Review Article

Non Cystic Fibrosis Bronchiectasis: Diagnosis and Management

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Summary

Bronchiectasis is characterized by abnormal permanent dilatation of bronchi. In any patient presenting with suspected symptoms, the diagnosis of bronchiectasis can be confirmed by HRCT. MRI is a radiation free alternative investigation. Early detection of bronchiectasis and its cause is crucial in preventing progression of disease. All adults with diffuse bronchiectasis have to be tested for ABPA, Immune deficiency diseases and ciliary dysfunction. In children it is mandatory to rule out foreign body aspiration and Cystic fibrosis (CF). Treatment of bronchiectasis is multimodality. Proper education, physiotherapy and pulmonary rehabilitation are useful non pharmacologic measures that should not be neglected. Antibiotics are the most important treatment modality during exacerbations. Anti inflammatory therapy is gaining popularity as it is effective in reducing exacerbations and progression of the disease. Mucolytics has only limited role. Colonization by Pseudomonas aeruginosa and Nontuberculous Mycobacteria (NTM) are often overlooked and can result in rapid worsening. Resectional surgery can be curative in localized disease. In patients presenting with complications like hemoptysis, there is no contraindications for surgery even if disease is bilateral if general condition and PFT permit. Overall prognosis is better than COPD with a well planned therapeutic approach.

Key words : Bronchiectasis, NonCysticfibrosis(NonCF), High resolution computerized Tomography(HRCT), Allergic brochopulmonaryaspergillosis(ABPA),Potentially Pathogenic microorganism(PPM)

Bronchiectasis is characterized by an abnormal permanent dilatation of bronchi with destruction of the muscles and elastic tissue[1]. First description of the disease was by Laennec in 1819[2]. It was considered as an *orphan* disease with no definite management protocols or break through therapeutic approaches until recently[3]. The major studies in bronchiectasis were on CF, as it is the commonest in the West which was later extrapolated to non CF bronchiectasis. In India most bronchiectasis are non CF[4].

Recognizing lack of clear protocols in the diagnosis and management of non CF bronchiectasis, British Thoracic Society in 2010 published a guideline based on the available literature[5]. Since then there were lot of publications about non CF bronchiectasis highlighting importance of this common disease.

Prevalence

Some years ago it was thought that non CF bronchiectasis was becoming an extinct disease in most of the developed countries[6]. Wide spread availability of High Resolution Computerized Tomographic (HRCT) scanning of thorax disproved this concept. In India in spite of liberal antibiotic policy, it continues to be a major respiratory problem with significant morbidity and mortality[4].

Due to paucity of data, the overall prevalence of bronchiectasis in many parts of the world is still unknown. There are at least 1,10,000 non CF bronchiectasis in US as per their database. The overall prevalence was found to be 52 per 100,000 population[7]. As age advances prevalence also found to increase. In another study from US, annual

age adjusted hospitalizations due to bronchiectasis from 1993 to 2006 were 16.5 per 10,000 population. The annual increase in hospitalization varied from 2.4 for males and 3.0 for females. The annual rise in mortality rate was about 3% in a study from England and Wales. Both the hospitalization and mortality rates are most likely to be an underestimate of the actual facts. In a study conducted in India, 5% patients presenting with airway obstruction have bronchiectasis[8].

Pathogenesis and Pathology

The lung has direct communication with atmosphere which contains innumerable microorganisms and various pollutants. Fortunately the primary and secondary defense mechanisms are sufficiently equipped to keep the lower respiratory tract clean and sterile. Any event or series of events which can damage the bronchial epithelium or alter mucociliary escalator system can initiate a vicious cycle which can finally result in the irreversible damage of bronchi by recurrent transmural infection and inflammation[9]. In majority, the 4th and 5th generations of sub segmental bronchi are affected. Occasionally more proximal bronchi are affected as in Allergic Broncho Pulmonary Aspergilosis (ABPA)[10].The stagnation of secretions in the damaged bronchi with the associated infections, inflammation, thickening of the walls and neovascularization are responsible for most of the symptoms of bronchiectasis.

In 1898, Ewart classified bronchiectasis in to 3 forms based on the grossly dilated appearance of large airways: 1) Cylindrical 2) Fusiform 3) Saccular[9]. Later in 1950, it was regrouped by L M Reid based on the appearance to 1)Cylindrical with uniform dilatation of the affected bronchi 2) Varicose because of the resemblance to varicose veins 3) Cystic or Saccular characterized by dilated bronchi ending in cysts or grapelike clusters[1].(Fig 1). This classification has no clinical relevance except that cystic indicates more advanced form of the disease.

Causes

Bronchiectasis can occur from a variety of causes. Early identification of the cause may help in preventing the progression of the disease. Recognized causes of bronchiectasis are given in (table1)

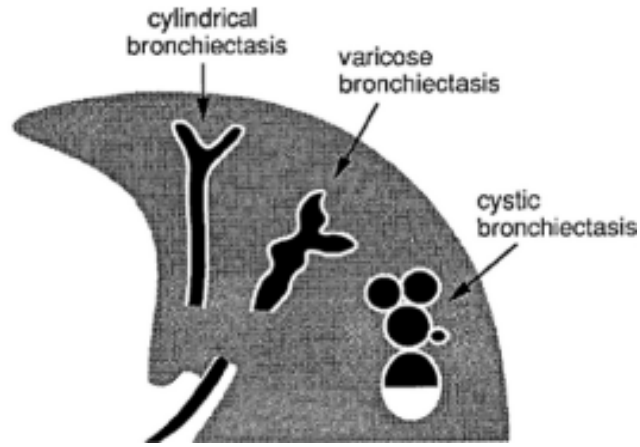

Fig 1

Clinical features

Most patients present with cough and sputum production. Expectoration of foul smelling sputum can occur in some patients. Hemoptysis, chest pain, breathlessness and weight loss are other associated symptoms[12].The three layered sputum with foamy upper layer, mucus middle layer and viscous purulent bottom layer is pathognomonic, but may not be seen in all patients. Some patients may present only with hemoptysis. This is often seen in upper lobe bronchiectasis and is known as bronchiectasis sicca. Symptoms can aggravate during exacerbations and on an average it is 1.5/year. Disease progression will be rapid if there is frequent exacerbations and colonization with bacteria. As the disease progress pulmonary hypertension and cardiac failure may follow. The most frequently described physical findings in bronchiectasis are finger clubbing and coarse crackles[13]. Air flow obstruction can also occur in association with bronchiectasis[14].

Any child presenting with persistent cough and sputum production lasting for more than 8 weeks, sputum culture yielding unusual organisms like S. aureus/ P.aeruginosa, atypical asthma, unexplained hemoptysis, recurrent or unresolving pneumonia, structural abnormalities of upper airways or esophagus needs evaluation for bronchiectasis[5].

Adults presenting with persistent cough without

Table 1: Commonly described causes of bronchiectasis[5]

Post infective	**Impaired mucociliary clearance**	**Immune deficiency**	**Exaggerated immune response**	**Congenital abnormalities of the bronchial wall**
1)Pneumonia 2)Tuberculosis 3)Pertussis 4)Measles	1)CF 2)Primary ciliary dyskinesia (PCD) 3)Young's syndrome	1)common variable immune deficiency syndrome(CVID) 2)Specific polysaccharide antibody deficiency 3)Secondary immunodeficiency, eg, malignancy (chronic lymphocytic leukemia) orHIV	1)Allergic Broncho Pulmonary Aspergillosis(ABPA) 2)Graft versus host disease 3)Inflammatory bowel disease (ulcerative colitis and Crohn's disease)	1)Mounier-Kuhn syndrome 2)Williams-Campbell syndrome 3)Marfan syndrome 4) Ehlers-Danlos syndrome
Inflammatory pneumonitis	**Fibrosis (traction bronchiectasis)**	**Mechanical obstruction**	**Connective tissue diseases**	**Miscellaneous conditions**
1)Aspiration of gastric contents 2)Smoke inhalation	1)Sarcoidosis 2)IPF	1)Foreign body 2)Tumor 3)Extrinsic compression(eg, lymph node)	1)Rheumatoid arthritis 2)SLE 3)Sjogren syndrome	1)Non Tuberculous Mycobacterium-MAC 2)Sequestration 3) Yellow nail syndrome 4)Alpha 1 AT deficiency

Primary etiologic factor cannot be established in 30-74% of patients[11].

obvious cause like smoking, unexplained hemoptysis, unusual microbes in sputum, recurrent pneumonia, associated COPD with recurrent and difficult to control infection are also candidates for bronchiectasis[5].

Diagnosis

The first part of the evaluation is identification of bronchiectasis, its extent and severity. This is mostly done by radiologic investigations. Second part is detection of underlying cause leading to bronchiectasis. This may be difficult but valuable in preventing further progression of the disease. Bronchiectasis is a final stage of lung damage and focus should be on its prevention.

Chest X-ray has only low sensitivity and specificity in the diagnosis of bronchiectasis[15]. In advanced disease thickened bronchi can be seen as tram line shadows in cylindrical bronchiectasis and ring shadows in cystic bronchography[15].The chest X-ray also helps in eliminating other diseases presenting as chronic cough. Earlier bronchogram was the gold standard investigation for the diagnosis of bronchiectasis. Today HRCT taken with the

standardized protocol is the radiologic investigation of choice[13]. Characteristic appearance of bronchiectasis in HRCT was first described by Nadich et al with minor modifications subsequently[16]. The most important evidence of bronchiectasis in HRCT is the signet ring sign where the airways internal diameter is larger than the accompanying pulmonary artery(Fig 2). Presence of dilated bronchi within a centimeter of pleural surface, lack of tapering of bronchi towards periphery, thickening of the walls, contour abnormalities like the tram line and cystic shadows, collections of secretions as evidenced by fluid levels are also indicators of bronchiectasis . Presence of few dilated bronchi alone has little relevance. The temporary dilatation and thickening of bronchial wall following pneumonia known as pseudo bronchiectasis may persist for 4 months. In order to avoid confusion it is advisable to do the scanning after a period of 4 months after pneumonia[17].

HRCT can also contribute to the specific diagnosis[18]. Bilateral bronchiectasis predominantly affecting lower lobe bronchi is suggestive of ciliary dyskinesia syndrome. Upper lobe bronchiectasis is more commonly seen in association with tuberculosis in India. Other causes for upper lobe bronchiectasis are ABPA and CF. Central bronchiectasis, presence of mucus plugging and tree in bud appearance are features of ABPA(Fig 3). Prominent nodularity with or without cavitations and tree in bud appearance often involving middle lobe are indicators of NTM. Focal bronchiectasis is more likely to be due to foreign body or slow growing neoplasm. An enlarged trachea with an internal diameter of more than 3 cm is diagnostic of Mounier-Kuhn syndrome. There is a scoring system put forward by Bhalla et al[19] for assessing severity of CF bronchiectasis which can also be used in non CF bronchiectasis. It is based on extent; severity of bronchial dilatation; wall thickening and the collection of fluid. MRI scan is a radiation free alternative to HRCT in the diagnosis and follow up[20]. Pulmonary function test is used for the functional assessment. Most common abnormality is airway obstruction with or without hyper-reactivity[5]. In the later stages of the disease there can be respiratory failure which can be detected by Pulse oximeter and Arterial Blood Gas (ABG) analysis

Box 1

Bronchiectasis HRCT finding

Direct signs

1) Signet ring sign

2) Lack of air way tapering > 2 cm distal to point of bifurcation

3) Air ways visible in peripheral lung fields

Indirect signs

1) Bronchial wall thickening

2) Mucoid impaction or fluid filled air ways-rounded/ tubular/ Y shaped structures with or without fluid levels

3) Bronchiolitis-ill defined centrilobular opacity with tree in bud configuration

4) Mosaic attenuation

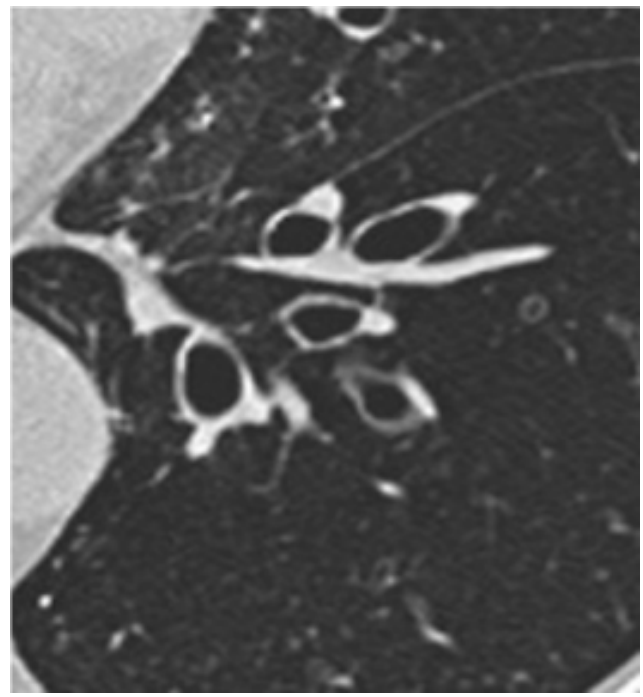

Fig 2 signet rig sign of bronchiectasis

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Recurrent respiratory infection is an accompaniment of bronchiectasis. Sputum culture is beneficial to identify the organism responsible for the infection. Occasionally colonization of lower respiratory tract by potentially

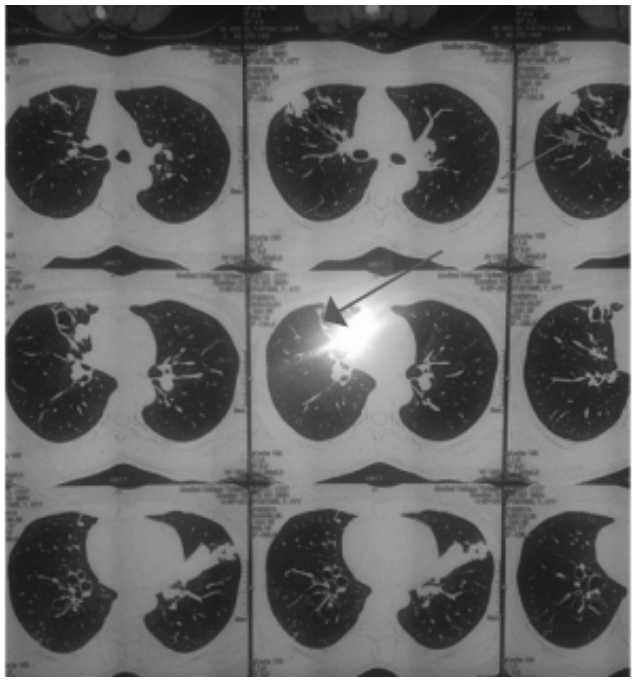

Fig 3 Bronchiectasis in ABPA
Areas of mucoid impaction (white arrow), bronchiectasis (red) arrow

pathogenic microorganisms (PPM) may occur. The common microorganisms causing infection and colonization are given in (Table 2)

Investigations in non CF bronchiectasis[5]

All patients	1) Chest X-ray
	2) Sinus radiography
	3) HRCT
	4) Routine blood tests and absolute eosinophil count
	5) Sputum smear for AFB
	6) Sputum eosinophils
	7) Sputum culture and sensitivity
	8) Pulse Oximetry
	9) Spirometry
	10) ECG /ECHO
	11) Immunologic tests, Immunoglobulin levels, specific antibody levels (both peptide &polysaccharide) & specific antibody response
	12) Aspergillus specific IgE & IgG
Selected patients	1) Bronchoscopy (localized bronchiectasis)
	2) Saccharine clearance test)/ nasal FeNO (cilia studies if abnormal)
	3) Sweat chloride test (Genetic studies if abnormal)
	4) Upper/lower GI scopy, Bairum swallow
	5) Semen analysis
	6) Second line immune deficiency test (accredited immunology lab)
	7) Tests for Collagen vascular disorders
	8) Alpha-1 Antitrypsin levels

Management

Main goal of therapy is to reduce the symptoms of the patient, improve the quality of life and prevent progression of the air way damage.

General measures

All patients have to be educated about the chronic nature of the disease, the risk of on and off exacerbation, importance of early treatment of infections and relevance of physiotherapy in clearing the secretions[5]. As in COPD, multidisciplinary pulmonary rehabilitation is beneficial in majority of patients. Non pharmacologic measures are as important as pharmacologic treatments.

Correction of underlying cause

Underlying cause if correctable has to be appropriately managed without any delay. Children with foreign body aspiration will benefit from its removal even if there is a delay in the diagnosis. Similarly patients with common variable Immunodeficiency, replacement therapy will prevent further progression. Early diagnosis of ABPA helps in preventing air way damage. Treatment options are limited in CF and Primary Ciliary Dyskinesia (PCD) syndromes at present. Fortunately in India it is very rare. Correction of underlying cause has little use in extensive disease.

Physiotherapy

Stagnation of secretions in the airways due to poorly functioning mucociliay clearance mechanism is responsible for most of the symptoms and the progression of the disease. Chest physiotherapy can be used to drain the secretions.

Table - 2

Organism	Nicotra et al 1995 (n=123)	Pasteur et al 2000 (n=150)	King et al 2007 (n=89)
H.influenza	30	37	45
P.Aeruoginosa	31	31	12
M.Catarrhalis	2.4	20	8
S.pneumoniae	10.6	13	7
S.aureus	7.3	14	4
No specific organism	-	23	21
Mycobacteria	17	0	2

A number of techniques are available for mobilizing secretions, such as postural drainage, Active Cycle Breathing Techniques (ACBT), positive expiratory pressure (PEP), oscillatory PEP devices, and high-frequency chest wall percussion. Regular chest physiotherapy in patients with non-CF bronchiectasis had small, but significant, benefits despite earlier negative systematic reviews[6]. ACBT is the most commonly used technique. Postural drainage can be combined with other physiotherapy measures for better results [5]. Patients who cannot do the postural drainage, autogenic drainage or modified postural drainage without head tilt can be tried.

Pharmacotherapy

Mucolytics

Most of the mucolytics has no definite role in non CF bronchiectasis. Bromhexine is probably the available best[5]. Human DNAse has no benefit and may be harmful in non CF bronchiectasis[5]. Inhalation of dry powder mannitol may facilitate clearance of secretions by altering the physical properties of the mucus[22]. Hypertonic saline (3% Sodium chloride) is an adjuvant that can be used to improve drainage of secretions before physiotherapy[29]. Both these agents can induce bronchospasm in some patients, which can be tackled by prior administration of nebulized bronchodilators[21].

Bronchodilators

A substantial number of patients can have associated bronchospasm which needs treatment by bronchodilators. Short and long acting beta 2 stimulants, methyl xanthenes and anticholinergic bronchodilators can be used to relieve bronchospsam. It is difficult to say which agent is superior due to paucity of well conducted studies. Montelukast has no proven role in non CF bronchiectasis.

Antibiotics

Acute exacerbation is a frequent accompaniment of all bronchiectasis and needs prompt treatment by antibiotics. As the common organisms causing infections are H.influenza, P.aeruginosa and S.aureus, one or two broad spectrum antibiotic covering these organisms is preferred. Amoxicillin plain or in combination with clavulanic acid is the best preferred initial antibiotic if FEV1 is >60% and sputum volume is less than 20 ml/day. Later depending on the culture and sensitivity reports antibiotics can be changed. Optimum duration of therapy is not defined, but most receive antibiotics for a period of 10-21 days depending on the severity and the nature of organism. Those with severe disease can be started on anti - pseudomonas antibiotic empirically. Very severe infections associated with respiratory failure and chronic infections not responding to oral antibiotics needs hospitalization and treatment with intravenous antibiotics. Coverage of anaerobic infection may be required in some patients. An inhaled antibiotic like gentamicin or tobramycin in combination with parenteral antibiotics has only limited benefit in the management of acute infections[22-24].

Prophylactic antibiotic is generally not preferred for fear of drug resistance and drug toxicities. Few recent studies are now favoring it especially in those with repeated infection requiring antibiotic use more than six times in a year. Some centers prefer that same antibiotic be given

for 7-14 days every month and certain others rotating antibiotic for 7-10 days every month[24]. Azithromycin 500 mg twice per week for 6 months was found to reduce the symptoms and number of exacerbations[25].

Coticosteroids

A Cochrane review concluded that there was insufficient evidence to recommend the routine use of Inhalational Corticosteroids (ICS) in adults with stable-state bronchiectasis, but a trial of this form of therapy may be justified in adults with difficult to control symptoms and in certain subgroups with significant air way hyper-reactivity[5]. The potential risks of high doses of steroids should not be neglected in such situation. In a recent study, combination inhaler of Long Acting Beta Agonist +ICS was found to be more superior in improving the quality of life compared to ICS alone[26]. Oral steroids are not recommended generally either in stable state or in acute exacerbations.

Vaccination

In children as well as adults there is little evidence favoring routine influenza vaccination. Such practices still prevail because of the benefit in the COPD patients which often has associated bronchiectasis. Pneumococcal vaccination is recommended in children and adults but it also does not have the support of well conducted clinical trials.[5]

Bacterial colonization

More than half of bronchiectasis patients have colonization with PPM of which the most harmful is Pseudomonas aeruginosa (PA) [27].The structural damage of airways, the micro organism's capacity for hyper mutability, formation of capsules, biofilims etc perpetuate colonization by PPM.

In colonization, bacterial organisms in bronchial mucosa doesn't evoke an inflammatory response. It can be classified as initial (1st positive culture done when there is no exacerbation), intermittent (alternate positive & negative culture by same PPM with at least one month between them) or chronic (3 or more consecutive culture positivity by same PPM separated by at least 1 month apart during a 6 month period while not on antibiotics). The latter will lead to chronic infection and inflammation by PPM followed by rapid deterioration of the general condition.

Intense antibiotic treatment with an intension to eradicate PA has to be tried even though evidences for this sort of treatment in non CF bronchiectasis is lacking. Oral ciprofloxacin(750 mg twice daily for 3 weeks), combination of two antipseudomonal antibiotics (piperacillin 4gm thrice daily+ tobramycin 3-5 mg /day for a period of 14-21 days), with or without inhalational antibiotics like gentamicin (80 mg twice daily) or tobramycin 3-5 mg / day cycles of 28 days) or colistin(1-3 million IU thrice daily) are the commonly recommended treatments[27].Nebulizing solutions are available for inhalational therapy. Intravenous preparation of antibiotics is not ideal for inhalation. Duration of inhalational therapy varies from 3-12 months.

Mycobacterium colonization

Colonization by opportunistic mycobacterium has been described in bronchiectasis. Occasionally this may later lead on to infection. A single AFB smear positivity alone is not an indication for treatment. Careful follow up is needed in such cases. Clinical deterioration, repeated culture and smear positivity, sudden decline in PFT and HRCT abnormalities like tree -in -bud appearance, cavitations of nodules along with failure to respond to usual treatment is an indication for treatment[5]. Among various opportunistic organism, MAC is the one that predominates in colonization and infection.

Surgical treatment

Surgery is considered only when medical management fails. It should be considered in localized disease when associated with hemoptysis, persistent infection, severe symptoms or failure to thrive. Comparison of surgery with conservative management is difficult due to paucity of studies[5]. With the improved surgical techniques it can be considered even in patients with bilateral disease if there are associated complications. Due consideration should be given to general condition and pulmonary function of these patients before selecting for surgery.

Prognosis

With the availability of effective antibiotics overall prognosis of patients has improved significantly. Prognosis of patients with bacterial colonization, ABG abnormality

and cor-pulmonale still remains poor. It is important to remember that a carefully designed therapeutic approach can alter the overall prognosis which is almost impossible in diseases like COPD.

References

1) Reid LM. Reduction in bronchial subdivision in bronchiectasis. Thorax 1950; 5:233247
2) Laennec RTH. A treatise on the disease of the chest. New York, NY: Library of the New York Academy of Medicine, Hafner Publishing, 1962; 78
3) Barker AF Bardana EJ. Bronchiectasis: update of an orphan disease. Am Rev Respir Dis 1988; 137:969978
4) Kabra SK et al Cystic fibrosis in India Pediatric pulmonology2007;42(12)1087-1094
5) 2010 BTS Guidelines on Non CF bronchiectasis Thorax 2010 Vol 65; supplement from the Finnish hospital discharge register. Eur J Public Health 1998;6:235e
6) Säynäjäkangas O, Keistinen T, Tuuponen T,et al. Evaluation of the incidence and age distribution of bronchiectasis from the Finnish hospital discharge register. Cent Eur J Public Health. 1998 Aug;6 (3):235-7
7) Weycker D, Edelsberg J, Oster G, et al Prevalence and economic burden of bronchiectasis. Am J RespirCrit Care Med 2004;169:A330.
8) JM Joshi,DV Shah et al Clinical profile of diseases causing chronic air flow limitation JAPI 2007;55:551-553
9) Cole PJ Inflammation a two edged sword the model of bronchiectasis ERJ Sppl 1986;147:6-15
10) Scadding JG. The bronchi in allergic aspergillosis.Scand J Respir Dis 1967;48:372-377
11) Pasteur MC, Helliwell SM, *et?al*.An investigation into causative factors in patients with bronchiectasis. A JRCCM 2000;162:1277-84.
12) MehmetAH,Aylin OU et al Clinical and Radiologic and functional evaluation of bronchiectasis 2011;6(3):131-136
13) AnneEODonnel bronchiectasis review article Chest 2008:138;815-823
14) Nicotra MB et al Clinical pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort *Chest*. 1995;108:955961
15) Feidman C Bronchiectasis new approaches to diagnosis and management Clinical Chest Medicine 2011;32(3):535-46
16) Naidich DP, McCauley DI, Khouri NF, et al. Computed tomography of bronchiectasis. J Comput Assist Tomogr 1982;6:437-44
17) Agarwal R Bronchiectasis in acute pneumonia Chest 2007;132:2054-55
18) Lee PH, Carr DH, Rubens MB, et al. Accuracy of CT in predicting the cause of bronchiectasis. ClinRadiol 1995;50:839e41
19) Bhalla M, Turcios N, Aponte V, et al. Cystic fibrosis: scoring system with thinsectionCT. Radiology 1991;179:783-788
20) Montella S ,Santamaria F et al Assessment of chest high field magnetic resonance imaging in children and young adults with noncysticfibrosiscronic lung disease compared to HRCT and corerelation with pulmonary function Invest Radiol 2009;44(9):532-538
21) Daviskas E, Anderson SD et al The 24-h effect of mannitol on the clearance of mucus in patients with bronchiectasis. Chest 2001:119;414
22) Bilton et al Addition of inhaled tobramycin to ciprofloxacin in acute exacerbation of PA in adult bronchiectaisChest 2006:130;1503
23) Expert Opinion pharmacotherapy 2000:8;3183
24) BarkerAF,Couch L et al Tobramycin solution for inhalation reduces sputum P.aeruginosa density in bronchiectasis AJRCCM 2000;162:481
25) Davies G, Wilson R. Prophylactic antibiotic treatment of bronchiectasis with azithromycin. Thorax. 2004;59:540-1.
26) Martínez-García MÁ et al Clinical efficacy and safety of budesonide-formoterol in non-cystic fi brosis bronchiectasisChest 2012;141: 461
27) JAngirill,CAgusti et al Bacterial colonization in patients with bronchiectasis,microbiologic pattern and risk factors Thorax 2oo2;57:15-19
28) Marinez- Garcia MA et al Treatment of Non CF bronchiectasis Arch. Bronconeumol. 2011;47: 599-609.
29) Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. Cochrane Database Syst Rev. 2006;CD002996.