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

Dr R Lakshmi Narasimhan
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
  \(\alpha_1\)-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
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 up to 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) BXGIS
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
<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Suggestive signs</th>
<th>Additional investigations</th>
<th>Expected abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
<td>Age under 40, malabsorption, poor growth, infertility in males, faecal masses on abdominal x-ray, diabetes</td>
<td>Sweat test</td>
<td>Positive sweat test: chloride concentration &gt;60 mEq/l</td>
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<td></td>
<td></td>
<td>Genetic testing</td>
<td>2 CFTR mutations</td>
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<td></td>
<td></td>
<td>NPD</td>
<td>Abnormal NPD</td>
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<tr>
<td>Congenital disorders</td>
<td>Primary ciliary dyskinesia: sinusitis, otitis media, hearing loss, poor sense of smell, middle lobe predominance</td>
<td>Nasal epithelial brushing or biopsy</td>
<td>Abnormal ciliary beat pattern and frequency of ciliogenesis in culture</td>
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<tr>
<td></td>
<td></td>
<td>Nasal NO measurement (&gt;5 years of age)</td>
<td>Nasal NO &lt; 150 ppb</td>
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<td></td>
<td></td>
<td>Saccharin test (no clinical value anymore)</td>
<td>Increased time (&gt;60 min) before tasting saccharin</td>
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<tr>
<td></td>
<td></td>
<td>Search for major and minor indicators of the disorder</td>
<td>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</td>
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<td>Genetic testing</td>
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<td>Levels below 150 mg/d</td>
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<td></td>
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<td>Scoliosis or pectus excavatum</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>Anatomical deformations: visible on clinical examination</td>
<td>α1-Antitrypsin deficiency</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Thoracic imaging</td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>Diarrhoea, abdominal pain, haematochezia, weight loss, arthritis, pyoderma gangrenosum, primary sclerosing cholangitis</td>
<td>Colonoscopy with biopsy of pathological lesions</td>
<td>Biopsy inflammation suggestive of IBD</td>
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<td></td>
<td></td>
<td>Gastrointestinal advice</td>
<td></td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>Malabsorption, chronic diarrhoea, failure to thrive in children, fatigue, mouth ulcers, anaemia, weight loss, dermatitis herpetiformis</td>
<td>tTG antibodies and IgA</td>
<td>Positive tTG antibodies test without IgA deficiency</td>
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<tr>
<td></td>
<td></td>
<td>Endoscopic duodenal or jejunal biopsies</td>
<td>Lymphocytic infiltration, villous atrophy</td>
</tr>
<tr>
<td>Post infectious</td>
<td>History of multiple pulmonary infections, tuberculosis or cough suppression</td>
<td>History or radiological evidence of previous infection</td>
<td>Radiological evidence of previous infection, history of cough suppression</td>
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<tr>
<td></td>
<td></td>
<td>Sputum with smear and culture for acid-fast bacilli</td>
<td>Positive for Mycobacterium avium complex or other mycobacteria</td>
</tr>
<tr>
<td>Aetiology</td>
<td>Suggestive signs</td>
<td>Additional investigations</td>
<td>Expected abnormalities</td>
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<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Immunological disorders</td>
<td>Primary: recurrent infections, developmental delay in children, particular organ problems</td>
<td>IgG and subclasses, IgA, IgM</td>
<td>Decreased values, depending on age of patient. Adult: IgG&lt;7.51 g/l; IgA&lt;0.82 g/l; IgM&lt;0.46 g/l. Lymphocyte or granulocyte deficit. Result suggestive of antibody presence or impaired function.</td>
</tr>
<tr>
<td></td>
<td>Secondary: lung transplant patients, patients under immunosuppressive therapy, HIV</td>
<td>Full blood count, Neutrophil antibody and function test, challenge with common humoral bacterial antigens</td>
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</tr>
<tr>
<td>ABPA</td>
<td>Asthma, wheezing, coughing up brownish mucoid plugs or blood, upper lobe predominance</td>
<td>IgG and subclasses, IgA, IgM</td>
<td>Decreased values, depending on age of patient. Positive HIV serology.</td>
</tr>
<tr>
<td></td>
<td>HIV testing</td>
<td>Total IgE, sputum sample</td>
<td>Raised total IgE&gt;1000 ng/ml, presence in sputum.</td>
</tr>
<tr>
<td></td>
<td>Specific serum IgE and IgG to Aspergillus fumigatus</td>
<td>Aspergillus fumigatus skin prick test</td>
<td>Raised Aspergillus IgE and/or IgG.</td>
</tr>
<tr>
<td></td>
<td>Autoimmune screening: rheumatoid factor, ANCA, ANAs and anti-citrullinated peptide antibodies</td>
<td>Rheumatological advice</td>
<td>Positive skin prick test.</td>
</tr>
<tr>
<td></td>
<td>Diagnosis depending on clinical examination combined with autoimmune screening results (positivity of rheumatoid factor, anti-citrullinated peptide antibodies, ANCA, ANA and/or ANA subtypes)</td>
<td>Spirometry, bronchodilation test</td>
<td>Obstructive lung function.</td>
</tr>
<tr>
<td>Rheumatic disorders (RA, SLE, Sjögren, ankylosing spondylitis, relapsing polychondritis)</td>
<td>RA: rheumatoid nodule, arthritis, synovitis, specific skeletal deformities, rheumatoid nodule, other skin symptoms, etc</td>
<td>Spirometry, bronchodilation test</td>
<td>Obstructive lung function.</td>
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<td>SLE: malar rash, ulcers, neuropsychiatric symptoms, etc</td>
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<td>COPD</td>
<td>Dyspnoea, Smoking history, Recurrent infections</td>
<td>Biopsy</td>
<td>Hilar lymphadenopathy, reticulonodular infiltrates, pulmonary infiltrates, fibrocystic or bullous changes, non-caseating granulomas, upper lobe predominance.</td>
</tr>
<tr>
<td>Traction, obstruction, inhalation</td>
<td>Sarcoidosis: fatigue, erythema nodosum, lupus pemio, arthralgia, uveitis, Bell's palsy, etc</td>
<td>Chest CT scan</td>
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<td></td>
<td>History of radiation therapy</td>
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<tr>
<td></td>
<td>History of inhalation/aspiration trauma</td>
<td></td>
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</tr>
<tr>
<td>YNS, Young’s syndrome, amyloidosis, endometriosis</td>
<td>YNS: yellow dystrophic nails, lymphoedema, sinusitis, pleural effusion</td>
<td>Bronchoscopy if imaging showing foreign body</td>
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<tr>
<td></td>
<td>Young’s syndrome: history of mercury contact, rhinosinusitis, infertility</td>
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<tr>
<td></td>
<td>Endometriosis: pelvic pain, infertility, cyclic haemoptysis/pain</td>
<td>Gynaecological evaluation</td>
<td></td>
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</tbody>
</table>
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. influenzae
• 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 viscosity 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

**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)

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

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

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.

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
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

Cough

UNSTICKING

COLLECTING

EVACUATING

Normal Breathing

Complete Exhalation

IRV

VT

ERV

RV
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

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
STEP 1

ciprofloxacin
750mg BD
2 weeks

Repeat sputum C/S

STEP 2

2 weeks IV anti-pseudomonal antibiotics [Table 4a]

STEP 2

Further 4 weeks ciprofloxacin
750mg BD
+ Nebulised colistin
2MU BD
3 months

STEP 2

Nebulised colistin
2MU BD
3 months

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

Suppressive 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

### Usual inhaled antibiotics used

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

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. Cochrane Database of Systematic Reviews 2007
<table>
<thead>
<tr>
<th>Study</th>
<th>Antibiotics</th>
<th>Duration</th>
<th>Bacteria</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARKER [9] and COUCH [20]</td>
<td>Tobramycin</td>
<td>4 weeks</td>
<td>PA</td>
<td>-4.56 (-5.44, -3.68)</td>
<td>21.05</td>
</tr>
<tr>
<td>HAWORTH [30]</td>
<td>Colistin</td>
<td>4 weeks</td>
<td>PA</td>
<td>-1.40 (-2.07, -0.73)</td>
<td>21.55</td>
</tr>
<tr>
<td>SERISIER [33]</td>
<td>Ciprofloxacin</td>
<td>4 weeks</td>
<td>PA</td>
<td>-4.12 (-6.54, -1.70)</td>
<td>15.53</td>
</tr>
<tr>
<td>TR02-107 [26, 27]</td>
<td>Amikacin</td>
<td>4 weeks</td>
<td>PA</td>
<td>-0.38 (-0.82, -0.06)</td>
<td>21.96</td>
</tr>
</tbody>
</table>

Overall ($I^2=95.2\%, p<0.001$)
Test for overall effect $Z=3.0$ ($p=0.003$)

Note: weights are from random effects analysis

**FIGURE 2** Effects of inhaled antibiotics on reduction of sputum bacterial load (log$_{10}$ CFU·g$^{-1}$). WMD: weighted mean difference; PA: *Pseudomonas aeruginosa*. 
<table>
<thead>
<tr>
<th>Study</th>
<th>Antibiotics</th>
<th>Duration</th>
<th>Bacteria</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk ratio [95% CI]</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DROBNIC [29]</td>
<td>Tobramycin</td>
<td>6 months</td>
<td>PA</td>
<td>4/20</td>
<td>4/20</td>
<td>1.00 [0.29–3.45]</td>
<td>22.33</td>
</tr>
<tr>
<td>ORRIOLS [32]</td>
<td>Ceftazidime + tobramycin</td>
<td>12 months</td>
<td>PA</td>
<td>0/7</td>
<td>0/8</td>
<td>1.13 [0.03–50.41]</td>
<td>5.24</td>
</tr>
</tbody>
</table>

Overall ($I^2=51.0\%, p=0.070$)

Test for overall effect $Z=2.97 \ (p=0.003)$

Note: weights are from random effects analysis

**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

**Reduced airway secretion**
- Reduced water secretion
- Modulation of mucin gene expression

**Reduced bacterial load and virulence**
- Inhibition of bacterial protein synthesis
- Suppression of quorum sensing proteins
- Reduced bacterial adherence
- Reduced bacterial toxin production
- Inhibition of bacterial biofilm function
- Reduced generation of oxygen free radicals

**Impaired mucociliary clearance**

**Acute/chronic respiratory infection**

**Persistent inflammation**

**Reduced chronic inflammation**
- Increased phagocytosis of apoptotic neutrophils
- Increased β-defensin levels
- Reduced production of pro-inflammatory cytokines
- Reduced neutrophil chemotaxis
- Downregulation of adhesion molecule expression
- Reduced production of oxygen species

**Inhibitory effect**
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 $\geq 2$ 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