Care of the Bronchiectasis Patient: Current State

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Disclosures

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

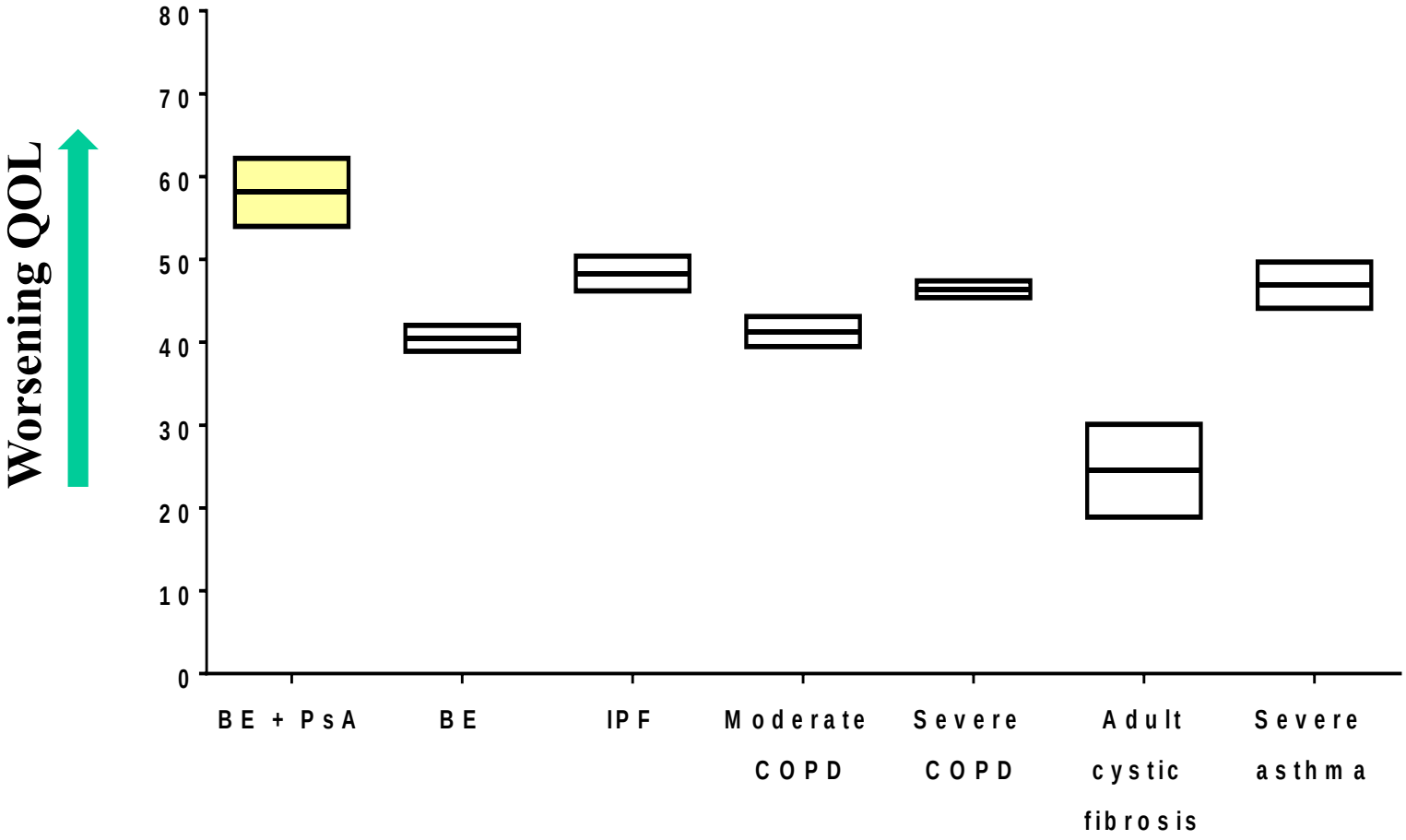
Bronchiectasis

- ✓ **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; 142:432-439**
- **Chalmers et al. *AJRCCM* 2013; 189.**

Bronchiectasis: Impact on Quality of Life

SGRQ total score



1. Kreuter, et al. *Respir Res.* 2017. 2. Kerwin, et al. *Intl J COPD*. 2017. 3. Magnussen, et al. *NEJM.* (Oct) 2014. 4. Padilla, et al. *Arch Bronconeumol.* 2007. 5. Ortega, et al. *NEJM.* (Sept) 2014.

Goals of Treatment

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

Challenges

- **Pulmonary function** - FEV_1 generally does not improve with therapy
  - Aim is to stabilize lung function
- **Quality of life** - No fully validated method of assessment
- **Exacerbations** - Difficult to define
  - Some progress has been made
- **Mortality** - Difficult to study in short term trials

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

Eur Resp J; 49, 2017

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

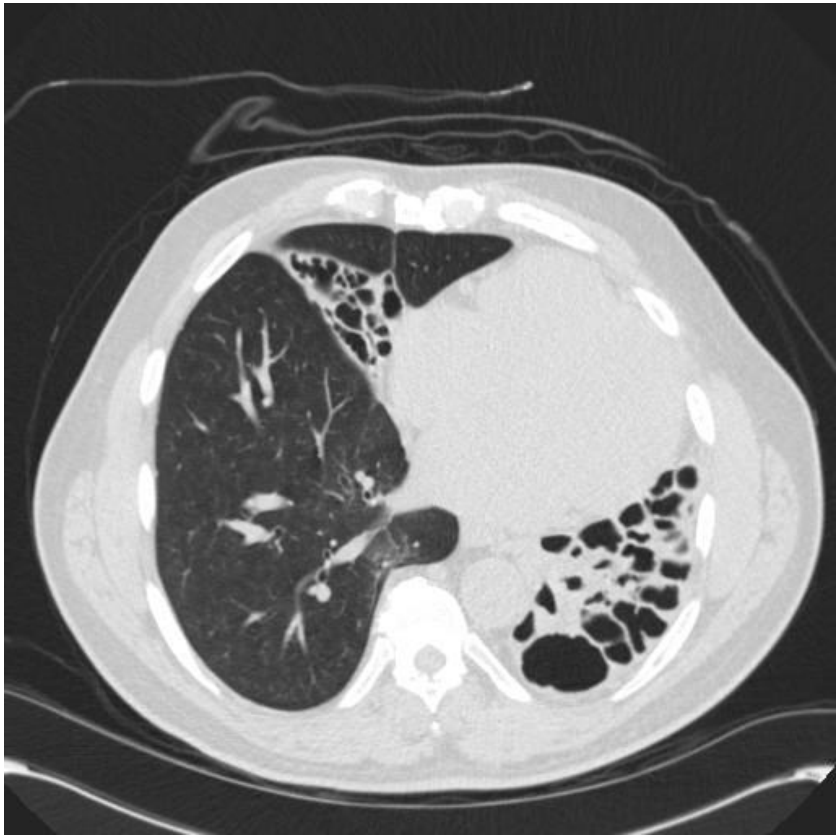
AND a clinician determines that a change in bronchiectasis treatment is required#

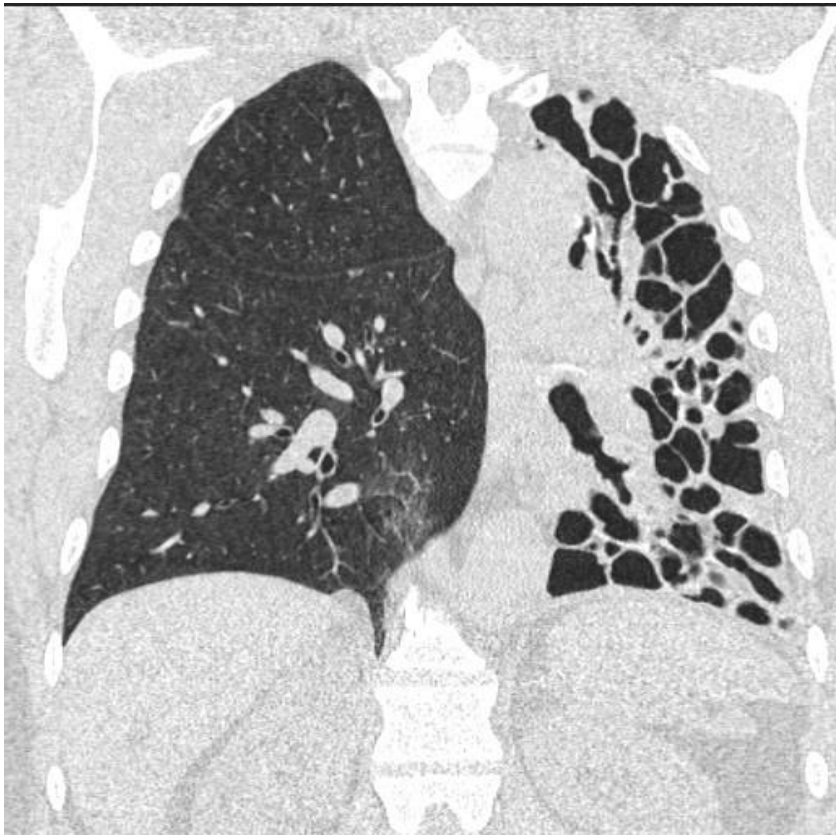
Current State

- ✓ There are no approved therapies
- ✓ Available guidelines regarding management are based on low quality of evidence
- ✓ Clinical trials for many of the pillars of treatment are lacking

77 y.o. African-American man:

- ✓ **Diagnosed with bronchiectasis at age 12 after a pneumonia at 18 months of age**





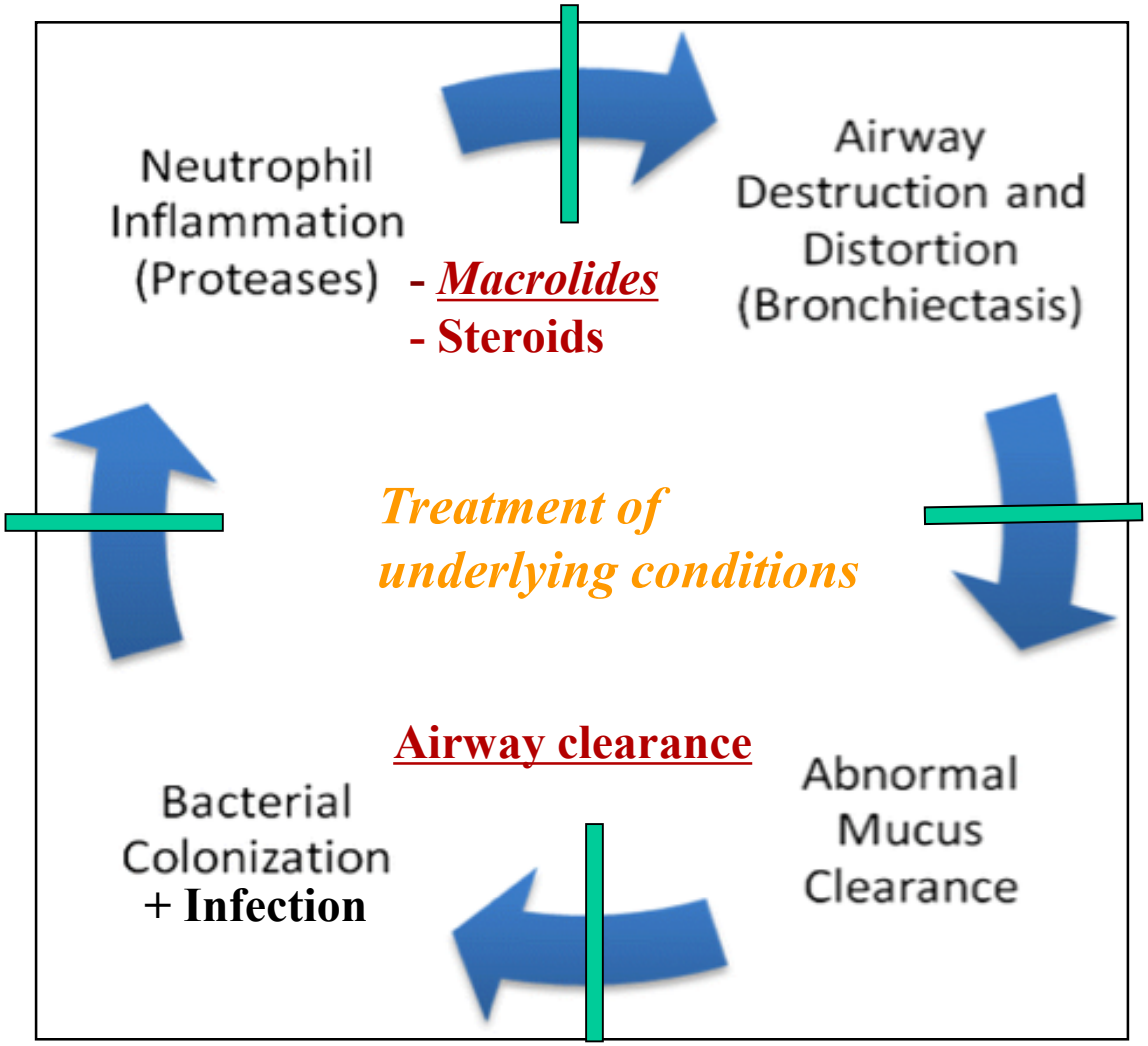
Clinical Course

- ✓ **Did well for many years**
- ✓ **Managed with rotating antibiotics + airway clearance**

Clinical Course

- ✓ **Has quinolone-resistant chronic *Pseudomonas aeruginosa* infection**
- ✓ **3-4 exacerbations per year often requiring IV antibiotics**
- ✓ **Daily sputum production - 40ml/day**
- ✓ **Perceives QOL as declining**

Bronchiectasis: Treatment



Am J Resp Crit Care Med 2013;188:647-656

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 physician-established diagnosis of bronchiectasis enrolled between 2008 and 2014

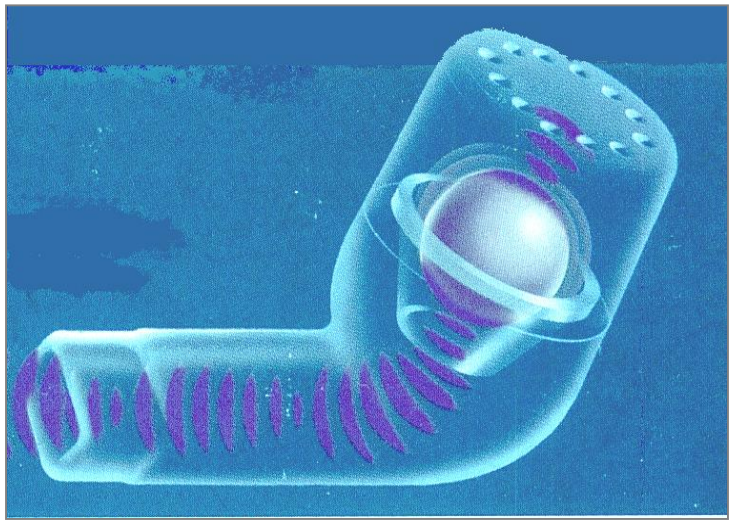
- ✓**Airway clearance - 56%**
- ✓**Antibiotics only for exacerbation - 41%**
- ✓**Suppressive antibiotics - 39%: 10% aerosol, 7% rotating oral regimen**
- ✓**Inhaled bronchodilators - 61%**
- ✓**Inhaled steroids - 39%, systemic steroids - 13%**

Airway Clearance Therapy

- ✓**Techniques designed to enhance mucociliary clearance**
  - **Considered mainstay of management**
  - **Little data**

    Cochrane Review 2015

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



Vibratory PEP Devices

PEP valve use most common in US Bronchiectasis Registry

High Frequency Chest Wall Oscillation

Airway Clearance: *Pharmacologic agents*

- ✓ **Hyperosmolar agents**
  - **Inhaled mannitol**
    - **Phase III trial: no significant reduction in exacerbation rates**
  - **Hypertonic saline**
    - **Improved sputum rheology, SGRQ, annual antibiotic usage**

- **Daviskas et al. Eur Resp J 2003; 18.**
- **Daviskas et al. *Respirology* 2005: 10.**
- **Bilton, Tino et al. *Thorax* 2014; 69.**
- **Cochrane Database Review, 2009**
- **Tarrant et al. *Respirology*, 2017; 22.**
- **Kellet, Robert. *Respir Med* 2011; 105.**

Pharmacologic agents

- ✓ **Bronchodilators**
  - **No long-term randomized controlled trial data to suggest efficacy**
- ✓ **Mucolytics**
  - **rh DNase not effective and potentially deleterious in non-CF patients**

O'Donnell et al. *Chest* 1998;113.

Airway Clearance Therapies

- ✓ **Target:**
  - **Symptomatic patients: cough, sputum production**
  - **Difficulty expectorating sputum**
  - **Impaired quality of life**
  - **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

Sputum analysis 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:

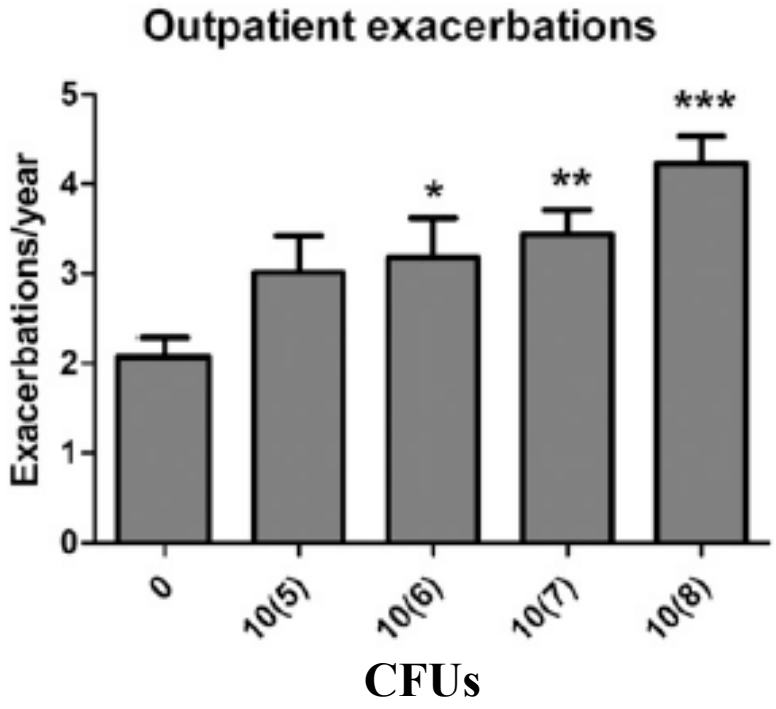
- ✓ ***Pseudomonas aeruginosa*** **and** ***S. aureus*** **infections can be especially challenging**
- ✓ **Adjust/narrow antibiotic if specific pathogen isolated**
- ✓ **Optimal duration unknown:**
  - **14 day course**
  - **Longer courses as dictated by clinical response**

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

Inhaled Antibiotic Therapy

Bacterial Load: Impact on Pulmonary Exacerbations

- ✓ **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; 186, 657-665.

“Frequent Exacerbator” Phenotype

- ✓ **2572 patients from 10 sites in Europe and Israel**
- ✓ **About 40% of patients had 0-1 exacerbations, 37% had 3 or more**
- ✓ **Prior and frequent exacerbations were strongest predictor of future exacerbations**

Chalmers et al. ***AJRCCM 2018; Epub.***

"Frequent Exacerbator" Phenotype

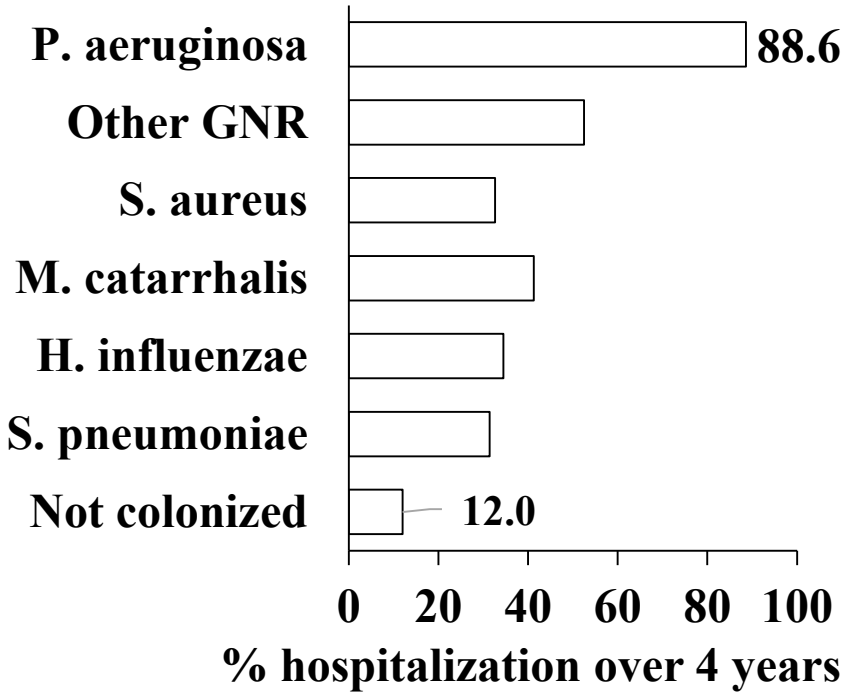
- ✓ **Other independent predictors:**
  - ***H. flu* and *P. aeruginosa* infection**
  - **Low FEV_1**
  - **Radiological severity**
  - **Co-existing COPD**

- ✓ **Frequent exacerbators also had worse QOL, high disease severity and increased mortality**

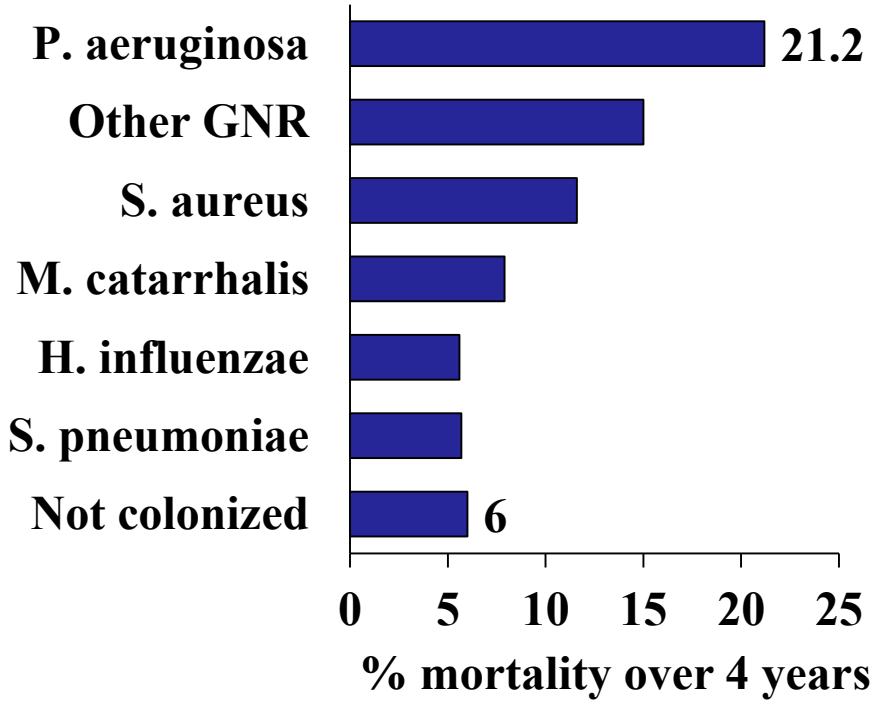
Chalmers et al. *AJRCCM 2018; Epub.*

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 in 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**

US Bronchiectasis Registry

	Patients with ≥2 exacerbations/year n=198 (18.9%)	Patients with <2 exacerbations/year n=851 (81.1%)
Baseline*		
Pseudomonas sputum isolation (% of patients)	50%	35%
Inhaled antibiotic (% of patients)	29%	13%
History of hospitalization (% of patients)	29.7%	17.2%
for exacerbation (% of patients)	79.2%	56.0%
During 2-year follow-up period:		
Average exacerbations (in 2 years) +/- SD	2.58 +/-0.97	0.32 +/-0.47
Hospital admissions per year (mean)	0.39	0.05

Cohort of patients with 2-year follow-up data (N=1049)
***information captured for events during the past 2 years**
Aksamit TR, et al, *Am J Respir Crit Care Med* 2017;195:A7304

Inhaled Antibiotics: Guidelines

- ✓**SEPAR: 2008**
  - **Chronic nebulized antibiotics when poor response +/or adverse effect of oral antibiotics, chronic *PA* infection**
- ✓**BTS: 2010**
  - **Long term nebulized antibiotics should be considered for ≥3 AE, fewer but severe exacerbations, *PA* colonization**
- ✓**TSANZ: 2015**
  - **Long term nebulized antibiotics should not be prescribed routinely; consider trial for frequent exacerbations +/or *PA* infection**

•Vendrell et al *Arch Bronco* 2008; 44.
•Pasteur et al. *Thorax*, 2010, 65.
•TSANZ Guidelines, *MJA* 2015.

Inhaled Antibiotics: Clinical Trials

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

Inhaled Tobramycin

- ✓ **Profound microbiologic impact on *P. aeruginosa;* no emergence of resistant organisms**
- ✓ **Improvement in symptoms and QOL suggested**
- ✓ **Efficacy as either maintenance therapy or treatment of acute exacerbations has not yet been established**
- ✓ **Adverse effects (cough, dyspnea, bronchospasm) well described**

- **Barker et al. *AJRCCM*; 162: 2000**
- **Scheinberg et al. *Chest*; 127: 2005**
- **Bilton et al. *Chest*; 130: 2006**

Inhaled Colistin

- ✓ **144 patients with *Pseudomonas* infection: inhaled colistin vs placebo daily for up to 6 months**
- ✓ **Enrolled within 21 days of an acute exacerbation**

- ✓ **<u>Primary endpoint</u>: time to exacerbation**
- ✓ **<u>Secondary endpoints</u>: time to exacerbation based on adherence (I-neb), bacterial density, SQRG total score, safety parameters**

Haworth et al. *AJRCCM* 2014; 189: 975.

Inhaled Colistin

- ✓ **Primary exacerbation endpoint not met in ITT group**
  - **Significant reduction in *Pseudomonas* CFU after 4 and 12 weeks**
  - **Improvement in SGRQ after 26 weeks (10. 5 units)**
  - **Well-tolerated; no emergence of colistin resistance**
- ✓ **In adherent patients (>80%)**
  - **Median time to exacerbation: 168 days in colistin group versus 103 days in placebo (p = 0.038)**
  - **Exacerbation rate: 50% in colistin group, 72% in placebo**

Haworth et al. *AJRCCM* 2014; 189: 975.

RESPIRE - 1, 2

- ✓ **Phase 3, PRDB trials: twice-daily ciprofloxacin DPI - 14 or 28 days on/off for 48 weeks**
- ✓ **$\geq$ 2 exacerbations in preceding 12 months; stringently defined**
- ✓ **7 pre-specified pathogens**
- ✓ **FEV_1: 30-90% predicted**

- ✓ ***Primary endpoints*:**
  - **Time to first exacerbation**
  - **Number of exacerbation events**

• DeSoyza et al. *ERJ*, 2016, *ERJ*, 2018: 51. • Aksamit et al. *ERJ*, 2018; 51.	**Respire - 1 (n = 416)**	**Respire - 2 (n = 521)**
Median time to first exacerbation	✓ 14 day on/off ***(336 vs 186 days)***	**NS**
Frequency of exacerbations	✓ 14 day on/off ***(39% reduction)***	**NS**

ORBIT - 3, 4

- ✓ **Phase 3, identical PRDB trials - once daily liposomal ciprofloxacin; 48 weeks, 6 cycles - 28 days on/off, then a 28-day open-label extension**
- ✓ **Chronic *P. aeruginosa* infection with at least 2 exacerbations in preceding 12 months**
- ✓ **Exacerbations and severity defined in protocol**

- ✓ ***Primary endpoint*: increase in median time to first pulmonary exacerbation (PE)**
- ✓ ***Secondary endpoint*: frequency of exacerbations over 48-week treatment period**

Haworth et al. ATS, 2017

Haworth et al. ATS, 2017.	ORBIT-3 (n = 304)	ORBIT-4 (n =278)	POOLED ANALYSIS
Median time to first exacerbation (all severities)	**NS**	✓ *(230 vs 136 days)*	**NS**
Frequency of exacerbations	**NS**	✓ *(37% reduction)*	✓ *(33% reduction)*
Median time to first PE requiring treatment with antibiotics	**NS**	✓	✓
Reduced sputum density of PA without attenuation of antibiotic activity during each treatment cycle over the 48-week trial	✓	✓	✓

Inhaled Antibiotics: Summary

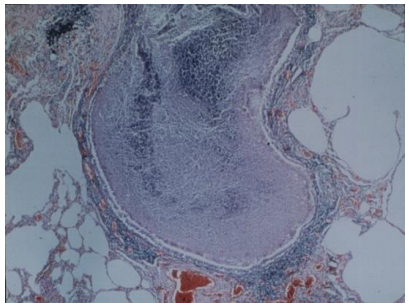
- ✓ **Clear microbiologic impact**
- ✓ **Clinical efficacy has not been proven conclusively in clinical trials thus far**
- ✓ **None currently approved by regulatory agencies**
- ✓ **Emergence of resistant pathogens has not been observed**

- ✓ **Target population:**
  - **Chronic GNR infection**
  - **Frequent exacerbations - >3/year**
  - **Other therapy optimized**
- ✓ **?daily versus on/off regimen**
- ✓ **Relationship to chronic macrolides has not been established**

Chronic Macrolide Therapy

Macrolides & Bronchiectasis

- ✓ **Scientific plausibility: 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 Rev*, 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
  - FEV1
  - 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**

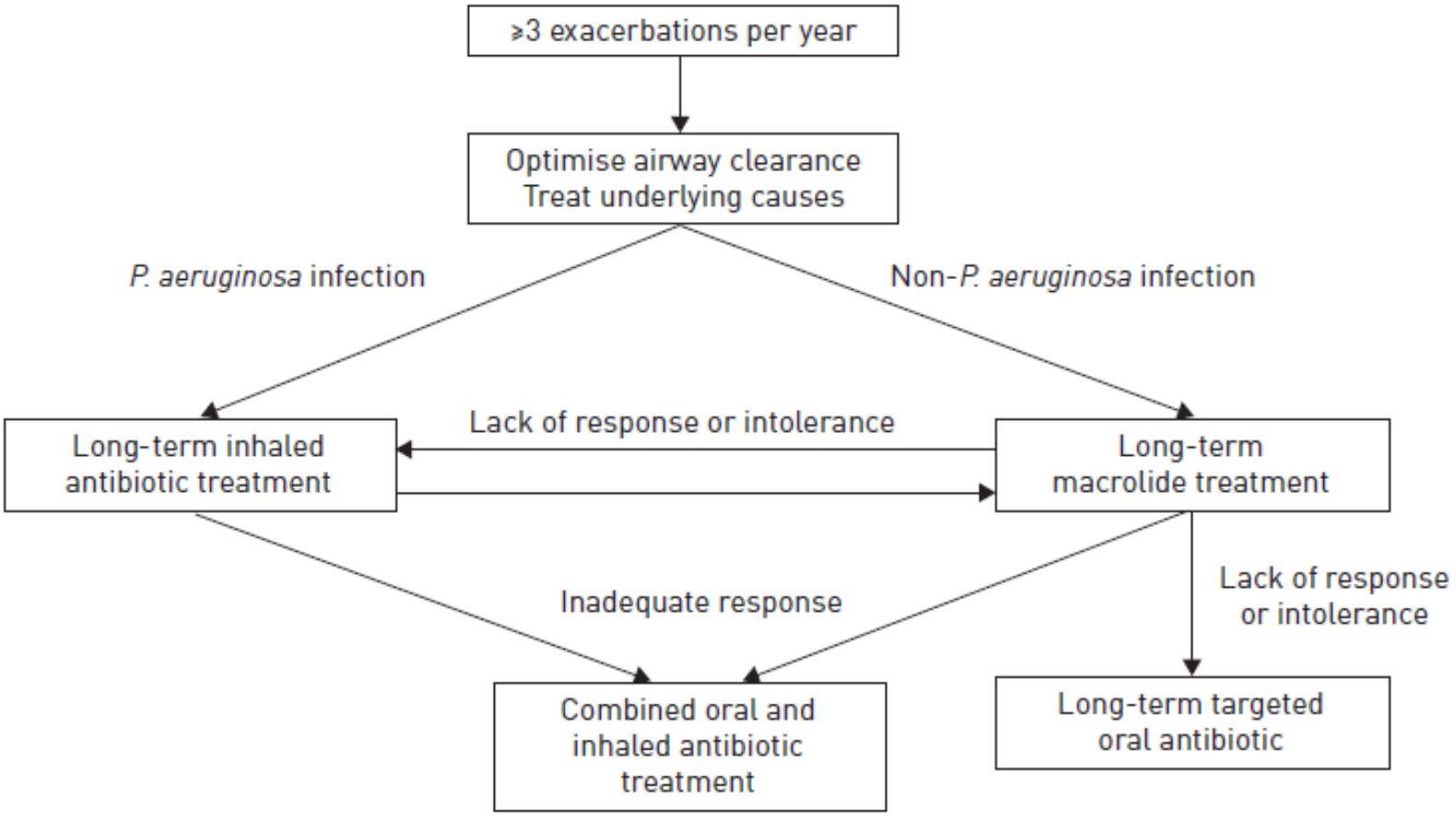
Macrolides: Target Patients

- ✓ **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**
  - **No convincing data to support routine use**
  - **Possible increased risk of NTM infection**

- **Kapur N, et al. *Cochrane Database Syst Rev*. 2009 Jan 21;(1):CD000996.**
- **Tsang KW, et al. *Thorax*. 2005;60:239-43.**
- **Andrejak et al. *Thorax*. 2013; 68: 256-62.**
- **Polverino et al . ERS Guideline. *ERJ* 2017; 50.**

Not Recommended

- ✓ **Chronic systemic antibiotics**
  - **No evidence-based data to support the use of systemic, non-macrolide, suppressive/maintenance therapy**

•**Wurzel et al.** ***Cochrane Review*** **2011**
•**TSANZ Guidelines,** ***MJA*** **2015**

- ✓ **Chronic systemic corticosteroids**

Surgery

An option for:

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

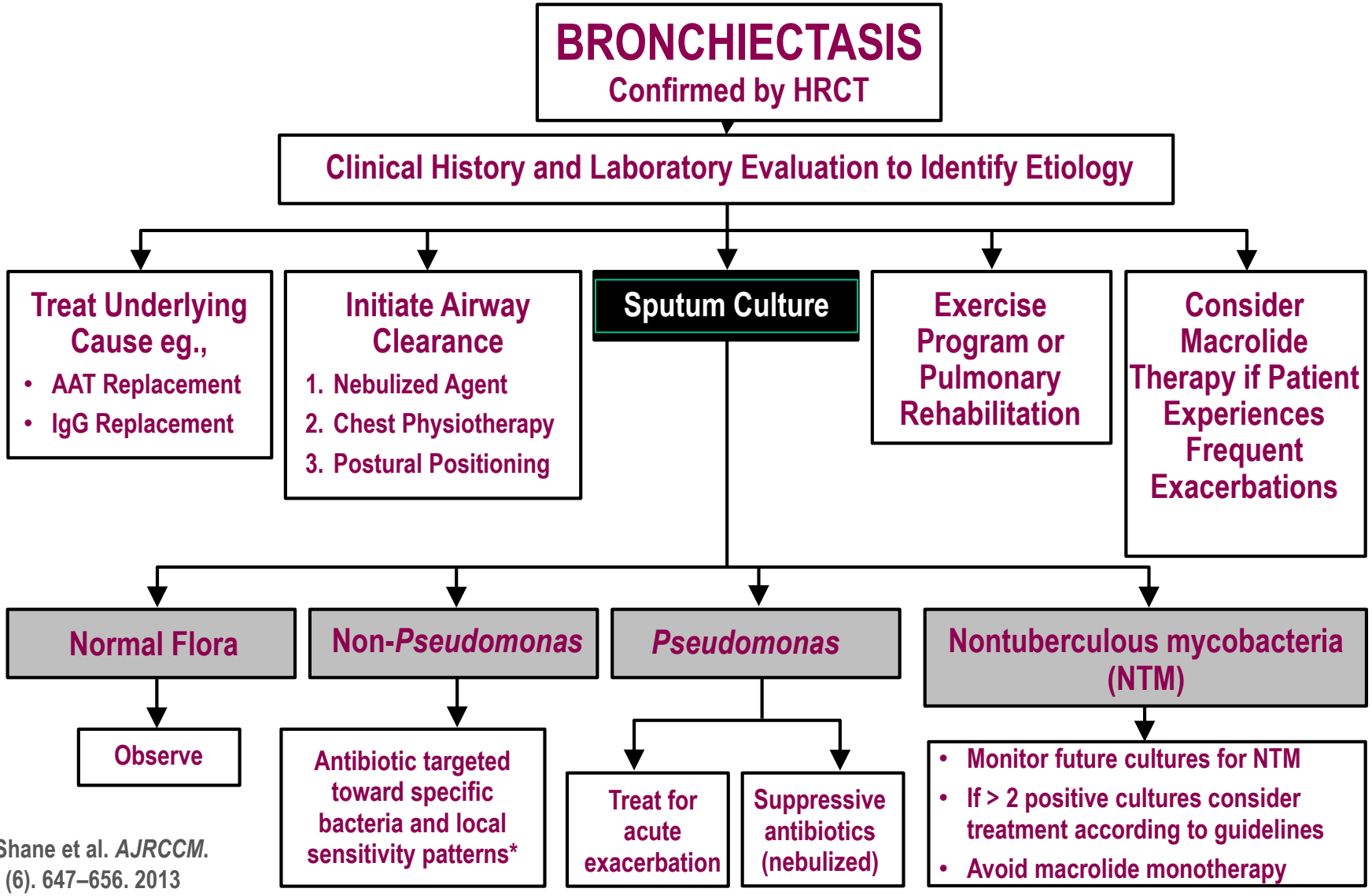
Acceptable morbidity and mortality reported

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

Supportive Measures

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

Proposed Treatment Algorithm



McShane et al. *AJRCCM*. 188 (6). 647–656. 2013

“The sobering reality is that patients with bronchiectasis suffer significant morbidity and mortality, and yet can be offered few proven, effective therapies.

Ultimately we need better characterization of our patients, more high-quality clinical trials to further define this entity, and, most crucially, better therapies - antimicrobial or otherwise.

The process of adoption of this orphan disease by clinicians and researchers needs be accelerated.”

***AJRCCM* 2018; 197**

Opportunities

- ✓ **Better characterize the epidemiology and natural history**
- ✓ **Strengthen support for and expand patient registries**
- ✓ **Rethink endpoints for clinical trials and address regulatory challenges**
- ✓ **Identify new targets for treatment**