction in the incidence of bronchiectasis, caused by these two infections.[17] Tuberculosis was among the most important causes of Bronchiectasis. Currently, the incidence of bronchiectasis, secondary to mycobarium tuberculosis, is declining due to effective antituberculous treatment. Lately, mycobarium avium-intracellulare complex (MAC), has been recognized to cause bronchiectasis. Allergic bronchpulmonary aspergillosis is associated with airway damage and bronchiectasis.[18]

**Immune dysfunction**

Immunodeficiency syndromes such as immunoglobulin deficiency, complement deficiency and chronic granulomatous disease, are associated with bronchiectasis.[19]Deficiency of IgG, IgM and IgA, put the patient at increased risk of recurrent pulmonary infections, that eventually end in bronchiectasis.[20]

**Cystic fibrosis**

Cystic fibrosis is well known to cause bronchiectasis, as a result of recurrent respiratory tract infections with Staphylococcus aureus and mucoid pseudomonas aeruginosa.[21] In addition, the gene responsible for cystic fibrosis (CF), the cystic fibrosis transmembrane regulator (CFTR), is shown to occur in high frequency in children with idiopathic bronchiectasis.[22]However, CFTR mutations alone cannot be responsible for bronchiectasis, as the heterozygotes for this gene mutation were not found to be at increased risk of bronchiectasis.[23]It is suggested that CFTR

**Bronchiectasis : Etiology and pathogenes[15]**

| Pathogenic mechanisms | Etiology |
|---|---|
| Primary infective insult | Bronchitis/brnchiolitis<br>Pertussis<br>Measles<br>Adenovirus<br>Pneumonia<br>Tuberculosis |
| Primary impairment of<br>Mucous clearance<br>Genetic,biochemical<br>Genetic,ultrastructural | <br>Cystic fibrosis<br>Primary ciliary dyskinesias |
| Immunodeficiency syndrome,<br>Congenital and acquired | Common varied<br>Immunodeficiency<br>Selective immunoglobulin<br>deficiency<br>Functional immune<br>Deficiency<br>Secondary<br>Hypogammaglobulinaemia<br>Human immunodeficiency<br>Virus infection |
| Hyperimmune response | Allergic bronchopulmonary<br>mycoses |
| Infection secondary to bronchial<br>Obstruction<br>Intraluminal<br>Extraluminal | <br>Slow-growing tumour,<br>Aspirated foreign body<br>Lymphadenopathy |
| Miscellaneous inflammation<br>Autoimmune disease | <br>Inflammatory bowel disease<br>Coeliac disease<br>Systemic lupus erythematosus<br>Rheumatoid disease<br>Cryptogenic fibrosing alveolitis<br>Primary biliary cirrhosis<br>Thyroiditis<br>Pernicious anaemia |
| Inhalation/aspiration injury | Toxic fumes<br>Gastric contents |
| Developmental defects<br>Structural | <br>Pulmonary agenesis<br>Sequestrated segment<br>Tracheobronchomegaly<br>Bronchomalacia |
| Biochemical | $\alpha_1$-Antitrypsin deficiency |

mutation acts with other factors (genetic, environmental) to contribute to bronchiectasis.[22]

**Immotile Cilia syndrome/Kartagener's syndrome**

Inherited as an autosomal recessive disease, immotile cilia syndrome can lead to bronchiectasis, as a result of recurrent pulmonary infections due to retained secretions.[17]Approximately 50% of patients with immotile cilia syndrome, have Kartagener's syndrome. It consists of sinusitis, bronchiectasis and situs inversus.[24]

**Chronic obstructive pulmonary disease**

Patients with advanced chronic obstructive pulmonary disease (COPD) may have

bronchiectasis; the literature reports rates between 30% and 50% .[25] These patients more often suffer from dyspnea and show poorer lung function. CT-morphologically, bronchiectasis in COPD differs from classic bronchiectasis, since theectasis is less pronounced but the peribronchial infiltration is more pronounced.[3] With the rising global prevalence of COPD, bronchiectasis is of increasing importance.

**Rheumatoid arthritis**

The association between rheumatoid arthritis and bronchiectasis, has recently received considerable interest. Bronchiectasis can occur, before or after the onset of Rheumatoid arthritis.[26]It has been suggested that, if bronchiectasis occurs before the onset of Rheumatoid arthritis, that chronic suppurative infection leads to triggering an immune response to the synovial membrane, causing rheumatoid arthritis.[27]In contrast, those patients who develop bronchiectasis after the onset of rheumatoid arthritis, may have increased susceptibility to respiratory infections caused by rheumatoid arthritis itself or its treatment. The recurrent pulmonary infections eventually lead to airway damage and bronchiectasis. This association is still controversial.[28]The combination of rheumatoid arthritis and bronchiectasis carries a poor prognosis.

**Inflammatory bowel disease**

Pulmonary involvement in inflammatory bowel disease is uncommon.[29]Interestingly, some patients with inflammatory bowel disease, develop bronchiectasis after colectomy.[30]It has been suggested, that bronchiectasis in inflammatory bowel disease, is due to an autoimmune process and infection has a minor role in its pathogenesis. This may explain the occurrence of bronchiectasis, post-colectomy, as the inflammatory and autoimmune processes shift from the bowel to the lung.[31]

**Clinical features:**

Patients with bronchiectasis complain of chronic cough, sputum production, and lethargy. Hemoptysis, chest pain, weight loss, bronchospasm, dyspnea, and impaired physical performance have also been observed.[32] The often mentioned three-layer sputum consisting of a foamy upper layer, mucous middle layer, and viscous purulent bottom layer is pathognomonic, but does not always occur.[3] Some patients are

symptom free in everyday life and become clinically conspicuous only during exacerbations.[3] Mild cases of bronchiectasis often have no abnormal physical signs. When the disease is sufficiently developed, the characteristic finding is that of persistent early and mid-inspiratory crackles.[15] Clubbing of the fingers and/or toes is a feature of gross disease with prolonged bronchial infection.[33] Nowadays finger clubbing in

bronchiectasis, other than that associated with CF, is uncommon in more developed countries.[15] Signs of collapse and fibrosis may be present in advanced cases.[15]

Exacerbation is defined as the presence of four or more of the symptoms listed in Box 2.[34]

**Box 2**

| Symptoms of exacerbation |
|---|
| • Increase of sputum with cough |
| • Increased dyspnea |
| • Raised temperature >38° C |
| • Increased wheezing |
| • Lowered physical resilience |
| • Fatigue |
| • Deterioration in lung function |
| • Radiological signs of infection |

**A minimum of 4 symptoms are the defining criteria foran exacerbation**

Complication:

Complications of bronchiectasis includes ( Box-3)

Complications

- Hemoptysis
- Cor-pulponale
- Resoiratory Failure
- Amyloidosis
- Secondary visceral abscess at distant sites ( i.e Branin)

**Investigation:**

**1.CT Scan** - High resolution CT scan of the chest is the confirmatory test for diagnosis of bronchiectasis. Findings include bronchial wall thickening with dilatation of bronchi to a diameter greater than that of accompanying arteriole (signet ring sign), lack of normal tapering of bronchi on sequential slices and visualization of bronchi in the the outer 1-2 cm.[35]Cases of allergic bronchopulmonary aspergillosis have central bronchiectasis while cystic fibrosis cases have upper zone bronchiectasis. ( Fig- 1)

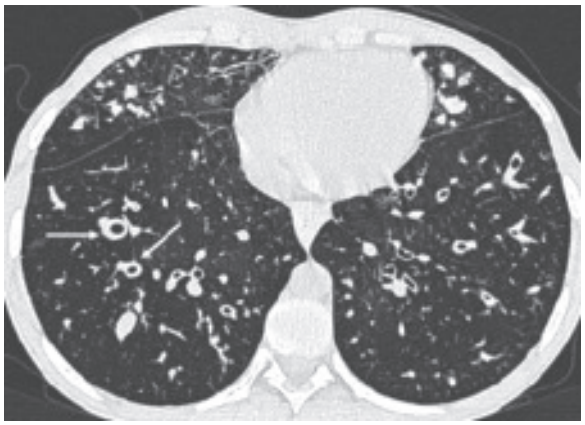

Figure- 1

**2. Chest X-ray** - This is useful as a baseline to monitor disease progression and at times of exacerbations. X-rays may show tram

lines or ring shadows[36] ( Fig- 2).

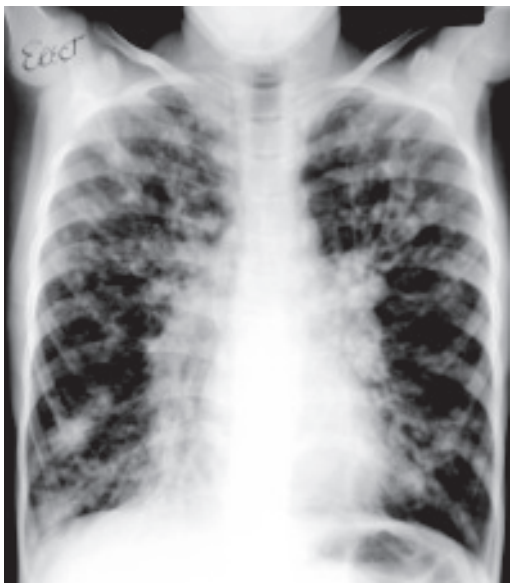

Figure- 1

**3. Blood tests** - Full blood count may show anaemia (of chronic disease). IgE levels may be raised in cases of allergic broncho-pulmonary Aspergillosis associated bronchiectasis. Aspergillus precipitin tests, Immunoglobulin levels and subclasses, Alfa 1 anti trypsin levels are other tests done to investigate etiology of brocnhiectasis.

**4. Sweat tests and genetic tests** may be done if cystic fibrosis is suspected. Other specific genetic tests and tests of ciliary functions are requested in appropriate clinical contexts.

**5. Sputum examinations**: Routine cultures are helpful in finding the colonizing bacteria e.g. *H influenza, S pneumonae and Pseudomonas aeruginosa*. AFB cultures are done to exclude *Mycobacterium tuberculosis* and also to consider the possibility of infection by Environmental Mycobacteria.

**6. Lung function tests** - These are useful in assessing severity of airflow obstruction and in monitoring disease progression.

Management:

The aims of treatment for bronchiectasis are:

- Improving mucociliary clearance or drainage of secretions
- Treating the infection
- Treating airway obstruction
- Treating the chronic inflammation that leads to disease progression.
- Treating the underlying disease.[3]

**Draining secretions**

Breathing therapy and physiotherapeutic measures are the basic treatments for bronchiectasis, to improve drainage of secretions and deal with dyspnea. The mainstay of treatment is sufficient administration of fluids for secretolytic purposes. This can be supported by inhalation of hypertonic saline solution. Especially inhaling hyperosmolar solutions has been found to be beneficial.[3] Studies using 7% saline for inhalation by CF patients have shown improved lung function and secretion clearance .[37]

In contrast to other hyperosmolar solutions, mannitol has the advantage of a longer half life within the airways. In an open label, non-

controlled study over 12days, quality of life, lung function, and sputum viscosity were notably improved.[38] A disadvantage of mannitol is the fact that hyperresponsiveness increases during inhalation. Currently, further studies are being conducted in order to gain licensing approval for the substance. Evidence base for n- Acetyl cysteine is very limited. Dornase-alfa may be harmful in non cystic fibrosis bronchiectasis althogh it is well established in cystic fibrosis.[39]

**Vaccinations:**

Influenza and pneumococcal vaccination are recommended as per national schedules

**Antibiotics:**

Antibiotics are the mainstay of treatment in exacerbations caused by infections. Choice of antibiotics depends on previous and current sputum culture results. Intravenous antibiotics may be used in cases with severe exacerbations or in cases not responding to oral antibiotics. Treatment with maintenance antibiotics in bronchiectasis can be directed at simply reducing the increased bacterial load, since chronic colonisation has been found to coincide with enhanced inflammation and worse clinical outcome.[40]

Macrolides, because of their anti-bacterial and anti-inflammatory properties, have long been thought ideal to intervene in the vicious circle of infection and inflammation that underlies bronchiectasis.[40]

Inhaled antibiotics are standard treatment for patients with CF who have been colonized with *Pseudomonas aeruginosa* [41] .Since 25% of patients with non-CF bronchiectasis are colonized with *Pseudomonas aeruginosa*, this therapeutic principle may offer an advantage in this setting. Significant clinical improvement has been shown, with a reduced density of pathogens and eradication of *Pseudomonas aeruginosa* in up to 35% of cases [42] .Choice of antibiotics depends on previous and current sputum culture results. Intravenous antibiotics

may be used in cases with severe exacerbations or in cases not responding to oral antibiotics.Box provides an overview of inhaled antibiotics.

**Anti-obstructive therapy:**

If a patient's airways are obstructed, anti-obstructive treatment similar to COPD should be considered. Parasympatholytics and beta-sympathicomimetics constitute the treatment of choice. Long-acting substances (tiotropium bromide or salmeterol/formoterol) seem

superior to short-acting substances.[3]

**Inhibiting inflammation:**

Oral corticosteroids are often administered in acute exacerbations of bronchiectasis. For inhaled steroids, long-term usage seems to confer benefits. [3]

**Treating the underlying disease:**

If possible, the underlying disease should be treated first. This primarily applies to immunodeficiency syndromes.[3]

**Allergic bronchopulmonary aspergillosis**

Allergic bronchopulmonary aspergillosis (ABPA) is arare but typical complication in bronchiectasis.

**Box4:** *Selection of the most researched inhaled antibiotics*

| Substance | Results | Source |
|---|---|---|
| Tobramycin | Eradication in 13-35%,reduction of pathogenic load, improved lung function | 42<br>43 |
| Colistin | Rise in FEV1,eradication in 3 of 18 cases,fewer exacerbations,reduction of pathogenic load | 44<br>45 |
| Aztreonam | CF:improved lung function,longer interval to exacerbation | 46 |
| Liposomal ciprofloxacin<br>Ciprofloxacin | Reduction of pathogenic load<br>Reduction of pathogenic load | 47<br>48 |
| Gentamycin | Fewer exacerbations,improved quality of life<br>Eradication of P.a. in 30.8% improved quality of life | 49<br>50 |

Bronchiectasis can be a sequela of ABPA, but it can also predispose to ABPA. Acute exacerbation of ABPA usually requires treatment with systemic steroids for a long period of time [51].In order to prevent recurrence, long-term oral therapy with itraconazole is indicated in patients with pulmonary colonization; several studies have shown the effectiveness of this treatment in CF. Inhaled amphotericin B is the subject of studies. Individual reports have documented successful treatment with a monoclonal antibody against IgE (omaluzimab).[3]

**Surgical therapy**

Surgery is the method of choice in unilateral and localized bronchiectasis. Several studies have shown that resection of the bronchiectasis improved symptoms.[52]In the different studies, mortality varied from 1% to 8.6%.[33] Complications included pneumonias, postoperative hemorrhage, atelectasis, bronchopulmonary fistula, and wound infection. In particular cases, the resection of bilateral bronchiectasis may be the aim,but the lesions should be limited and completely resectable.[52] In severe complications, such as life threatening hemorrhage or fungal infection, surgical therapy can be used as the method of last resort.Hemoptysis, which is mostly caused by bleeds from hypertrophied vessels of the inflamed mucosa, can becontrolled by bronchial artery embolization (coiling) if required. This should only be done in specialized centers.

**Lung transplantation in advanced disease**

Lung transplantion can be a useful intervention in very advanced non-CF bronchiectasis. It is of vital importance to identify the right time for putting the patient on the transplant list. In accordance to the guidelines, the following criteria should be met:

- FEV1 < 30 % and an exacerbation with inpatient admission to intensive care, or
- More than three exacerbations per year, or
- Recurrent pneumothorax, or
- Hemoptysis requiring—and receiving—intervention .[53]

A double lung transplant is the method of choice in more than 90% of cases. In case only one lung is transplanted, there is a risk that pathogens are transferred from the native lung into the transplanted lung. Experiences from large centers have shown that he long-term prognosis does not differ much from that of other indications, with 5-year survival rates between 55% and60% .[55]

**Conclusion:**

Bronchiectasis is still, one of the frequently seen chronic lung diseases, that can affect the life quality and expectancy of the affected person. Multiple conditions are associated with the development of bronchiectasis, but all require both an infectious insult plus impairment of drainage, airway obstruction and/or a defect in host defense. Treatment of bronchiectasis is aimed at controlling infection and improving bronchial hygiene. Surgical extirpation of affected areas may be useful in selected patients.

**References:**

1. Bronchiectasis: diagnosisand management in 21st century. Postgrad Med J 2010; 86:493–501.

2. Laennec RTH. De'Auscultation Mediate ou Traite du Diagnostic des poumons et du Coeur (On Mediate Auscultation or Treatise on the Diagnosis of the Diseases of the Lungs and Heart). Paris, Brosson and Chaud'e ;1819.

3. Rademacher J, Welte T: Bronchiectasis—diagnosis and treatment. Dtsch Arztebl Int 2011; 108(48): 809–15. DOI: 10.3238/arztebl.2011.0809

4. Bilton D: Update on non-cystic fibrosis bronchiectasis. Curr Opin Pulm Med 2008; 14: 595–9.

5. Twiss J, Metcalfe R, Edwards E, et al.: New Zealand national incidence of bronchiectasis „too high" for a developed country. Arch Dis Child 2005; 90: 737–40.

6. Department of Health. Hospital edipsode statistics. Avaialble from:http://www.hesonline.nhs.uk (accessed 5 September 2016).

7. Quint JK, Millett ER, Joshi M et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016; 47(1) :186-93.

8. Stockley RA. Bronchiectasis-new therapeutic approaches based on pathogenesis. Clin Chest Med 1987;8:48194. Back to cited text no. 1 [PUBMED]

9. Evans DJ, Greenstone M. Long-tem antibiotics in the management of non-CF bronchiectasis-do they improve outcome? Respir Med 2003;97:851-8. Back to cited text no. 3 [PUBMED]

10. Stockley RA, Hill SL, Morrison HM, Starkie CM. Elastolytic activity of sputum and its relationship to purulence and to lung function in-patient with bronchiectasis. Thorax 1984;39:408-13.

11. Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: A double blind, placebo-controlled study, Eur Respir J 1997;10:994-9. Back to cited text no. 2 [PUBMED] [FULLTEXT]

12. Reid LM. Reduction in bronchial subdivision in bronchiectasis. Thorax 1950;5:233-47. Back to cited text no. 11 [PUBMED]

13. AL-Shirawi N,AL-Jahdali HH,Al-Shimemeri A.Pathogenesis,etiology and treatment of bronchiectasis.2006;1:41-51.

14. Pasteur M, Helliwell S, Houghton S et al. An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000; 162(4 Pt 1): 1,277-84.

15. Seaton A,Seaton D,Leitch AG.Crofton and Douglas's respiratory diseases.Fifth edition.2000;1:794-828.

16. Kauffman BY, Tomee JF, Vander Werf TS, de Monchy JG, Koeter GK. Review of fungus-induced asthmatic reactions. Am J Respir Crit Care Med 1995;151:2109-16. Back to cited text no. 15

17. Barker AF. Bronchiectasis. N Engl J Med 2002;346:1383-93. Back to cited text no. 4 [PUBMED] [FULLTEXT]

18. Chauhan B, Knutsen AP, Hutcheson PS, Slavin RG, Bellone CJ. T cell subsets, epitope mapping and HLA-restriction in patients with allergic bronchopulmonary aspergillosis. J Clin Invest 1996;97:2324-31. Back to cited text no. 16

19. Stockley RA. Bronchiectasis-new therapeutic approaches based on pathogenesis. Clin Chest Med 1987;8:481-94. Back to cited text no. 1 [PUBMED]

20. Cunningham-Rundles C, Bodian C. Common variable immuno deficiency: Clinical and immunological features of 248 patients. Clin Immunol 1999;92:34-48. Back to cited text no. 21 [PUBMED] [FULLTEXT]

21. Davis PB, Drumm M, Konstan MW. Cystic fibrosis. Am J Respir Crit Care Med 1996;154:1229-56. Back to cited text no. 24 [PUBMED]

22. Ninis VN, Kylync MO, Kandemir M, Daoly E, Tolun A. High frequency of T9 and CFTR mutations in children with idiopathic bronchiectasis. J Med Genet 2003;40:530-9. Back to cited text no. 25

23. Castellan C, Quinzii C, Altieri S, Mostella G, Assael BM. A pilot survey of cystic fibrosis clinical manifestations in CFTR mutation heterozygotes. Genet Test 2001;5:249-54. Back to cited text no. 26

24. Bush A, Cole P, Hariri M, Mackay I, Phillips G, O'Callaghan C, et al . Primary ciliary dyskinesia: diagnosis and standards of care. Eur Respir J 1998;12:982-8. Back to cited text no. 33

25. Patel IS, Vlahos I, Wilkinson TM, et al.: Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 15; 170: 400–7.

26. Bamji A, Cooke N. Rheumatoid arthritis and chronic bronchial suppuration. Scand J Rheumatol 1985;14:15-21. Back to cited text no. 36 [PUBMED]

27. McMahon MJ, Swinson DR, Shettar S, Wolstenholme R, Chattopadhyay C, Smith P, et al . Bronchiectasis and rheumatoid arthritis: A clinical study. Ann Rheum Dis 1993;52:776-9. Back to cited text no. 37

28. Van Albada-Kuipers GA, Linthorst J, Peeters EA, Breedveld FC, Dijkmans BA, Hermans J, et al . Frequency of infection among patients with rheumatoid arthritis versus patients with osteoarthritis or soft tissue rheumatism. Arthritis Rheum 1988;31:667-71. Back to cited text no. 40

29. Cohen M, Sahn SA. Bronchiectasis in systemic disease. Chest 1999;116:1063-74. Back to cited text no. 12 [PUBMED] [FULLTEXT]

30. Camus P, Piard F, Ashcroft T, Gal AA, Colby TV. The lung in inflammatory bowel disease. Medicine 1993;72:151-83. Back to cited text no. 42 [PUBMED]

31. Kinnear W, Higenbottam T. Pulmonary manifestations of inflammatory bowel disease. Intern Med spec 1983;4:104-11. Back to cited text no. 47

32. Goeminne P, Dupont L: Non-cystic fibrosis. A clinical, roentgenologic and pathologic study. *Arch Intern Med* 1941;68: 395

33. Ogilvie AG. The natural history of bronchiectasis1. Kumar V, Abbas Abdul K, Fausto N. Robbins and Cotran pathological basis of disease 7th edition. Saunders;2005.

34. O'Donnell AE, Barker AF, Ilowite JS, et al.: Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group.Chest 1998; 113: 1329–34.

35. Dagli E. non cystiv fibrosis bronchiectasis. *Paediatr Respir Rev*. 2000;1:64-70. 9. Nicotrs MB, Rivera M, Dale AM et al. Clinical, pathophysiologic

36. Nicotra MB, Rivera M, Dale AM, et al. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. *Chest*. 1995; 108: 955-61.

37. Donaldson SH, Bennett WD, Zeman KL, et al.: Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 2006; 354: 241–50

38. Daviskas E, Anderson SD, Gomes K, et al.: Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. Respirology 2005; 10: 46–56.

39. Wills PJ, Wodehouse T, Corkery K, et al. Short term recombinant human DNase in bronchiectasis. Effects on clinical state and in vitro sputum transportability. *Am J Respir Crit Care Med*. 1996;154:413-7.

40. Altenburg et al.Non-cystic fibrosis bronchiectasis.2015;73:4

41. Ratjen F, Munck A, Kho P, et al.: Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE Trial. Thorax 2010; 65: 286–91.

42. Drobnic ME, Suñé P, Montoro JB, et al.: Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa. Ann Pharmacother 2005; 39: 39–44.

43. 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.

44. Steinfort DP, Steinfort C: Effect of long-term nebulised colistin of lung function and quality of life in patients with chronic bronchial sepsis. Intern Med J 2007; 37: 495–8.

45. Dhar R, Anwar GA, Bourke SC, et al.: Efficacy of nebulised colomycin in patients with non-cystic fibrosis bronchiectasis colonised with Pseudomonas aeruginosa. Thorax 2010; 65: 553.

46. McCoy KS, Quittner AL, Oermann CM, et al.: Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. Am J Respir Crit Care 2008; 178: 921–8.

47. Bilton D, Bruinenberg P, Otulana B, et al.: Inhaled liposomal ciprofloxacin hydrochloride significantly reduces sputum pseudomonas aeruginosa density in CF and Non-CF bronchiectasis. Am J Respir Crit Care Med 179; 2009: A3214.

48. Wilson R, Welte T, Polverino E, et al.: Randomized, placebocontrolled, double-blind, multi-center study to evaluate the safety and efficacy of Ciprofloxacin dry powder for

inhalation (Ciprofloxacin DPI) compared with placebo in patients with non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 183; 2011: A6407.

49. Antoniu SA, Trofor AC: Inhaled gentamicin in non-cystic fibrosis bronchiectasis: effects of long-term therapy. Expert Opin Pharmacother 2011; 12: 1191–4.

50. Tsang KW, Tan KC, Ho PL, et al.: Inhaled fluticasone in bronchiectasis: a 12 month study. Thorax. 2005; 60: 239–43.

51. Agarwal R: Allergic bronchopulmonary aspergillosis. Chest 2009; 135: 805–26.

52. Bagheri R, Haghi SZ, Fattahi Masoum SH, et al.: Surgical management of bronchiectasis: analysis of 277 patients. Thorac Cardiov Surg 2009; 58: 291–4.

53. Orens JB, Estenne M, Arcasoy S, et al.: Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and LungTransplantation. J Heart Lung Transplant 2006; 25: 745–55.