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Bronchiectasis, Causes, Pathogenesis,Clinical Manifestations and Update Management

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Abstract: ***Bronchiectasis is a recognized congenital and acquired lung condition. The congenital entity is unavoidable while the acquired type could be prevented by complete childhood immunization against bacterial and viral infections. Early diagnosis of chest infections and prompt antibiotic treatment to prevent complications like lung abscess or bronchiectasis. Once there is the development and established bronchiectasis, it is irreversible. Management is with antibiotics, postural drainage, mucolytics, and supportive nebulized bronchodilators. Radio-imaging is an important tool for diagnosing bronchiectasis including CT-scan Chest. Progression or response to treatment is gauged with radio-imaging especially serial chest x-rays, but alternatively, the clinical wellbeing of the patient can be gauged with decreasing volume of sputum expectorated per 24 hours.***

Keywords: congenital, acquired, bronchiectasis, respiratory failure, high resolution CT-Chest

1. Introduction

Lungs are the most exposed organ of the body to outer environment after skin. Most of the lung diseases are due to underlying causes related to genetics, smoking and infections. Bronchiectasis is an uncommon disease, which results most often as a complication of infectious process in large majority of acquired causes. First time, it was described by Laennec in 1819 and later by Sir William Osler in the late 1800s, and further by Reid in the 1950s.There has been significant changes in the prevalence, causes, presentation and treatment of bronchiectasis in recent times[1]Congenital or acquired bronchiectasis is defined as permanent dilatation of the proximal and medium sized bronchi (<2mm diameter)[1]. The condition is characterized by variable chronic cough and excessive expectoration associated with progressive parenchymal lung damage. Permanent bronchial distortion and impaired mucocilliary escalator function leads to recurrent infections and bacterial colonization leading to further progressive lung damage and morbidity which over the years culminate in respiratory insufficiency warranting a need for lung transplantation in severe cases.[2,3].Diagnosis of this condition is based on variable but chronic history of cough with expectoration and needs specific investigations for confirmation like bronchography and nowadays radio-imaging with high resolution CT-Chest is the gold standard. Bronchoscopy has special role to exclude foreign body in young patients having recurrent chest infections and having localized pneumonias at the same site. Main stay of treatment is short courses of antibiotics and chest physiotherapy besides surgery in few selected patients having limited disease. We review the, causes, clinical manifestations, pathophysiology of this condition along with specific investigations and update modalities of treatment.

Characterized by permanent dilatation of the bronchi, thickening of bronchial walls, impaired muco-cilliary drainage, and airway obstruction, bronchiectasis is a chronic and progressive disease manifesting clinically as chronic cough and copious variable expectoration with associated lung damage leading to further bronchial distortion fibrosis and respiratory insufficiency.[4,5,6,7,8].

Acquired bronchiectasis because of chest infections has been more common during pre-antibiotic era, although exact prevalence remains unknown. Among many factors one is its association with smoking related chronic bronchitis and chronic obstructive lung disease leading to under investigation of bronchiectasis.[9,10,11].Compared to the past, there has been significant drop in the prevalence of acquired bronchiectasis in the present times [12,13,14,15,16].This drop in prevalence is said to be because of less frequent childhood infections due to expanded vaccination program, availability of affective broad spectrum antibiotics, early diagnosis and prompt treatment of pulmonary tuberculosis with modern antituberculous medications[17,18].Even at present this disease still remains common among populations having frequent respiratory infections including tuberculosis, due to inadequate healthcare facilities in less developed regions and high populations[19].A study on adults referred to a pulmonary clinic in Saudi Arabia by Al-Mobeireek etal reported bronchiectasis as a cause of chronic cough and expectoration in 5% of patients [20].

Patho-Classification of Bronchiectasis

Being a syndrome of chronic cough with variable expectoration bronchiectasis is associated with irreversible bronchial distortion and thickening of bronchial walls. Often it is initiated by an infectious event subsequently perpetuated by impairment of drainage, manifesting with airway obstruction and recurrent chest infections due to abnormal defense mechanisms.

Typical pathogens known to cause bronchiectasis are,*Klebsiella, Staphylococcus, Mycobacterium tuberculosis, Mycoplasma Pneumoniae, non-tuberculous mycobacteria* (more common in HIV and reported in immunocompetent old age female nonsmokers in their 60s, sputum is positive for AFB and on radio-imaging ,small regular nodules and findings consistent with bronchiectasis on CT- Scan

Chest),others being measles virus, pertussis virus, influenze virus, herpes simplex virus and adenovirus.[21,22,23,24]. Colonization in established bronchiectasis is with *Hemophilus influenza* (47-55%), *Pseudomonas species*(18-26%) [25,26].Colonization leads to accelerated lung damage and hence progression of the disease[27].People having gastroesophageal reflex disease and associated infection by *Helicobacter pylori* are reported more prone to develop bronchiectasis because of recurrent chest infections [28,29,30].

Exact typing of bronchiectasis remains debatable, but pathologically, dependent on contrast chest radio-imaging studies, bronchiectasis is classified in to four types despite of its clinical irrelevance by Reid in 1950 [31,32]**Table-1**.First being called follicular type is more common in children, due to inflammation of lymphoid tissue and nodular appearance of the bronchial walls.2nd type is called tubular or cylindrical bronchiectasis, characterized by tram track pattern radiating from the hila, there is uniform dilatation of the bronchi with signet-ring appearance. The diameter of the airways seen is larger than the adjacent vessel. The diameter of the bronchus is normally 1-1.5 times that of adjacent vessel, a diameter greater than 1.5 times that of adjacent vessel is highly suggestive of bronchiectasis. The third type is called varicose type, and is charaterized by irregular outline and alternating areas of dilatation and narrowing, described as beaded appearance. The fourth type is called cystic or saccular bronchiectasis, which is the most severe form of the disease , these contrast with subpleural blebs in emphysema, which has thin walls and are not accompanied by proximal bronchial abnormalities seen in bronchiectasis. The bronchi dilate, forming large cysts, which appear radiologicallike fluid and air filled cavities. [33}.

Table 1: Types of Bronchiectasis based on Radio-imaging (Reid-1950)

Type	Features
Lymphoid	--- heaped up thick walls of bronchi
Tubular/cylindrical	--- uniform dilated bronchi
Cystic /sacular	--- cavity looking appearance .some time with air fluid levels
Varicose/beaded	--- areas of narrowing & dilatations

Bronchiectasis may manifest as a localized as seen in post foreign body type, or diffuse unilateral or bilateral disease as seen in systemic or immune deficiency states. Sometimes due to extrinsic compression of the bronchus, for example middle lobe syndrome caused by enlarged regional lymph nodes in tuberculosis or other infections. Other type of apical localized bronchiectasis is called bronchiectasis sicca seen often due to healed tuberculosis.[34].Diffuse bronchiectasis usually bilateral called polycystic lung disease is associated either with congenital lung conditions or ,congenital deficiency of immunoglobulins or due to associated systemic diseases [35,36]

Clinical manifestations:

Clinical manifestations of bronchiectasis include, chronic history of cough and variable foul smelling expectoration with associated hemoptysis at times. Among recognized constitutional features of bronchiectasis are fever, shortness of breath, chest pain, poor appetite, and weight loss. In advanced cases there is marked decline in lung function leading to respiratory failure and cor-pulmonale coupled with increased morbidity and mortality and requiring lung transplantation.About half of the patients having peripheral sub-pleural bronchiectasis manifest as having pleuritic chest pain as part of sub-pleural pneumonitis and may complicate in to pneumothorax[37,38].Secondary amyloidosis causing proteinuria is the end result in chronic suppurative lung diseases like bronchiectasis causing significant weight loss. Physical findings are not marked except digital clubbing seen in about 2-3% of patients having moderately severe disease. Course crackles, wheez and sub-pleural rubs are some of the findings on auscultation of the chest show a mixed restrictive and obstructive lung disease[39].

Causes of Bronchiectasis:

Development of bronchiectasis is multifactorial, Table-**2**.Non-cystic bronchiectasis mostly is acquired due to recurrent chest infections especially during childhood. In many patients the cause remains unknown called idiopathic bronchiectasis ,especially this has been the case before availability of modern radio-imaging diagnostic tools where half of the patients remained undiagnosed. On the other hand, primary immunoglobulin-deficiency is the predisposing cause along with some genetic pre-dispositions. A dry type bronchiectasis called sicca is seen in the apical parts of the lung after treated pulmonary tuberculosis having negligible to no expectoration but associated sometimes with life threatening hemoptysis due to fungus growth(aspergilloma) in the residual cavities.

Infections&immunesystem:

More frequent childhood infections during pre-antibiotic era, like measles, whooping cough (pertussis), adeno and respiratory synsitial viral infections causing lower respiratory problems were main causes of bronchiectasis. [40,41,42].The incidence has declined after expanded vaccination program and availability of broad spectrum antibiotics. Chronic infections like tuberculosis,aspergillosis and human immunodeficiency virus (HIV), may also lead to permanent lung damage and recurrent chest infections and hence bronchiectasis [43,44,45]. Among other important causes of bronchiectasis detected by CT-Scan Chest and sputum direct microscopy and culture, are Mycobacterium avian-intracellulare complex and allergic bronchopulmonary aspergilosis endemic in certain parts of the world like USA [46;47,48].

Demographics:

There are no racial pre-dilections for bronchiectasis but socioeconomic conditions do matter.Non CF-bronchiectasis is said to be more severe and common among American thin body frame females older than 60 years. This kind of bronchiectasis is often caused by Mycobacterium avium complex and is called Lady Windermere syndrome. [49,50,51]. In the pre-antibiotic era, bronchiectasis used to be frequent in first decade of life and this continues even today in under developed communities ,but in developed countries ,the age of onset has moved in adult populations exception being cystic fibrosis [52].Old age above 60 years has been related to increased number of bronchiectasis cases in some epidemiological studies in the United States

especially during 1933 to 2006. No single specific underlying cause could be found for this increase [53].The age related difference in the prevalence of bronchiectasis in persons above 60 years is likely the reflection of under lying causes like lung diseases by atypical mycobacteria,and vulnerability to recurrent and chronic infections[54].

Immune dysfunction :
Congenital or acquired immunodeficiency conditions like common gamma globulin G (IgG) subclass deficiency, X-linked agammaglobulinemia, immunoglobulin A(IgA) deficiency, immunoglobulin M(IgM) deficiency, Immunoglobulin E (IgE) deficiency, complement deficiency and chronic granulomatous disease, are all associated with bronchiectasis due to recurrent chest infections in early age. Whereas deficiency of individual immunoglobulins or their subclasses are said to be cause of recurrent chest infections leading to bronchiectasis, Sub-class IgG deficiency but normal total IgG levels leads to bronchiectasis is still not clear. HIV patients are also prone to chest infections leading in some cases to bronchiectasis[55,56,57].According to Chalmer etal,Vitamin D deficiency is frequent and correlates with severity of bronchiectasis[58,59].Those having low vitamin D levels are more prone to get acute exacerbations and colonization with Pseudomonas aeroginosa and had lower FEV1 (forced volume in 1 second).[60,61,62].

Bronchiectasis&inherited Cysticfibrosis:
It is a common condition with autosomal recessive mode of inheritance affecting 1:2500 whites and 1:17000 blacks, is a well-known cause of early childhood bronchiectasis associated with obstructive and restrictive lung disorder. It is associated with recurrent chronic respiratory infections with *Staphylococcus aureus* and *Pseudomonas aeroginosa* as a sign post of chronic chest.[63,64,65].Gene responsible for cystic fibrosis called Cystic fibrosis transmembrane regulator (CFTR) has been established as a frequent underlying cause in children with bronchiectasis of unknown cause.[66,67,68] for 28,29.30 of nehad].CFTR gene mutation in itself is not associated with increased risk of bronchiectasis rather it requires additional factors like genetic and environment[69,70,71].

Alpha-1 antitrypsin deficiency:
Another condition associated with bronchiectasis is a1-antitrypsin deficiency despite of absent emphysema. [72,73,74]. Shin, et al has suggested that gene expression may cause emphysema which subsequently casues bronchiectasis due to recurrent bronchitis especially in those having recurrent chest infections.[75,76,77,78]. However frequency of a1-antitrypsin deficiency gene was not found to be different in patients having bronchiectasis and controls in a study by Cuvelier, et al [79,80,81].

PrimaryImmotileCiliasyndrome(Kartagener'ssyndrome)
Autosomal recessive disorder also called immotile cilia syndrome although rare could lead to bronchiectasis as a result of dysfunctional pulmonary muco-ciliary escalator. It may affect 1in 15,000-30,000 population. As a result of retained bronchial secretions leads to recurrent and frequent respiratory infections leading to bronchiectasis. [82,83,84]. About half of the patients with immotile cilia syndrome, have associated sinusitis, bronchiectasis and sinus inversus,called Kartagener's syndrome. Other anomalies include inguinal hernias and rectal prolapse are also common in these patients [85, 86].

Young syndrome:
It is similar to cystic fibrosis or its genetic variant. It is often observed among middle aged male population of North America and is rated as a leading underlying cause of male infertility in these patients [87].

Miscelaneous congenital anatomical lung conditions:
Some of the congenital lung conditions also can lead to development of bronchiectasis due to recurrent chest infections in young age, although some cases has been diagnose in late age. These include bronchopulmonary sequestrations (intra or extra-lobar) and lobar atresias. [88]. Other conditions are William-Cambell syndrome having congenital cartilage deficiency, Swer-James syndrome giving rise to hyperlucent lung, and tracheobronchomegaly in Mounier-Kuhn syndrome. Another condition although rare could cause bronchiectasis and exudative pleural effusion [89,90,91]

Connective disorders & Rhematoid arthritis:
Bronchiectasis associated with rheumatoid arthritis has been a subject of interest in recent times. In one study by Walker et al reported that the incidence of bronchiectasis in rheumatoid arthritis is 3.2-35% [92,93,94].A figure of 3.1% has been quoted elsewherein patients as compared to 0.3% in patients with osteoarthritis.[95].Bronchiectasis in rheumatoid arthritis is a sign of bad prognosis[96].Sjogrens syndrome is also associated with bronchiectasis due to increased viscosity of bronchial secretions.[97].On the other side Solanki et al has reported that the incidence of rheumatoid arthritis related bronchiectasis was 5.2%.[98]. Bronchiectasis may pre-cede or follow onset of rheumatoid arthritis.[99,100].Bronchiectasis pre-ceding rheumatoid arthritis due to chronic suppurative infections may trigger development of rheumatoid arthritis and vice versa.[101,102].On the other side those who develop bronchiectasis after onset of rheumatoid arthritis, are more prone to respiratory infections ,primarily due to rheumatoid arthritis itself or as a complication of treatment especially immunomodulating therapies leading to development of bronchiectasis and acute and chronic infections.Irrespective of being controversial this association leads to a bad prognosis due to overwhelming infections with decline in 5 year survivals[103,104,105].According to a recent study in Saudi Arabia by Suzan etal, in 2015,on 100 patients of confirmed rheumatoid arthritis having no respiratory symptoms, 35% of these had underlying asymptomatic bronchiectasis. Various predictors of underlying bronchiectasis were age above 50years, duration of rheumatoid disease more than years and male gender, $P<0.001$, $p<0.006$ and $P<0.028$ respectively [106].

Lung involvement in seronegative arthritis like ankylosing spondylitis and inflammatory bowel disease although rare is a recognized feature.[107].The majority of cases of inflammatory bowel disease ,ulcerative colitis as well as Crohn's disease are reported, having pulmonary airway disease especially bronchiectasis in up to 25% patients having lung involvement even before or after collectomy

[108,109,110,111,112].Underlying mechanisms are suggested to be a combination of inflammation and autoimmunity rather than infections[113,114].

Systemic lupus erythromatosis is associated with bronchiectasis in about 21% of cases [115], while ankylosing spondylitis in a minority of cases only[116].Relapsing polychondritis causes secondary bronchiectasis due to recurrent infections[117].Sarcoidosis is reported associated with bronchiectasis by various underlying mechanisms, like fibrosis, granulomatous inflamation and extrinsic bronchial compression[118]. Marphans syndrome and autosomal dominanat polycystic kidney disease are also associated with bronchiectasis due to bronchial wall weakness [119,120].A unique variety called tractional bronchiectasis is associated with advanced stages of interstial lung disease,such type of bronchiectasis is more marked in upper lobes in case of radiations and sarcoidosis while in lower lobes in intersticial lung disease or idiopathic pulmonary fibrois (ILD/IPF)[121].

Pathogenesis of Bronchiectasis:

There is no systemic data as regards incidence or prevalence of bronchiectasis, in general ,with expanded vaccination program and availability of antibiotics during 20th century resulted in drop of rates of bronchiectasis.[122] .The best data till-todate suggest that prevalence of bronchiectasis reflects the socioeconomic conditions of the communities under study[123,124].Despite of many underlying conditions associated with bronchiectasis, in about half of the cases exact underlying mechanisms may still remain unknown. All conditions leading to bronchiectasis are orchestrated either by altered pulmonary defense or inflammation [125].Under these circumstances there is defective mucociliary escalator and thus increased susceptibility to chest infections and colonization as a sign post of chronic chest with associated lung parenchymal damage and bronchiectasis [126]. Continous Inflamation and recurrent infections in bronchiectasis are said to be due to underlying defect in antigen presenting cells macrophages and neutrophils resulting in progressive lung damage [127, 128, 129].

All most all patients of bronchiectasis have impaired mucocilliary dysfunction with variable excessive expectoration due to progressive inflammation and recurrent infections. Some of these patients have intermittent events but some with colonization and high inflamtory markers have persistant and progressive respiratory symtoms [130,131]. Still, Colonization is not a rule in all patients [132,133] .Due to persistant inflammation there is increased vascular permeability leading to exudation of serum proteins in the alveoli resulting in high sputum protein content .There is also increased number of neutrophils and their products like elstases and superoxide radicals.[134,135].These neutrophil contents has been associated closely with development of bronchiectasis, emphysema and adult respiratory syndrome like conditions. There is increased expectoration due to hypertrophy of mucous glands, hyperairway secretion ,epithelial cilliary damage and more and more airway inflammation [136,137,138].

A study by Tsang and co-workers reported strong correlation between elastase enzyme activity, degree of daily expectoration, and number of lung lobes affected .There is poor lung function in patients having severe and persisting inflamation and high elstase levels in the sputum.According to the same study, sputum elastase activity correlated with the 24-h sputum volume and the number of lung lobes affected by bronchiectasis[139]. This can explain the worse lung function in patients who have persistently high levels of elastase in their sputum. High elastases secreted by neutrophils renders the epithelial secretary IgA dysfunctional thus encouraging further colonization. Thus excessive bacterial growth leads to more lung parenchymal tissue.This in part is also due to altered phagocytic opsonization and reduced complement activity mediated by IgG[140,141].

Besides these mechanisms endogenous nitric oxide production is said to be another cause of respiratory diseases by its direct cytotoxic effects as well as its interaction with superoxide[142,143].Tsang et al, reported that there is reduced nitric oxide in patients having bronchiectasis and colonization by Pseudomonas aeruginosa SP due to reduced activity of nitric oxide synthetase.[144].Colonization in bronchiectasis is different than that in chronic bronchitis,it include *Haemophilus influenza, Moraxella catarrhalis, Staphylococcus, Pseudomonas aeroginisa*,and less commonly *Streptococcus Pneumoniae* [145,146].

Various inflammatory mediators like interleukin (IL-8), interleukin IB(IL-1B) inter leukan 10(IL-10)interleukin 6(IL-6) tumour necrosis factor a (TNF-a) and leukotriene B4(LT-B4).These mediators leads to neutrophils recruitment and destruction by acting together. [147,148,149,150,151]. Another feature associated with bronchiectasis is hyper-reactive airways[152,153].

Majority of these patients having bronchiectasis in advanced stages and with pseudomonas colonization develop associated hyperreactive airways disease. One study in Saudi Arabia reported ,that in those patients of bronchiectasis having co-existing pseudomonas colonization ,reactive airways disease, was more common than those who did not had pseudomonas colonization. Subsequently exacerbations and respiratory failure were also more common in cases having associated obstructive airways disease increasing morbidity and mortality [154].

The diagnosis of bronchiectasis is supported by history of chronic respiratory complaints of cough with purulent copious expectoration rich in neutrophil elastases and albumin on sputum analysis .Besides radio-imaging, to recognize the underlying etiology, requires quantitative immunoglobulin levels estimation, serum alpha 1-antitrypsin levels, autoimmune screening, besides aspergillus precipitins and total serum IgE levels for the diagnosis of allergic bronchopulmonary asepergillosis (ABPA).

Chest-Radiography

About 90% of patients having respiratory symptoms consistent with bronchiectasis has abnormal chest x-rays. Among the radiological patterns are ring shadows, tram line

shadows, increased linear reticular shadows, pneumonitis and sometimes atelectasis.[155,156].

High-Resolution CT-Scan:
It is one of the modern and reliable radioimaging diagnostic tools of choice which has replaced old bronchography in diagnosis of bronchiectasis. A routine chest x-ray may not be able to show detectable findings required to make the diagnosis of bronchiectasis. Utility of chest x-ray and high resolution CT-Chest (HRCT) were compared by Bruggen-Bogaarts etal, who reported that a normal chest x-ray excludes presence of bronchiectasis with a sensitivity of 87.8%, where no further investigation is warranted. They advocated that in the presence of a normal chest x-ray and absence of history suggestive of bronchiectsis, a HRCT is rarely required. However HRCT of the chest has become investigation of choice while diagnosing bronchiectasis in the presence of abnormal chest x-ray having a linear relationship [157,158,159].To exclude motion artifacts modality of choice is spiral CT-Scan chest [160,161].

Pulmonary Function Tests:
Whereas mild and localized bronchiectasis retains normal pulmonary function on spirometry, more severe cases of bronchiectasis show associated obstructive or mixed obstructive as well as restrictive pattern on spirometry [160].Reduced diffusion capacity and hyperinflation are other features seen in about one third to two third of those having bronchiectasis. Hyperactive air disease is other manifestation manifested on challenge studies [162,163].

Sweat Chloride Test:
Patients in early childhood having persistant respiratory symtoms or recurrent chest infections are diagnosed for cystic fibrosis by sweat chloride test in about 70% of cases during first year of life.[164]. A sweat chloride below 40 millimoles is reported normal, a range from 40-60 millimoles is reported as borderline while the levels above 60 millimoles are reported grossly abnormal and diagnostic in 90% of cases of cystic fibrosis [165,166].In some of the cases having chronic respiratory symptoms and having even normal sweat test require further investigations to exclude gene mutations[167,168,169].

Bronchoscopy:
Various bronchoscopic studies on findings in bronchiectasis have reported airways appearances like inflamed bronchial mucosa, bronchomalacia, obliterative lesions. The site of these findings correlated well with high resolution CT - chest. Bronchoscopy has important therapeutic and diagnostic role especially in young children having recurrent chronic respiratory symptoms and localized bronchiectasis at the same side or site, to exclude suspected foreign body impaction [170]. In addition bronchoalveolar lavage and brushings help to collect secured uncontaminated specimens for reliable cultures.

Microbiology of Bronchiectasis
When compared with healthy non-smokers, about 64% (Angrill & co-workers) patients having bronchiectasis has chronic colonization with potentially pathogenic flora in their lower respiratory airways[171,172,173].These microorganisms cause progressive lung parenchymal tissue damage resulting in bronchiectasis. Among the most prevalent micro-organisms include *Haemophilus Influenzae*(55%), *Pseudomonas aeroginosa* (26%) and *streptococcus pneumonia*(12%).One third of these bugs were resistant to antibiotics Various risk factors for chronic colonization are young age below 14 years, associated obstructive airways disease having FEV1 < 80% of predicted and presence of cystic bronchiectasis [174].Presence of *Pseudomonas aeroginosa* is the sign post of chronic chest. On the other hand all those having bronchiectasis and colonized with these bugs don't develop infection due to these organisms .This differentiation between colonization and infection has therapeutic and prognostic value. Chronic infection due to these organisms leads to development of antibodies, which are unfortunately non-protective and are a sign of bad prognosis being the sign post of chronic chest suppuration correlating with clinical features.[175]. In colonization the levels of these antibodies are negligible, and these levels differentiate between the two i.e Infection and colonization by a sensitivity and specificity of 75% -Carballero et al [176].Another study by Ho etal reported that presence of *Pseudomonas* on sputum culture in patients of bronchiectasis is associated with more copious expectoration ,more morbidity and worse lung function having a FEV1/FVC ratio below 60% in the large majority of patients[177].Similar observations has been reported by Wilson and co-workers [178].Another well recognized microorganism in patients of cystic bronchiectasis in particular is *Burkholderia Cepacia* ,which is also common in immunocompromized patients as well as those requiring mechanical ventilation [179].Chronic colonization in non-cystic bronchiectasis has not been reported. A case of *Burkholderia.Cepacia* associated bronchiectasis has been reported by Ledson et al, in a mother of two children having cystic fibrosis and colonized with *Burkholderia.Cepacia*, she was not found to have immune deficiency or cystic fibrosis, author postulated that it was as a result of direct transmission of infection from her children [180].

Update Management of Bronchiectasis:
Preventive strategies are more powerful than cure in acquired non-cystic bronchiectasis. As compared to pre-antibiotic era, where there has been high mortality in the tune of 49% in a group of patients followed for 3-6 years [181].Severity of bronchiectasis in terms of sputum output is gauged by daily measuring 24 hour sputum output. A sputum output of < 10ml is seen in mild, 10-150 ml moderate and sputum above 150ml is seen as severe bronchiectasis. Main stay of treatment is chest physiotherapy and antibiotics courses of 7-10 days[182].Antibiotics in respiratory infections are used by parenteral, oral and nebulized routes. Nebulized tobramycin is reported a safe and affective therapy in pseudomonas colonization, collistin and gentacin being other choices [183,184,185,186]. Only few conditions causing non-cystic bronchiectasis respond to medical treatment like allergic bronchopulmonary asepergillosis, immune deficiencies, and non-tuberculous Mycobacterial infections [187,188]. Now the prognosis of bronchiectasis has improved immensely as a result of advances in medical care comprising large scale vaccination, availability of broad spectrum antibiotics and surgical expertise [189].Allergic Bronchopulmonary aspergilosis(ABPA) is treated with glucocorticoids and

antifungal medications. American thoracic society recommends treatment of *Mycobacterium avium complex* (MAC) infection with combination of Clarithromycin, Rifampicin and Ethambutol, sometimes even streptomycin as 4rth drug in severe cases, but relatively young patients to avoid toxicity. Treatment is continued upto (usually 18-24 months) until the sputum culture results have been negative by one year[190].

Acute exacerbations are marked with increased sputum output, fever and are treated with intravenous antibiotics after taking sputum for culture sensitivity and inhaled bronchodilators. Antibiotics in high doses given as short courses (7-10 days) do help control exacerbations [191, 192, 193] but long term antibiotics are controversial and non-useful [194].

Bronchopulmonary hygiene requires various modalities to encourage drainage of retained secretions. It involves use of mucolytics, antibiotics nebulized or systemic and nebulized bronchodilators along with inhaled corticosteroids. Chest physiotherapy, involving chest wall vibratory devices, oscilatiing jackets or airways air resonance devices combined with postural drainage are recognized treatment modalities [195]. Chest percussion physiotherapy and postural drainage has been reported very useful in clearing bronchial secretions by monitoring daily sputum output especially after good hydration, mucolytics like bromhexine and nebulized bronchodilators[196,197].Use of aerolized recombinant human DNase is found useful in cystic fibrosis type bronchiectasis, while it has not been recommended in cases of non-cystic fibrosis bronchiectasis.[198].

Bronchiectasis is a mixed restrictive as well as obstructive lung disorder and obstructive element unfortunately remains poorly reversible .Monotherapy with salbutamol like short acting beta-agonists (SABAs) or long acting beta-agonists (LABAs} has been reported largely non-beneficial [199,200]. However long acting beta-agonists combined with inhaled corticosteroids has been reported relatively useful [201]. Studies on mono-therapy with inhaled corticosteroids like fluticasone 1000mcgm ,budesonide and beclamethasone, daily has been reported beneficial by Tsang et al and Elborn-coworkers respectively [2002,203]. Usefullness of leukotrien receptor blockers has not been proved by any trials.[204]. Role of oral steroids has not been studied in trials but are said to be beneficial in patients having allergic bronchopulmonary *aspergillosis* and especially during acute exacerbation when used under the umbrella of short course intravenous broad spectrum antibiotics[205].

Excessive, viscid and thick expectoration is hall mark of bronchiectasis which is difficult to spit out due to associated mucocilliary escalator dysfunction especially in the presence of obstructive airways disease. Expectorants increase bronchial secretions and loosen phlegm by reducing its viscosity to facilitate expectoration .Adjuvant treatment with expectorants, decongestants along with long acting beta agonists bronchodilators and inhaled corticosteroids(LABAS+ICS) are expected to be promising [2006].

Surgical treatment is one of the therapeutic options in carefully selected patients having localized and unilateral bronchiectasis. Mortality rates reported in chest surgery are 1-8.6% [207,208,209,210,211]. An operative morbidity of 14 to 53% is reported in different case series [212,213,214].

One study by Ashour et al, in Saudi Arabia on patients having unilateral and localized bronchiectasis treated surgically reported no mortality but 15% operative morbidity. Cured by thoracic surgery were 72.5% while 27.5% got improved [215]. These findings are in agreement with outcomes reported by others [216]. Surgical option as modality of treatment is used when there is limited disease, medical treatment fails or there is an obstructive mass lesion, foreign body impaction or hemorrhage. Surgery is also used to remove parts of lung affected by resistant tuberculosis and *Mycobacterium avium sp complex* [217, 218, 219, 220].

Classification of bronchiectasis remains controversial as regards selection of patients for surgery. However selection of patients for surgery is done, based both on hemodynamic studies (perfused vs non-perfused) and morphological patterns (cystic vs non-cystic) seen on radio-imaging like Contrast HRCT-scan chest findings [221,222]. Patients having cystic and localized disease treated by surgery showed remarkable improvement (>73%) with negligible morbidity and morbidity [223,224]. Treatment with antibiotics, decrease bacterial burden and this results in reduced levels of neutrophil elastases and protein transudation and hence low sputum albumin contents [225]. [6,38 cited above for 3 of nehad cited above].Both Hill etal [226] and Stockley et al [227], demonstrated that high bacterial loads and excessive volumes of the daily sputum output in bronchiectasis require high doses of antibiotics, their sputum volume not only become less in volume but non-mucoid in consistency. Post antibiotic period was associated with improved FEV1 as well with a sense of wellbeing in clinical terms. After discontinuing antiobiotics, after some time again an increased sputum production was observed, thick in consistency, rich in neutrophil elastases and alubumin. Study by I.P et al on a group of 12 patients of bronchiectasis ,demonstrated that when an acute exacerbation is treated for 2 weeks courses of antibiotics ,there is a significant drop, both in neutrophilic chemotactic activity and elastase activity. After stopping antibiotics levels of these markers returned [228] Kelly etal also observed similar observations when treated their patients with amoxicillin, besides showing that there was improvement in degree of obstructive airways seen in better FEV1[229].

In several recent reports use of macrolides has shown reduction in the obstructive airway diseases and degree of inflammation in patients of bronchiectasis [230, 231, 232].The underlying mechanism of macrolides actions is unclear but is considered due to their antimicrobial and antiinflamtory effects [233,234,235,236,237].

Vaccines:

Preventive approaches are stronger than curative efforts, therefore role of *Polyaccharide pneumococcal* vaccinations in those (age above 2 years) having chronic lung conditions

is well established [238]. Whitney and co-workers has examined benefits of pneumococcal vaccination and has reported a significant (32%) decrease in the incidence of pneumococcal infections especially in elderly [239].

Again use of *influenza A & B* vaccines in those having chronic lung diseases, especially in elderly patients can reduce the risk of recurrent respiratory viral infections and hence complications and death by 70-85%[240,241].

Lung transplantation: In advanced end stage lung damage with FEV1 <30% of the predicted ,morbid respiratory failure in relatively young patients single or double lung transplant has been used but still on limited scale at specialized centres.

Pulmonary rehabilitation:
Besides pharmacological and preventive interventions, non-pharmacological approaches has also been reported very beneficial. It involves psychological support light exercises, chest physiotherapy, smoking cessation, nutrition and long term oxygen therapy. These patients are better cared by multidisciplinary teams along with patient education to teach them coping strategies, under the theme of stop wishing start learning.

Prognosis:
Mortality and morbidity has been high with in the first 5 years of life in the pre-antibiotic era. The period between 1930 and 1981 has been the era of thoracic surgery, when even tuberculosis was being treated by many surgical procedures including phrenic crush, plumbage, thoracoplasty and lobetomies etc. A study in 1940 on 400 patients of bronchiectsis reported a mortality rate above 30%, majority within 2 years [242]. In comparison a retrospective study in 1981, when antibotics were being used on large scale, reported a mortality of 13% [243]. Another study on patients suffering from bronchiectasis from Finland, reported in late 1990s an increased mortality compared to Br.asthma and chronic obstructive pulmonary disease(COPD).Reported mortality rates for bronchiectasis, asthma and COPD were, 28%, 20% and 38% respectively [244, 245].

Overall the prognosis of bronchiectasis has improved with early antibiotics especially in compliant patients, and other adjuvant modalities of management .Although prognosis varies with underlying cause and pre-disposing conditions. However CF related bronchiectasis has worse prognosis. Complications like recurrent pneumonias requiring frequent hospital admissions, empyema, lung abscess, respiratory failure and corpulmonale are less common these days. Risk of complications like pneumothorax remains the same especially in cystic bronchiectasis. Hemoptysis is another dreadful complication. Amyloidosis and metastatic abscess after availability of broad spectrum antibiotics has become rare these days. Mortality these days is related to progressive respiratory failure and right heart failure (cor-pulmonale) in advanced cases .Those on long term oxygen therapy before 65years of age and requiring admission in intensive care unit are reported having poor outcomes[246].A higher mortality was reported in one study done on patients with non-CF bronchiectasis in 2007,and factors for increased mortality were advanced age, poor functional status, extensive disease on radio-imaging, in the presence of hypoxemia and hypercapnia(mixed respiratory failure).On the other hand regular vaccinations as part of prevention, regular follow up with the treating physician and optimum body mass index range 19-24 were associated with better prognosis and lower mortality[247].

2. Conclusion

Till-today, bronchiectasis remains a common lung condition associated with great morbidity and mortality particularly in high populated and resource poor regions. Besides congenital conditions associated with bronchiectasis, other conditions favoring development of bronchiectasis are smoking and chest infections being the commonest .Viral or bacterial respiratory infections in childhood are the most common pre-disposing causes in early age besides congenital muco-cilliary escalator dysfunction in minority of patients. Poor immune host defense and obstructive airways, leading to impaired drainage and superadded recurrent infections. Once established it is a progressive condition. Use of antibiotics to control infection and chest physiotherapy to facilitate postural drainage are the main modalities of treatment with addition of bronchodilators combined with inhaled coticosteroids during acute exacerbations. Surgery has a limited but definite role in selected patients having localized disease. Lung transplant in relatively young patients having advanced and bilateral bronchiectasis coupled with respiratory failure, yet remains a possible option at specialized centres , but with limited survival promise besides complications associated with immunosuppressive medications used in organ transplant cases.Clinical improvement in exacerbations is best gauged by recording 24 hour sputum output than repeated chest x-rays ,a quantitative and qualitative change is noticed in response to combined therapy including chest physiotherapy,antibiotics,bronchodilators.Figures-1,2,3.

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Figure 1: Change in consistency and color of the sputum

Figure 2: Change in consistency and color of the sputum

Figure 3: Change in consistency and color of the sputum