Evaluating and Treating Bronchiectasis Patients

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Penn Medicine

CELEBRATING 250 YEARS
1765–2015
Perelman School of Medicine
UNIVERSITY of PENNSYLVANIA

Disclosures

- ✓ **Research grant support:**
  - **Bronchiectasis Research Registry/COPD Foundation**
- ✓ **Advisory Board:**
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  - **Aradigm**
  - **Cipla**

Bronchiectasis

- ✓ **Characterized pathologically by airway inflammation and permanent bronchial dilatation, and clinically by productive cough**
- ✓ **Heterogeneous entity with multiple etiologies**
- ✓ **Prevalence is increasing**
- ✓ **Clinical course punctuated by exacerbations**
- ✓ **Associated with notable QOL impairment, and significant morbidity and mortality**

- **Seitz et al. *Chest* 2012; 142**
- **Chalmers et al. *AJRCCM* 2013; 189.**

EVALUATION

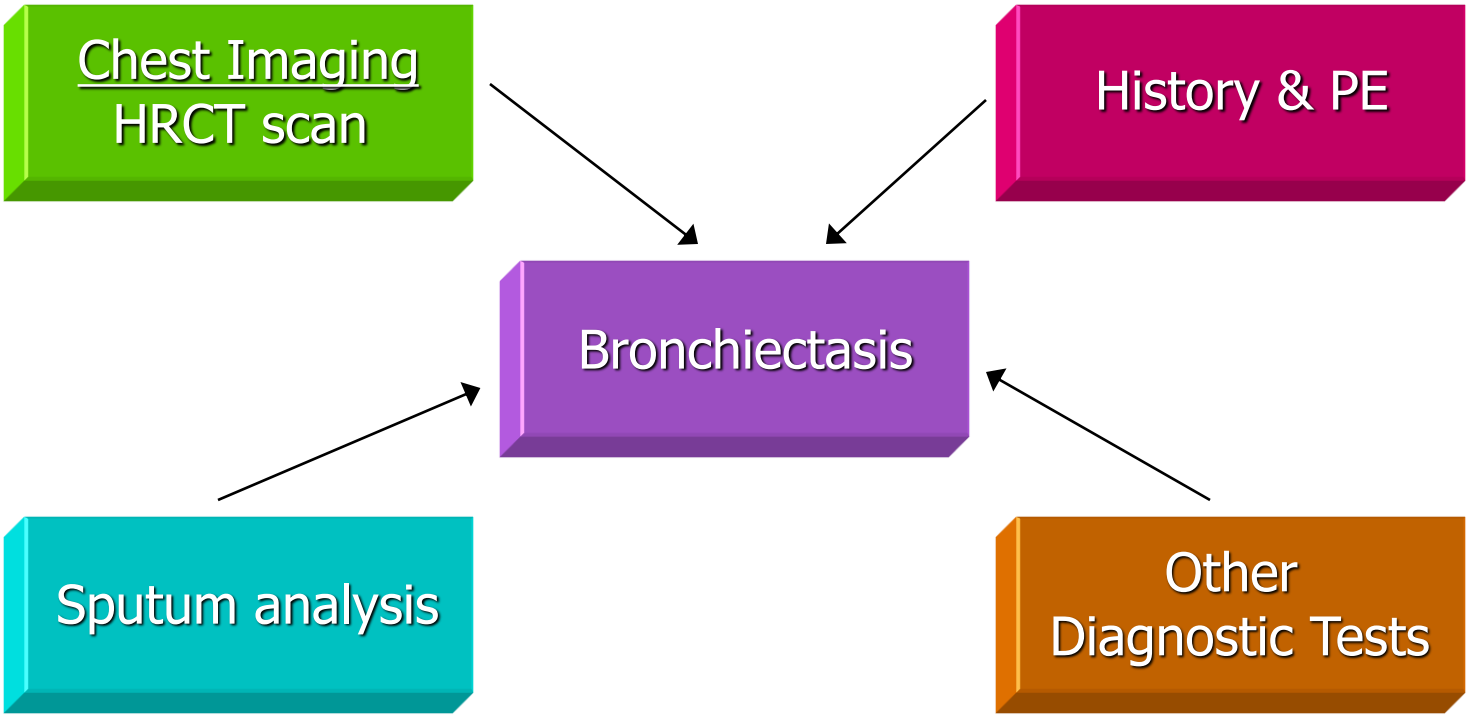
Get the Diagnosis Right

1) Establish presence of bronchiectasis

2) Identify underlying cause

- Successful in a majority of cases
- May impact treatment in as many as 40% of patients

Bronchiectasis: Diagnosis

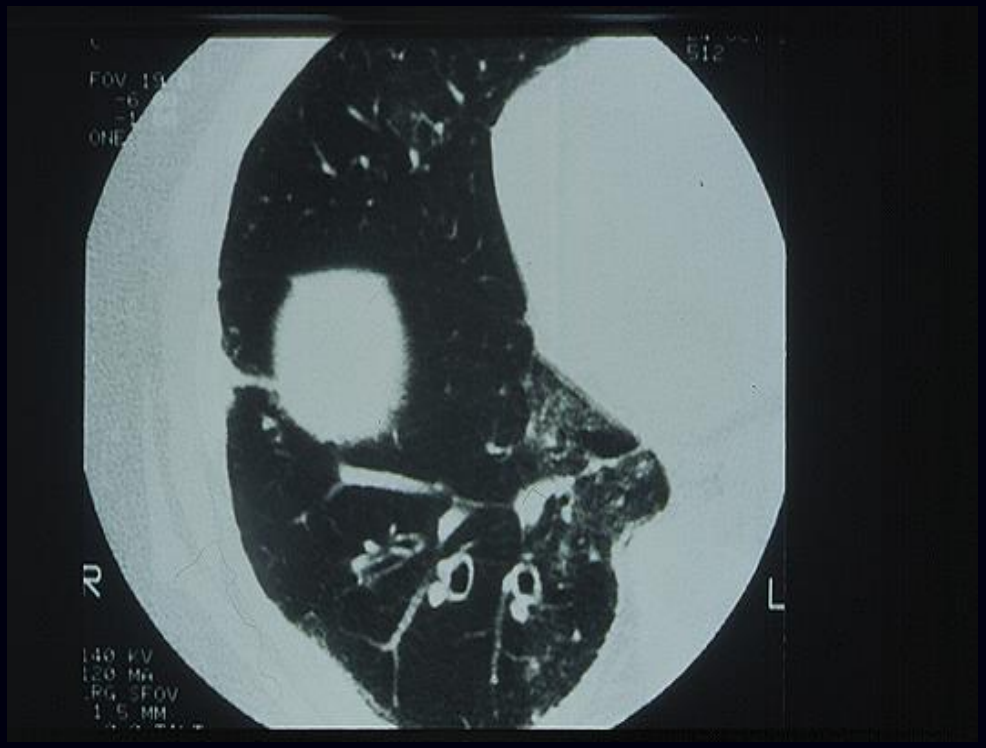


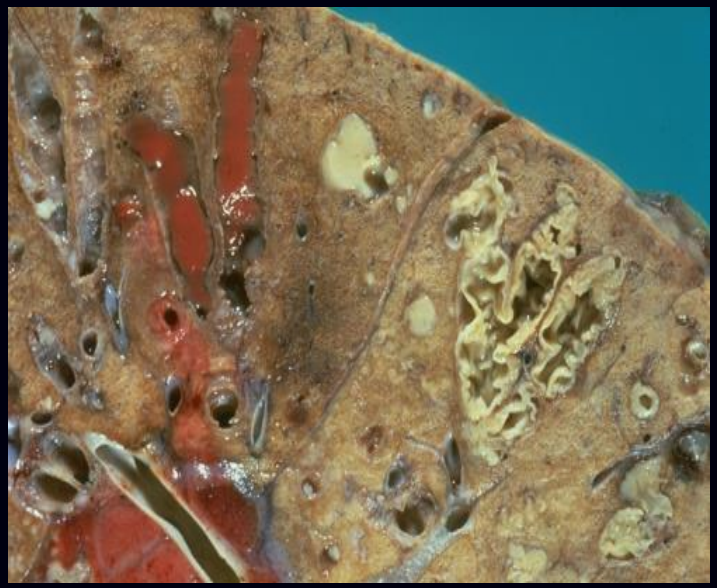
Clinical Profiles

- ✓ **Persistent productive cough**
  - **Daily sputum production**
  - **Symptoms for many years**
  - ***Pseudomonas aeruginosa* by sputum culture**
- ✓ **Recurrent respiratory tract infections**
- ✓ **Non-smokers thought to have COPD with recurrent exacerbations**
- ✓ **Unexplained hemoptysis**

BTS Guideline. Pasteur et al. *Thorax* 2010; 65.

HRCT scan





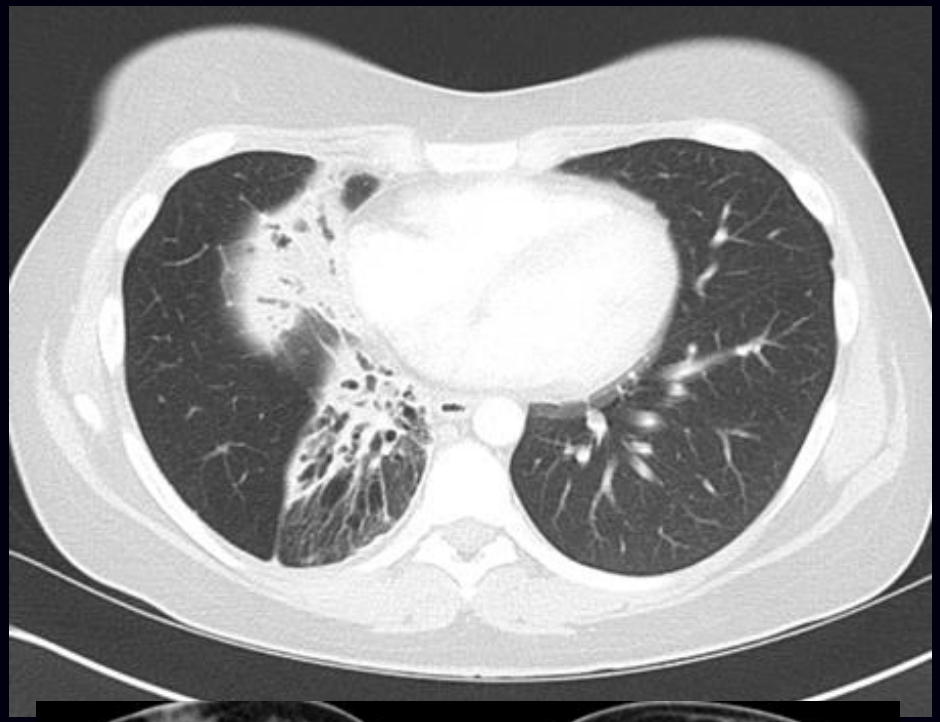
Radiological Distribution

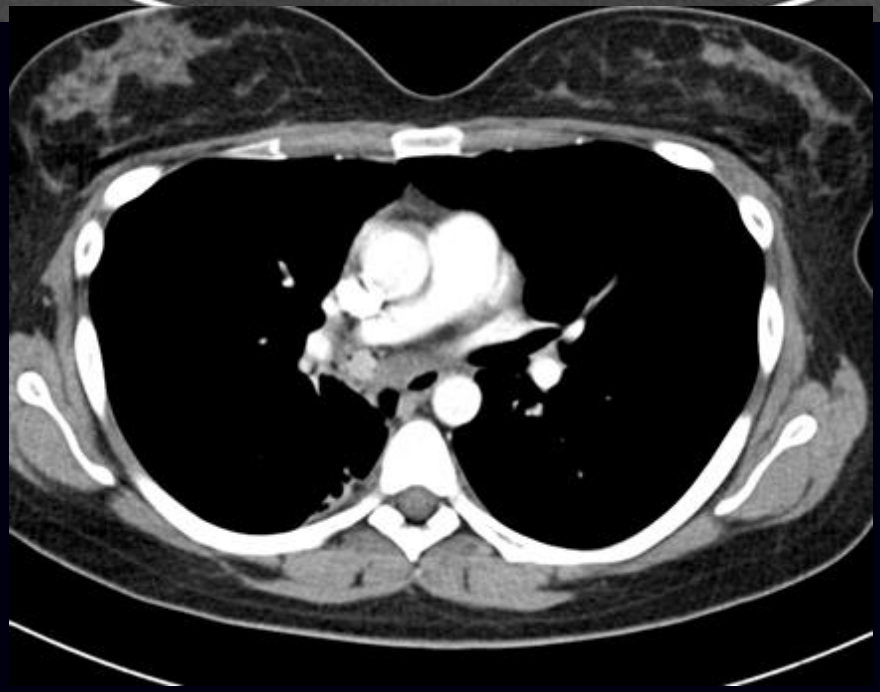
Focal Disease

- ✓ **Postinfectious**
  - **Bacterial**
  - **Viral**
  - **Mycobacterial (TB, NTM)**
- ✓ **Airway obstruction**
  - **Foreign body**
  - **Bronchial stricture (i.e., RML syndrome)**
  - **Endobronchial mass**

Focal disease is rarely due to genetic causes

•Barker AF. *N Engl J Med.* 2002;346.
•Mysliwiec V, Pina JS. *Postgrad Med*. 1999; 106.
•Pasteur MC, et al. *AJRCCM*. 2000; 162.





Radiological Distribution

Focal Disease

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  - Viral
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  - Foreign body
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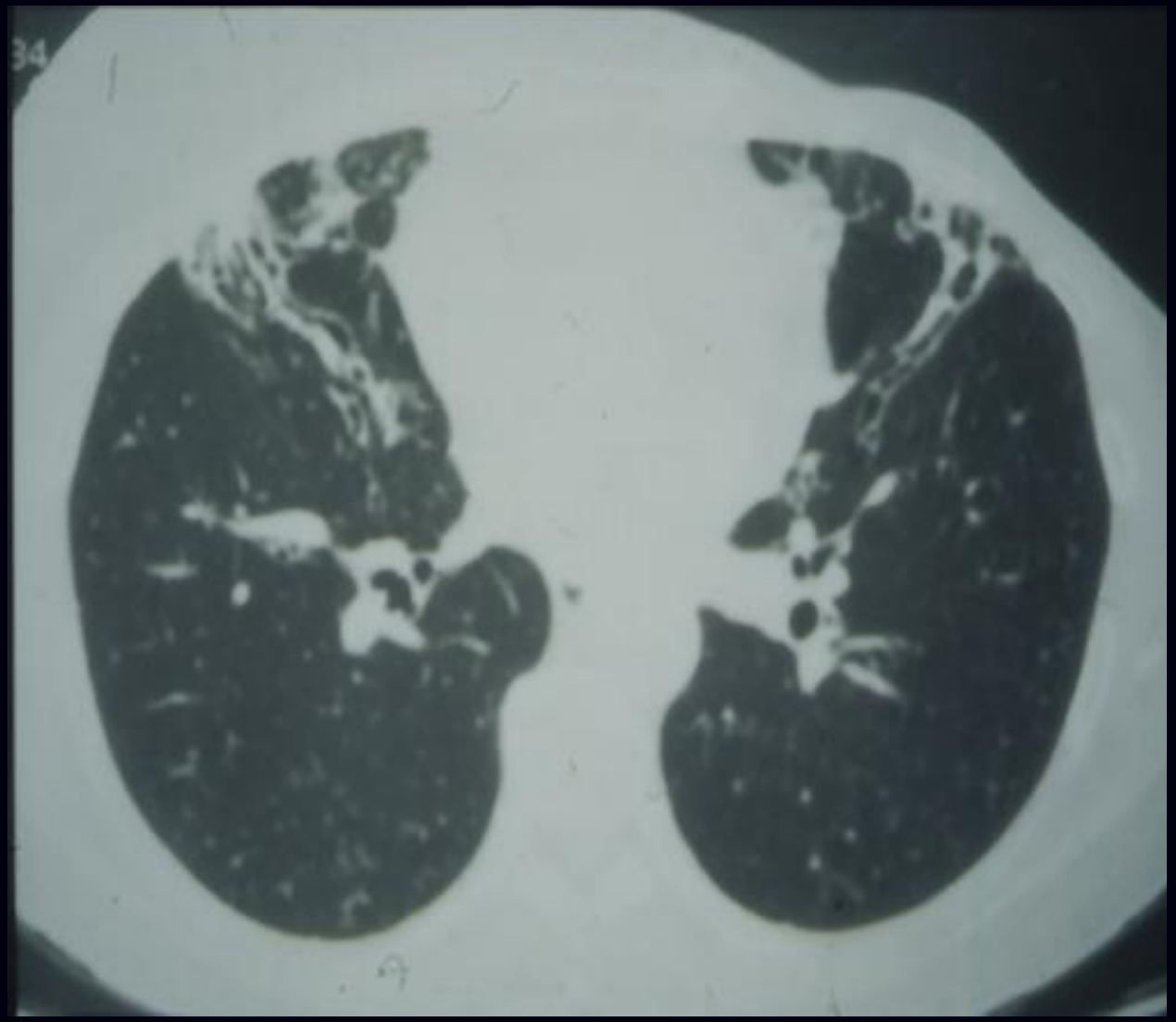
  - Endobronchial mass

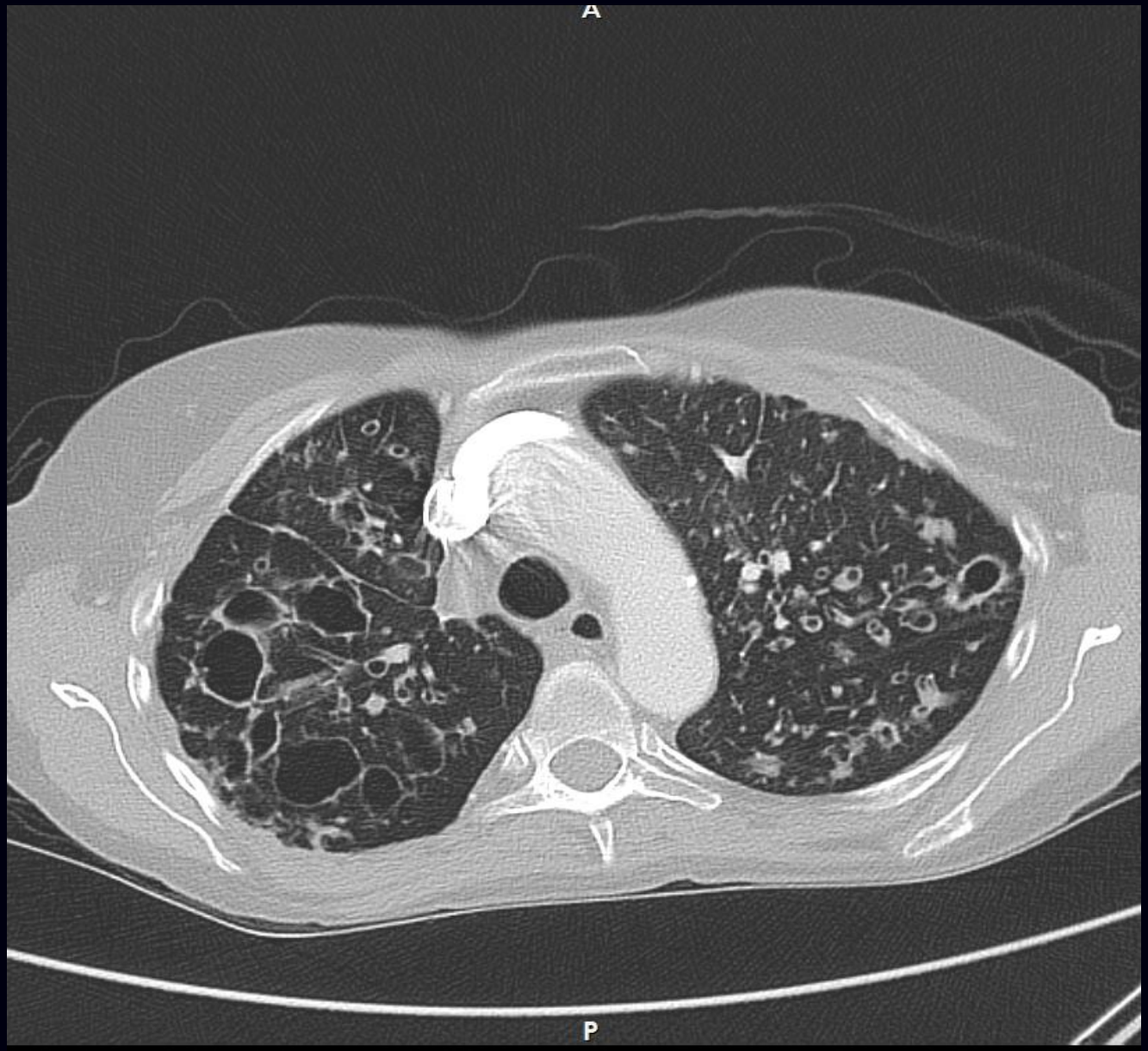
Multifocal Disease

- ✓ **Postinfectious**
  - Measles, pertussis
  - Mycobacterial (TB, NTM)
- ✓ **Congenital syndromes**
  - Cystic fibrosis
  - Primary ciliary dyskinesia
- ✓ **Immunodeficiency states**
  - Immunoglobulin deficiency/CVID
  - HIV/AIDS
- ✓ **Immune-mediated diseases**
  - ABPA
  - Rheumatoid arthritis
  - Sjogren's syndrome
  - Inflammatory bowel disease
- ✓ **GERD/Aspiration**

•**Barker AF. *N Engl J Med.* 2002;346.**
•**Mysliwiec V, Pina JS. *Postgrad Med*. 1999; 106.**
•**Pasteur MC, et al. *AJRCCM*. 2000; 162.**

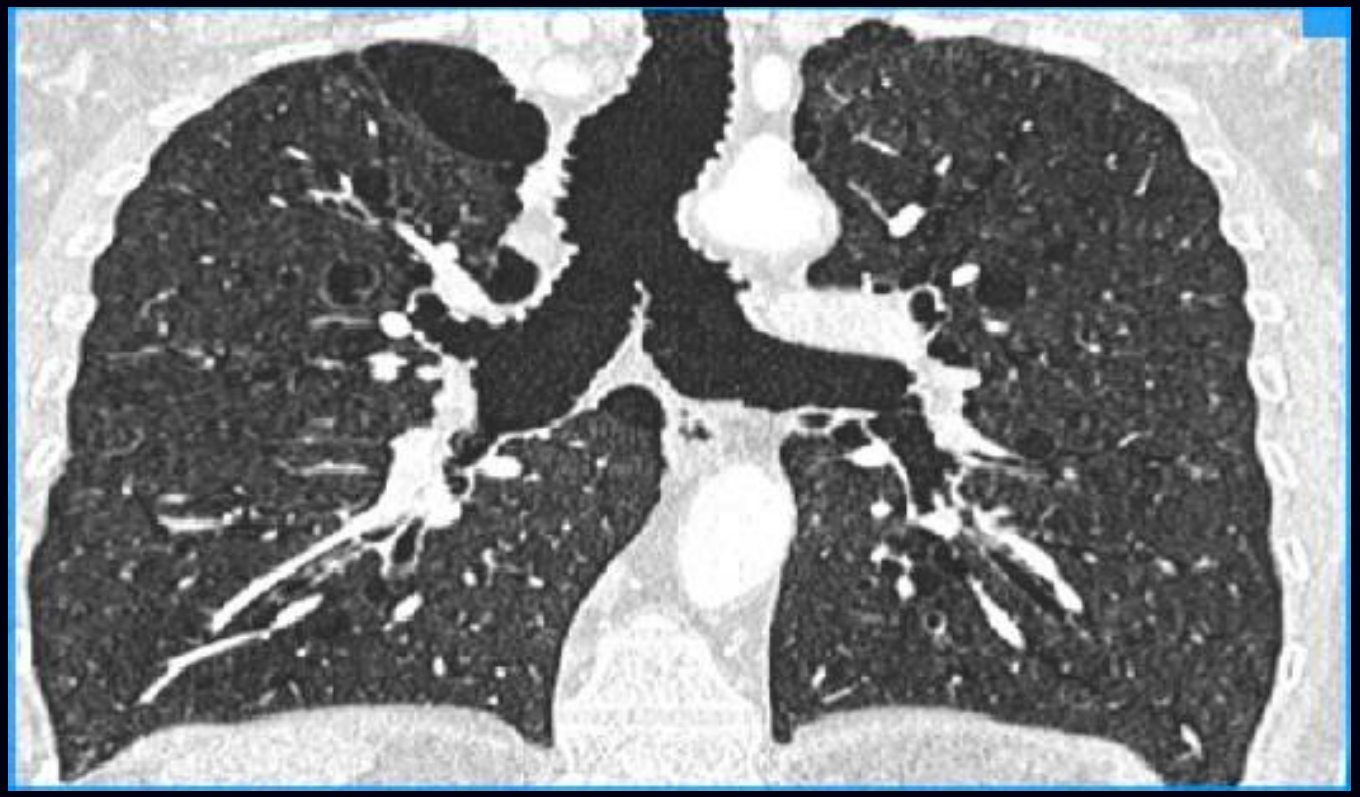


MAC Infection

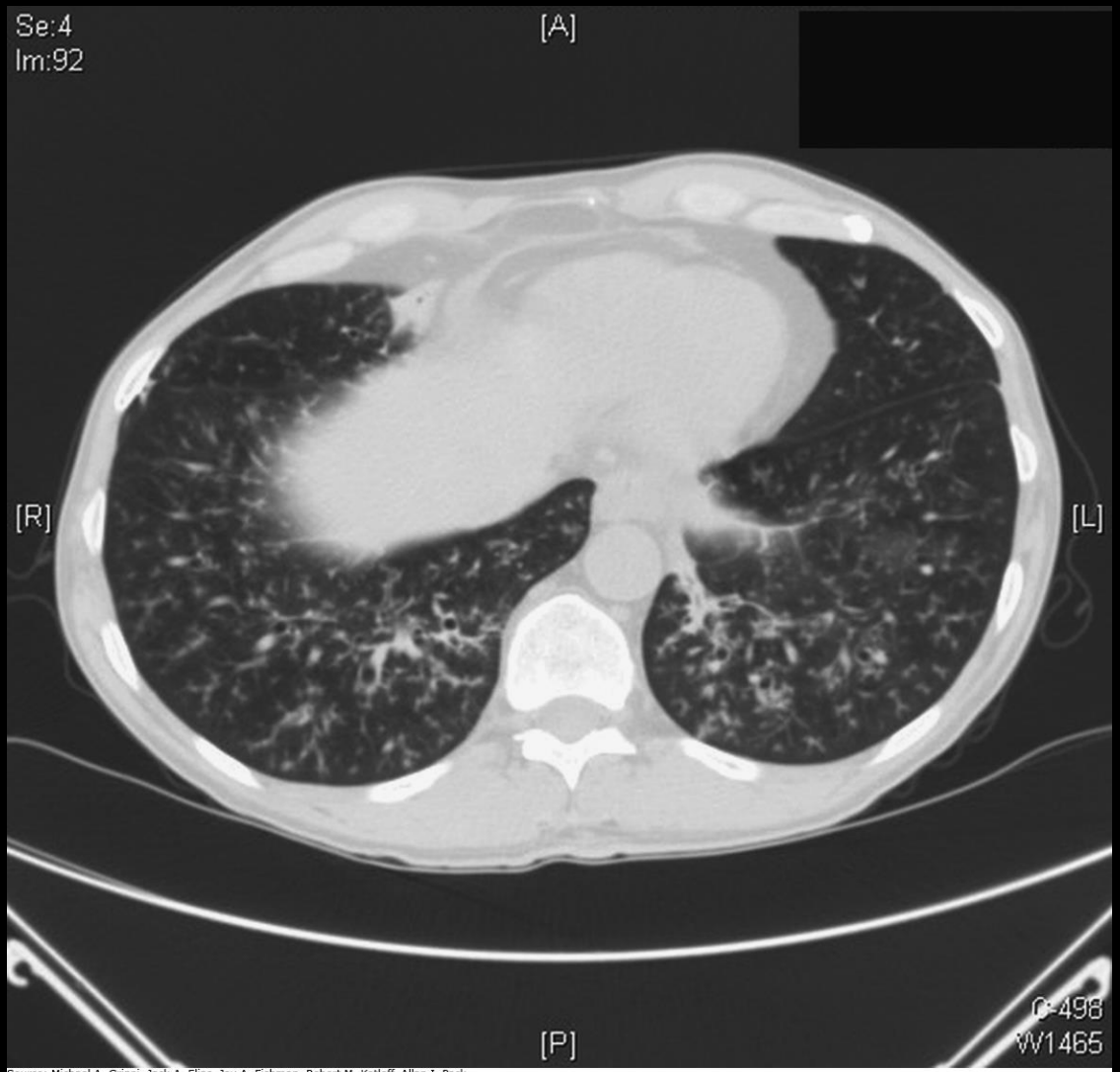


Cystic Fibrosis

ABPA



Mounier-Kuhn Syndrome



Aspiration

Approach to Diagnosis

- ✓ **Age of the patient**
- ✓ **Presence of extrapulmonary signs of symptoms**
- ✓ **Presence of associated conditions**
  - **ABPA, RA, COPD**
- ✓ **Microbiology**

Work-up: ERS Guidelines

✓ **Minimum bundle**

- **CBC with differential count**
- **Serum immunoglobulins (A, G, M)**
- **ABPA testing: serum IgE level, specific IgE and IgG, *Aspergillus* skin test**
- **Routine sputum culture**

Other testing as dictated by clinical data

ERS Guideline. Polverino et al. *Eur Resp J* 2017; 50.
Conditional recommendation

- ✓ **CF testing (*both* sweat chloride tests and CFTR genetic mutation analysis):**
  - **All children and all adults up to the age of 40**

- ✓ **Consider CF testing in others with:**
  - **Upper lobe bronchiectasis**
  - **Persistent isolation of *S. aureus* in sputum**
  - **Features of malabsorption**
  - **Male primary infertility**
  - **Recurrent pancreatitis**

BTS Guideline. Pasteur et al. *Thorax* 2010; 65.
ERS Guideline. Polverino et al. *Eur Resp J* 2017; 50.

- ✓ **PCD testing:**
  - **Neonatal respiratory distress**
  - **Chronic rhinosinusitis or otitis media**
  - **Infertility or dextrocardia**

- ✓ **Work-up for gastric aspiration should be considered in selected patients**

- ✓ **Bronchoscopy: not routinely warranted**

BTS Guideline. Pasteur et al. *Thorax* 2010; 65.
ERS Guideline. Polverino et al. *Eur Resp J* 2017; 50.

TREATMENT

Goals of Treatment

- ✓ Control symptoms: cough, sputum characteristics
- ✓ Reduce exacerbations
- ✓ Improve quality of life
- ✓ Maintain lung function
- ✓ Reduce mortality
- ✓ Reduce cost of care

Treatment Targets

- ✓ **Impaired sputum clearance**
- ✓ **Acute and chronic lung infection**
- ✓ **Airway inflammation**
- ✓ **Underlying condition**

Adult Patients With Bronchiectasis

A First Look at the US Bronchiectasis Research Registry

Timothy R. Aksamit, MD; Anne E. O'Donnell, MD; Alan Barker, MD; Kenneth N. Olivier, MD; Kevin L. Winthrop, MD; M. Leigh Anne Daniels, MD, MPH; Margaret Johnson, MD; Edward Eden, MD; David Griffith, MD; Michael Knowles, MD; Mark Metersky, MD; Matthias Salathe, MD; Byron Thomashow, MD; Gregory Tino, MD; Gerard Turino, MD; Betsy Carretta, MPH; and Charles L. Daley, MD; for the Bronchiectasis Research Registry Consortium

***Chest* 2017; 151.**

1826 patients with bronchiectasis enrolled between 2008 and 2014

- ✓**Airway clearance - 56%**
- ✓**Antibiotics only for exacerbation - 41%**
- ✓**Suppressive antibiotics - 39%: 10% aerosol, 7% rotating oral regimen**
- ✓**Inhaled bronchodilators - 61%**
- ✓**Inhaled steroids - 39%, systemic steroids - 13%**

Airway Clearance Therapy

- ✓ **Techniques designed to enhance mucociliary clearance**
  - **Widely considered a mainstay of management**
  - **Little data regarding efficacy**

    Cochrane Review 2015

- ✓ **Number of modalities in use:**
  - **Mechanical methods**
  - **Pharmacologic**

Airway Clearance Therapy

- ✓ **Target population:**
  - **Symptomatic patients: cough, sputum production**
  - **Difficulty expectorating sputum**
  - **Frequent acute exacerbations**

ERS Guideline. Polverino et al. *ERJ* 2017; 50
Weak recommendation

Recommend a modality that will maximize patient adherence

Systemic Antimicrobial Therapy for Exacerbations

Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research

Eur Resp J 2017; 49.

Adam T. Hill[1,26], Charles S. Haworth[2,26], Stefano Aliberti[3], Alan Barker[4], Francesco Blasi[3], Wim Boersma[5], James D. Chalmers[6], Anthony De Soyza[7], Katerina Dimakou[8], J. Stuart Elborn[9], Charles Feldman[10], Patrick Flume[11], Pieter C. Goeminne[12,13], Michael R. Loebinger[14], Rosario Menendez[15], Lucy Morgan[16], Marlene Murris[17], Eva Polverino[18], Alexandra Quittner[19], Felix C. Ringshausen[20], Gregory Tino[21], Antoni Torres[18], Montserrat Vendrell[22], Tobias Welte[20], Rob Wilson[14], Conroy Wong[23], Anne O'Donnell[24,27] and Timothy Aksamit[25,27] for the EMBARC/BRR definitions working group

Definition of a bronchiectasis pulmonary exacerbation for clinical trials

A person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h:

1) Cough
2) Sputum volume and/or consistency
3) Sputum purulence
4) Breathlessness and/or exercise tolerance
5) Fatigue and/or malaise
6) Haemoptysis

AND a clinician determines that a change in bronchiectasis treatment is required#

Sputum culture is critical

Table 1
Bacteriology of bronchiectasis

Organisms	Study/Year (n)			
	Nicotra et al,[5] 1995 (n = 123)	Pasteur et al,[6] 2000 (n = 150)	King et al,[4] 2007 (n = 89)	Li et al,[7] 2005 (n = 136)
H influenza	30	35	47	39
P aeruginosa	31	31	12	11
M catarrhalis	2	20	8	2
S pneumoniae	11	13	7	22
S aureus	7	14	4	4
No organism	Not specified	23	21	Not specified
Mycobacterium	17	0	2	Not specified

US BRR:

- ***P. aeruginosa* - 33%**
- ***S. aureus* - 11.3%**

- **O'Donnell. *Clin Chest Med* 2012.**
- **Metersky et al. *Ann ATS* 2018; 15.**
- **Aksamit et al. *Chest* 2017; 151.**

Antimicrobial Therapy

General Principles:

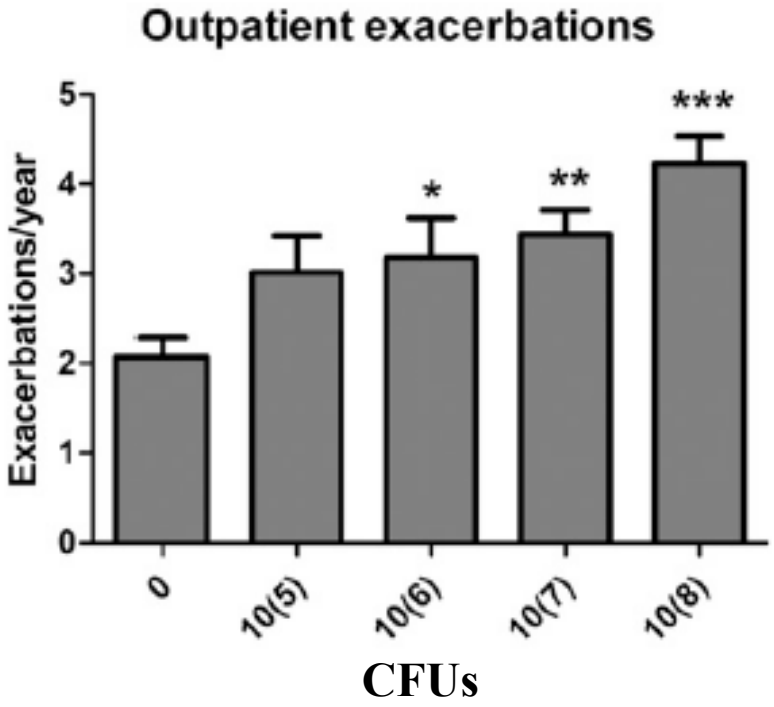
- ✓ **Let sputum analysis be your guide**
- ✓ **Adjust/narrow antibiotic if specific pathogen isolated**
- ✓ **Optimal duration is uncertain:**
  - **14 day course**
  - **Longer courses as dictated by clinical response**
- ✓ ***Pseudomonas aeruginosa* and *S. aureus* infections can be especially challenging**

ERS Guideline. Polverino et al. *ERJ* 2017; 50.
Conditional recommendation

Inhaled Antibiotic Therapy

Bacterial Load: Impact

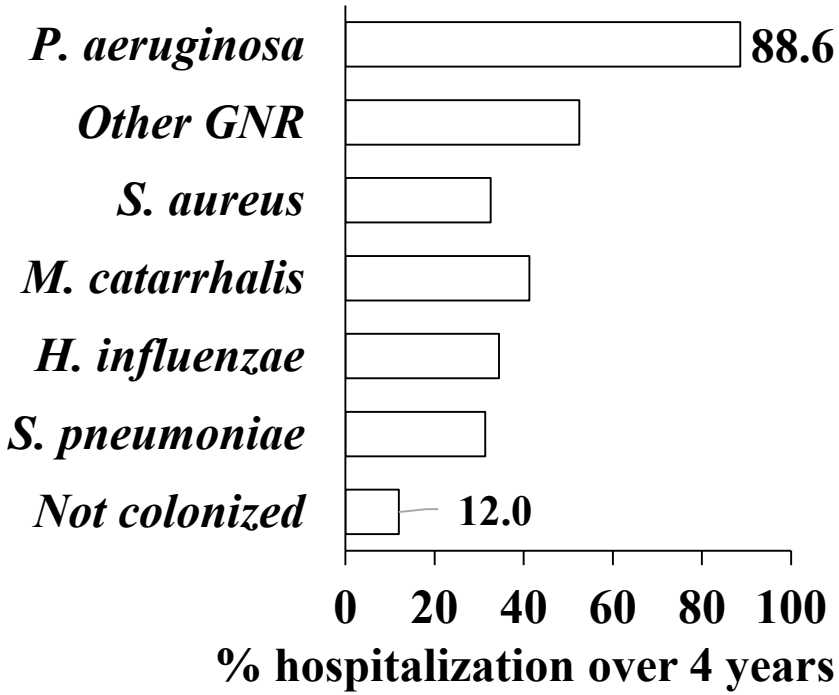
- ✓ **High bacterial load (CFUs) linked to:**
  - **Risk of future exacerbations**
  - **Future hospitalizations for exacerbations**
  - **Markers of lung inflammation**



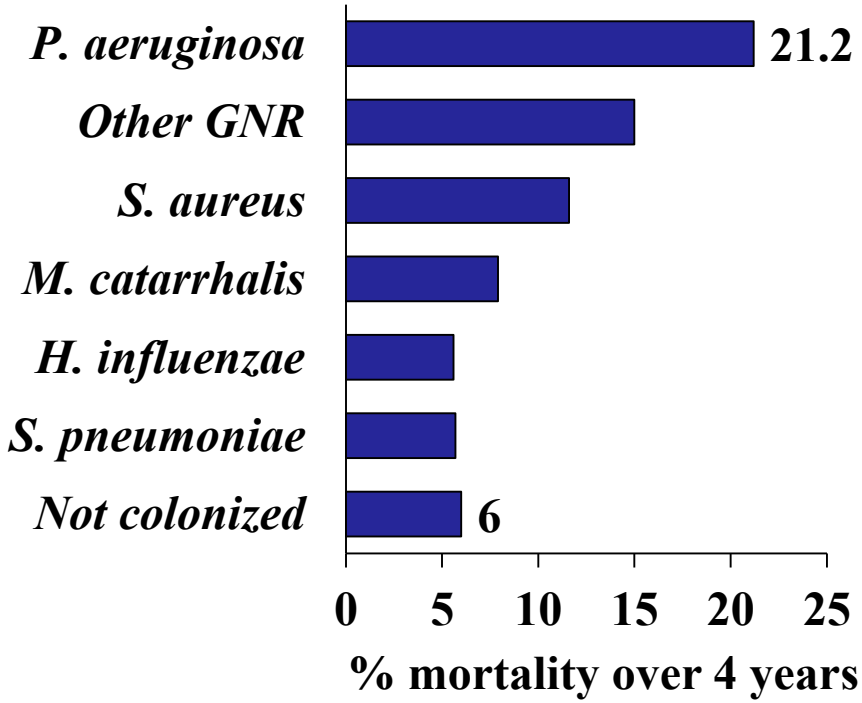
Chalmers, et al. *Am J Respir Crit Care Med* 2012;.

Impact of *Pseudomonas* Infection

7× Higher Risk of Hospitalization



3× Higher Mortality



- Chalmers, et al. *AJRCCM.* 2014; 189.
- Finch, et al. *Annals ATS.* 2015; 12.

Inhaled antibiotics have been standard of care for CF patients with *P. aeruginosa* infection

- ✓ **Tobramycin:** Ramsey et al. *NEJM*, 1999; 340
- ✓ **Aztreonam:** McCoy et al. *AJRCCM*, 2008; 178

Inhaled Antibiotics

Pros:

- ✓ **High concentration in the airway**
- ✓ **Reduced systemic absorption**
- ✓ **Reduced systemic toxicity**

Cons:

- ✓ **Airway side effects**
- ✓ **Possible emergence of resistance**

Inhaled Antibiotics: Clinical Trials

- ✓Tobramycin
- ✓Gentamicin
- ✓Aztreonam for inhalation solution
- ✓Levofloxacin
- ✓Colistin
- ✓Dry powder ciprofloxacin (RESPIRE)
- ✓Liposomal ciprofloxacin (ORBIT)

Inhaled Antibiotics: Summary

- ✓ **Clear microbiologic impact**
- ✓ **Clinical efficacy not proven conclusively in clinical trials thus far**
  - **Reduction of exacerbations**
    - **Colistin, RESPIRE-1, ORBIT-4**
  - **Improved quality of life**
    - **Colistin: improvement in SGRQ after 26 weeks (10. 5 units)**

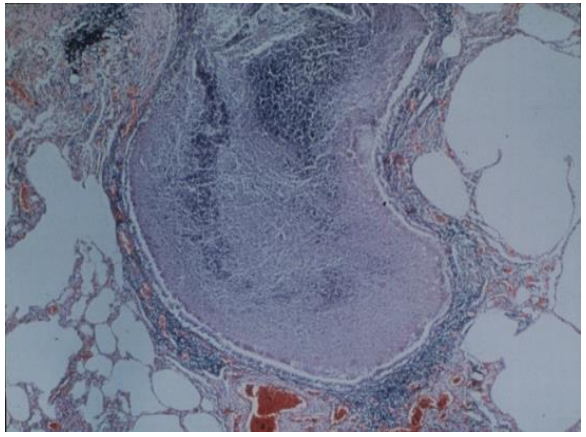
Inhaled Antibiotics: Summary

- ✓ **Adverse effects (cough, dyspnea, bronchospasm) well described**
- ✓ **Emergence of resistant pathogens has not been observed**
- ✓ **None currently approved by regulatory agencies**

- ✓ **Target population:**
  - **Chronic GNR infection**
  - **Frequent exacerbations: > 3/year**
  - **Other therapy optimized**

- ✓ **Daily versus on/off regimen**
- ✓ **Role versus chronic macrolides has not been established**

Chronic Macrolide Therapy



Macrolides & Bronchiectasis

- ✓ **Myriad anti-inflammatory and immunomodulatory properties**
  - **Inhibit mucus hypersecretion**
  - **Reduce IL-8 and neutrophil elastase**
  - **Inhibit neutrophil adhesion to epithelial cells**
  - **Inhibit biofilm formation**
  - **Inhibit production of reactive oxygen species from neutrophils**
- ✓ **Precedent for their use in other airways diseases: CF, DPB, post-transplant OB, COPD**

Kanoh, Rubin. *Clin Microbiol R*ev, 2010

EMBRACE

(Wong et al. *Lancet* 2012: 380)

- 141 patients
- At least 1 exacerbation in past year
- Azithromycin 500mg thrice weekly for 6 months
- Co-primary endpoints:
  - Event-based exacerbation frequency
  - FEV_1
  - SGRQ

BAT

(Altenburg et al. *JAMA* 309, 2013)

- 83 patients
- At least 3 exacerbations in past year
- Azithromycin thrice weekly for 12 months
- Primary endpoint:
  - # of infectious exacerbations

BLESS

(Serisier et al. *JAMA* 309, 2013)

- 107 patients
- At least 2 exacerbations in past year
- Erythromycin 400mg twice daily for 48 weeks
- Primary endpoint:
  - Mean rate of exacerbations/year

All three studies reported decrement in exacerbations

Macrolides & Bronchiectasis: Concerns

- ✓ **Bacterial antibiotic resistance**
- ✓ **NTM macrolide resistance**
- ✓ **Cardiac risk**
- ✓ **Other adverse effects**
  - **GI tract**
  - **Ototoxicity**

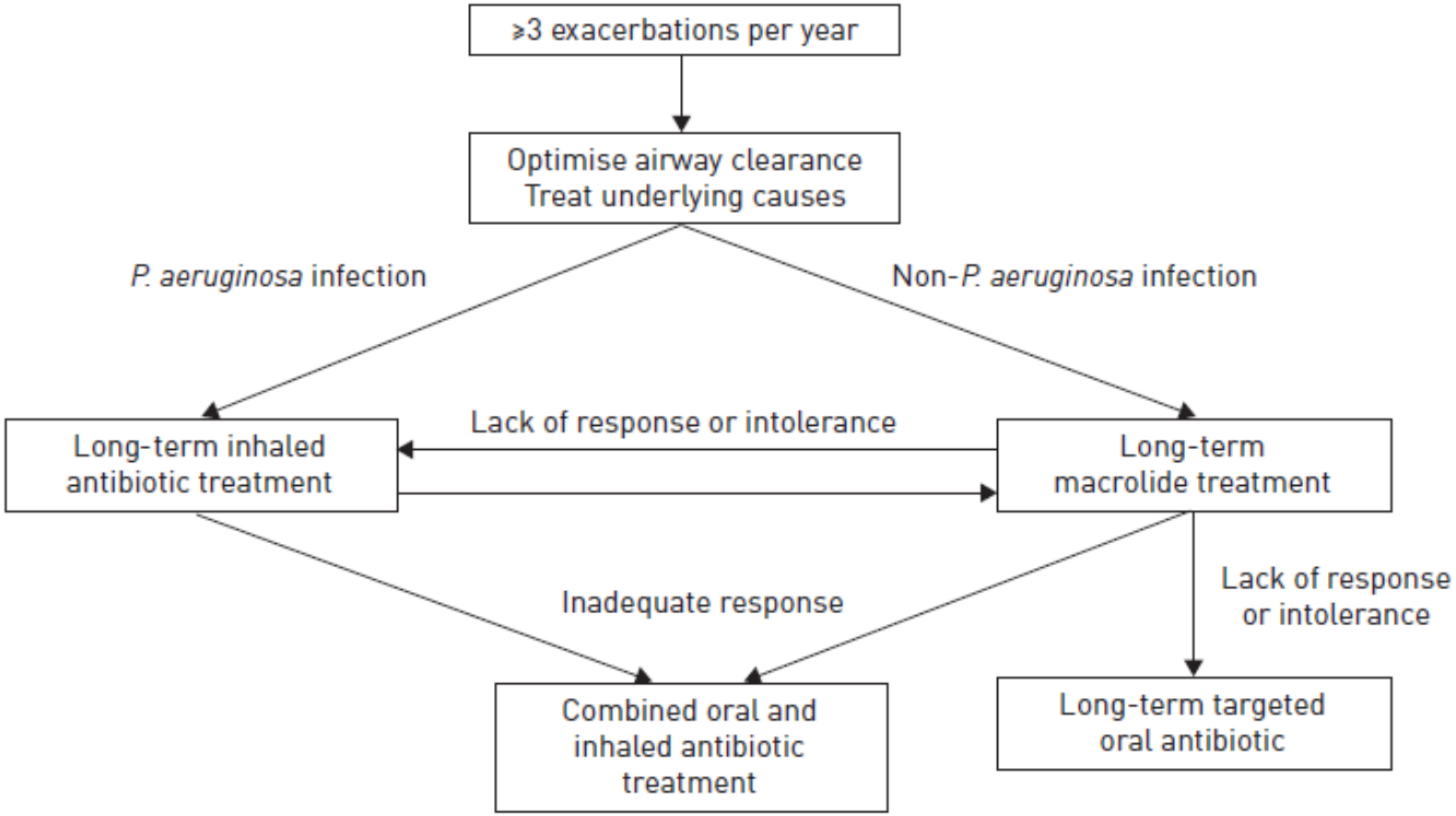
Macrolides: Target Patients

- ✓ **Frequent exacerbations (> 2-3 per year)**
  - **No subgroup data; role in other settings ?**
- ✓ **No significant underlying cardiac disease and normal EKG/QTc**

- Avoid in patients with known or strongly suspected NTM infection.

- Duration of therapy has not been established

Long-term Antibiotic Treatment



ERS Guideline. Polverino et al . *ERJ* 2017; 50.
Conditional recommendations

Not Recommended

- ✓ **Inhaled corticosteroids**
  - **Possible increased risk of NTM infection**
- ✓ **Chronic systemic corticosteroids**
- ✓ **Chronic non-macrolide systemic antibiotics**

- **Kapur N, et al. *Cochrane Database Syst Rev*. 2009 Jan 21.**
- **Tsang KW, et al. *Thorax*. 2005;60.**
- **Andrejak et al. *Thorax*. 2013; 68.**
- **Polverino et al . ERS Guideline. *ERJ* 2017; 50.**
- **Wurzel et al. *Cochrane Review* 2011**
- **TSANZ Guidelines, *MJA* 2015**

Surgery

An option for:

- **Localized disease, frequent exacerbations despite medical therapy**
- **As an adjunct to medical therapy for NTM infection**
- **Refractory, massive hemoptysis**

Acceptable morbidity and mortality reported

ERS Guideline. Polverino et al. *ERJ* 2017; 50.
Weak recommendation

Other Measures

- ✓ Specific therapy for underlying conditions when appropriate
- ✓ Short-course systemic steroids for some exacerbations
- ✓ Exercise /pulmonary rehabilitation
- ✓ Supplemental oxygen
- ✓ Lung transplantation

Summary

- ✓ **An organized diagnostic approach is important**
- ✓ **Treatment options are evolving and need to be individualized; phenotyping may provide guidance**
- ✓ **We need more research! The sobering reality is that patients with bronchiectasis suffer significant morbidity and mortality, and yet can be offered few proven, effective therapies.**