Management of Non-CF Bronchiectasis (NCFB) in 21st century

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Outline

- Overview
- Workup including etiology
- Airway clearance
- Specific pharmacotherapy
- Immunization
- Exacerbations
- NIV
- Surgery

Definition

- Bronchiectasis is defined as permanently dilated airways due to chronic bronchial inflammation caused by inappropriate clearance of various microorganisms leading to recurrent or chronic infection
- Characterised by thickening of the bronchial wall, leading to increased sputum production and chronic cough
- It is a pathological endpoint that results from many disease processes

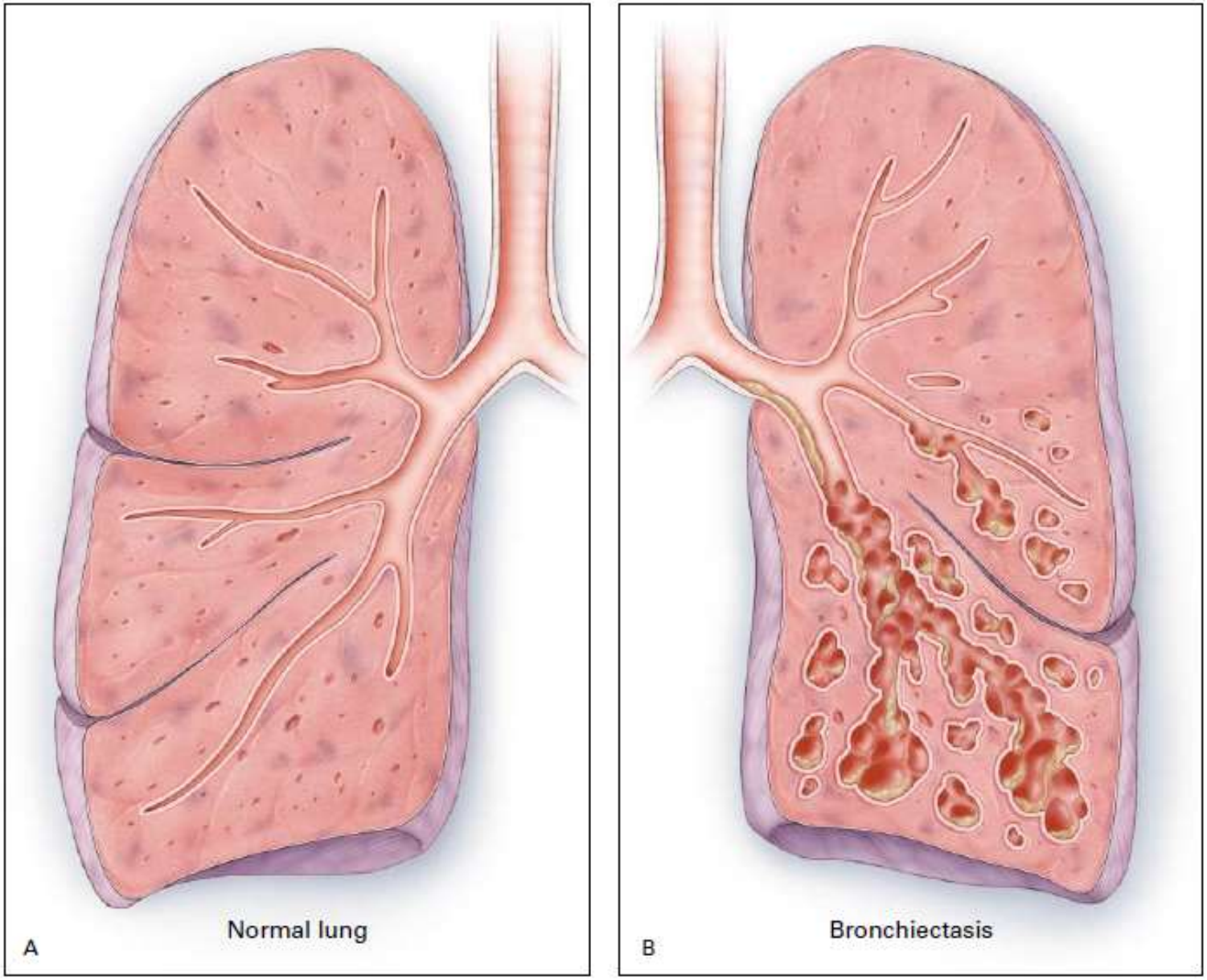


Figure 2. Normal Lung and Airways (Panel A) and the Lung of a Patient with Bronchiectasis (Panel B).
In Panel B, bronchiectasis is primarily in the lower lobe, which is the most common distribution. The saccular dilatations and grape-like clusters with pools of mucus are signs of severe bronchiectasis.

Bronchiectasis – Historical perspective

- Laennec first described bronchiectasis in 1819

  '…the dilated bronchi lose their natural shape, and present themselves under the form of a cavity, capable of containing a hemp-seed, a cherry-stone, an almond, or even a walnut'.

- A Famous patient with NCFB was William Osler, who died in 1919 of lung abscess and empyema – BXSIS was later confirmed on his autopsy

- 1920s - introduction of contrast bronchography by Jean Athanase Sicard, permitting precise imaging of destructive changes in airways

- 1950s - Lynne Reid linked bronchography with pathological specimens

- 1980s-1990s – advent of HRCT

Epidemiology

- Incidence varies widely: from 3.7/100000 children in New Zealand to 52/100000 adults in the USA to 272/100000 in older UK studies
- The prevalence increases with age – peaks at 80 yrs
- Prevalence fell from 1960s-1990s in the West but recently increasing prevalence documented (annual increase of 8.74%)
- Debatable whether this is a true increase in number of patients with bronchiectasis or increased recognition due to more frequent use of HRCT
- 15-30% patients labelled as “COPD” had bronchiectatic changes on HRCT

Epidemiology

- In US studies prevalence higher in women and remained so after logistic regression controlling for race and number of CT scans (odds ratio = 1.36)
- No Indian epidemiological data available
- In US, bronchiectasis was highest in prevalence in Asian populations - probably the result of high rates of severe respiratory infections at an early age, rather than a racial predisposition
- Reasons for this high prevalence include isolation, poverty, household overcrowding and poor living conditions

Etiology of NCFB

- Autoimmune disease
  - Rheumatoid arthritis
  - Sjögren's syndrome
- Cilia abnormalities
  - Primary ciliary dyskinesia
- Connective tissue disease
  - Tracheobronchomegaly (Mounier-Kuhn syndrome)
  - Marfan's disease
  - Cartilage deficiency (Williams-Campbell syndrome)
- Hypersensitivity
  - Allergic bronchopulmonary aspergillosis (ABPA)
- Immune deficiency
  - Immunoglobulin deficiency
  - HIV infection
  - Job's syndrome
- Inflammatory bowel disease
  - Ulcerative colitis
  - Crohn's disease
- Injury
  - Pneumonia/childhood infections
  - Aspiration
  - Smoke inhalation
- Malignancy
  - Chronic lymphocytic lymphoma
  - Stem cell transplantation; graft-versus-host disease
- Obstruction
  - Tumor
  - Foreign body
  - Lymphadenopathy
- Other
  - α_1-Antitrypsin deficiency
  - Yellow nail syndrome
  - Young's syndrome

Pathogenesis - Cole's vicious cycle

- Infection and inflammation are key components in the aetiopathogenesis of bronchiectasis

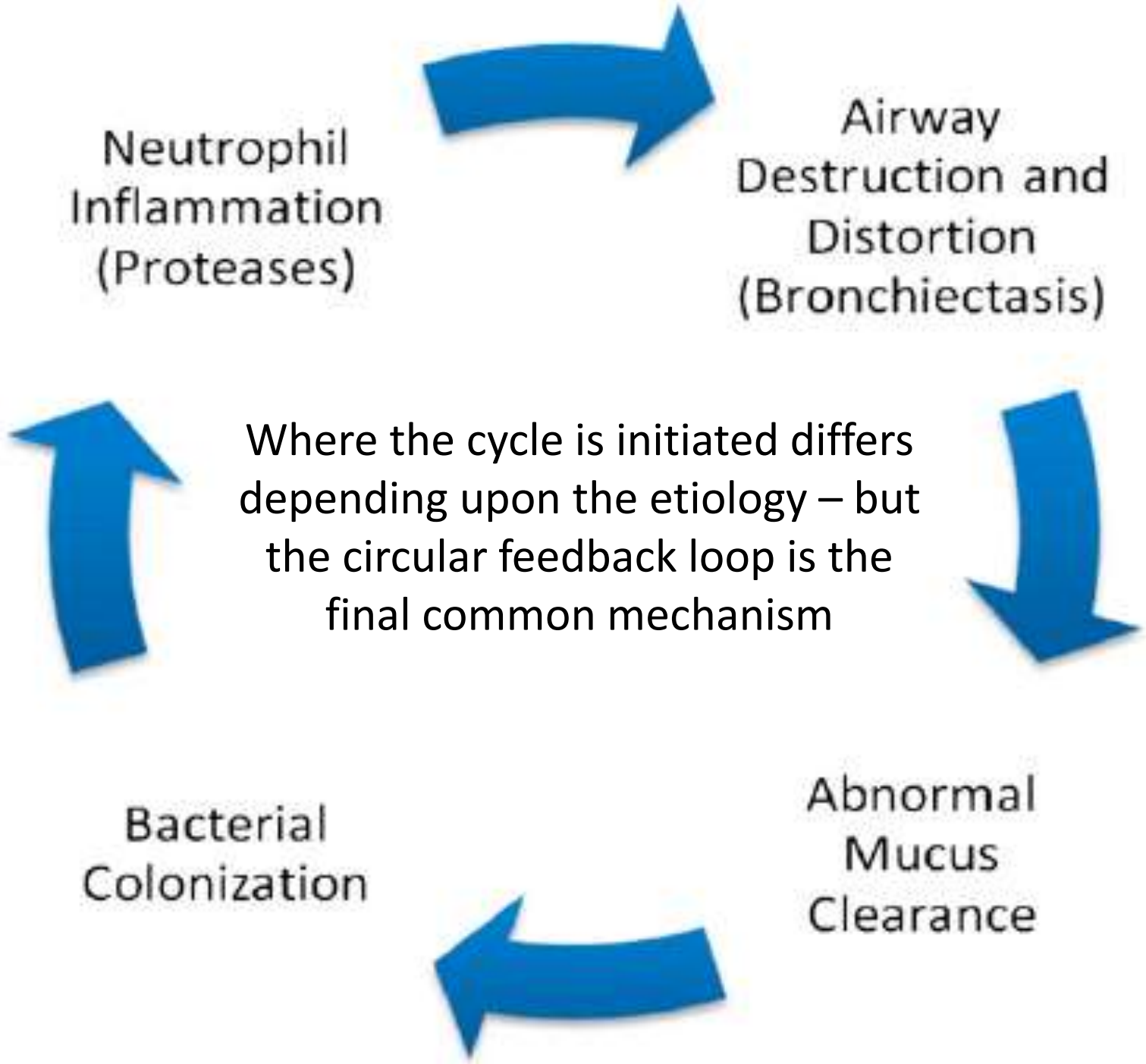
- A predisposed individual develops a robust inflammatory response to pulmonary infection or tissue injury – the resulting inflammation is partially responsible for structural damage to the airways

- Chronic bacterial infection elicits a systemic inflammatory response with local release of inflammatory cytokines (including TNF- and IL-8) causing migration of inflammatory cells such as neutrophils and lymphocytes

- Neutrophils release proteolytic enzymes e.g. neutrophil elastase and reactive oxygen species into the airway lumen which cause epithelial damage and stimulate mucous production

- The structural abnormalities allow for mucus stasis, which favors continued chronic infection

- Over time, retained sputum can cause mucous plugs and airway obstruction, obliteration, and damage resulting in more advanced bronchiectasis – and the vicious cycle persists


Neutrophil Inflammation (Proteases)
Airway Destruction and Distortion (Bronchiectasis)
Abnormal Mucus Clearance
Bacterial Colonization
Where the cycle is initiated differs depending upon the etiology – but the circular feedback loop is the final common mechanism

Workup

- Confirm the diagnosis of bronchiectasis in suspected patients
- Workup for etiology
- Sputum microbiology
- Lung function testing
- Role of bronchoscopy

Whom to Suspect?

- Chronic productive “wet” cough
- Purulent sputum
- Hemoptysis
- Frequent infective exacerbations
- “COPD” in non-smokers
- Young age of onset with long history
- Isolation of Pseudomonas, Burkholderia, etc.
- Poorly controlled asthma (ABPA)
- Clubbing, Coarse crackles

Imaging - CXR

- Rarely normal in overt clinical bronchiectasis (Only 7%)
- But lacks sensitivity and specificity
- CXR may be normal in upto 30% with “cryptic BXSIS” being treated as COPD
- Bronchial wall thickening may be seen as “tram-tracks” or ring shadows
- Crowding of the bronchi, loss of definition of the bronchovascular markings, oligaemia may also be seen
- In severe disease, honeycombing, air-fluid levels or fluid-filled nodules

CXR

- However may give clue to etiology:
  - Lobar/segmental collapse s/o obstruction
  - Congenital anomalies eg. Kartagener's, Mournier Kuhn syndrome, etc
  - Middle Lobe collapse/BXSIS in NTM
  - Fleeting infiltrates and mucus plugs in ABPA

Imaging - HRCT

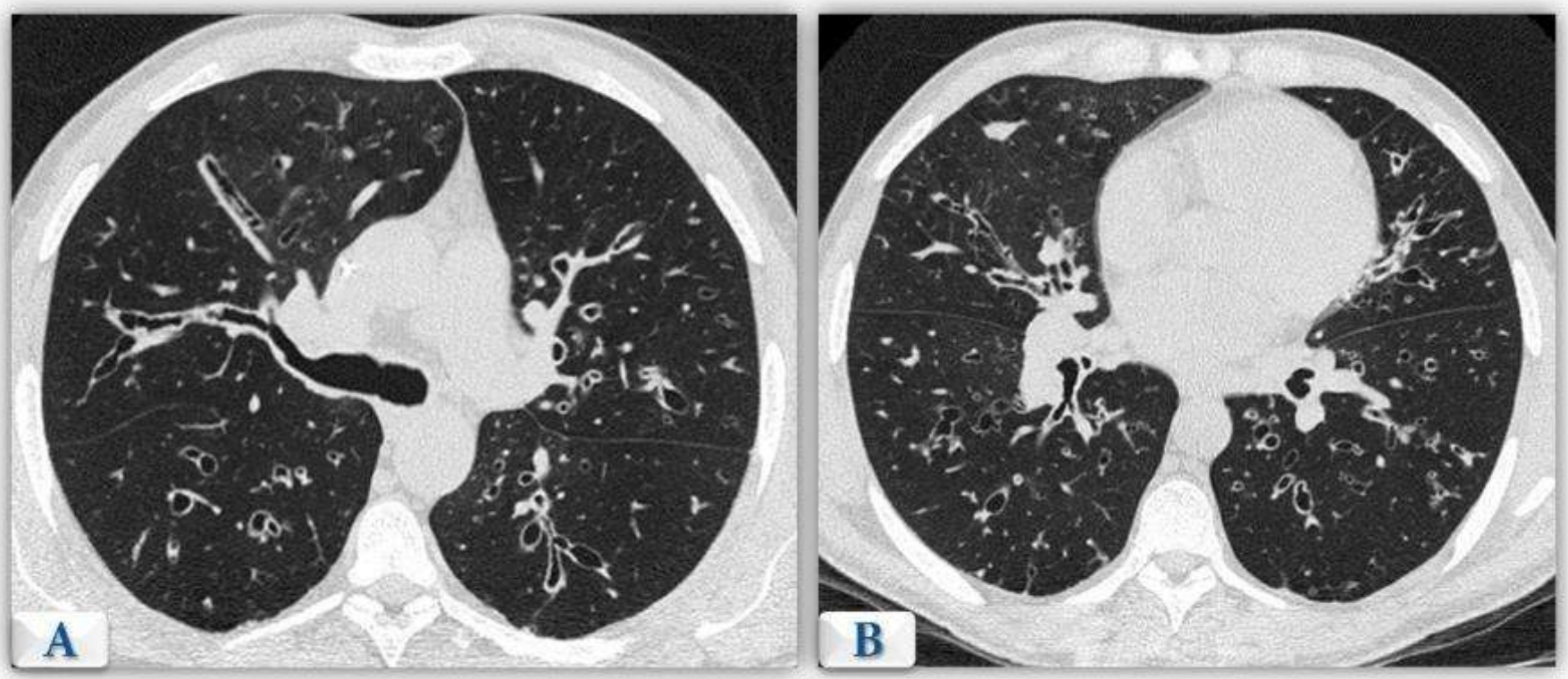
- HRCT has replaced bronchography as gold-standard of in-vivo diagnosis of BXSIS
- Criteria include:
  - The internal diameter of the bronchus is larger than that of its accompanying vessel; or
  - The bronchus fails to taper in the periphery of the chest
  - Peribronchial thickening i.e the wall thickness is equal to or larger than the diameter of accompanying vessel often present

HRCT - classification

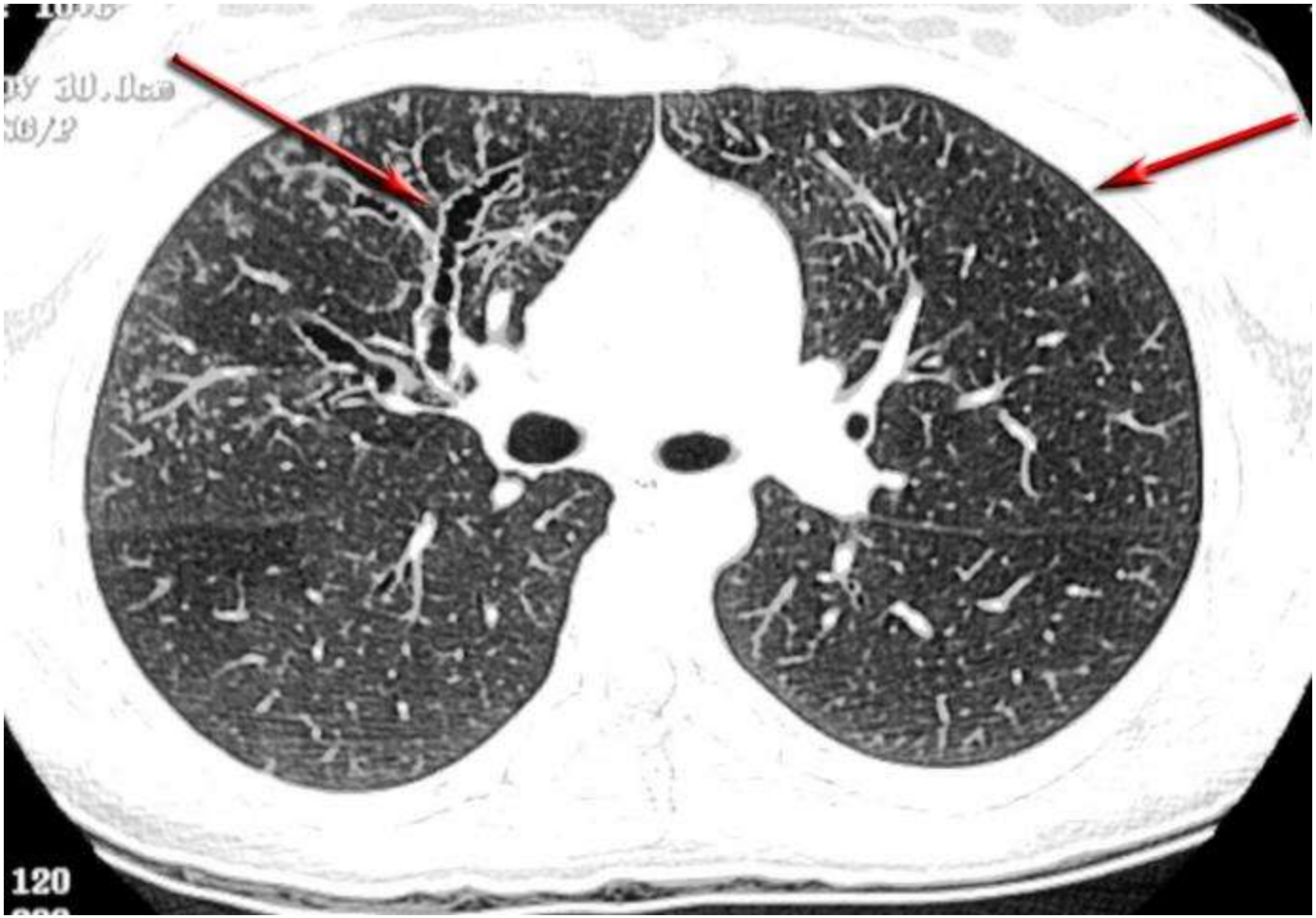
- Cylindrical (Tubular): Longitudinally ‘Tram lines’ or, in cross-section, thick-walled circular structures called ‘signet rings’
- Varicose: Typical beaded appearance
- Saccular (Cystic): Appear as a string of cysts, a cluster of grapes, or air-fluid levels due to retained secretions

All can coexist together

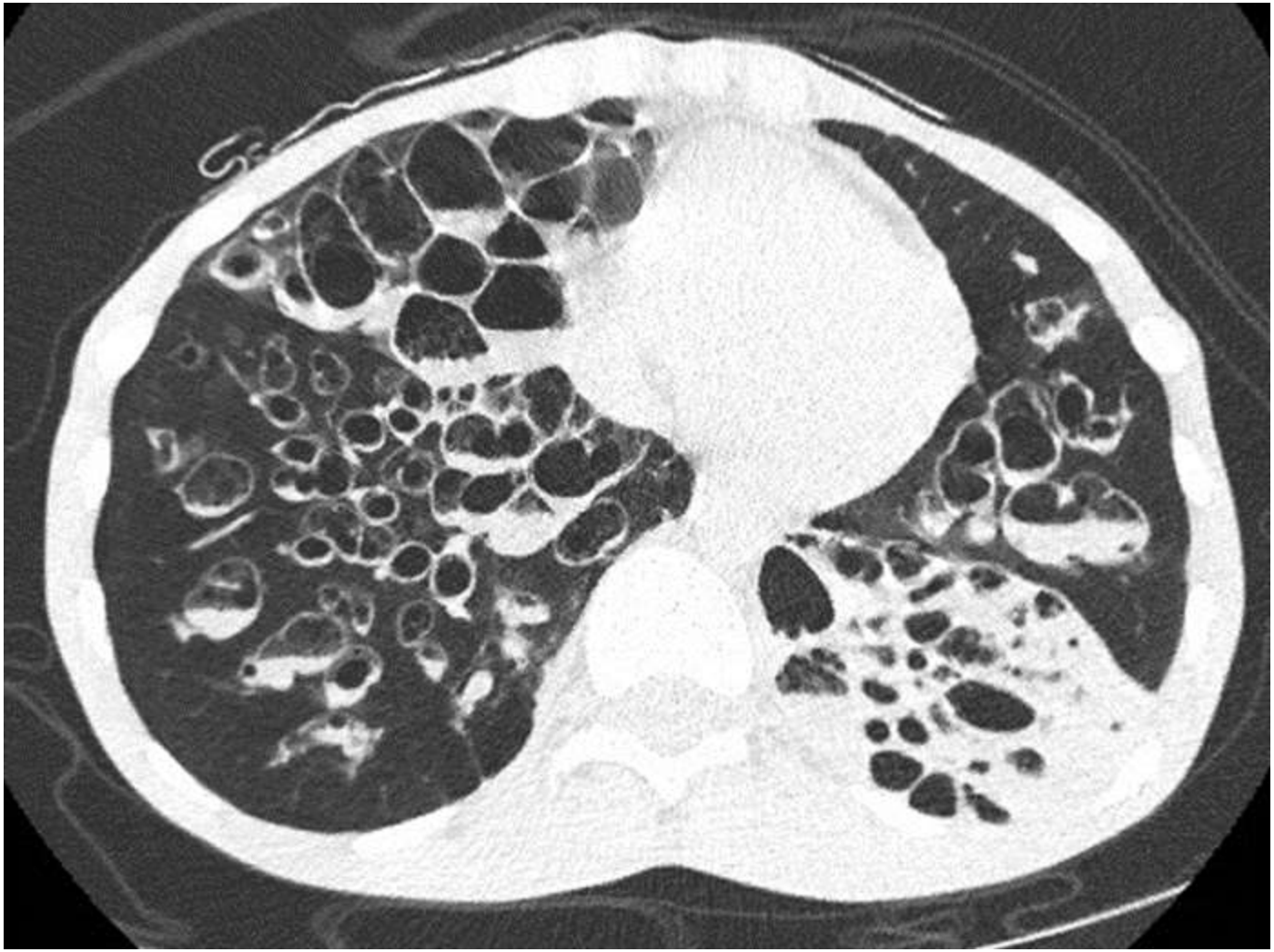
Cylindrical (Tubular) BXSIS



Varicose BXSIS



Saccular (Cystic) BXSIS



Other uses of HRCT

- Clue to etiology
  - Foreign body
  - Anatomical defects
  - Central BXSIS, upper lobe, HAM – ABPA
  - Middle lobes – NTM, PCD
  - Upper lobe, central – CF
  - Lower lobe emphysema – Alpha 1 antitrypsin
  - Centrilobular or random nodules, cavitation - NTM

Workup for etiology

- Must be done in all cases as any treatable cause eg. ABPA/ foreign body/ aspiration/ Ig deficiency etc must not be missed
- Also helps in genetic counselling and family screening
- Prognostication

Aetiology	Suggestive signs	Additional investigations	Expected abnormalities
Cystic fibrosis	Age under 40, malabsorption, poor growth, infertility in males, faecal masses on abdominal x-ray, diabetes	Sweat test	Positive sweat test: chloride concentration >60 mEq/l
		Genetic testing	2 CFTR mutations
		NPD	Abnormal NPD
Congenital disorders	Primary ciliary dyskinesia: sinusitis, otitis media, hearing loss, poor sense of smell, middle lobe predominance	Nasal epithelial brushing or biopsy	Abnormal ciliary beat pattern and frequency of ciliogenesis in culture
		Nasal NO measurement (>5 years of age)	Nasal NO <150 ppb
		Saccharin test (no clinical value anymore)	Increased time (>60 min) before tasting saccharin
	Marfan's syndrome: myopia, arachnodactylia, tall stature, thoracic deformations, glaucoma, abnormal joint flexibility, heart murmur	Search for major and minor indicators of the disorder	Diagnosis based on family history and a combination of major and minor indicators of the disorder, rare in the general population but occurring in one individual Genetic testing
	α1-Antitrypsin deficiency	α1-Antitrypsin deficiency	Levels below 150 mg/dl
	Anatomical deformations: visible on clinical examination	Thoracic imaging	Scoliosis or pectus excavatum
IBD	Diarrhoea, abdominal pain, haematochezia, weight loss, arthritis, pyoderma gangrenosum, primary sclerosing cholangitis	Colonoscopy with biopsy of pathological lesions	Biopsy inflammation suggestive of IBD
		Gastrointestinal advice	
Coeliac disease	Malabsorption, chronic diarrhoea, failure to thrive in children, fatigue, mouth ulcers, anaemia, weight loss, dermatitis herpetiformis	tTG antibodies and IgA	Positive tTG antibodies test without IgA deficiency
		Endoscopic duodenal or jenunal biopsies	Lymphocytic infiltration, villous atrophy
Post infectious	History of multiple pulmonary infections, tuberculosis or cough suppression	History or radiological evidence of previous infection	Radiological evidence of previous infection, history of cough suppression
		Sputum with smear and culture for acid-fast bacilli	Positive for *Mycobacterium avium* complex or other mycobacteria

Aetiology	Suggestive signs	Additional investigations	Expected abnormalities
Immunological disorders	Primary: recurrent infections, developmental delay in children, particular organ problems	IgG and subclasses, IgA, IgM	Decreased values, depending on age of patient. Adult: IgG<7.51 g/l; IgA<0.82 g/l; IgM<0.46 g/l
		Full blood count	Lymphocyte or granulocyte deficit
		Neutrophil antibody and function test, challenge with common humoral bacterial antigens	Result suggestive of antibody presence or impaired function
	Secondary: lung transplant patients, patients under immunosuppressive therapy, HIV	IgG and subclasses, IgA, IgM	Decreased values, depending on age of patient
		HIV testing	Positive HIV serology
ABPA	Asthma, wheezing, coughing up brownish mucoid plugs or blood, upper lobe predominance	Total IgE, sputum sample	Raised total IgE>1000 ng/ml, presence in sputum
		Specific serum IgE and IgG to *Aspergillus fumigatus*	Raised *Aspergillus* IgE and/or IgG
		Aspergillus fumigatus skin prick test	Positive skin prick test
Rheumatic disorders (RA, SLE, Sjögren, ankylosing spondylitis, relapsing polychondritis)	RA: rheumatoid nodule, arthritis, synovitis, specific skeletal deformities, rheumatoid nodule, other skin symptoms, etc	Autoimmune screening: rheumatoid factor, ANCAs, ANAs and anti-citrullinated peptide antibodies	Diagnosis depending on clinical examination combined with autoimmune screening results (positivity of rheumatoid factor, anti-citrullinated peptide antibodies, ANCAs, ANAs and/or ANA subtypes)
	SLE: malar rash, ulcers, neuropsychiatric symptoms, etc	Rheumatological advice	
COPD	Dyspnoea, Smoking history, Recurrent infections	Spirometry, bronchodilatation test	Obstructive lung function
Traction, obstruction, inhalation	Sarcoïdosis: fatigue, erythema nodosum, lupus pernio, arthralgia, uveitis, Bell's palsy, etc	Chest CT scan	Hilar lymphadenopathy, reticulonodular infiltrates, pulmonary infiltrates, fibrocystic or bullous changes, non-caseating granulomas, upper lobe predominance
	History of radiation therapy	Biopsy	
	History of inhalation/aspiration trauma	Bronchoscopy if imaging showing foreign body	
YNS, Young's syndrome, amyloidosis, endometriosis	YNS: yellow dystrophic nails, lymphoedema, sinusitis, pleural effusion	Exclusion diagnosis based on imaging and clinical findings	
	Young's syndrome: history of mercury contact, rhinosinusitis, infertility	Urological advice	
	Endometriosis: pelvic pain, infertility, cyclic haemoptysis/pain	Gynaecological evaluation	

Sputum Microbiology

- Gram stain and sputum bacterial culture must be done in all cases – specimens should reach lab < 3hrs to maximise yield of Pneumococcus and H. influenza
- Helps in:
  - Guiding choice of antibiotic therapy in case of future exacerbation
  - Helps in attempt to eradicate/decrease burden of colonisation
- P. aeruginosa shown to correlate with severe disease, a greater decline in lung function, more frequent exacerbations, and reduced quality of life compared with other bacteria*

*Evans SA et al. Lung function in bronchiectasis: the influence of Pseudomonas aeruginosa. *ERJ* 1996

Sputum Microbiology

- In adults, H influenzae is the most frequently isolated pathogen, being found in up to 35% of patients.
- Significantly higher isolation rate of Ps.aeruginosa than in children, this organism being isolated in 5-31% of patients.
- Others: S.pneumoniae, S.aureus, M.catarrhalis
- Aspergillus species found in a small number of patients
- CF: Staph spp., Burkholderia cepacia

Sputum for AFB/NTM

- NTM associated with BXSIS both as a cause and complication
- Inflamed airways in BXSIS predisposes to infection with environmental mycobacteria
- Sputum samples AFB stain and culture for TB/NTM should be sent in:
  - Fever, LoA, LoW
  - a new infiltrate or cavity on the chest x-ray which does not clear with regular antibiotics
  - unexplained deterioration in clinical status not responding to usual treatment
  - middle-aged or elderly women with chronic cough and CXR suggesting possible middle lobe bronchiectasis (M avium complex –> “Lady Windermere syndrome”)
  - adults with bronchiectasis due to PCD.

Lung function testing

- All patients with BXSIS should undergo spirometry with BDR +/- PEF
- Those with obstruction and significant BDR maybe candidates for ICS+LABA
- FEV1 should be monitored at least once a year
- Helps in monitoring treatment response and disease progression
- FEV1 < 30% with extensive BXSIS to be screened for lung Tx

Management

- General measures
- Specific treatment

Goals of Therapy:

  - Identify and treat underlying cause to prevent disease progression
  - Control symptoms and enhance QoL
  - Reduce exacerbations
  - Maintain lung function

Treatable Causes

- IVIg in humoral immunodeficiency
- ABPA
- NTM
- Autoimmune diseases

General measures

- Education
- Vaccination – Pneumococcal and Influenza vaccination (except in primary immunodeficiency)
- Hydration
- Nutrition
- Pulmonary Rehabilitation
- Airway clearance

Airway clearance

- The goal of airway clearance is to mobilize bronchopulmonary secretions and interrupt the vicious cycle of inflammation and infection
  - Inhaled agent
  - Postural drainage
  - Chest physiotherapy (manual or device)

Inhaled agents

Act by reducing osmolality of mucus and decrease its vscosity making it easier to clear

- Normal saline
- Hypertonic saline
- Mannitol
- Terbutaline
- Mucolytics

Normal Saline

- In an RCT*, the effectiveness of active cycle of breathing techniques (plus modified postural drainage) was significantly increased by the addition of nebulised NS prior to treatment.
- In this study, NS was not as effective as 7% hypertonic saline.
- However another study** found no difference between NS and 6 % hypertonic saline

*Kellett F, et al. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. Respir Med 2005

**Nicolson Chet al. The long term effect of inhaled hypertonic saline 6% in non–cystic fibrosis bronchiectasis. Respir Med 2012

Hypertonic saline

- Various studies using 3-14% saline available show contradicting results
- In addition to augmenting mucus clearance, hypertonic saline may have immune-modulating effects
- Reeves and colleagues showed reduced IL-8 concentrations in sputum and BAL in patients with CF after administration of hypertonic saline
- *In a 4 way RCT hypertonic saline resulted in significantly greater sputum weight and a greater reduction in sputum viscosity than other treatments alone (PEP/CPT)

*Kellett F, et al. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. Respir Med 2005

Mannitol

- *RCT of dry-powder mannitol nebulised 400 mg bd vs control
- The exacerbation rate was not significantly reduced on mannitol (rate ratio 0.92, p=0.31). However, time to first exacerbation was increased on mannitol (HR 0.78, p=0.022)
- SGRQ score also significantly improved on mannitol

*Bilton D et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax September 2014

Terbutaline

- Nebulised terbutaline may enhance sputum yield as a result of direct hydration and beta2 adrenergic stimulation
- In addition, the ensuing bronchodilation may enhance airway clearance by increasing expiratory flow rates and improving regional ventilation
- *The use of nebulised terbutaline (5 mg) immediately before CPT yielded significantly more sputum and increased radio aerosol clearance from the whole lung and from regions of interest than physiotherapy alone

*Sutton PP et al. Use of nebulised saline and nebulised terbutaline as an adjunct to chest physiotherapy. Thorax 1988

Mucolytics

- Study by O'Donnell and colleagues, who studied recombinant DNAse alpha in NCFB patients randomized to receive either dornase alfa or placebo for 6 months*
- Subjects treated with dornase alpha had more frequent exacerbations, hospitalizations, and antibiotic and corticosteroid courses than did subjects randomized to receive placebo

* O'Donnell et al. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase. Chest 1998;

Bromhexine

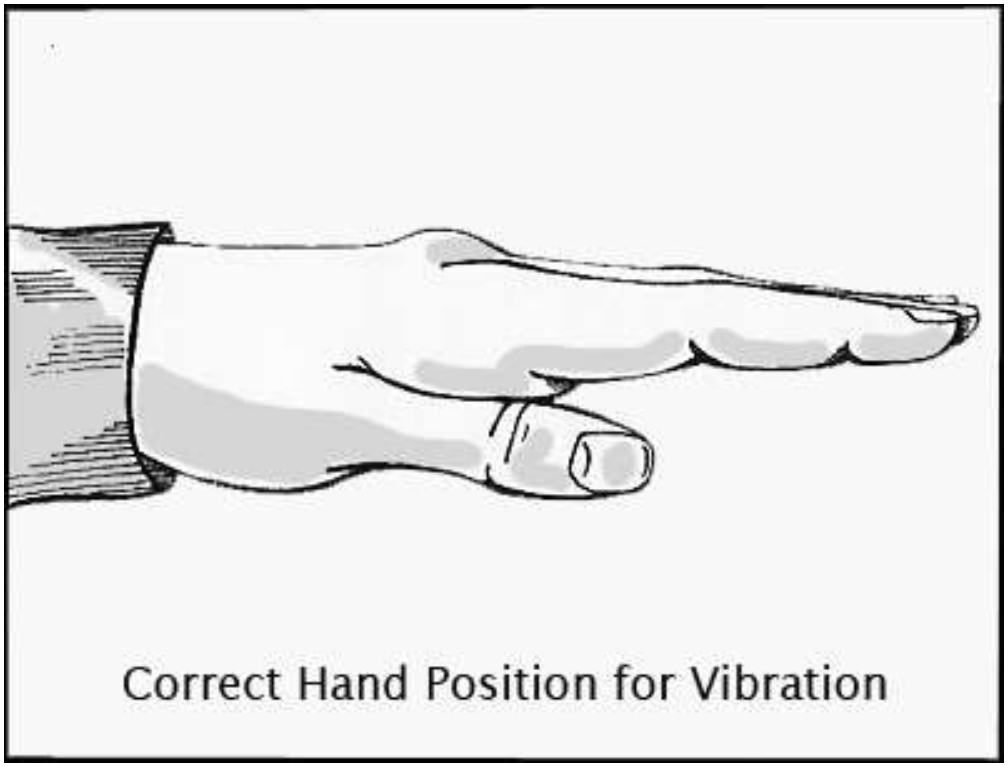
- Bromhexine has been studied in acute exacerbations as an adjunct to antibiotic therapy and showed additional benefit in lung function and sputum.
- *Cochrane database suggests that bromhexine is the only mucolytic so far shown to be beneficial in the treatment of bronchiectasis exacerbations.

* Crockett AJ et al. Mucolytics for bronchiectasis. Cochrane Database Syst Rev 2001;

Chest physiotherapy

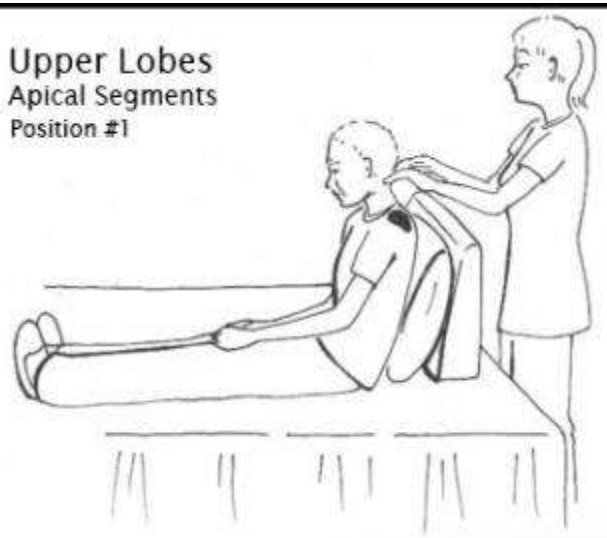
- Manual chest percussion
- High-frequency chest wall oscillation (HFCWO)
- Autogenic drainage
- Active cycle breathing with huff cough
- PEP device
  - PEP valve
  - Flutter device
  - Acapella
  - Lung flute

Postural drainage

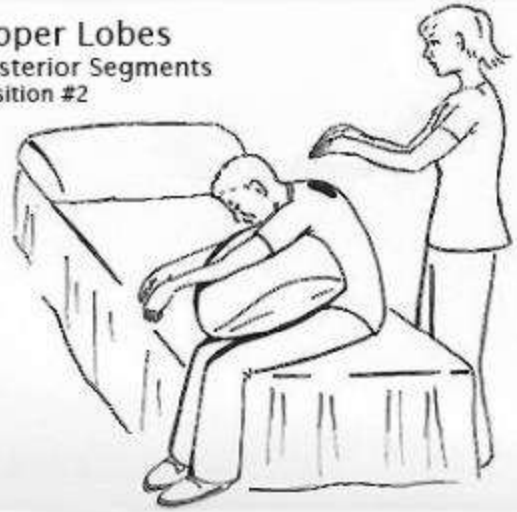


Correct Hand Position for Vibration

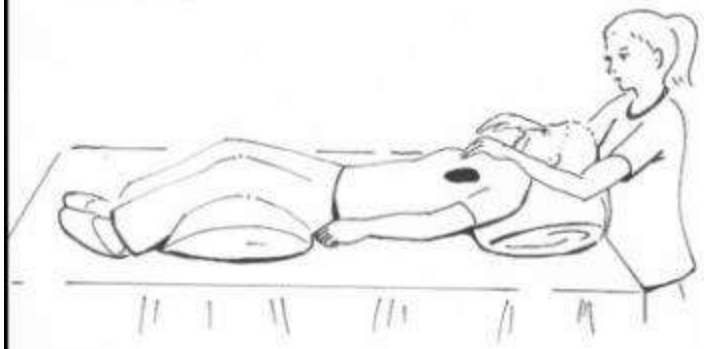
Upper Lobes
Apical Segments
Position #1



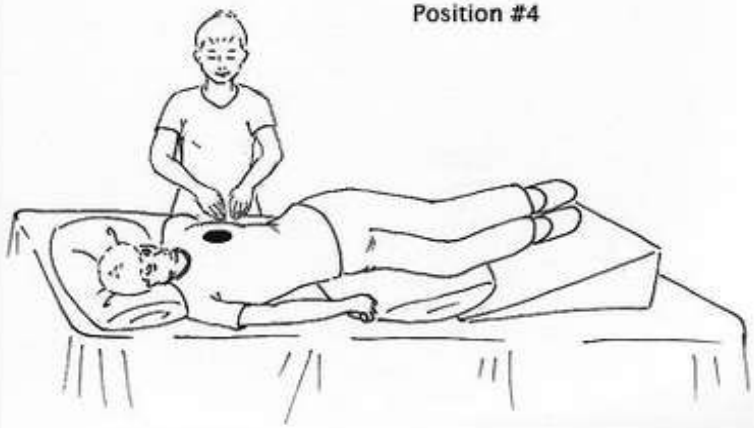
Upper Lobes
Posterior Segments
Position #2

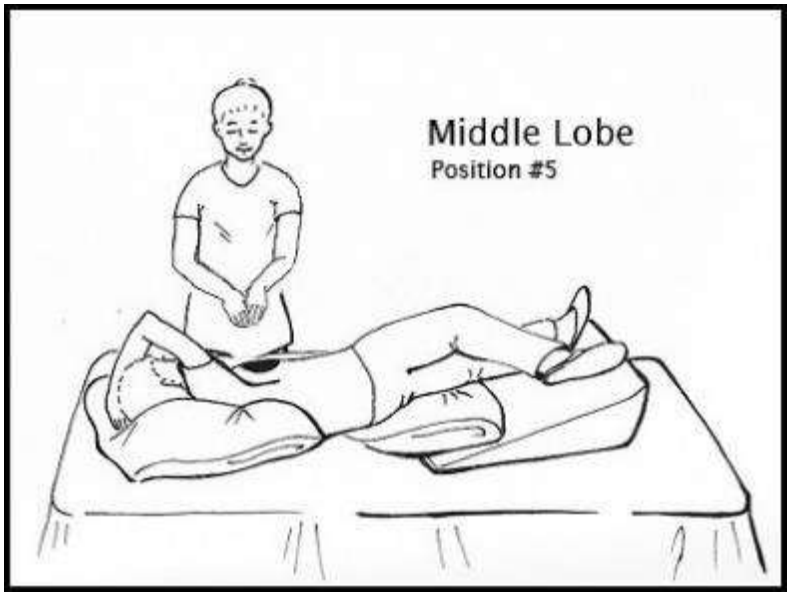


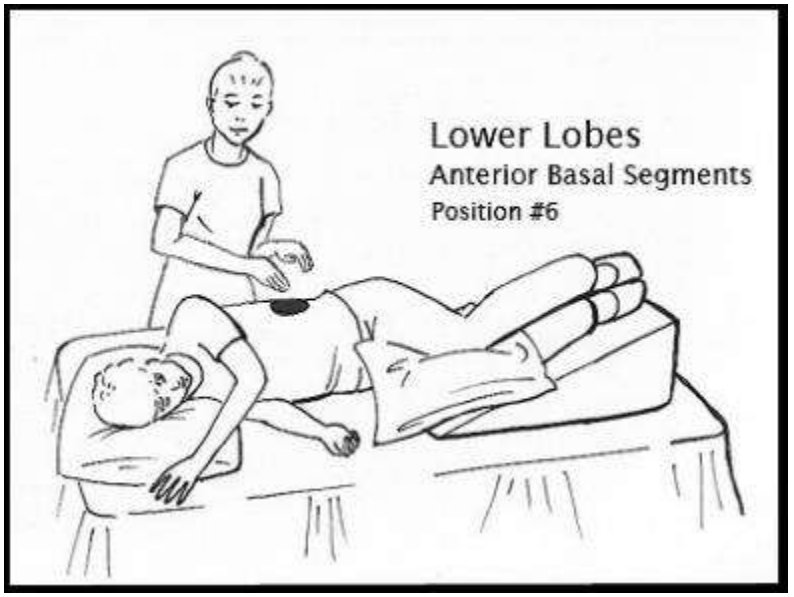
Upper Lobes
Anterior Segments
Position #3

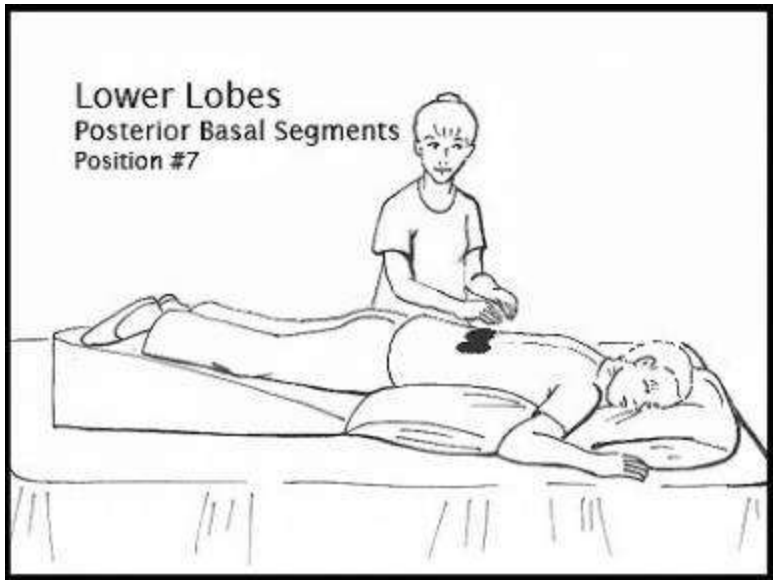


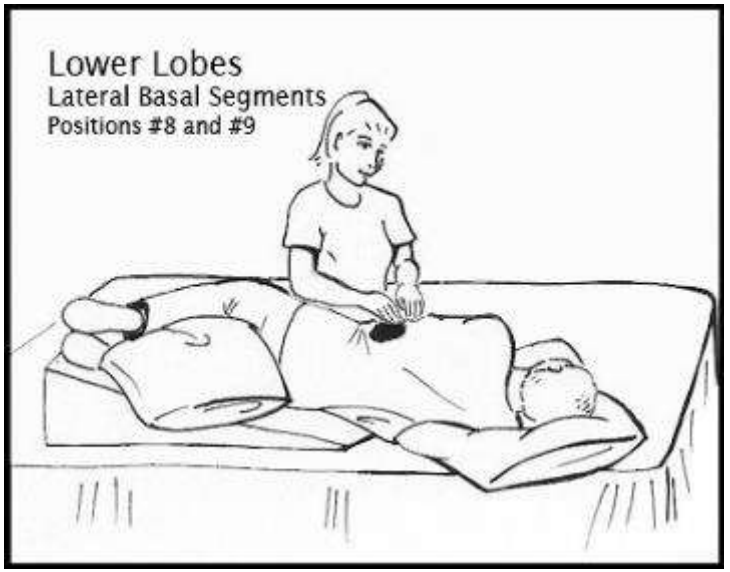
Lingula
Position #4

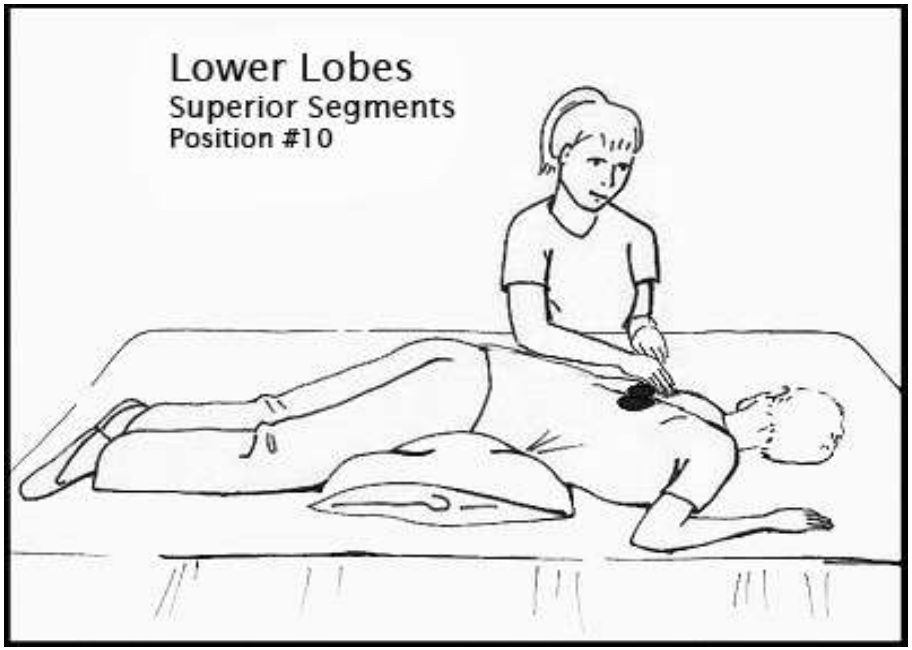



Middle Lobe
Position #5


Lower Lobes
Anterior Basal Segments
Position #6


Lower Lobes
Posterior Basal Segments
Position #7


Lower Lobes
Lateral Basal Segments
Positions #8 and #9


Lower Lobes
Superior Segments
Position #10

High frequency Chest-wall Oscillation

ABI “Vest” device

ABI Vest (HFCWO)

- The Vest® Airway Clearance System consists of an inflatable garment connected by Air Hoses to an Air Pulse Generator.
- The Air Pulse Generator rapidly inflates and deflates the inflatable garment, gently compressing and releasing the chest wall up to 25 times per second.
- Applies High Frequency Chest Wall Oscillation to entire thorax; moves mucus from peripheral to central airways
- Used independently or with minimal caregiver supervision
- Portable
- Time required: 15-30 minutes

PEP valve

- Positive Expiratory Pressure
- Action: splints airways during exhalation
- Can be used with aerosolized medications
- Technique dependent
- Portable
- Time required: 10 - 15 minutes

Flutter device

Flutter

- Action: loosens mucus through expiratory oscillation; positive expiratory pressure splints airways
- Used independently
- Technique dependent
- Portable
- May not be effective at low airflows
- Time required: 10 - 15 minutes

Acapella device

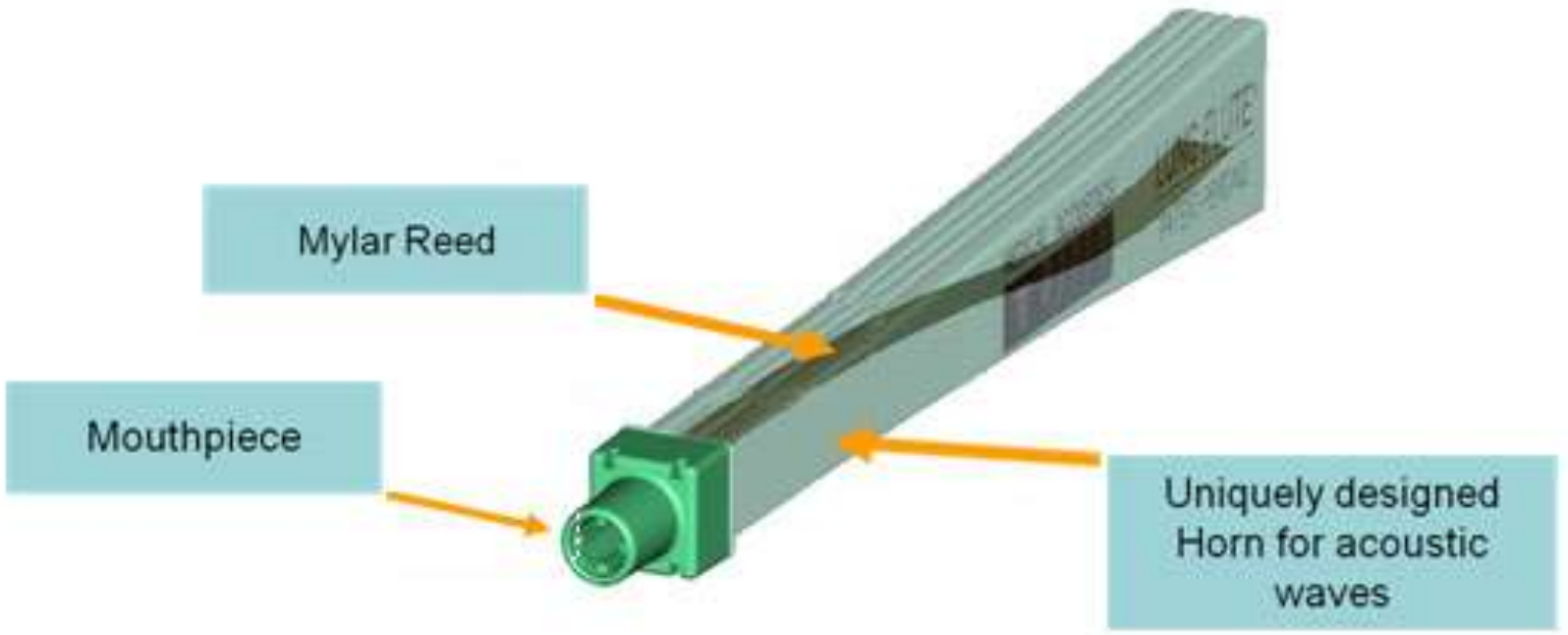
Acapella

- Acapella® is a small hand held device for airway clearance.
- It has both resistive and vibratory features, which help loosen and clear secretions.
- When patient breathes out through Acapella®, the airflow causes the rocker to move in one direction. The rocker, counterweighted by the magnet, moves back into its original position with a see-saw action.
- This causes the vibration and resistance to airflow which is then transmitted to lungs.

Acapella

- The resistance to airflow keeps the airways open to get air behind the sputum and help it move upwards
- The vibrations help to loosen secretions from airways and move them up more easily for effective chest clearance
- The dial at the end of Acapella® varies the resistance to airflow
- How to use:
  - 8-10 breaths followed by 1-2 huffs→cough out sputum
  - Repeat for 15-20 mins
  - 2 times/day

Lung Flute


Mylar Reed
Mouthpiece
Uniquely designed Horn for acoustic waves

1

- Sit up straight
- Tilt your head slightly downward

2

- Inhale a little deeper than normal
- Gently blow as if trying to blow out a candle
- You will hear the reed flutter

3

- Remove mouth piece
- Quickly inhale and blow again

4

- Wait for 5 seconds
- Take several normal breaths

5

- Repeat 20 sets of 2 blows for adequate results

6

- Several minutes of coughing should bring up secretions

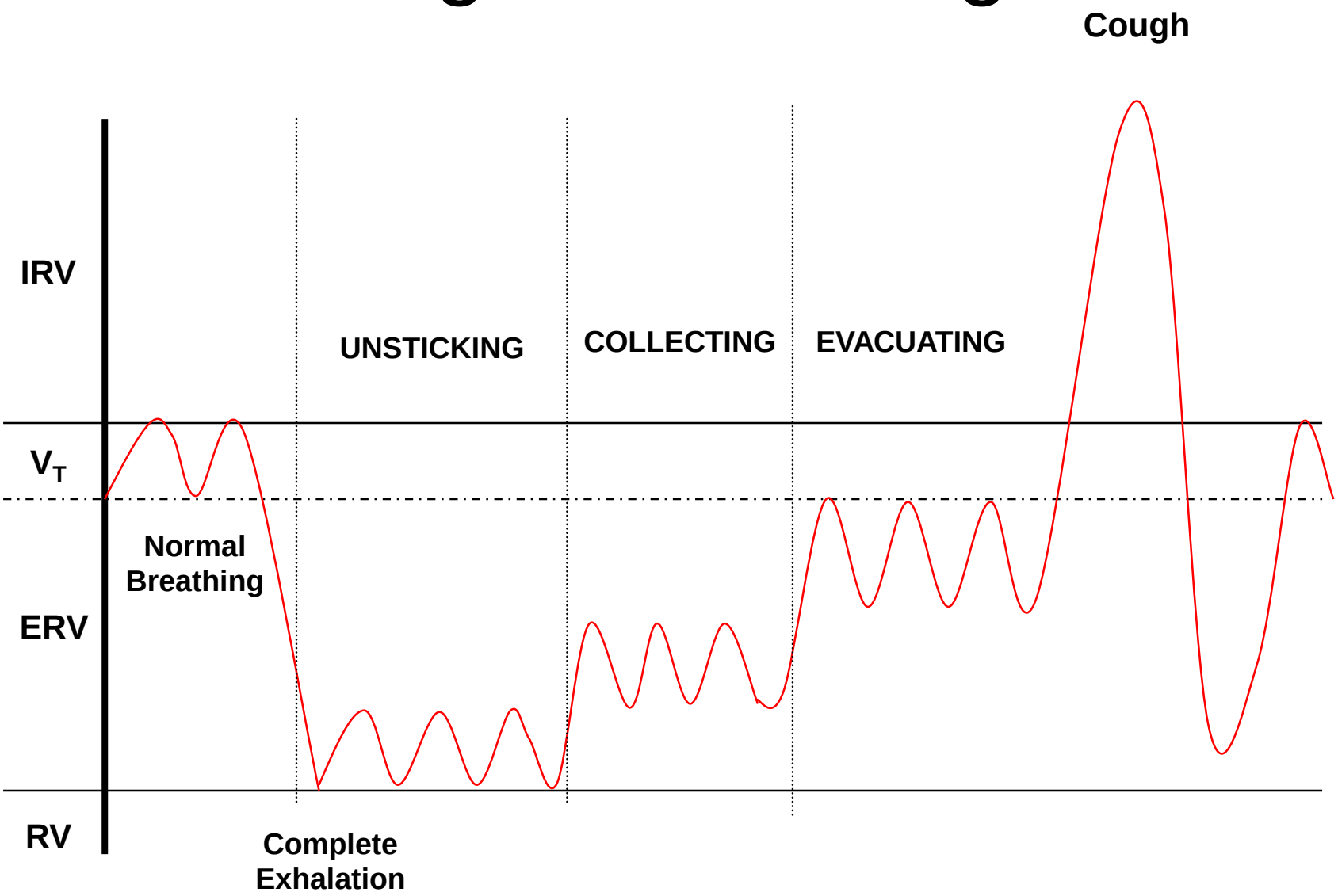
Active Cycle of Breathing Technique

- Three steps:
  - Breathing control
  - Thoracic expansion / breath hold
  - Forced expiratory technique
- May be performed independently
- Easily tolerated

Autogenic Drainage

- Three phases
  - Unsticking
  - Collecting
  - Evacuating
- May be performed independently
- Harder to teach and to learn than other techniques
- May be difficult for very sick patients to perform

Autogenic Drainage



Specific Therapy

- Antibiotics
- Macrolides
- Oral Steroids
- ICS (+/-LABA)
- Bronchodilators (SABA/LABA)
- Surgical management

Antibiotic Therapy

Antibiotics are used in the following scenarios:

- In an attempt to *eradicate* Pseudomonas and/or MRSA
- To *suppress* the burden of chronic bacterial colonization
- To *treat exacerbations*.

Rationale to use long term antibiotics

- The chronic host inflammatory response to colonising microbes causes lung damage and impaired bronchial clearance
- This further increases the colonising microbial load → Vicious cycle progresses
- Antibiotics can potentially halt the bacterial infection and subsequently limit ongoing neutrophilic inflammation
- Symptoms could thus be reduced by interrupting or stopping the “vicious cycle”

Antibiotics for eradication

- Colonisation with P.aeruginosa associated with worse symptoms and QoL scores and may lead to accelerated decline in FEV1*
- Retrospective review of 30 patients from 2004-2010**
- IV regime: IV gentamicin 4 mg/kg/d plus ceftazidime 2g tds for 2 wks, f/b nebulised colistin 2 MU bd for 3 months +/- oral ciproflox 500 mg bd for 3 months
- Oral regime: Ciprofloxacin 500 mg bd for 3 months f/b nebulised colistin 2 MU bd for 3 months
- Pseudomonas was initially eradicated in 80% of patients
- At follow-up (median, 14.3 mo), 50% remained Pseudomonas free.
- Reduced exacerbation frequency was seen (3.93 vs 2.09, p=0.002), even in the group that remained colonized with Pseudomonas

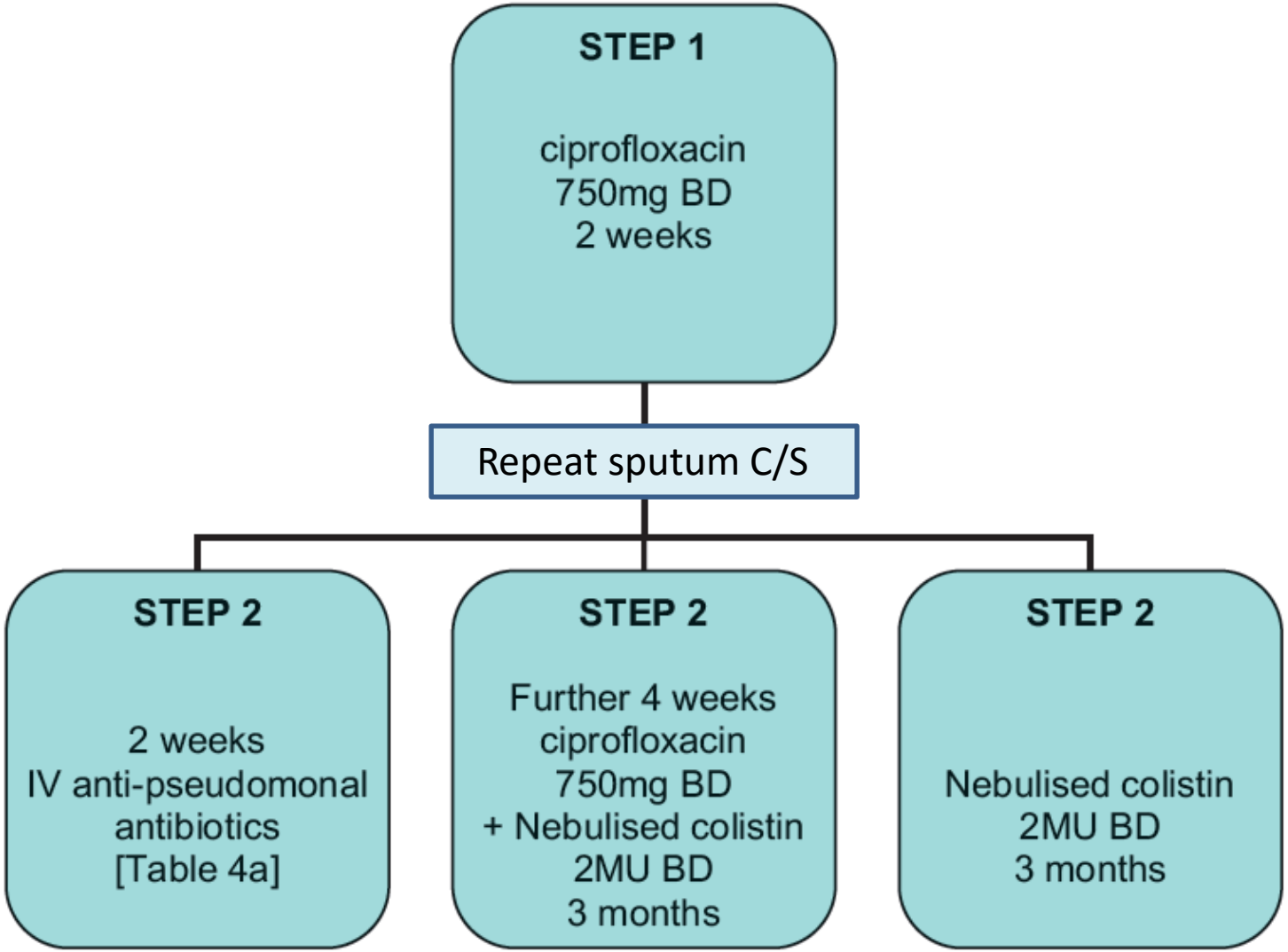
*Evans SA et al. Lung function in bronchiectasis: the influence of Pseudomonas aeruginosa. *ERJ* 1996

**White L et al. Outcomes of Pseudomonas eradication therapy in patients with non–CF bronchiectasis. Respir Med 2012

BTS guidelines – Good Practice Point

- In patients who have P.aeruginosa isolated for the first time, an attempt should be made to eradicate using 14 days of oral ciprofloxacin
- Failure to eradicate P aeruginosa with oral treatment may lead to consideration of intravenous and/or nebulised eradication therapy
- For patients in whom MRSA is isolated in the sputum, an attempt to eradicate the organism should be made with drug, dose and duration guided by local microbiological advice

Pasteur MC et al; BTS Bronchiectasis Non-CF Guideline Group. BTS guideline for non- CF bronchiectasis. Thorax 2010



Pasteur MC et al; BTS Bronchiectasis Non-CF Guideline Group. BTS guideline for non- CF bronchiectasis. Thorax 2010

Supressive long term antibiotics

- Direct relationship between bacterial load and levels of airway and systemic inflammation
- Goal of suppressive antibiotic therapy is to
  - reduce the bacterial burden for patients in whom eradication of the organism is not successful
  - improve symptoms
  - reduce the frequency of exacerbations

McShane PJ et al. Non-CF bronchiectasis. Am J Respir Crit Care Med, Sep 15, 2013

Supressive long term antibiotics

- May be oral/inhaled
- Defined as > 4 wks duration
- Inhaled antibiotics are safe and effective in reducing sputum bacterial load over the long term because they deliver a high concentration of drug to the airway
- Reduced systemic absorption, thereby reducing the risk of systemic side effects

McShane PJ et al. Non-CF bronchiectasis. Am J Respir Crit Care Med, Sep 15, 2013

Usual inhaled antibiotics used

Antibiotic	Dose	NS (ml)	Sterile water (ml)	Total volume (ml)	Daily adult dose
Colistin	1-2 MU	2-4	-	2-4	2 MU bd
Gentamicin (40 mg/ml)	80 mg	2	-	4	160 mg bd
Amoxicillin dry powder	500 mg	-	5	5	500 mg bd
Tobramycin (40 mg/ml)	80/160 mg	2/4	-	4/8	80-160 mg bd
Tobamist/Tobi	300 mg	-	-	5	300 mg bd
Ciprofloxacin DPI	32.5 mg	-	-	-	32.5 mg bd
Ciprofloxacin liposomal	100-150 mg	-	-	5 ml	100-150 mg od

Pasteur MC et al; BTS Bronchiectasis Non-CF Guideline Group. BTS guideline for non- CF bronchiectasis. Thorax 2010

Effects of long term antibiotics

- Greater reduction in sputum bacterial load – Maximum with aminoglycosides/ciplox
- Higher chance of achieving eradication
- Better clinician assessed response rates
- Fewer exacerbations (RR=0.72, p=0.01) and hospital admissions (NNT=5)
- No improvement in FEV1/FVC/SGRQ
- MC ADR – Bronchospasm (RR=2.96, p=0.01) – Seen in aminoglycosides, not with colistin/ciplox

*Brodt AM et al. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review ERJ 2014
** Evans DJ et al. Prolonged antibiotics for purulent bronchiectasis in children and adults. CochraneDatabase of Systematic Reviews 2007

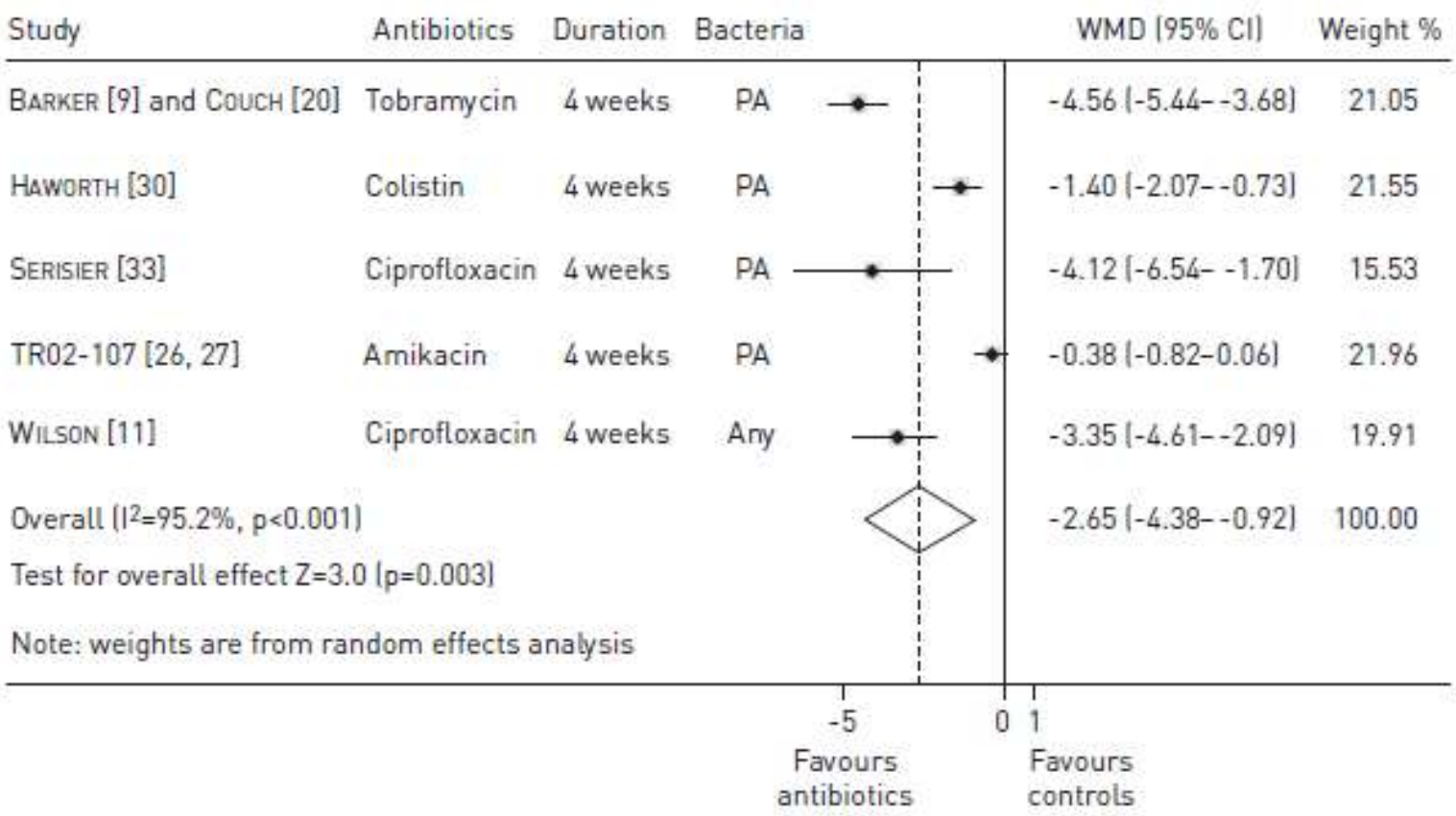


FIGURE 2 Effects of inhaled antibiotics on reduction of sputum bacterial load (log_{10} CFU·g^{-1}). WMD: weighted mean difference; PA: *Pseudomonas aeruginosa*.

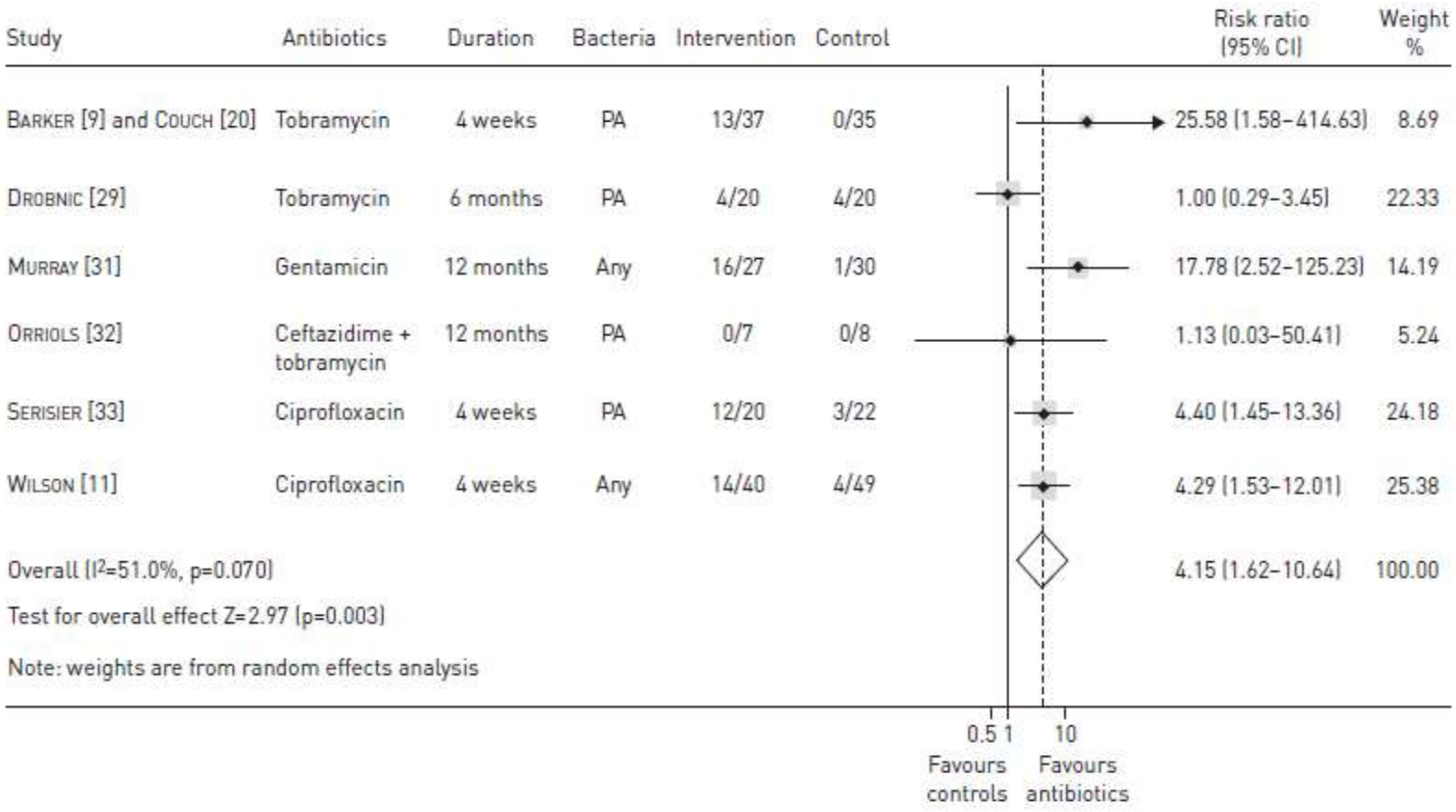


FIGURE 3 Effects of inhaled antibiotics on bacterial eradication from sputum. PA: *Pseudomonas aeruginosa*.

BTS recommendations - C

- Patients having >/=3 exacerbations per year requiring antibiotic therapy or patients with fewer exacerbations that are causing significant morbidity should be considered for long-term nebulised antibiotics.
- In such patients, long-term nebulised antibiotics should be considered if chronically colonised with P.aeruginosa.
- The choice of antibiotic should be guided by the antibiotic sensitivity results. Further studies are needed to address the optimal antibiotic choice and doses and duration required

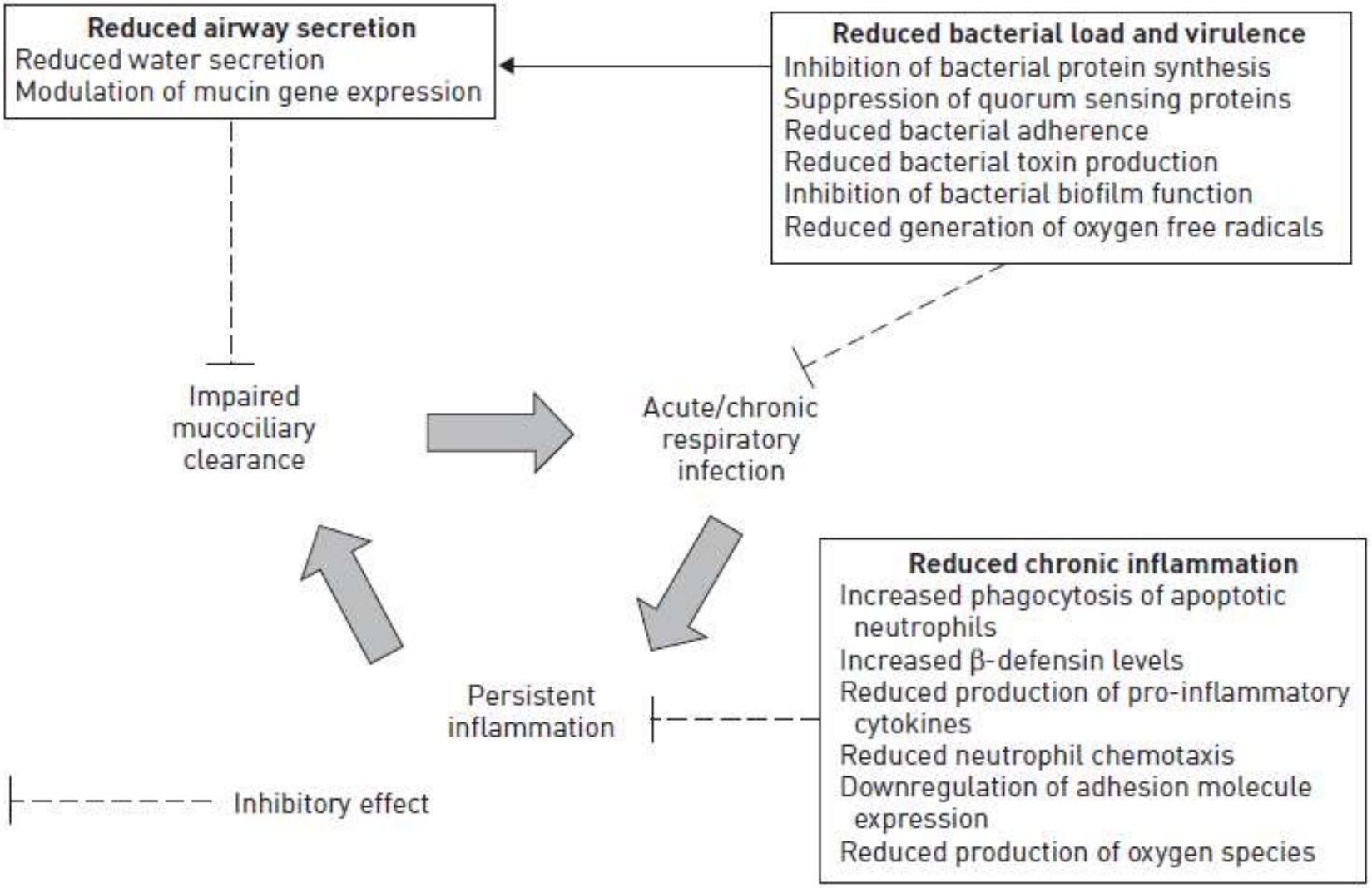
Macrolides

- Macrolide antibiotics belong to a family of compounds chemically characterised by the presence of a macrocyclic lactone ring of >12 elements
- Given their favourable bioavailability via the oral route, excellent tissue penetration and broad efficacy against many lung pathogens macrolides are widely used as first-line agents in the therapy of respiratory infections

Macrolides

- The immunomodulatory and antiinflammatory effects of macrolides, are seen with 14-(erythromycin, clarithromycin and roxithromycin) and 15-members (azithromycin)
- Reduce airway mucus secretion and viscosity
- Decrease airway neutrophil accumulation through a reduction in pro-inflammatory cytokines expression and adhesion molecule production
- May take several weeks to manifest
- First observed in DPB – now DoC for DPB

Macrolides break the vicious cycle



Studies on macrolide therapy

Effect of Azithromycin Maintenance Treatment on Infectious Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis
The BAT Randomized Controlled Trial

Azee 250 mg od

Erythromycin 400 mg bd

Effect of Long-term, Low-Dose Erythromycin on Pulmonary Exacerbations Among Patients With Non–Cystic Fibrosis Bronchiectasis
The BLESS Randomized Controlled Trial

Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial

Azee 500 mg 3 times/wk

Conroy Wong, Lata Jayaram, Noel Karalus, Tam Eaton, Cecilia Tong, Hans Hockey, David Milne, Wendy Fergusson, Christine Tuffery, Paul Sexton, Louanne Storey, Toni Ashton

Summary of results from studies

- Decreased exacerbation rates (33 - 43%) in patients with >/=2 exacerbations/year
- FEV1 and FEVC improvement (1% per 3 months)
- Better QoL (SGRQ and LRTI-VAS score) – only BAT
- Decrease in sputum weight – only BLESS
- More GI side-effects
- Higher risk of macrolide resistance (25-50% increase)
- No other side effects significant

Potential hazards of macrolide therapy

- Ototoxicity
- Drug Interactions
- QT prolongation and arrhythmias (esp in elderly)
- Hepatotoxicity (rare)
- Macrolide resistance in the community
- Risk of pathogenic MDR NTM eg Mycobacterium abscessus

In whom should macrolides be used?

- Selected patients with non-CF Bronchiectasis with >/= 2 exacerbations per year requiring antibiotics/hospital admission
- Preferably avoid in elderly/drug interactions
- Duration – at least 6 months

ICS

- Anti-inflammatory effects – shown to decrease sputum inflammatory markers (leukocyte density and IL-1, IL-8, and LTB4)
- Role well established in Asthma
- However earlier Cochrane review of ICS in CF showed no benefit and affected growth in children

Effects of ICS in non-CF BXSIS

- Improvement in clinical parameters – sputum/dyspnea and HRQoL
- Decrease in sputum volume
- Small improvement in FEV1 and FVC (0.09L) at 6 months – not sustained later
- No effect on exacerbation rates
- No sufficient evidence to recommend long term use

Kapur N, Bell S, Kolbe J, Chang AB. Inhaled steroids for bronchiectasis. *Cochrane Database of Systematic Reviews 2009*

ICS + LABA

- Double blind parallel group RCT of 40 patients compared budesonide with formoterol+budesonide for 6 months
- Improvement seen in – SGRQ, symptom control
- No change in exacerbation rates/FEV1

Goyal V et al. Combination inhaled corticosteroids and long-acting beta2-agonists for children and adults with bronchiectasis. *Cochrane Database of Systematic Reviews 2014*