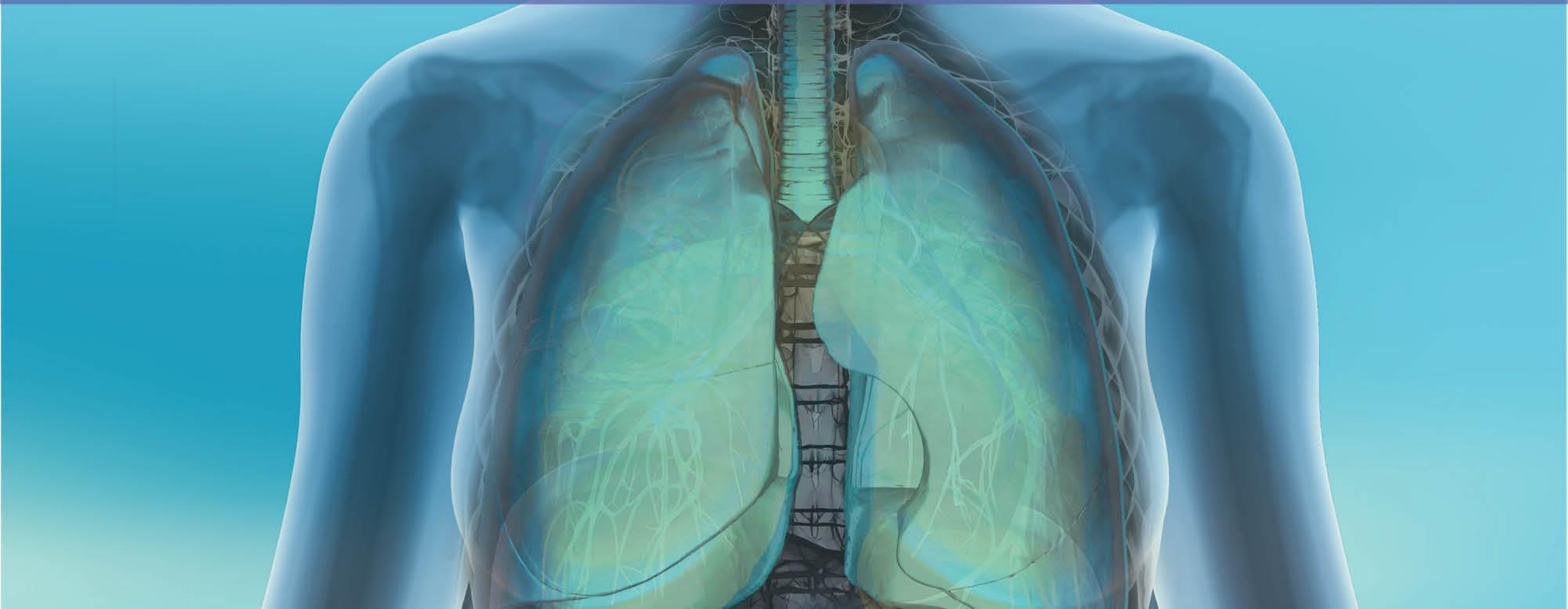
# NTM Lecture Series for Providers

April 27-28, 2023
NATIONAL JEWISH HEALTH



# INTRODUCTION TO BRONCHIECTASIS



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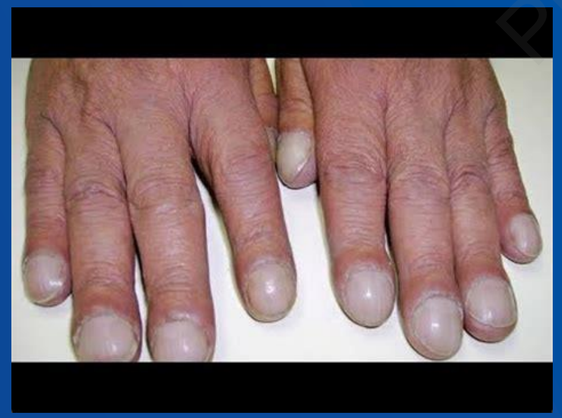
# Learning Objectives

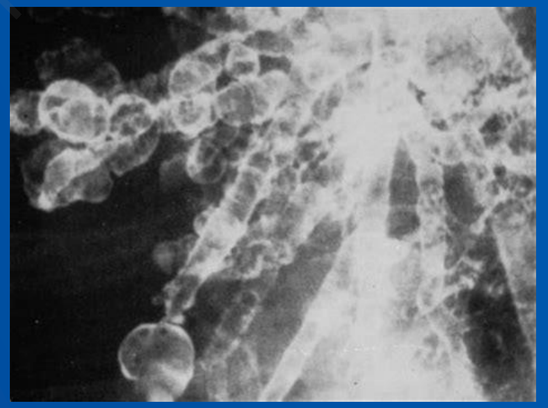
1. Define and recognize the various aetiologies of bronchiectasis
2. Understand the evaluation of Bronchiectasisis
3. Identify the cornerstones of treatment for Bronchiectasis

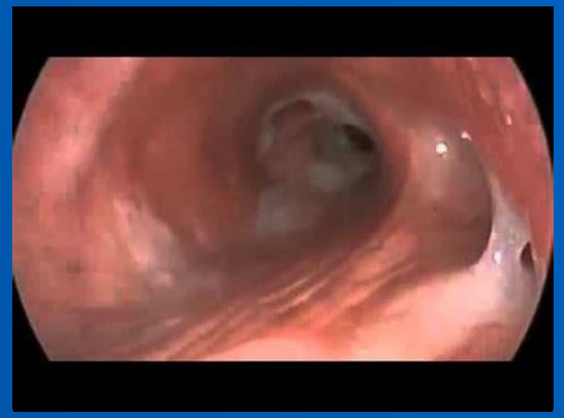
# BRONCHIECTASIS

1. Definition
2. Causes
3. Evaluation
4. Treatment



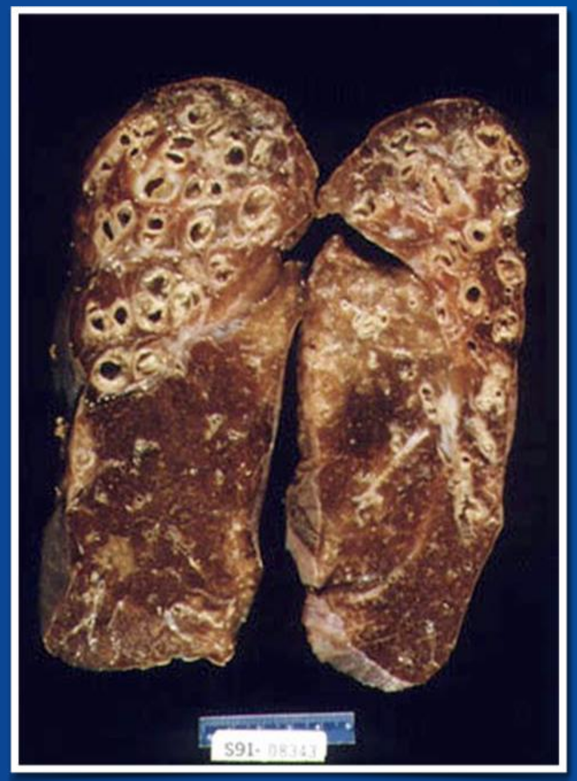


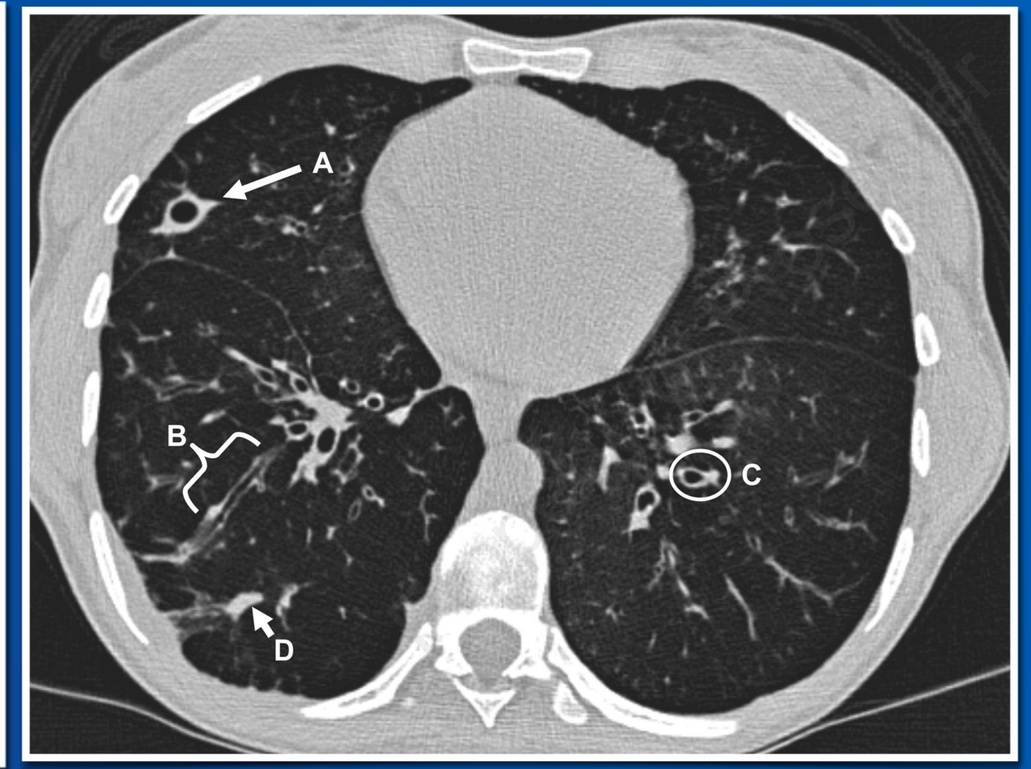




René-Théophile-Hyacinthe Laennec
(1781-1826)

Progressive respiratory disease characterized by permanent dilatation of the bronchi and associated with a clinical syndrome of cough, sputum production and recurrent respiratory infections

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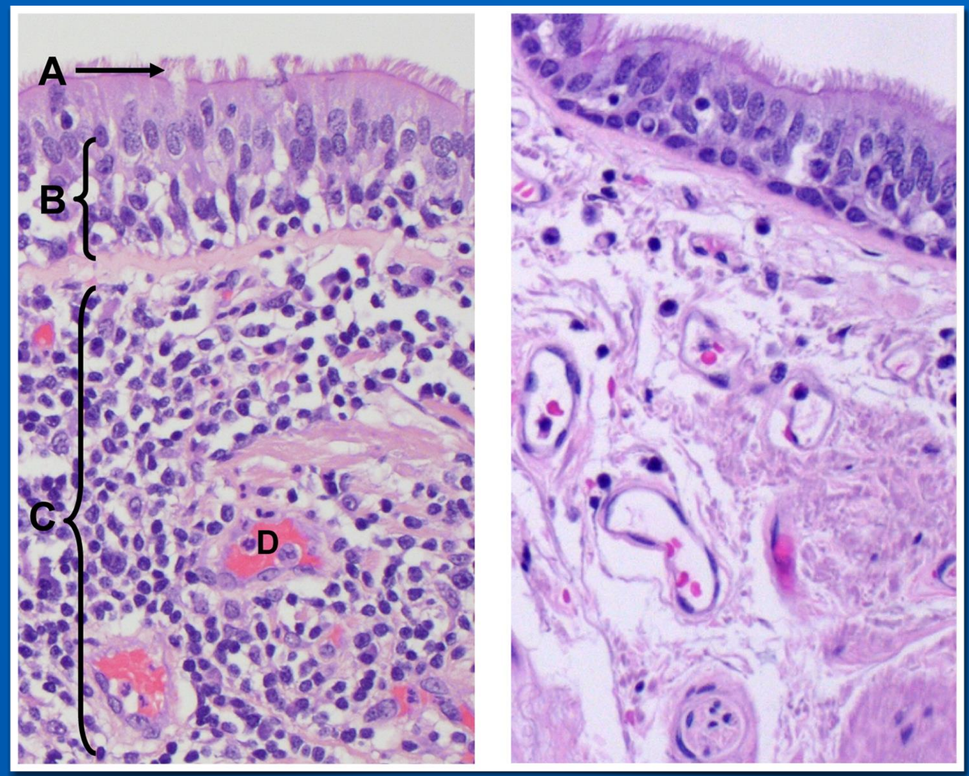
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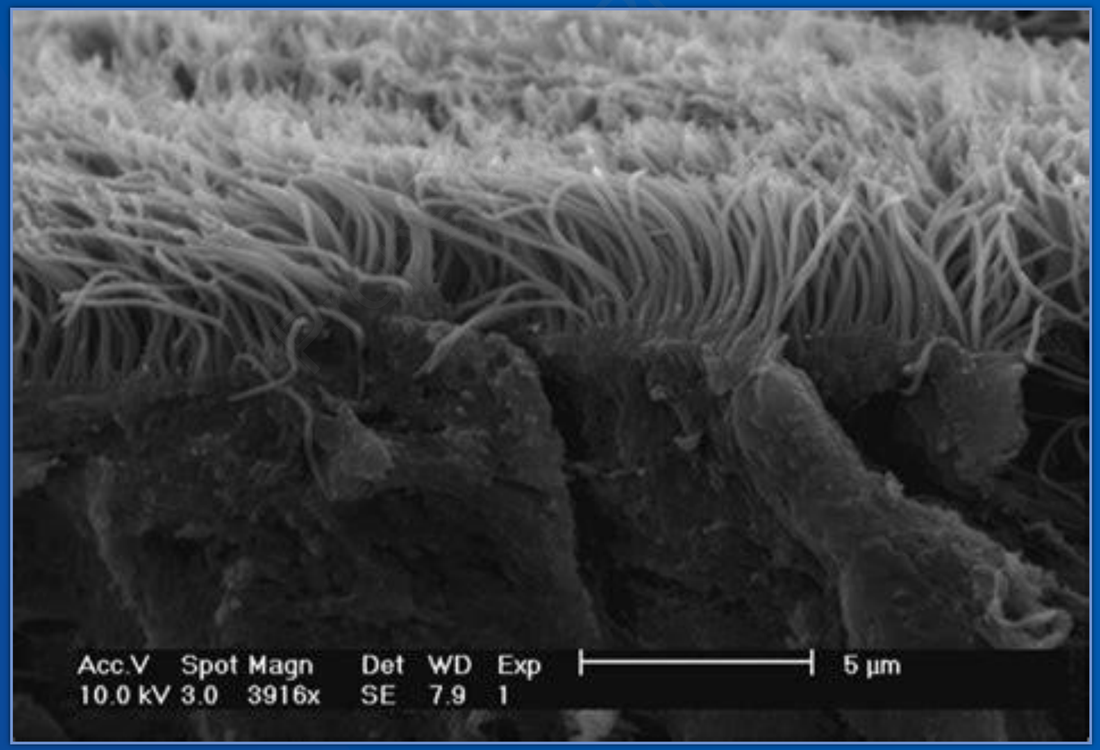
# Abnormalities of Airway Defense Mechanisms

## Muco-cilliary clearance

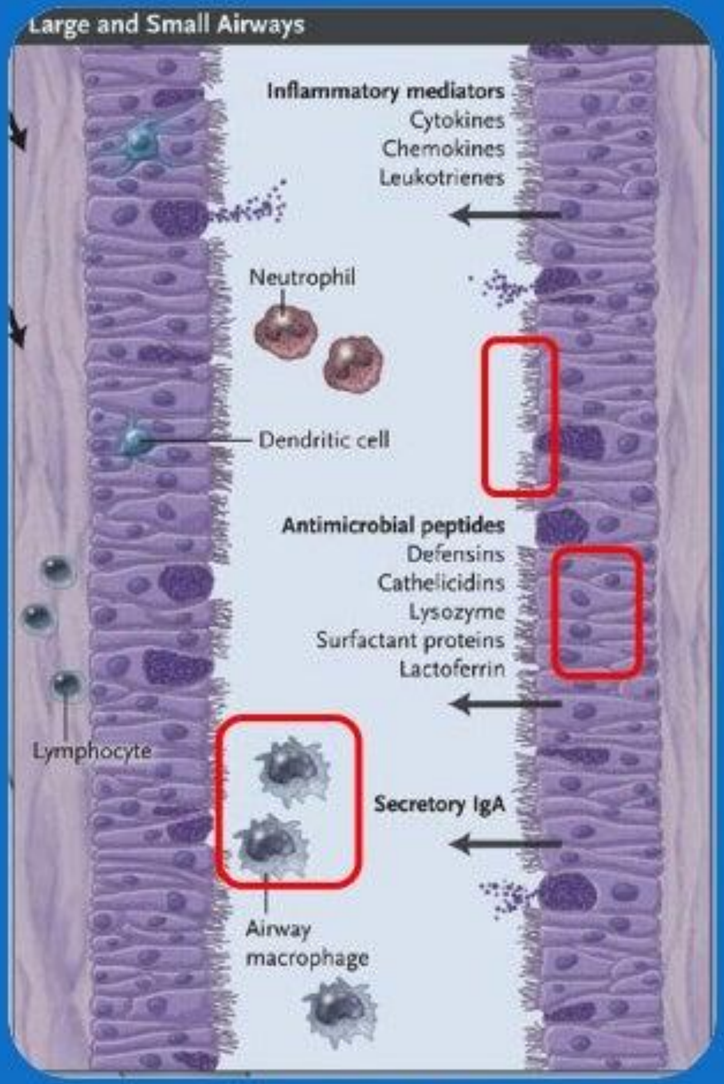


## Innate Immunity

- Cellular : Neutrophils ; Macrophages ; NK cells
- Proteins: TLR, Cytokines, Antimicrobial proteins

## Adaptive Immunity

- Immunoglobulins
- T and B Lymphocytes




Adapted from Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* . 2008;359:22.

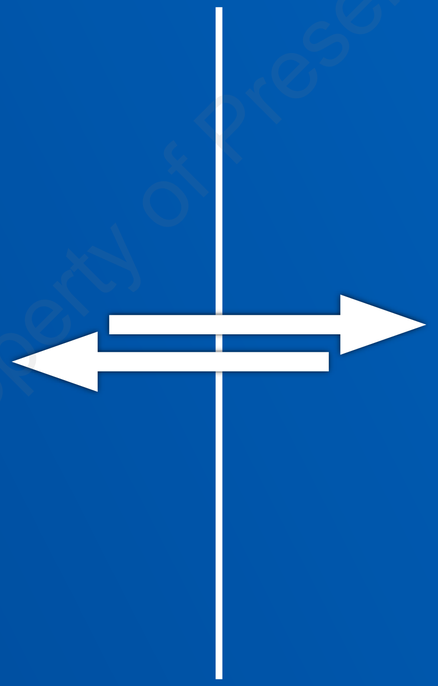
## Causes:

# Two Hit Hypothesis

### Mucocilliary Defects
CF
PCD

### Immune Defects
Primary - CVID
Secondary - ChemoRx

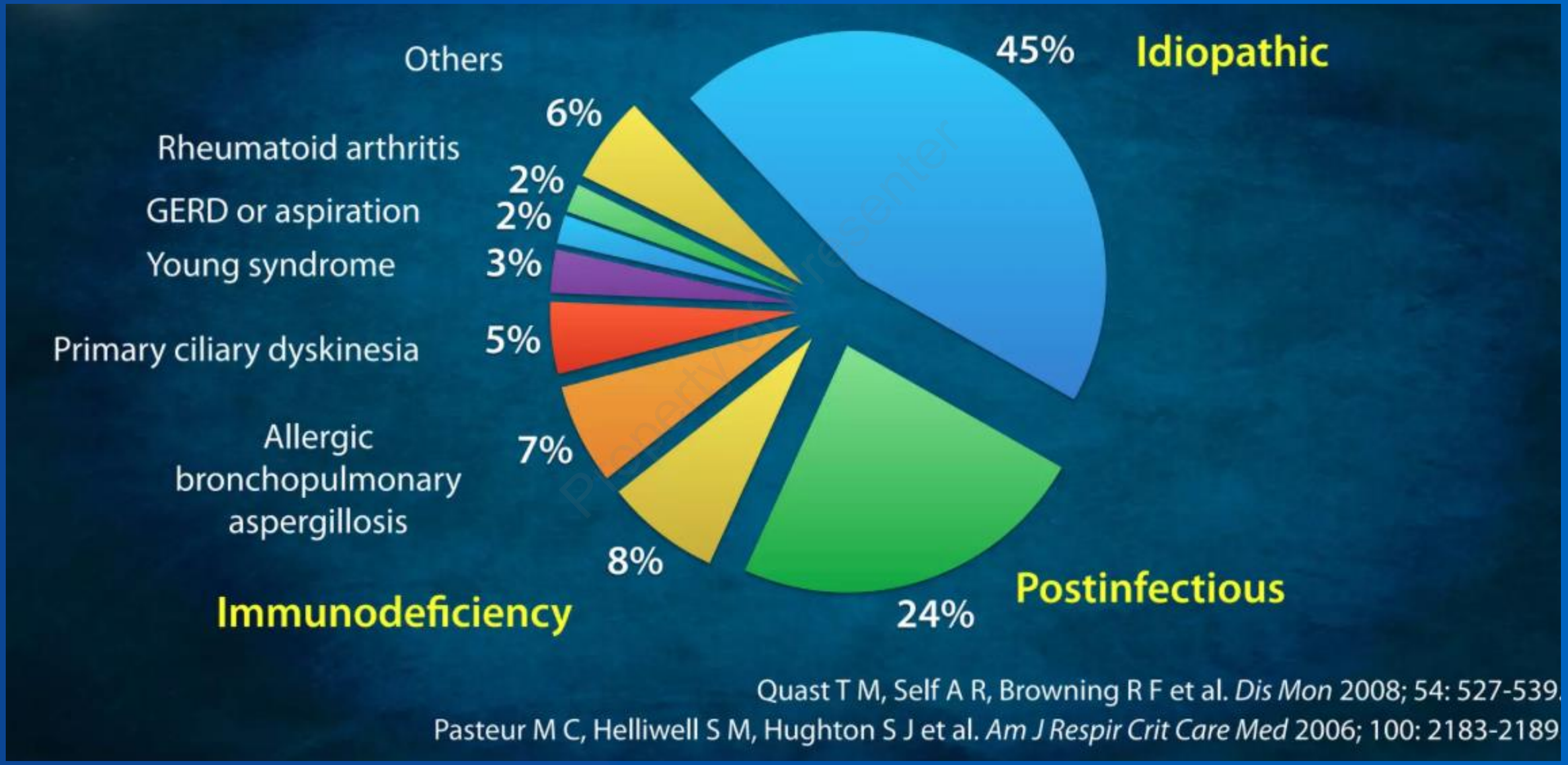
### Other Conditions
RA
Sjogren's
IBD



### Acute /Severe
Infection - Viral
Inhalation / Radiation

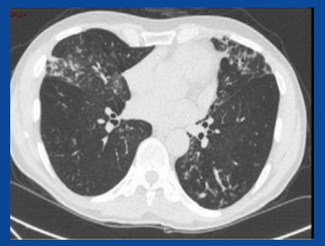
### Recurrent
Aspiration
Infection

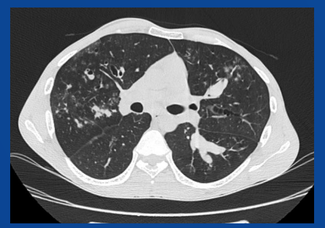
### Persistent
ABPA
TBM
Bronchial Obstruction



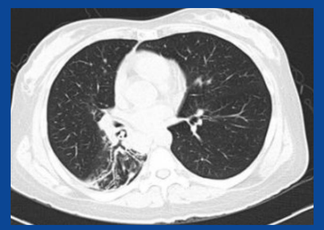

Quast T M, Self A R, Browning R F et al. *Dis Mon* 2008; 54: 527-539.

Pasteur M C, Helliwell S M, Hughton S J et al. *Am J Respir Crit Care Med* 2006; 100: 2183-2189

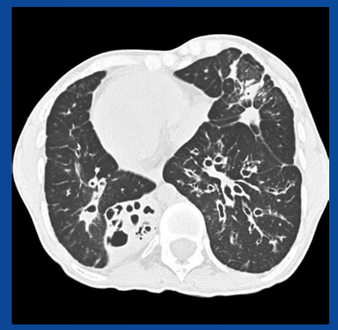


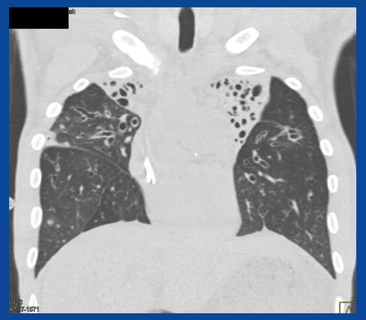


| | Cause | Notes | Specific Rx |
|---|---|---|---|
| Post-Infectious | Viral, Bacterial, Fungal | May be unilobar | - |
| NTM | Abscessus and Avium | Middle-aged Female, RML, Lingula, Cavitation, TIB | + |
| Post-TB | MTB | Upper lobe | + |
| ABPA | A.Fumigatus, | Central BE, Fleeting infiltrates, Mucus plugging, Asthma, S.Aureus | + |



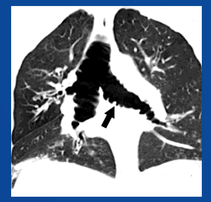
| | Cause | Notes | Specific Rx |
|---|---|---|---|
| COPD | Smoking, Biomass | Lower lobe, Tubular, Airflow obstruction | +- |
| Asthma | Controversial | Neutrophilic, frequent exacerbations | + |
| Airway Obstruction | Tumours, Collapse | Can be unilobar | + |
| Aspiration | FB, Gastric contents | Lower Lobe | + |

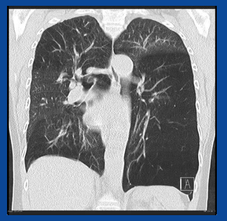




| | Cause | Notes | Specific Rx |
|---|---|---|---|
| PCD | Genetic | Early symptoms, Middle lobe and lower lobe, rhinosinusitis; otitis media; situs inversus, infertility, ectopic preg | +- |
| Adult CF | CFTR Mutations | Upper lobe, Non-Pulmonary manifestations, PSE or S.Aureus, infertility, malabsorption, pancreatitis, nasal polyposis | +- |

| | Cause | Notes | Specific Rx |
|---|---|---|---|
| Immunodeficiency | Primary (CVID, HyperIgE, etc), Secondary (Drugs, Malig, HIV) | Depending on cause | + |
| Autoimmune | RA, Sjogren's, SLE, Sarcoidosis | Depending on cause | + |
| Diffuse Panbronchiolitis | Idiopathic | Far east | + |
| IBD | UC, Crohn's, Coeliac | Prominent sputum, Steroid responsive | + |





| | Cause | Notes | Specific Rx |
|---|---|---|---|
| Airway | Mounier-Kuhn, Marfan's, Williams-Campbell | Specific radiographs | + |
| A1ATD | PiZZ | Emphysema + BE | + |
| Yellow-Nail | Lymphatic Obstruction | Dystrophic nails, Pleural effusion, Rhinosinusitis | + |
| Young's Syndrome | Unknown | Rhinosinusitis, Obstructive azoospermia | + |

# Evaluation of Bronchiectasis : General Considerations



1. Definitive Diagnosis
2. Determining Aetiology
3. Underlying / Associated Conditions
4. Severity of Disease
5. Microbiology
6. Non-Respiratory issues

# 1. Definitive Diagnosis : HRCT

CT imaging protocol

- Slice thickness: ≤1mm
- Reconstruction algorithm: – high spatial frequency
- kVp: 100-140
- mAs (or effective mAs): 100 – 200
- Gantry rotation time: <0.5s

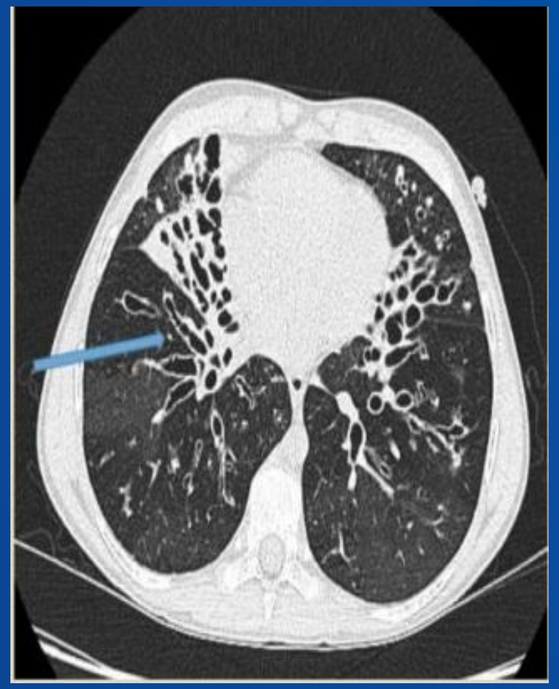
CT features of bronchiectasis

- Defined by bronchial dilatation as suggested by one or more of the following:
    1. Bronchoarterial ratio >1 (internal airway lumen vs adjacent pulmonary artery)
    2. Lack of tapering
    3. Airway visibility within 1cm of costal pleural surface or touching mediastinal pleura

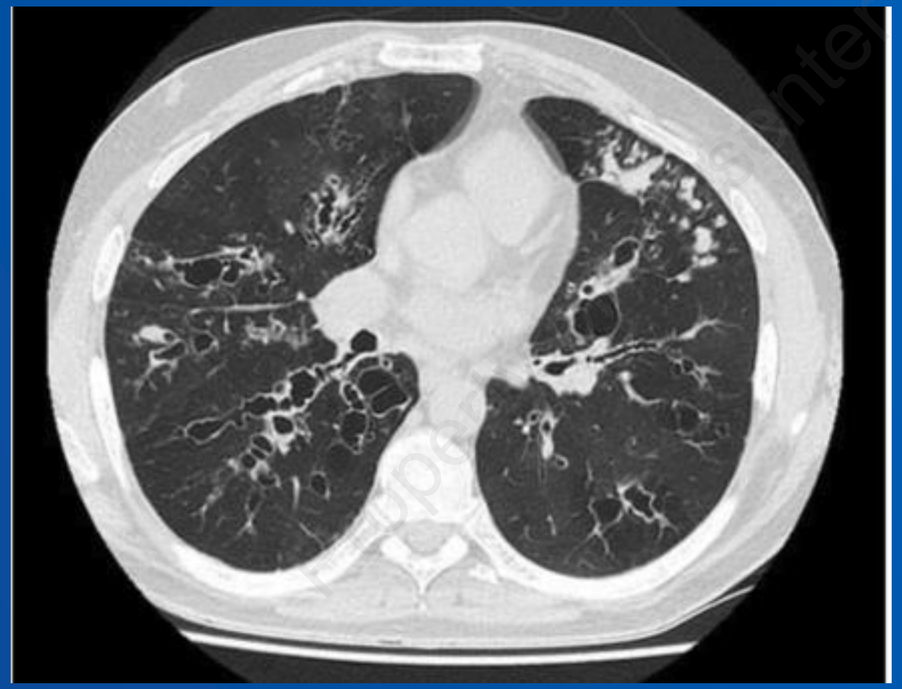
The following indirect signs are commonly associated with bronchiectasis:

- Bronchial wall thickening
- Mucus impaction
- Mosaic perfusion / air trapping on expiratory imaging

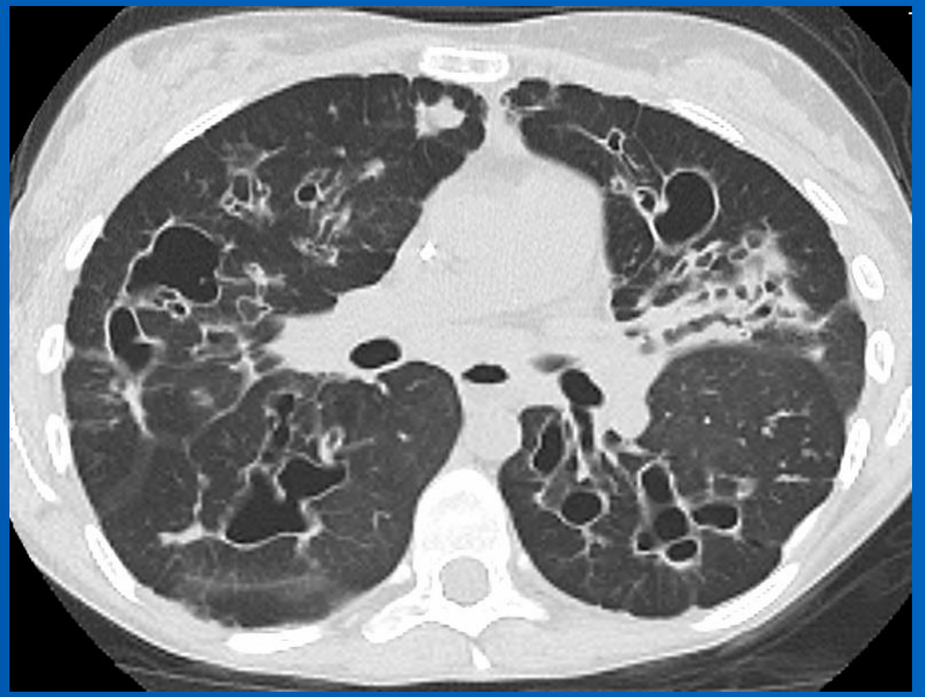
# Radiographic Phenotypes



Cylindrical/tubular



Varicose



Saccular/cystic

# 2. Determine Aetiolgy

## History:

Neonatal symptoms

Infertility

Previous pneumonia or viral illness in childhood

Gastric aspiration

Asthma

Autoimmune symptoms

Family history

Recurrent oto-sino-pulmonary infections

Situs abnormalities

## Exam

Wheezing - Focal or Diffuse

Clubbing

Situs Abnormalities

Arthritis, Sicca, Raynaud's

Nail Abn.

# HRCT : Diagnostic Clues

Upper lobe predominant
- CF
- Sarcoidosis
- Pneumoconiosis
- Tuberculosis

Central
- ABPA
- NTM

Lower lobe predominant
- PCD
- Hereditary Immunodeficiency
- A1AT deficiency
- Chronic aspiration

# Investigations : Adapted from BTS and ERS

**Diagnostic laboratory:**

- CBC+Diff
- IgG / A / M
- Total IgE and Aspergillus Specific IgE / IgG / Skin testing
- Consider measuring baseline specific antibody levels against capsular polysaccharides of Streptococcus pneumoniae. If low, immunize with 23 valent polysaccharide pneumococcal vaccine, followed by measurement of specific antibody levels 4–8 weeks later
- Consider HIV
- RF/Anti-CCP, ANA, SSA, SSB, ANCA : BTS but not ERS

**Conditional:**

- A1AT if coexisting emphysema
- SPEP if Ig Elevated
- Test for CF in patients with supporting clinical features (early onset, male infertility, malabsorption, pancreatitis)
- Test for PCD if supporting clinical features (Neonatal distress, childhood symptoms, Recurrent otitis / rhinosinusoitis, infertility)

Sputum

Expectorated or Induced

Bacteria

Mycobacteria

BAL

Cannot produce sputum

Suspected infection

Doing Poorly

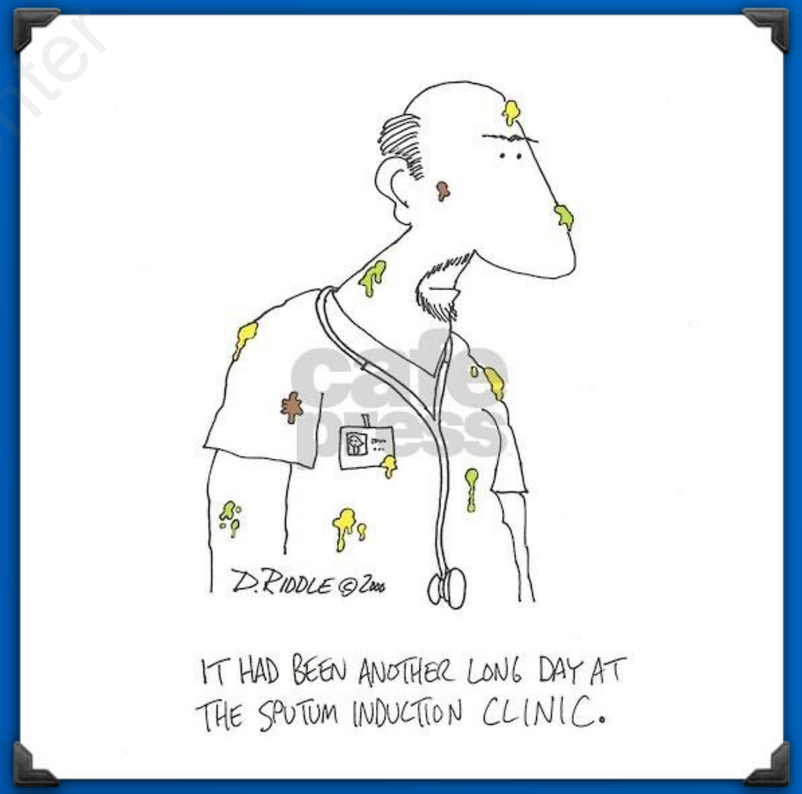
Suspected NTM by CT with negative sputa

Other

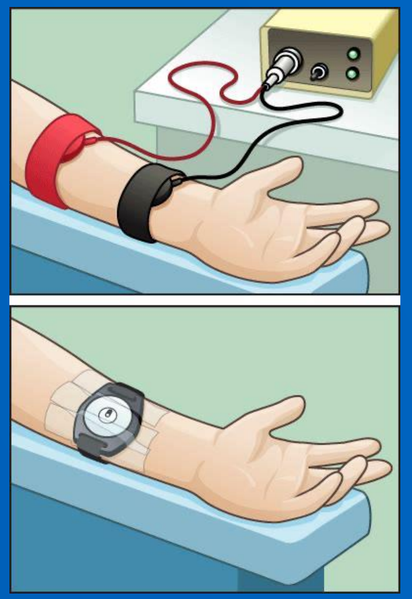
Reflux and aspiration if symptoms

Spirometry

Bronchscopy : Concern for Obstruction

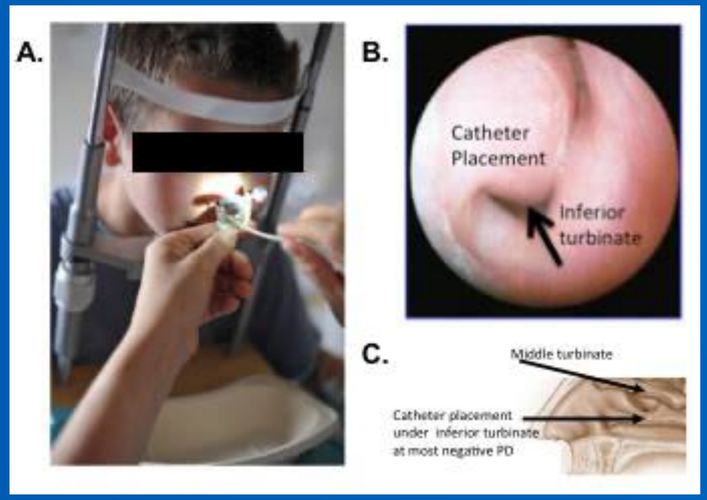


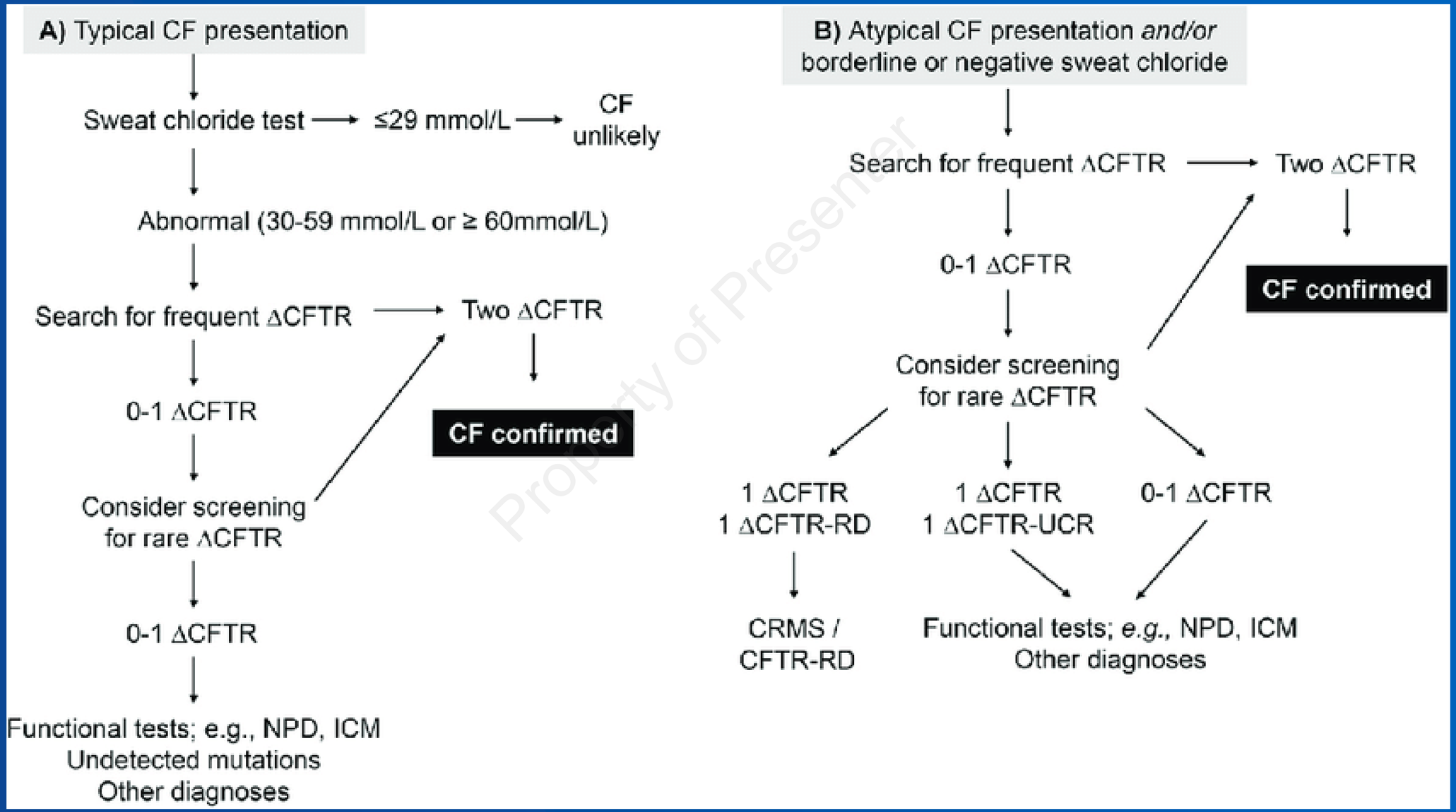
## Test for CF in patients with supporting clinical features, (for example, early onset, male infertility, malabsorption, pancreatitis)

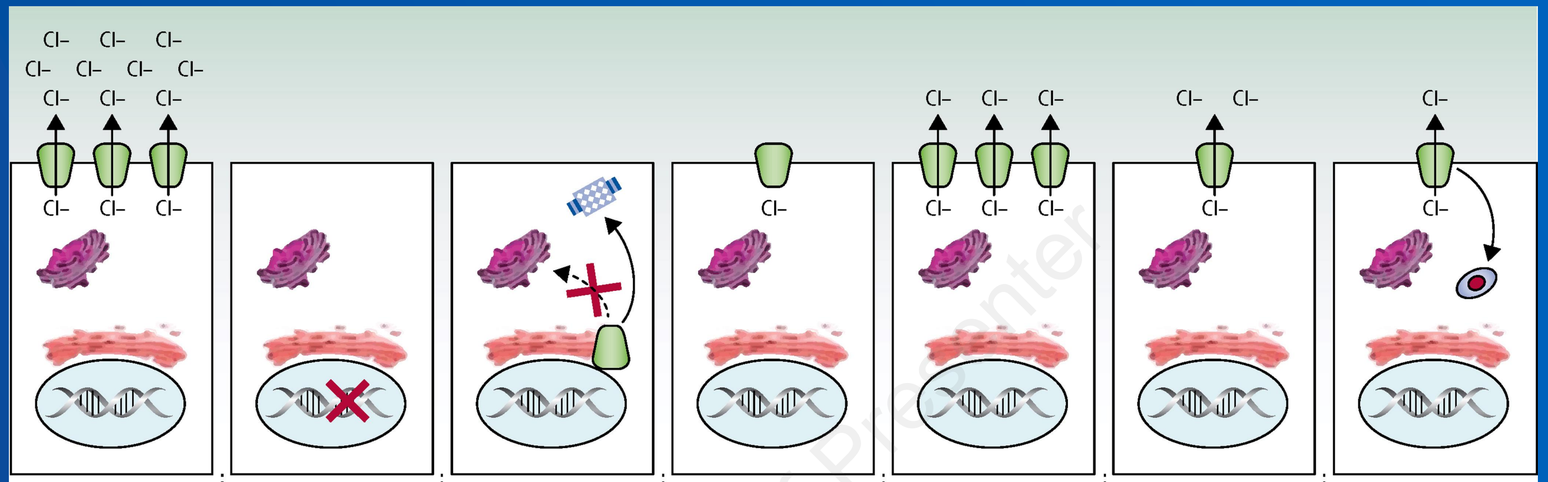


**Two sweat chloride measurements :**

- Two measurements greater than 60 mmol/L are diagnostic of CF.
- Values not exceeding 29-59 mmol/L require follow-up genetic testing as cases of genetically proven CF have been associated with results below 40 mmol/L.
- **Functional Abnormalities** can be tested using Nasal Potential Difference or Intestinal Current Measurement (ICM)
- Abnormalities may occur with idiopathic bronchiectasis and normal sweat chloride levels with either one, two, or no CFTR mutations.








| Wildtype CFTR | I | II | III | IV | V | VI |
|---|---|---|---|---|---|---|
| Defect types | No protein | No traffic | No function | Less function | Less protein | Less stable |
| Mutation examples | Gly 542 x<br>Arg 553 x<br>Trp 1282 x | Gly 85 Glu<br>Δ Ile 507<br>Δ Phe 508<br>Asn 1303 lys | Val 520 Phe<br>Ser 549 Arg<br>Gly 551 Asp | Arg 117 His<br>Arg 334 Trp<br>Ser 1235 Arg | Ala 455 Glu<br>1680–886 A→G<br>2657+5 G→A | Δ Phe 508<br>Gln 1412 x |
| Required approaches | Rescue protein synthesis | Correct protein folding | Restore channel conductance | Restore channel conductance | Maturation or correct misplicing | Promote protein stability |
| Approved drugs | .. | Lumacaftor, Tezacaftor | Ivacaftor | Ivacaftor | .. | .. |



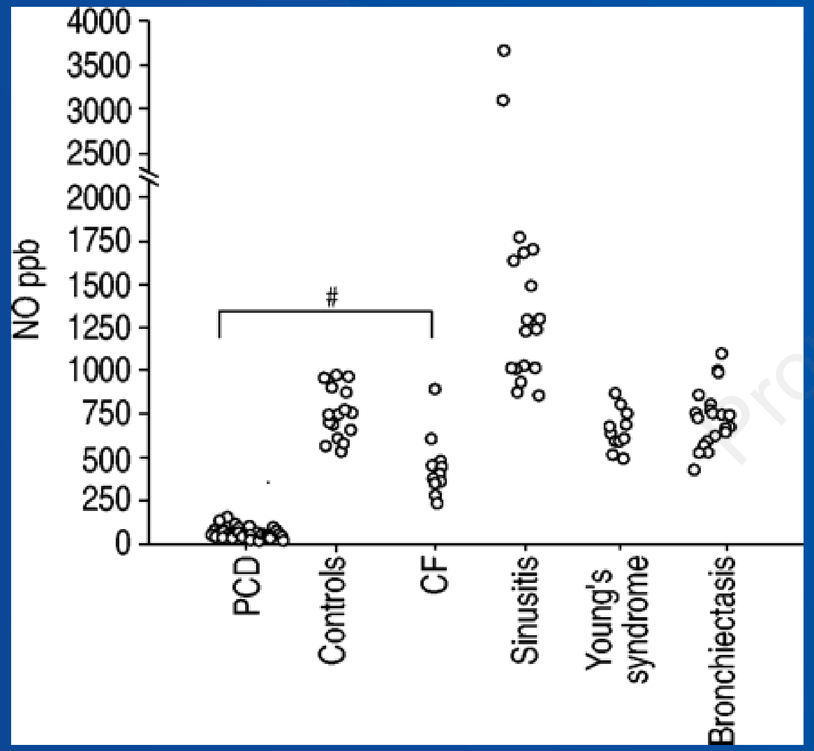
Elexacaftor/tezacaftor/ivacaftor (Trikafta): Ages 6 and older who have at least one copy of the F508del mutation or at least one copy of 177 specified mutations

Tezacaftor/ivacaftor and ivacaftor (Symdeko): Ages 6 and older with two copies of the F508del mutation, or with a single copy of one of 154 specified mutations.

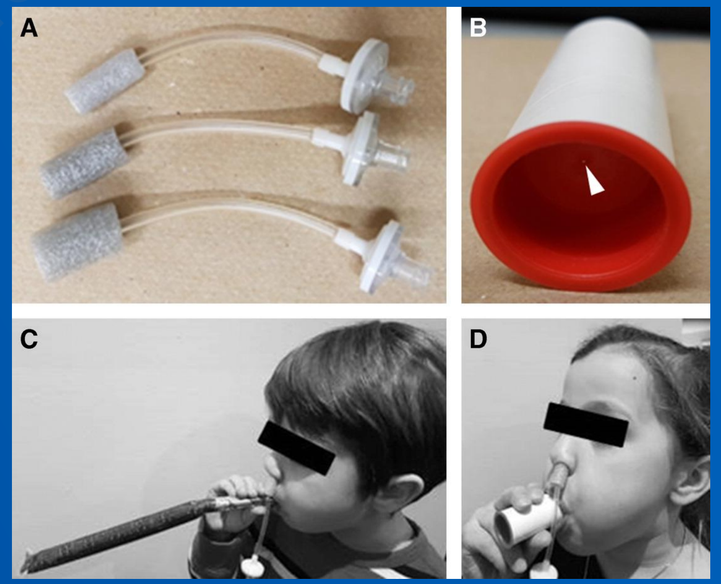
Lumacaftor /ivacaftor (Orkambi): Ages 1 and older who have two copies of the F508del mutation.

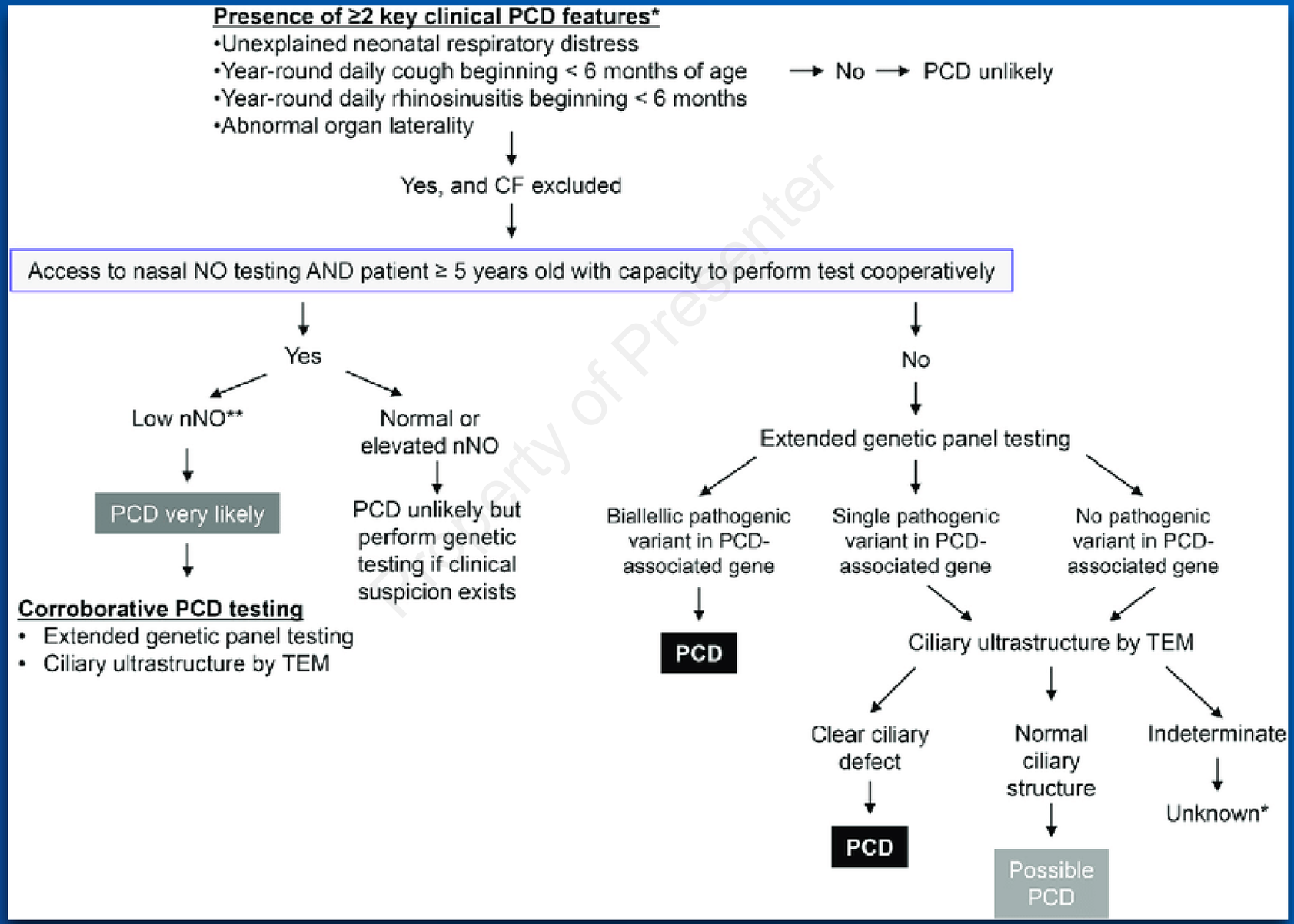
Ivacaftor (Kalydeco): Ages 4 months and old who have one of 97 specified mutations.

# Test for PCD if supporting clinical features (Neonatal distress, childhood symptoms, Recurrent otitis / rhinosinusoitis, infertility)




T. Wodehouse, S.A. Kharitonov, I.S. Mackay, P.J. Barnes, R. Wilson, P.J. Cole
European Respiratory Journal 2003 21: 43-47





# 3. Assessing Severity of Bronchiectasis



Bronchiectasis Severity Index:

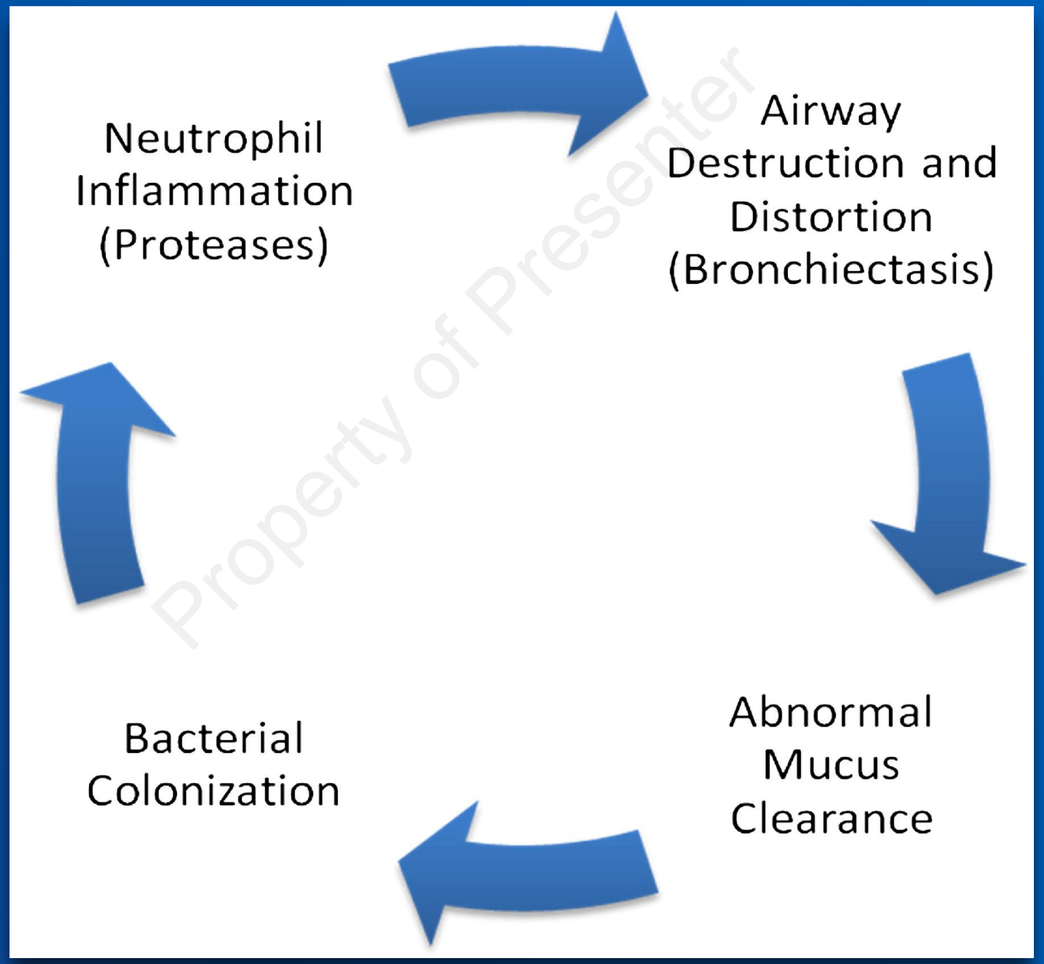
1. Age
2. BMI
3. FEV1
4. Hospitalization
5. Number of exacerbations
6. Breathlessness Score
7. Pseudomonas
8. OtherOrganisms
9. Number of involved Lobes

0-4
Mild Bronchiectasis
1 year outcomes: 0 - 2.8 % mortality rate, 0 - 3.4 % hospitalisation rate
4 year outcomes: 0 - 5.3 % mortality rate, 0 - 9.2 % hospitalisation rate

5 - 8
Moderate Bronchiectasis
1 year outcomes: 0.8 - 4.8 % mortality rate, 1.0 - 7.2 % hospitalisation rate
4 year outcomes: 4 % - 11.3 % mortality rate, 9.9 - 19.4 % hospitalisation rate

9 +
Severe Bronchiectasis
1 year outcomes: 7.6 % - 10.5 % mortality rate, 16.7 - 52.6 % hospitalisation rate
4 year outcomes: 9.9 - 29.2 % mortality, 41.2 - 80.4 % hospitalisation rate

# 4. Therapeutic Principles






"vicious cycle hypothesis" first proposed in 1986 by Cole, remains central to our understanding

There are currently no guidelines for the management of bronchiectasis in the United States. Comprehensive guidelines were presented in the United Kingdom in 2010 (Update 2019) and Australia and New Zealand provided guidelines in 2015. The European Respiratory Society guidelines for the management of bronchiectasis were published in September 2017.



Thorax. 2019 Jan;74(Suppl 1):1-69. British Thoracic Society Guideline for bronchiectasis in adults

Eur Respir J. 2017 Sep 9;50(3). European Respiratory Society guidelines for the management of adult bronchiectasis

# Treatment : General Considerations

1. Underlying Cause
2. Antibiotics
3. Macrolides
4. Mucoactive agents
5. Anti-inflammatory agents
6. Bronchodilators
7. Airway Clearance
8. Pulmonary Rehabilitation
9. Emerging Therapies

# 1. Causes of bronchiectasis that have specific treatment.

| Condition or cause | Specific therapeutic measures |
|---|---|
| Allergic bronchopulmonary aspergillosis | Systemic corticosteroids, antifungal agents |
| Ciliary dyskinesia | Auditory monitoring, cardiac evaluation , genetic counceelling |
| Associated diseases (asthma, COPD, collagen diseases, inflammatory bowel disease, etc.) | Treatment of the underlying disease |
| Alpha-1 antitrypsin deficiency | Avoid tobacco exposure; consider replacement therapy. |
| Cystic fibrosis | DNase; consider CFTR modulator |
| Immunodeficiencies | Periodic immunoglobulin replacement |
| Nontuberculous mycobacterial infection | Treatment according to species and in accordance with guidelines |
| Bronchial obstruction | Bronchoscopic clearance or surgical treatment |
| Gastroesophageal reflux disease | Inhibitor of acid gastric secretion; consider surgery |

## 2. Antibiotics

Antibiotics (oral, intravenous or nebulised) can be used in three situations:

1. To treat exacerbations
2. To attempt eradication of new airway isolates
3. As a long term maintenance for suppression of chronic colonization

# 2.1. Acute Exacerbations:

## 14 days of antibiotics (conditional recommendation, very low quality of evidence).

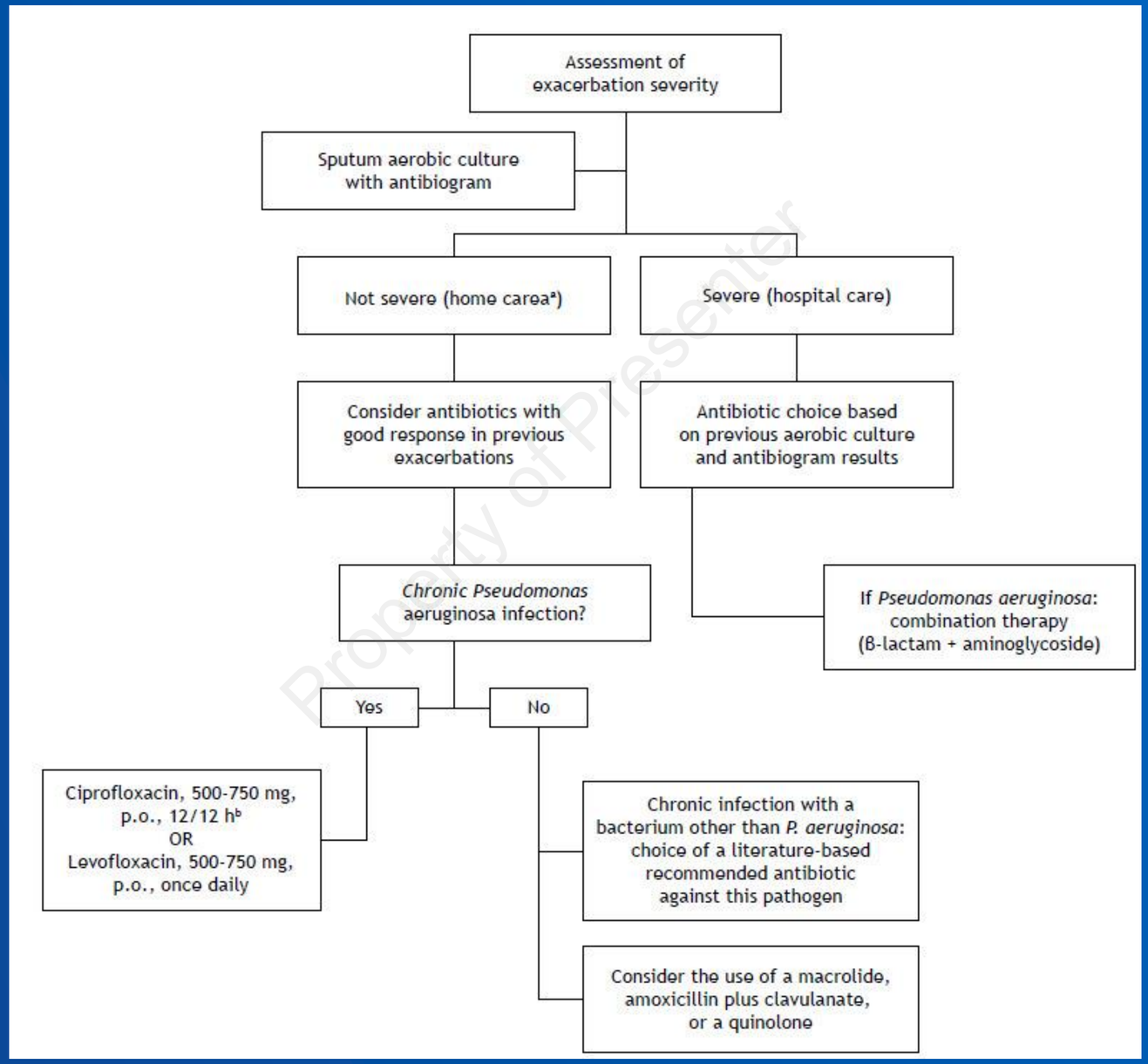
Summary of the evidence

- No direct data comparing longer and shorter courses of antibiotics, we suggest continuing the usual practice of treating acute exacerbations of bronchiectasis with 14 days of antibiotics on the basis of the patient's prior microbiology testing and the severity of the exacerbation.

- Shorter Course : Mild exacerbations, exacerbations in mild patients, those associated with pathogens more sensitive to antibiotics (e.g. S. pneumoniae), or patients with a rapid return to baseline.

- In patients with lack of recovery by 14 days of antibiotic therapy - re-evaluation of the patient's clinical condition and a new microbiological investigation.

- Severe exacerbations require intravenous antibiotic therapy and/or hospitalization (tachypnea ; worsening hypoxemia, fever, hemoptysis >25ml/24hrs, Sepsis criteria)





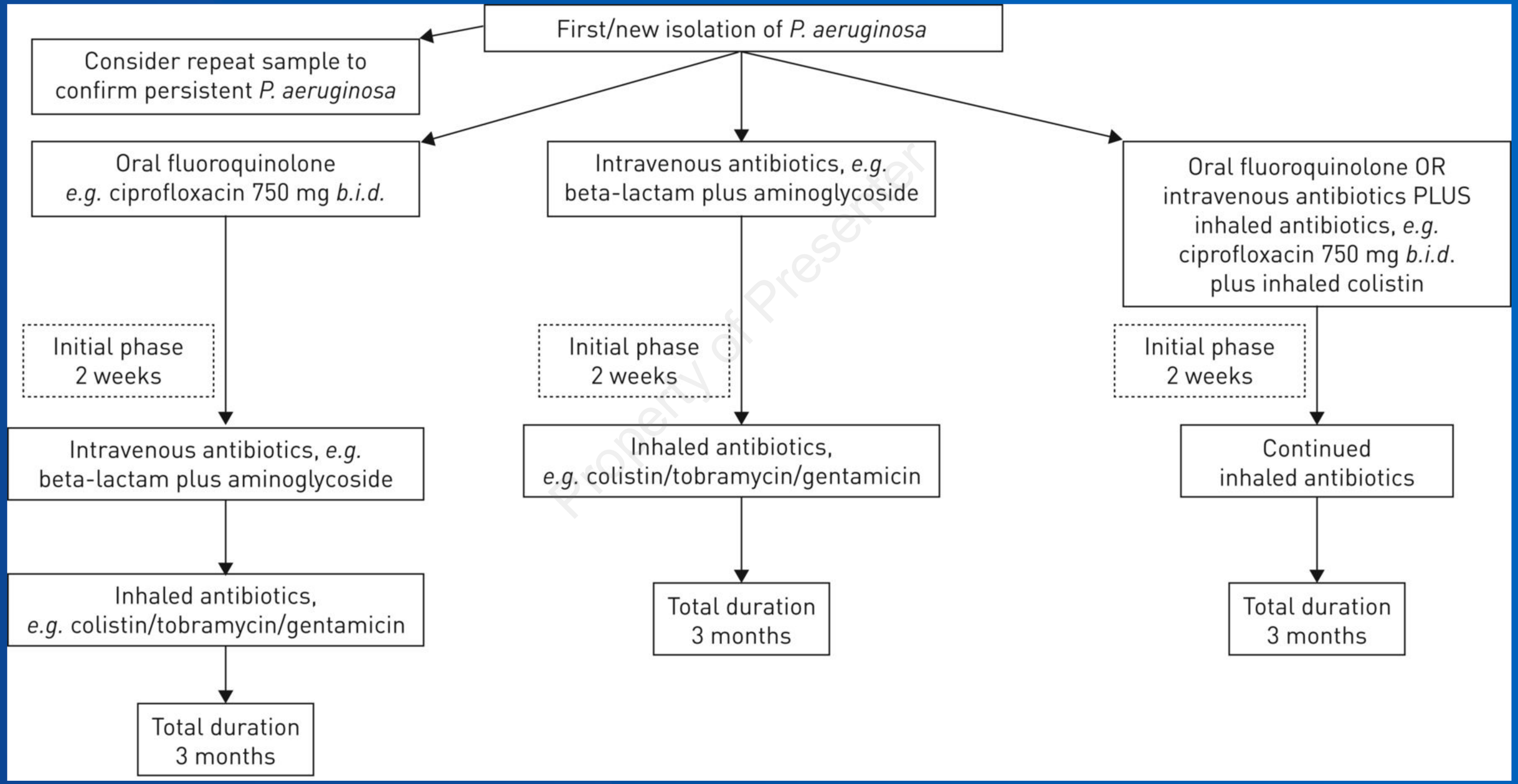

Brazilian consensus on non-cystic fibrosis bronchiectasis. J Bras Pneumol. 2019 Jul-Aug; 45(4)

## 2.2. *Eradication of new isolates.*

1. The optimal eradication regime for Pseudomonas aeruginosa has not been determined however, in practice, two weeks of oral ciprofloxacin based regimen is often used. This may be escalated in cases of persistently positive cultures.
2. There is currently no evidence to support the eradication of other organisms

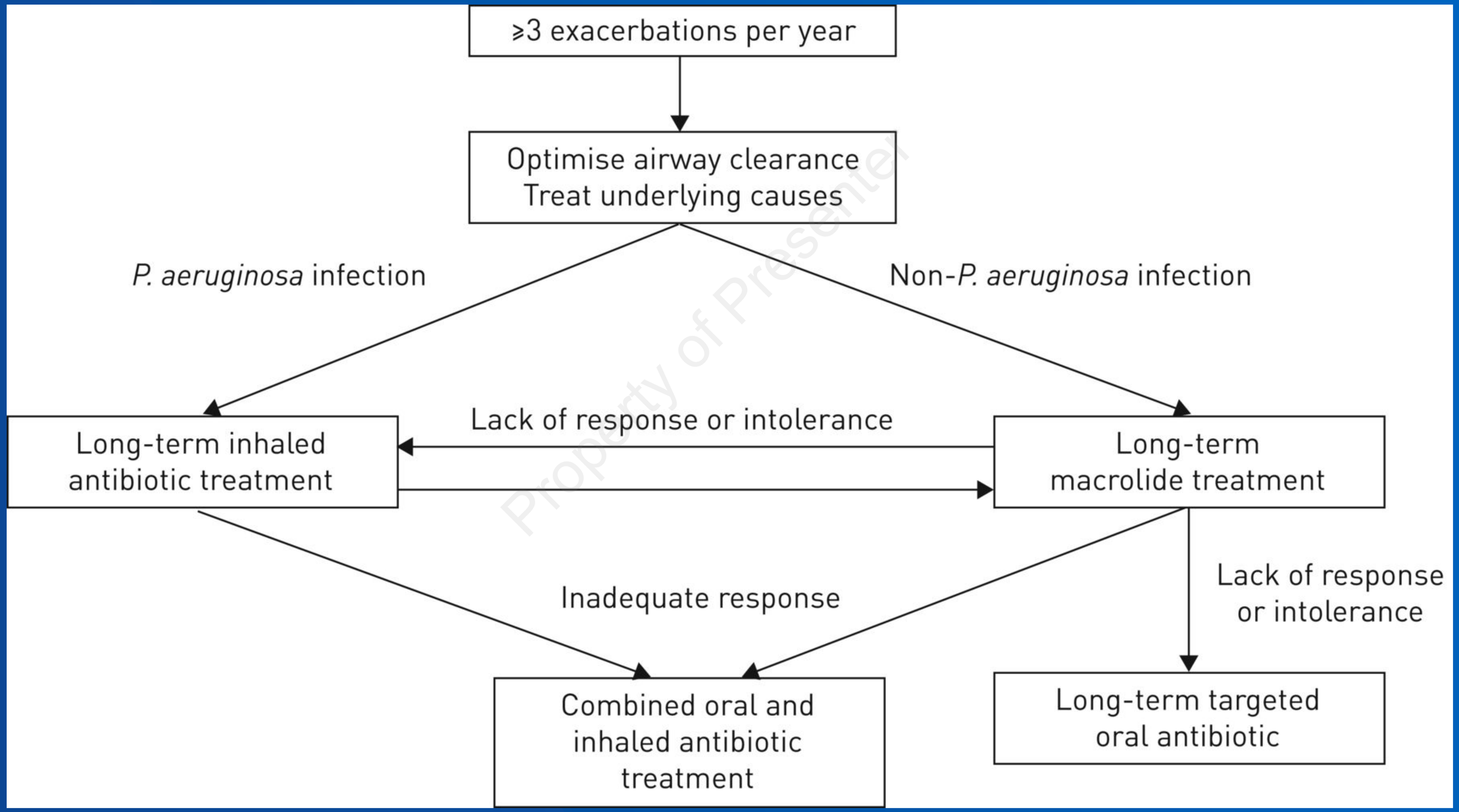
# Regimens for primary *Pseudomonas aeruginosa* infection.

| Treatment regimen | Dose | Frequency |
|---|---|---|
| Oral antibiotic + inhaled antibiotic | | |
| Oral:<br>Ciprofloxacin<br>+ | 500-750 mg | 14-21 days |
| Inhaled:<br>Gentamicin or<br>Nebulized tobramycin or<br>Colistimethate** | 80 mg<br>300 mg<br>1,000,000 IU | 3 months |
| Intravenous antibiotic (antipseudomonal beta-lactam + aminoglycoside) + inhaled antibiotic | | |
| Intravenous:<br>Ceftazidime or<br>Cefepime or<br>Piperacillin + tazobactam or<br>Meropenem<br>+ | 2 g<br>2 g<br>4.5 g<br>2 g | 14 days |
| Intravenous:<br>Amikacin or<br>Gentamicin or<br>Tobramycin<br>+ | 20-30 mg/kg/day (max 1.5 g/day)<br>3-5 mg/kg/day (max 160 mg/day)<br>10 mg/kg/day (max 660 mg/day) | 14 days |
| Inhaled:<br>Gentamicin or<br>Nebulized tobramycin or<br>Colistimethateb | 80 mg<br>300 mg<br>1,000,000 IU | 3 months |



## 2.3. Maintenance suppression of persisting microbial colonists

- Once established in the airway long term colonizers may be difficult to eradicate.
- A therapeutic trial of pathogen-targeted inhaled antibiotics (Tobramycin / Colistin/ Gentamicin / Ciproflxacin ) may be considered in selected patients e.g. those with established Pseudomonas aeruginosa colonisation and frequent exacerbation.
- Nebulised antibiotics are associated with a 10% – 30% risk of bronchospasm. Bronchodilators may be required prior to nebulised antibiotics



| Antibiotic and formulation | Dose | Frequency |
|---|---|---|
| Nebulized colistimethate | 1,000,000 IU | 1/12 h continuously |
| Gentamicin | 80 mg | 1/12 h continuously (or in alternating cycles of 28 days) |
| Dry powder tobramycin | 112 mg | 1/12 h in alternating cycles of 28 days |
| Nebulized tobramycin | 300 mg | 1/12 h in alternating cycles of 28 days |



Brazilian consensus on non-cystic fibrosis bronchiectasis. J Bras Pneumol. 2019 Jul-Aug; 45(4)

# 3. Macrolides for bronchiectasis.

1. Macrolide antibiotics target both inflammation and infection and have been shown to have beneficial clinical effects in patients with bronchiectasis.
2. Macrolide antibiotics (erythromycin, clarithromycin, azithromycin) have antimicrobial, anti-inflammatory and immunomodulatory properties
3. They are efficiently delivered to sites of infection and achieve high tissue concentrations, particularly Azithromycin.
4. Three major randomised controlled trials in adults and one in children have shown that azithromycin and erythromycin are effective in preventing pulmonary exacerbations (reduced by 40-60%) in patients with bronchiectasis (Wong et al 2012, Altenburg et al 2013, Serisier et al 2013, Valery et al 2013). Meta-analyses of these and smaller studies also show modest improvements in quality of life and lung function (Wu et al 2014, Gao et al 2014).



Li W, et al. Azithromycin or Erythromycin? Macrolides for Non-Cystic Fibrosis Bronchiectasis in Adults: A Systematic Review and Adjusted Indirect Treatment Comparison. *Chronic Respiratory Disease.* 2018:16: 1-9.

## Adverse Effects.

1. Gastrointestinal effects (mainly diarrhoea) are common but are generally mild.
2. Hearing impairment has not been evaluated in bronchiectasis but has been reported in a study of azithromycin in COPD patients.
3. Cardiac arrhythmias : risk is very small with oral treatment. Caution should be taken with patients who have prolonged QTc interval.
4. Resistance to macrolides is very likely to develop with prolonged macrolide treatment. However, the negative consequences of macrolide resistance for individual patients treated with macrolides are unclear.

Dose regimens vary according to different studies and have not been standardised.

Azithromycin

- 500 mg 3 times a week (Monday, Wednesday, Friday)
- 250 mg 3 times a week (if patient is unable to tolerate higher dose)
- 250 mg daily

- The optimal duration of treatment is not clear. Positive clinical trials have treated for 6 or 12 months.
- The maximum benefit of macrolide treatment is thought be attained after at least 3 months of treatment.
- One approach to treatment is to give macrolide treatment over the cooler months, when the risk of exacerbations is highest, with a drug holiday over the summer months

## Checklist prior to starting treatment:

- ☑ Frequent exacerbations (3 or more exacerbations in past year)
- ☑ Exclude non-tuberculous mycobacterial infection (sputum culture x3)
- ☑ Assess cardiac risks (QTc interval, arrhythmia) – ECG

# 4. mucoactive treatment

## Recommendation

- Trial long-term mucoactive treatment (≥3 months) in adult patients with bronchiectasis who have difficulty in expectorating sputum and poor quality of life and where standard airway clearance techniques have failed to control symptoms (weak recommendation, low quality evidence).

- Clinically, significant benefits can be achieved in the following patient scenarios:
  - Frequent exacerbations
  - Difficulty clearing secretions
  - Chronic colinization, in particular Pseudomonas aeruginosa
  - Substantial sputum burden

## 4.1. Mucoactive agents

- The following mucoactive agents can be used to assist with airway clearance in patients with bronchiectasis:
  - Isotonic saline (0.9%)
  - hypertonic saline (3% – 7%)
  - Mannitol, Hyaluronic Acid
- There is no evidence to support the use of N-acetylcysteine or guaiafenesin in bronchiectasis.
- Avoid recombinant human DNase to adult patients with bronchiectasis (strong recommendation, moderate quality evidence)



Dornase, the recombinant DNase as an example has been evaluated in two trials showing no benefit in one trial and a worsening in FEV1 and increase in exacerbation frequency in the other in Dornase treated subjects (O'Donnell 1998, Wills 1996). In contrast, case reports however have suggested some benefit for Dornase treatment in primary ciliary dyskinesia (Desai 1995, El-Abiad 2007)

## Mechanism of action of HS

Not fully understood, theories include:

- Increases the osmotic gradient of water to the bronchial surface, rehydrating and increasing the volume of the epithelial lining fluid
- Decreases mucus viscosity
- Stimulates cough
- Accelerates mucociliary clearance via electrostatic interactions with mucins
- Inhibits epithelial sodium channels
- Possible anti-inflammatory effects
- Activation of antimicrobial peptides
- Inhibition of Pseudomonas aeruginosa growth due to an antimicrobial effect

## Practicalities

- Optimal salt concentration of HS ?
- A salt concentration of 12% is at the higher limit of patient tolerability, and the most commonly used concentrations are 6% or 7%.
- The volume is usually 4 ml to 5 ml.
- Mostly HS is used twice a day (some studies : once a day, or four times a day).
- Nebulization system, the most commonly used : Jet type

- Inhaled hypertonic saline (7%) as an adjuvant to respiratory therapy for 4 weeks was more effective in promoting expectoration than was isotonic saline.
- In another study, the use of hypertonic saline compared with 0.9% saline improved quality of life and pulmonary function, as well as reduced emergency room visits.
- However, a 12-month study comparing the use of hypertonic saline with 0.9% saline showed that there were no differences in exacerbation rates, quality-of-life scores, $FEV_1$, or reduction in bacterial colonization of sputum.



Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31
Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011; 105: 1831–1835.
Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667

Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31

No differences in $FEV_1$ and FVC between IS and HS

- ↑ weight of the sputum obtained in HS group than in IS group
- ↑ ease to expectorate and ↓ viscosity of sputum in HS group

24 bronchiectasis patients for 4 weeks separated by one washout week

Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011; 105: 1831–1835.

In the HS group versus the IS group:

- ↑ in $FEV_1$ percentage and FVC compared with baseline
- ↑ in global SGRQ score and in domains

randomized, single-blind, crossover study from the same research group analyzed 30 patients over a period of 8 months

Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667

There were no differences between the HS and the IS groups in:

- FEV1 and FVC
- The activity, impact and symptoms domains of the SGRQ
- Physical and social domains of the LCQ
- Frequency of annual exacerbations, exacerbations that required antibiotics,
- Frequency of cough
- Percentage of patients with potentially pathogenic microorganisms in sputum

single-center, randomized, double-blind, parallel group study of 12 months duration and 48 patients, comparing treatment of 5 ml twice-daily IS versus 6% HS. Each treatment arm had 20 patients,

# Lung function (HS vs IS)

- No significant differences in FEV1 and FVC were found in the initial work of Kellett and colleagues.
- In a study published in 2011, these authors found statistically significant differences in favor of HS in the FEV1 and FVC
- Nicolson and colleagues found no significant differences in absolute FEV1 and absolute FVC between HS and IS after 3, 6, or 12 months.
- Paff and colleagues did not find differences in FEV1 or FVC between the groups.



Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31
Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011; 105: 1831–1835.
Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667
Paff et al. A randomised controlled trial on the effect of inhaled hypertonic saline on quality of life in primary ciliary dyskinesia. Eur Respir. J.2017 Feb 23;49(2):1601770.

## Quality of life (HS vs IS)

- Kellett and colleagues reported a significant benefit in the overall SGRQ
- Nicolson and colleagues found no differences in the SGRQ at 3, 6, and 12 months. However, QoL improved significantly with respect to baseline with both saline solutions in all the SGRQ and LCQ domains at 3, 6, and 12 months.
- Paff and colleagues did not find significant differences in SGRQ score but In the Bronchiectasis Quality of Life Questionnaire (QoL-B), the study found clinically and statistically significant differences in favor of HS



Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31
Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011; 105: 1831–1835.
Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667
Paff et al. A randomised controlled trial on the effect of inhaled hypertonic saline on quality of life in primary ciliary dyskinesia. Eur Respir. J.2017 Feb 23;49(2):1601770.

## Exacerbations and use of antibiotics

- Kellett and colleagues: Significant difference in favor of HS (2.14 exacerbations/year vs 4.85 in the IS group). There was also a reduction in the use of antibiotics in favor of the group treated with HS
- Nicolson and colleagues: No differences between both groups
- Paff and colleagues: No differences were found



Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31
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Paff et al. A randomised controlled trial on the effect of inhaled hypertonic saline on quality of life in primary ciliary dyskinesia. Eur Respir. J.2017 Feb 23;49(2):1601770.

## Hospital admissions

- The only work that studied hospital admissions was that of Nicolson and colleagues, who showed that there were no significant differences

- Four of the participants in the study (10%) had to be hospitalized, one in the group treated with HS for 68 days, and three in the group treated with IS for 3, 5, and 61 days.



Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667

## Cough and expectoration

- Both solutions, added to respiratory physiotherapy, were better than physiotherapy alone to facilitate expectoration:
  - Reduce sputum viscosity, and increase the amount of expectorated sputum.[14]

- However, there were no differences between groups with respect to the frequency of cough at 3, 6, and 12 months.[16]



Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31
Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011; 105: 1831–1835.
Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667

## Microbiology

- The percentage of patients with potentially pathogenic microorganisms in the sputum samples decreased from 55% and 60% at the beginning of the study in the HS and IS groups, respectively, to 15% at the end of the study in both groups.

- No significant differences between HS or IS

## Inflammatory markers

The study by Paff and colleagues analyzed inflammatory markers but did not observe any change after the treatment with HS.[17]



Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31
Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011; 105: 1831–1835.
Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667
Paff et al. A randomised controlled trial on the effect of inhaled hypertonic saline on quality of life in primary ciliary dyskinesia. Eur Respir. J.2017 Feb 23;49(2):1601770.

## Adverse events

- Kellett and colleagues:  No intolerance to HS or significant reduction in $FEV_1$ following HS inhalation.
- In the 2011 study: 2 out of 32 patients were excluded for initial intolerance to HS.
- Nicolson and colleagues: 1 patient out of 48 in the initial screening was excluded because for significant reduction in FEV following HS inhalation. 2 withdrew from the HS group due to bronchoconstriction and intolerance to salbutamol.



Kellett F, Redfern J, Niven R. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with bronchiectasis. Respir Med 2005; 99: 27–31
Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011; 105: 1831–1835.
Nicolson CH, Stirling RG, Borg BM, et al. The long-term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 661–667

# 5. Anti-Inflammatories

## 5.1. Inhaled corticosteroids. (1,3)

- Should not be prescribed routinely unless there is an established diagnosis of coexisting asthma.
- Placebo-controlled studies of ICS in BE identified no beneficial effects.
- Patients with bronchiectasis had a nearly 200-fold increased risk of acquiring NTM infection compared with the general population and independently, use of ICS increased risk by 29-fold, increasing to an almost 50-fold increase in risk when taking higher-dose ICS (> 800 µg/d)

## 5.2. Macrolides (2)

- Three large randomized clinical trials of long-term use of macrolides (azithromycin or erythromycin) showed a reduction in the frequency of exacerbations in adults with bronchiectasis who had had one to three exacerbations in the previous year

## 5.3. No benefit to Statins (4)



(1) Lasserson, T, et al. Oral steroids for bronchiectasis (stable and acute exacerbations). Cochrane Database Syst Rev. 2001; 4: CD002162
(2) Polverino E, et al. European Respiratory Society Guidelines for the Management of Adult Bronchiectasis. European Respiratory Journal. 2017;50: 1700629.
(3) Kapur N, et al. Inhaled Corticosteroids for Bronchiectasis. Cochrane Database of Systematic Reviews. 2018, Issue 5. Art. No.: CD000996.
(4) Mandal P, et al. Atorvastatin as a Stable Treatment in Bronchiectasis: A Randomized Controlled Trial. The Lancet. 2014;2: 455-463.

# 6. Bronchodilators

- No evidence to support the routine use of bronchodilators in patients without dyspnea
- No evidence to support the routine use of anticholinergics.
- Recommend Long-acting bronchodilators in symptomatic patients with airflow obstruction
- Spanish guidelines recommend the use of short-acting bronchodilators prior to respiratory therapy and prior to the use of inhaled hypertonic solutions and/or inhaled antibiotics.



Arch Bronconeumol (Engl Ed). 2018 Feb;54(2):88-98. Spanish Guidelines on Treatment of Bronchiectasis in Adults

## 7. Airway Clearance

- Mobilize secretions and interrupt the vicious cycle of inflammation and infection.
- Inhaled agent (7% HS) + chest physiotherapy, such as : oscillatory positive expiratory pressure (PEP) device, high-frequency chest wall oscillation (HFCWO, OLE, autogenic drainage, active cycle breathing with huff coughs or manual chest percussion.

Convincing the new grad that pulmonary toilet means it's his turn to clean the dept bathroom – priceless!

# Benefits of Airway Clearance

- Improvements in quality of life scores and exercise capacity in patients using the PEP device twice daily for 3 months.
- HFCWO produced statistically significant improvements in the Breathlessness, Cough, and Sputum Scale and COPD Assessment test, improved FEV1 and FVC, and reduced C-reactive protein and sputum neutrophils compared with the PEP device.
- Adding postural drainage to CPT has been shown to augment the amount of sputum produced during airway clearance.
- Any of the airway clearance modalities can be tailored to fit the specific preferences of the patient but in all cases, patient education is a paramount factor in the success of therapy.



Maggie McIlwaine , et al. Cochrane Database Syst Rev. 2019 Nov 27;2019(11)

# 8. Physical Exercise / Pulmonary Rehabilitation

- Incremental shuttle walk distance and quality-of-life scores were found to improve, but these benefits were not sustained at 6 months.
- The frequency of exacerbations over 12 months was reduced.
- No effect on cough or symptom related quality of life.
- Pulmonary rehabilitation initiated during an exacerbation had no impact on exacerbation frequency or mortality.
- European guidelines recommend that patients who have exertional limitation (mMRC scale score > 1) should be encouraged to exercise regularly and participate in pulmonary rehabilitation.



European Respiratory Journal 2017 50: 1700629.

## Order of medications

A general guide is:

1. Bronchodilator inhalers (e.g. Albuterol)
2. Nebulised saline
3. Other inhaled medications (preventors)
4. *Nebulised antibiotics (Tobramycin, Colistin)
5. *The airway clearance routine should be done before inhaled antibiotics

# FOLLOW-UP AND MONITORING

Perform spirometry with bronchodilator use every 6 months, lung volume assessment annually, and the six-minute walk test

Collect samples from the lower respiratory tract (sputum, for example) at regular intervals of 3-4 months and during pulmonary exacerbations for aerobic culture, as well as annually for culture for fungi and mycobacteria. If the patient is being treated with chronic macrolide therapy, culture for mycobacteria should be performed every 4 months

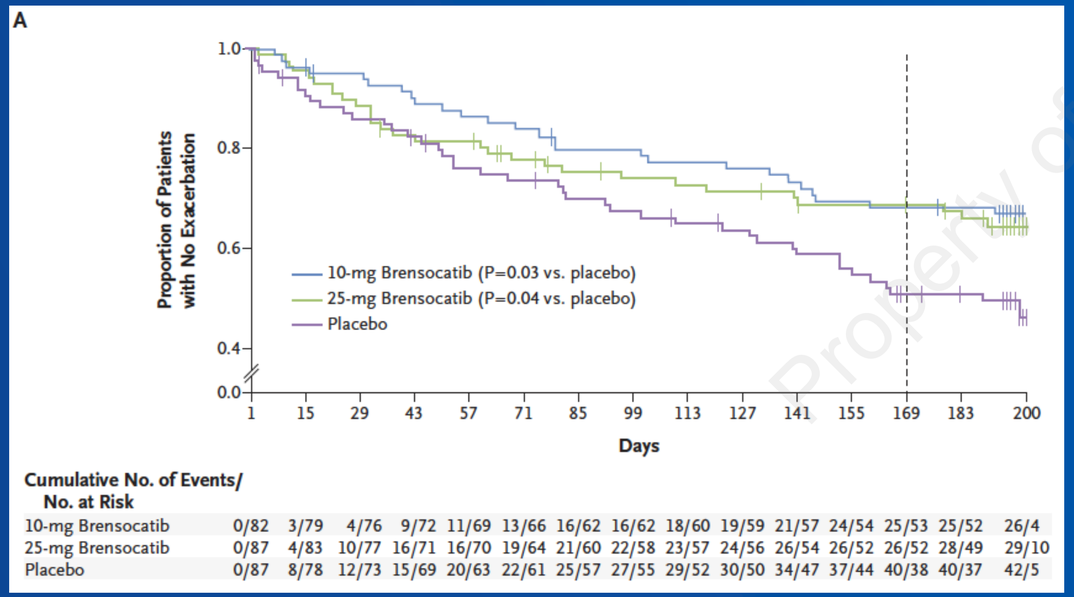
A severity score and a prognostic estimate should be calculated at the time patients are diagnosed with bronchiectasis. Periodic calculation of the score (annually, for example) aids in therapeutic management.

# WILLOW Study – Primary and Secondary Outcomes

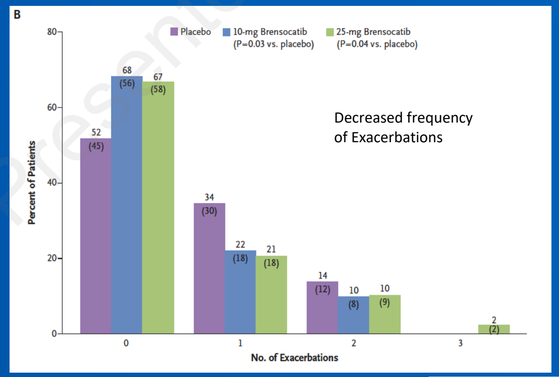
- ASPEN Trial : completed enrollment

BRENSOCATIB : Inhibitor of dipeptidyl peptidase 1 (DPP-1) required for activation of Neutrophil Serine Proteases

## Prolonged time to first exacerbation c/w placebo:

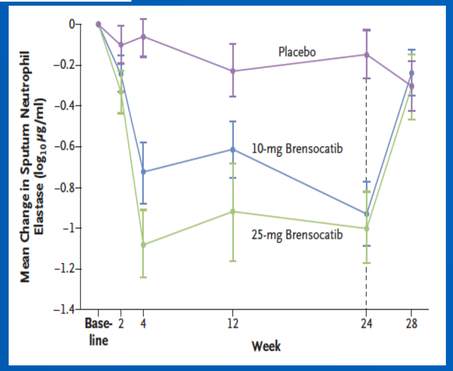



| Cumulative No. of Events/ No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10-mg Brensocatib | 0/82 | 3/79 | 4/76 | 9/72 | 11/69 | 13/66 | 16/62 | 16/62 | 18/60 | 19/59 | 21/57 | 24/54 | 25/53 | 25/52 | 26/4 |
| 25-mg Brensocatib | 0/87 | 4/83 | 10/77 | 16/71 | 16/70 | 19/64 | 21/60 | 22/58 | 23/57 | 24/56 | 26/54 | 26/52 | 26/52 | 28/49 | 29/10 |
| Placebo | 0/87 | 8/78 | 12/73 | 15/69 | 20/63 | 22/61 | 25/57 | 27/55 | 29/52 | 30/50 | 34/47 | 37/44 | 40/38 | 40/37 | 42/5 |




Decreased frequency of Exacerbations

Decreased Sputum Neutrophil Elastase






Chalmers JD, et al. N Engl J Med 220;383:2127-37

## Future Therapies – Clinical Trials

| Drug | | Phase | Status |
|---|---|---|---|
| CSL787 | Nebulized, plasma derived immunoglobulin | 1 | Recruiting |
| ARINA-1 | Inhaled ascorbic acid, glutathione, | 2a | Recruiting |
| roflumilast | phophodiesterase-4 inhibitor | 2 | Recruiting |
| icenticaftor | CFTR potentiator | 2 | Recruiting |
| BI 1291583 | cathespsin C inhibitor | 2 | Recruiting |
| mepolizumab | Anti-IL5 | - | Recruiting |
| S-1226 | Inhaled CO2 enriched air + Perflubron | 2 | Recruiting |
| BCG | TB vaccine | 2 | Recruiting |
| hypertonic saline, carbocysteine | mucolytic | 3 | Recruiting |
| AZD5069 | CXCR2 antagonist | 2 | Completed |

THE END