מרכז שניידר לרפואת ילדים בישראל
مركز شنايدر لطب الأطفال في إسرائيل
Schneider Children's Medical Center of Israel

CLALIT 100 years
The Best For Your Family

INHALED ANTIBIOTICS THERAPY IN NON-CF LUNG DISEASE

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Chipap 18th February 2015

Inhaled antibiotic therapy:

- Direct delivery to the airways
- High local drug concentration
- Low systemic concentration
- more efficacious
- With less side effects

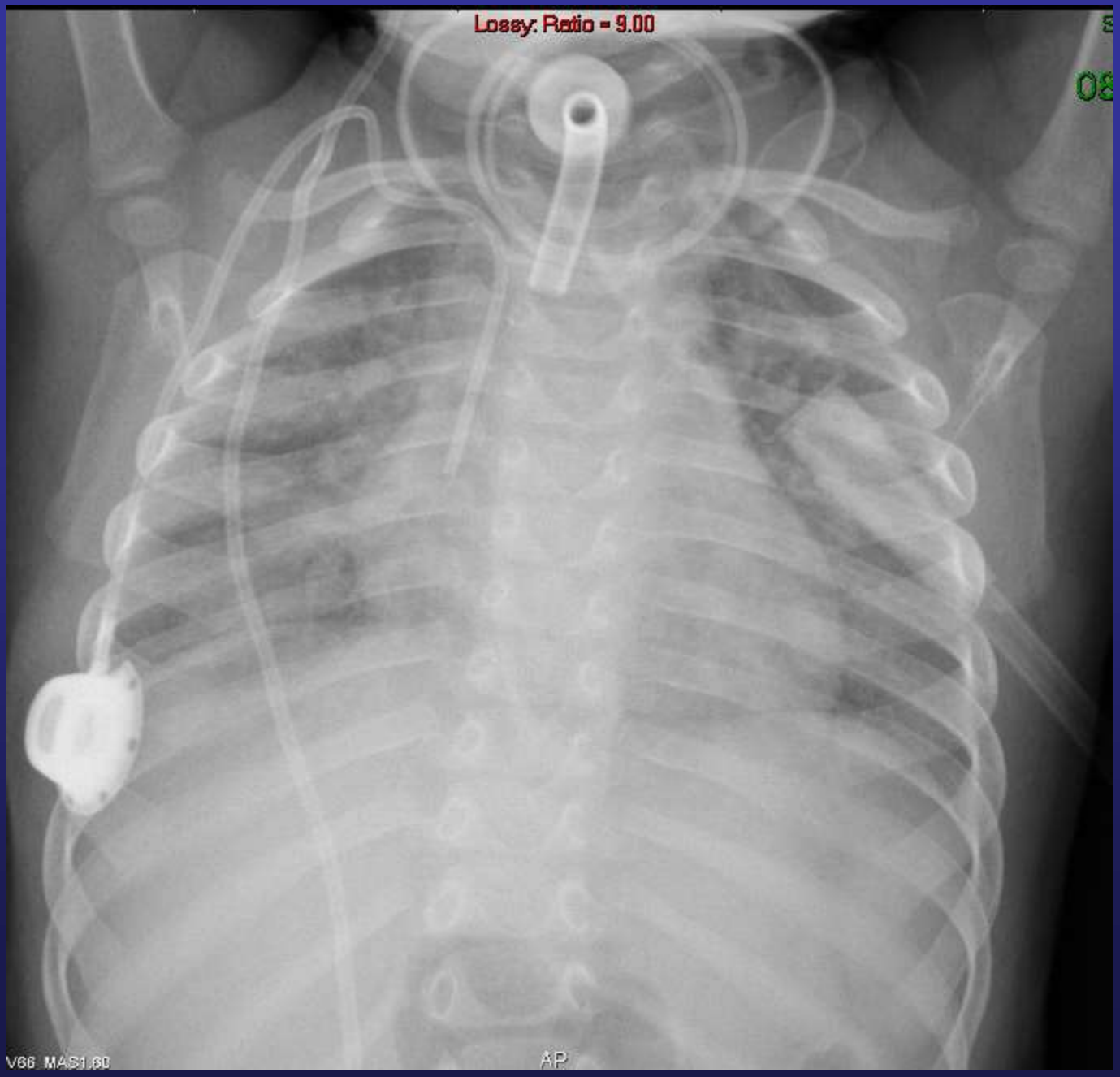
Inhaled antibiotics

- Standard treatment for CF with chronic PA colonization
- Up to 25% non CF bronchiectasis are colonized with PA – thus this may be a good therapy.
- Far less advanced studies or clinical experience

At Schneider's, inhaled antibiotics used for many years for non CF lung disease

Case 1

- At 10 months, malignant ependymoma posterior fossa resected + radiation
- Vocal cord paralysis, no gag reflex
- Tracheostomy, PEG
- Chronic severe lung disease: O2 saturation dropped to 70%,
- Oxygen dependent
- Sputum culture: *P. aeruginosa, P. putida, S. aureus, S.pneumonia, K. pneumonia, S. maltophilia*


Lossy: Ratio = 9.00
AP

- 18 months inhaled colistin 1 X10^6 units x2/day

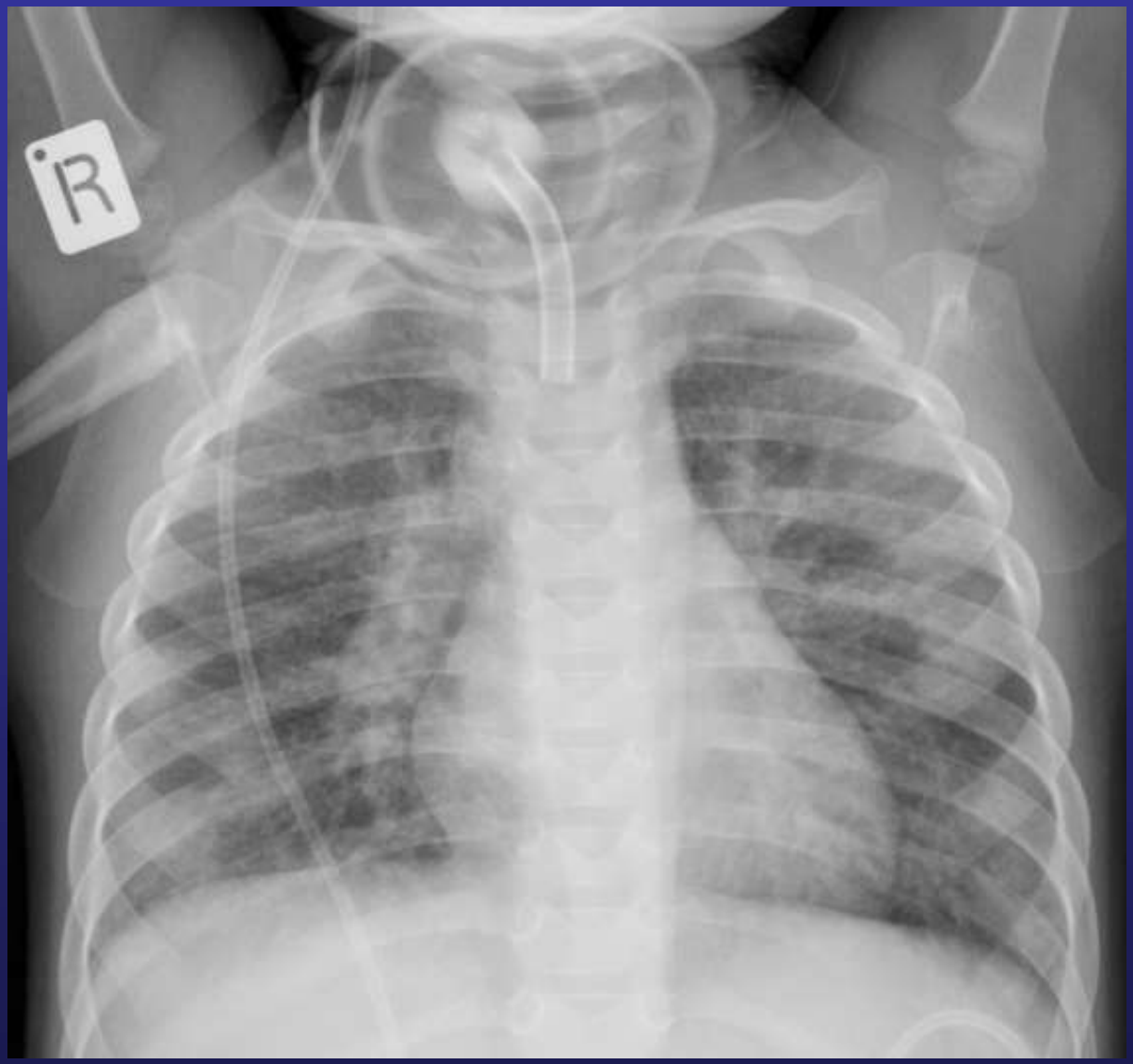
Oral Cipro/cefuroxime/ flagyl

Occasional hospitalizations For IV antibiotics

Physiotherapy

Ventolin, aerovent , budesonode

2011



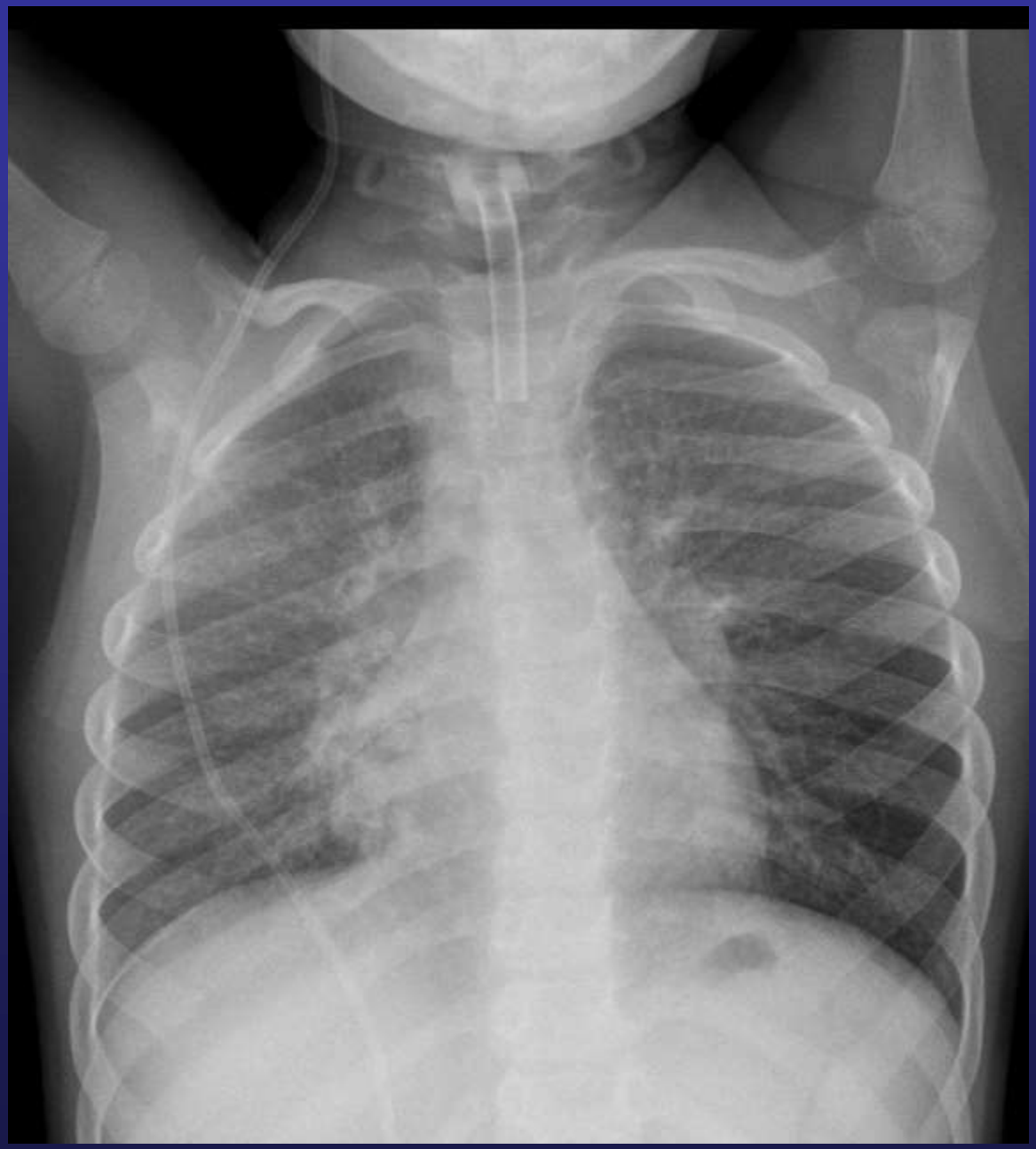
No longer oxygen dependent

Gag returned

Still vocal cord paralysis

Still on intermittent Cipro
And inhaled colistin
- thus avoids hospitalization

Chronic lung disease



2014

Case 2

- Diagnosed in infancy with pseudohypo-aldosteronism type 1 (epithelial sodium channel –ENaC defect).
- PICU with RSV at age 2 months. Ventilated
- 2 more PICU admissions
- Recurrent severe respiratory distress.
- Frequent hospitalizations
- Sputum: *P. mirabilis,* chronic *P. aeruginosa, K. oxytoca, S. aureus, Providencia*

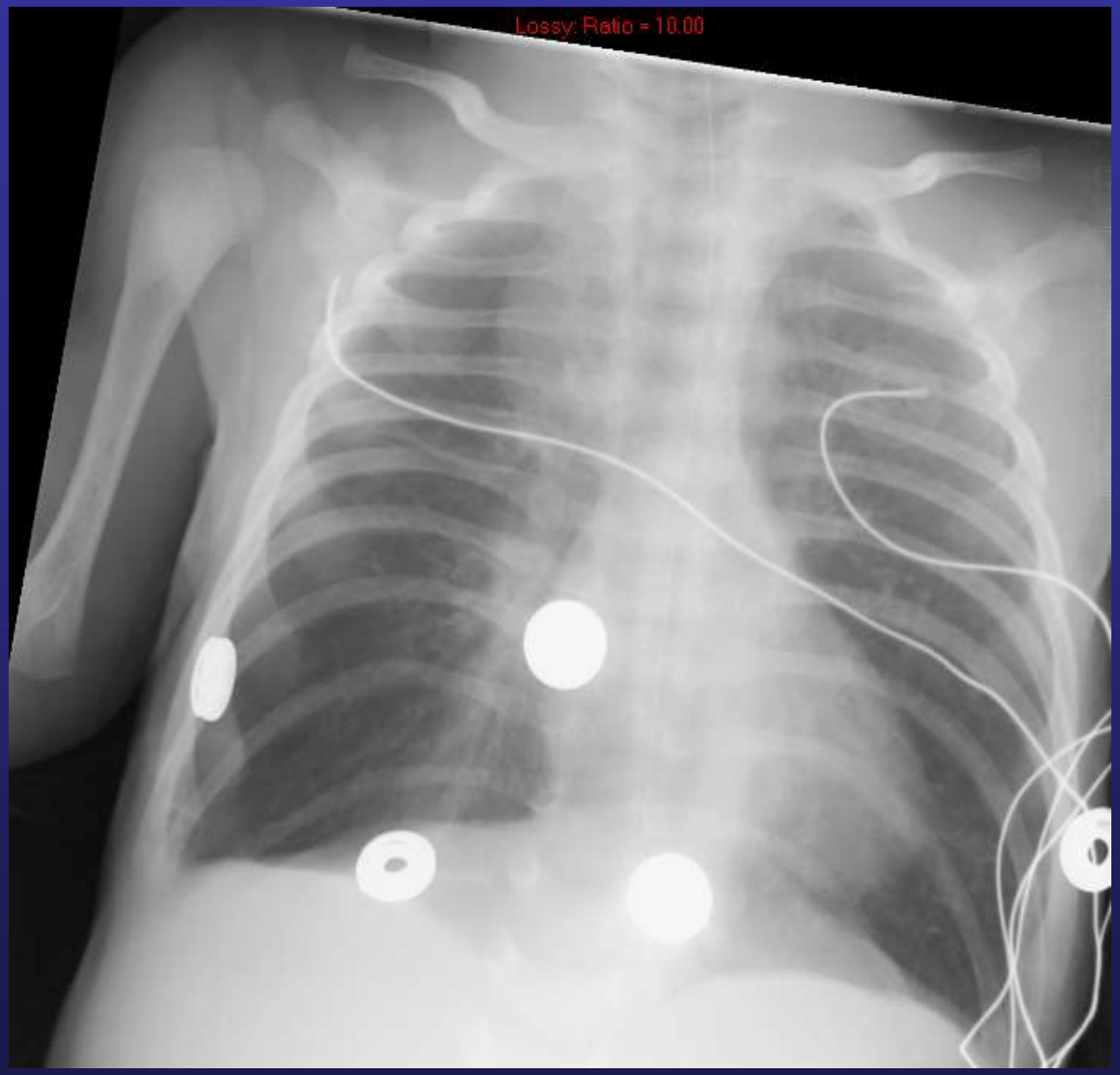
Severe hyperinflation, atelectasis during RSV

IV antibiotics

Then maintained on:

Inhaled colistin

Oral ciprofloxacin
Physiotherapy
Hypertonic saline inh
aerovent



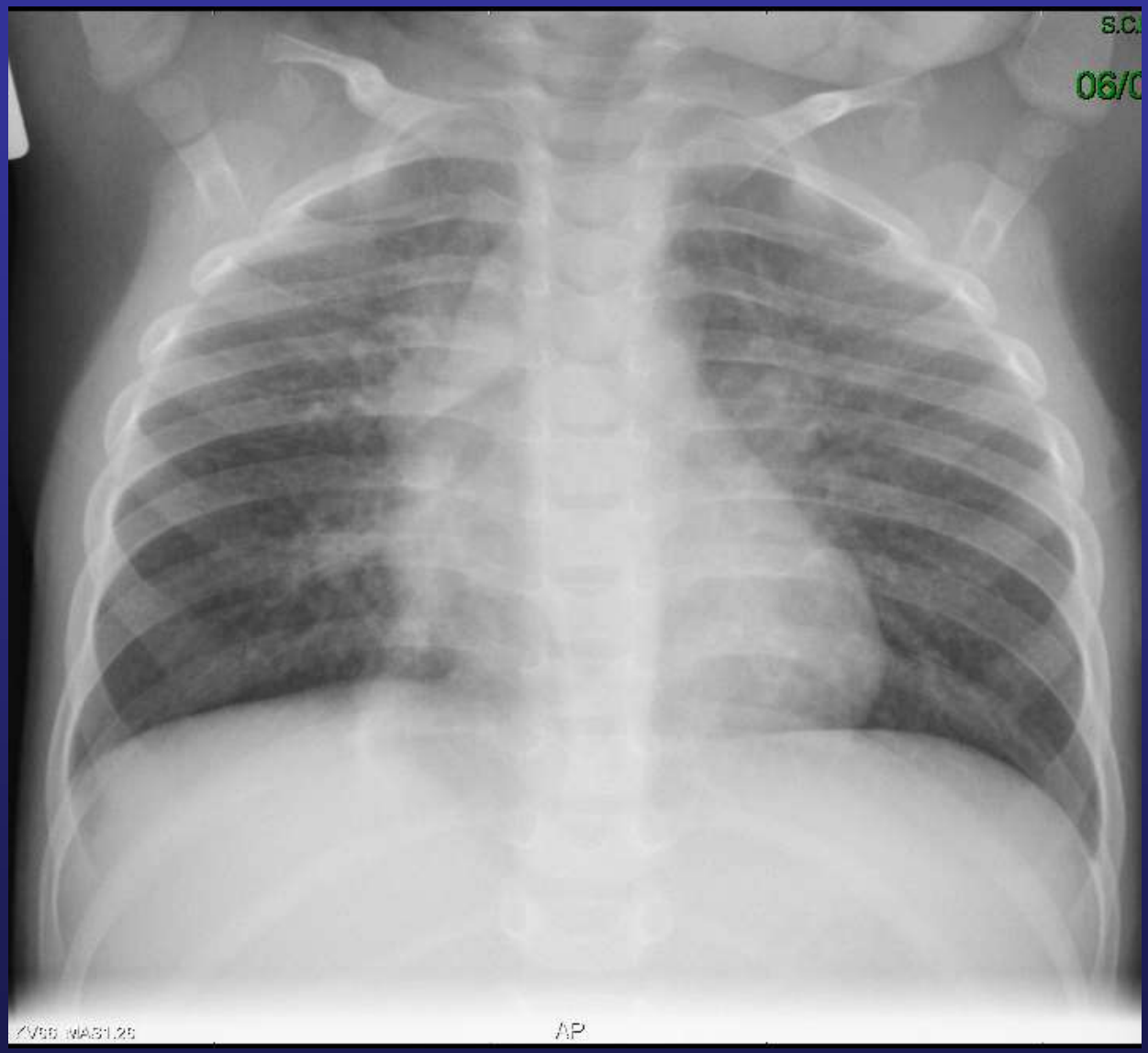
2011

Chronic lung disease

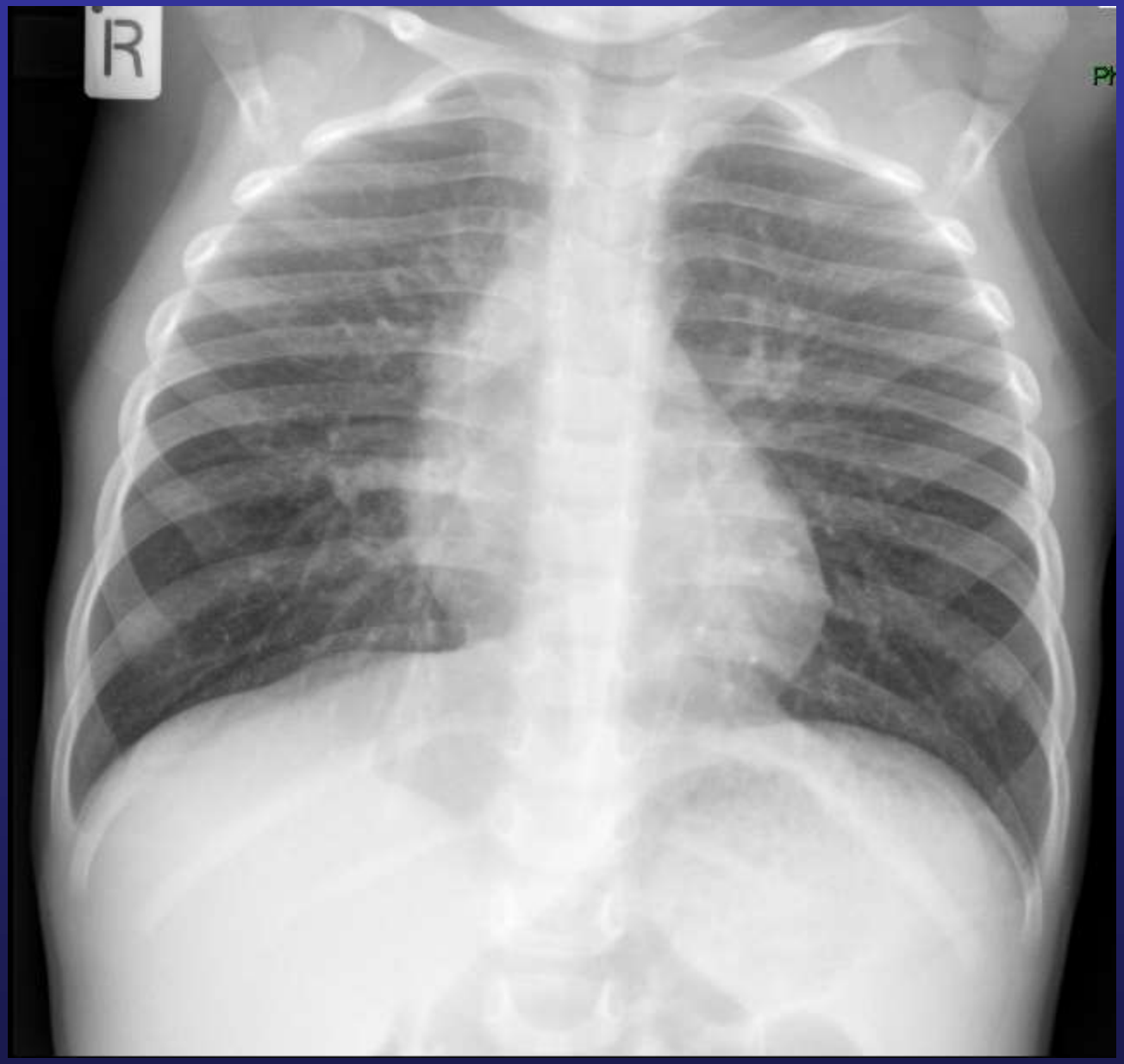
Inhaled colistin for 20 months

Attempting to stop:
Prolonged admission
O_2 dependent

By 3y,
Intermittent colistin



2013



Nov 2014

Aim: to review inhaled antibiotic use at Schneider's

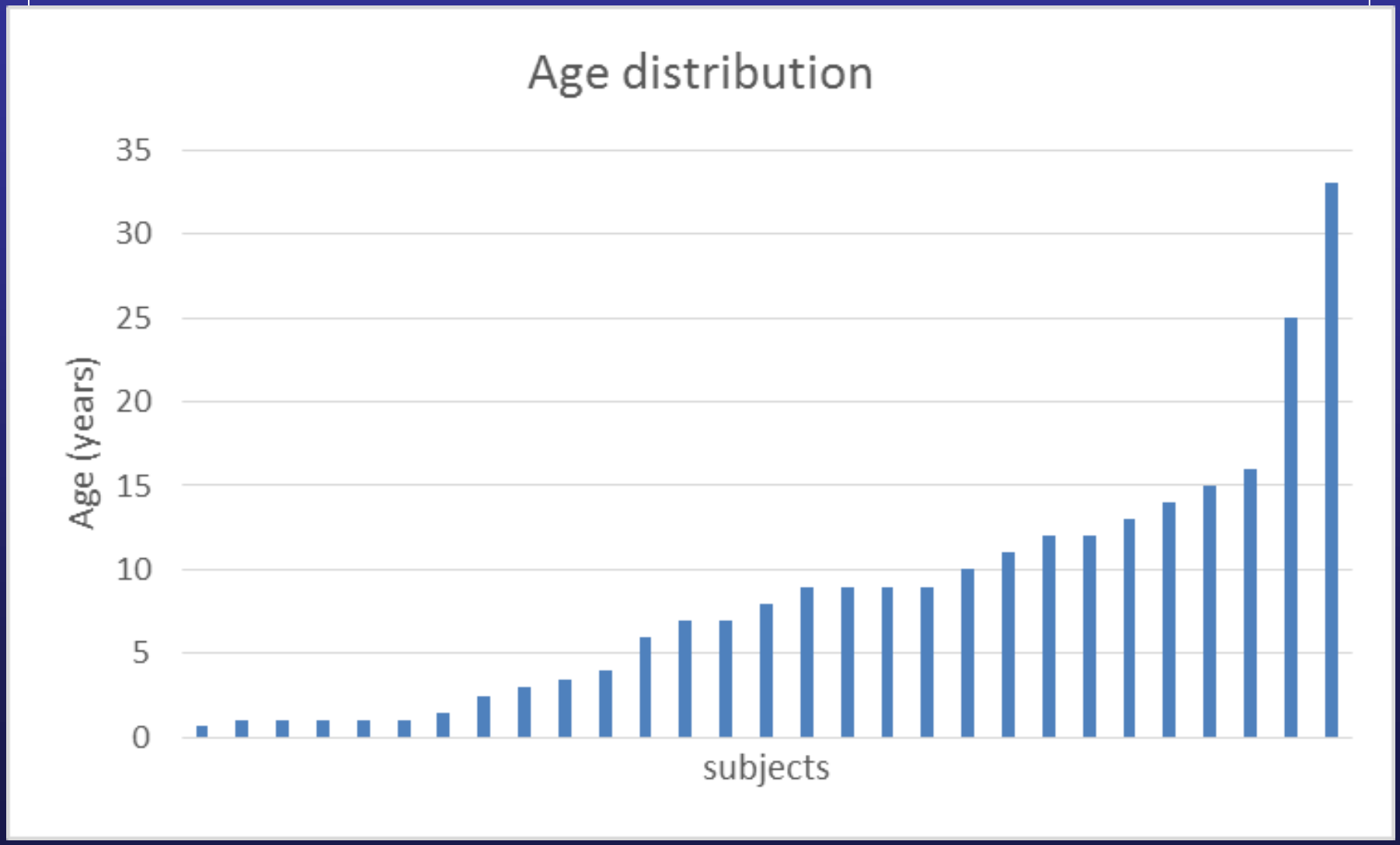
- 2010-2014
- Included: patients followed in Pulmonary Unit
- non-CF chronic lung disease
- Chose colistin inhalation as the index drug
- Excluded: single consults e.g. oncology, in-patients; those where prescribed but not taken; those without bacterial culture
- Sputum cultures: by expectoration, or induced sputum with suction + physiotherapy

Demographics

- 29 patients, 18 male

- 14 chronic therapy (>2 months)
- 5 recurrent intermittent, 1-2 mths each cycle
- 10 short term ($\leq$ 2 months)

age range: 0.7-33y, n=29



Diagnoses, n=29

- Bronchiectasis: 14
    - PCD: 6
    - Post adenovirus: 2
    - Post liver transplant: 1
    - Idiopathic: 3
- Recurrent aspiration pneumonia 12
  - Congenital myopathy: 4
  - Neurodegenerative or HIE: 6
  - Vocal chord paralysis 1
  - FD: 1
- Immune disorder: 3
- Pseudohypoaldosteronism: 2

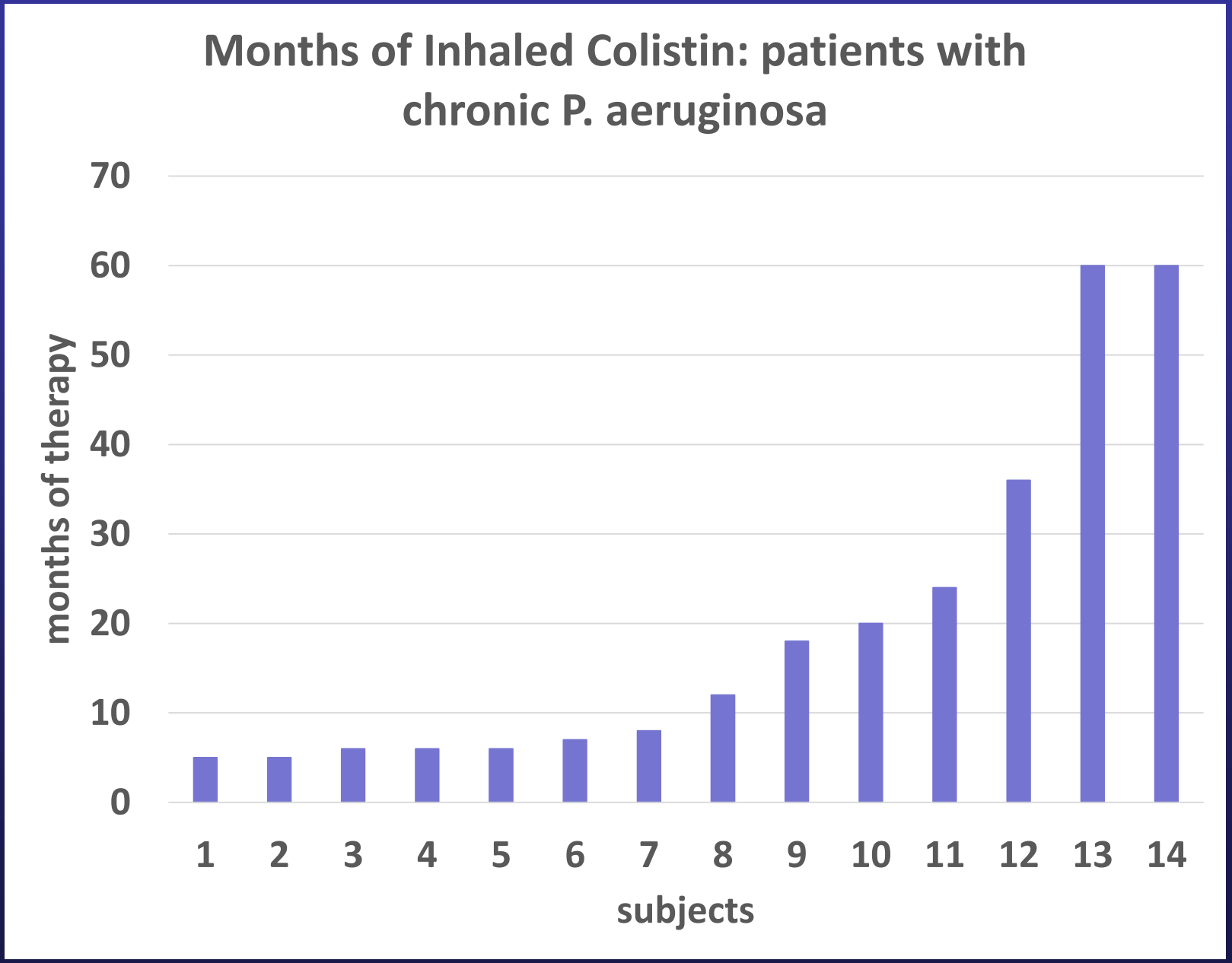
Diagnoses <5y (n=10)

- Myopathy 2
- Neurodegenerative 3
- Vocal cord paralysis (ependymoma) 1

- Immune deficiency 2
- Pseudohypoaldost 2

Bacterial infection

- *P. aeruginosa* 28/29
- Co-infection or subsequent cultures:
- *K. pneumonia*
- *Enterobacter*
- *Acinetobacter*
- *S. aureus, S. pneumonia, H. influenza*
- *S. maltophilia*
- *P. mirabilis*
- *Serratia*


Months of Inhaled Colistin: patients with chronic P. aeruginosa
70
60
50
40
30
20
10
0
months of therapy
1
2
3
4
5
6
7
8
9
10
11
12
13
14
subjects

Eradication of *P. aeruginosa*

- Of 14 with short term or intermittent infection, 11 were eradicated

- Of 15 with persistent or chronic infection, only 9 were eradicated

Subjective improvement:

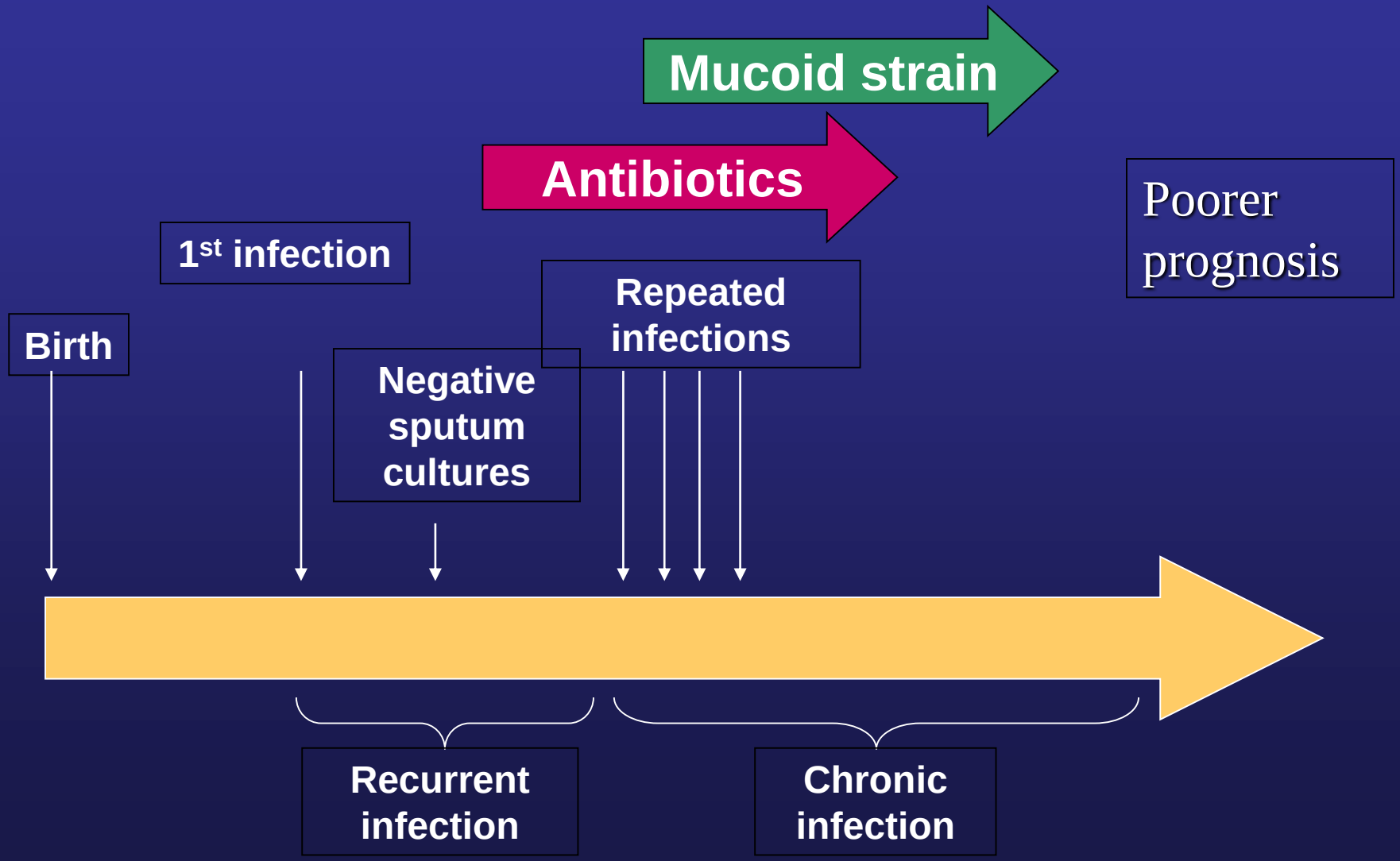
In most cases, at least temporarily

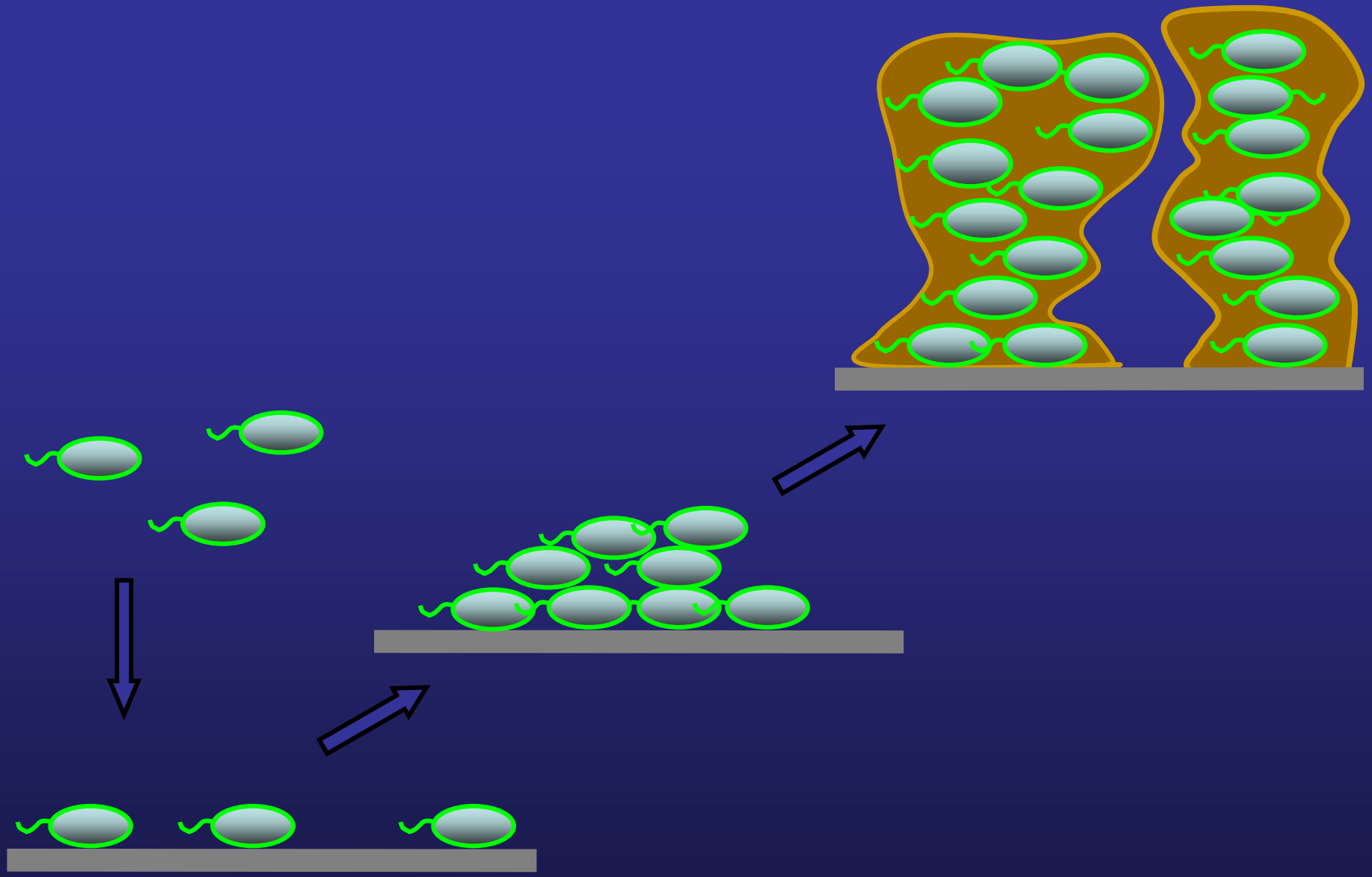
Non- CF Bronchiectasis

- common: 1:20,000 in the young
  to 1:200 >75yo
- underdiagnosed (‘asthma’, ‘COPD’)
- high morbidity
- reduced HrQoL
- management: few RCT
  mainly from consensus expert opinion
  or extrapolated from CF

RCT in children – almost absent

Development chronic Pseudomonas aeruginosa lung infection

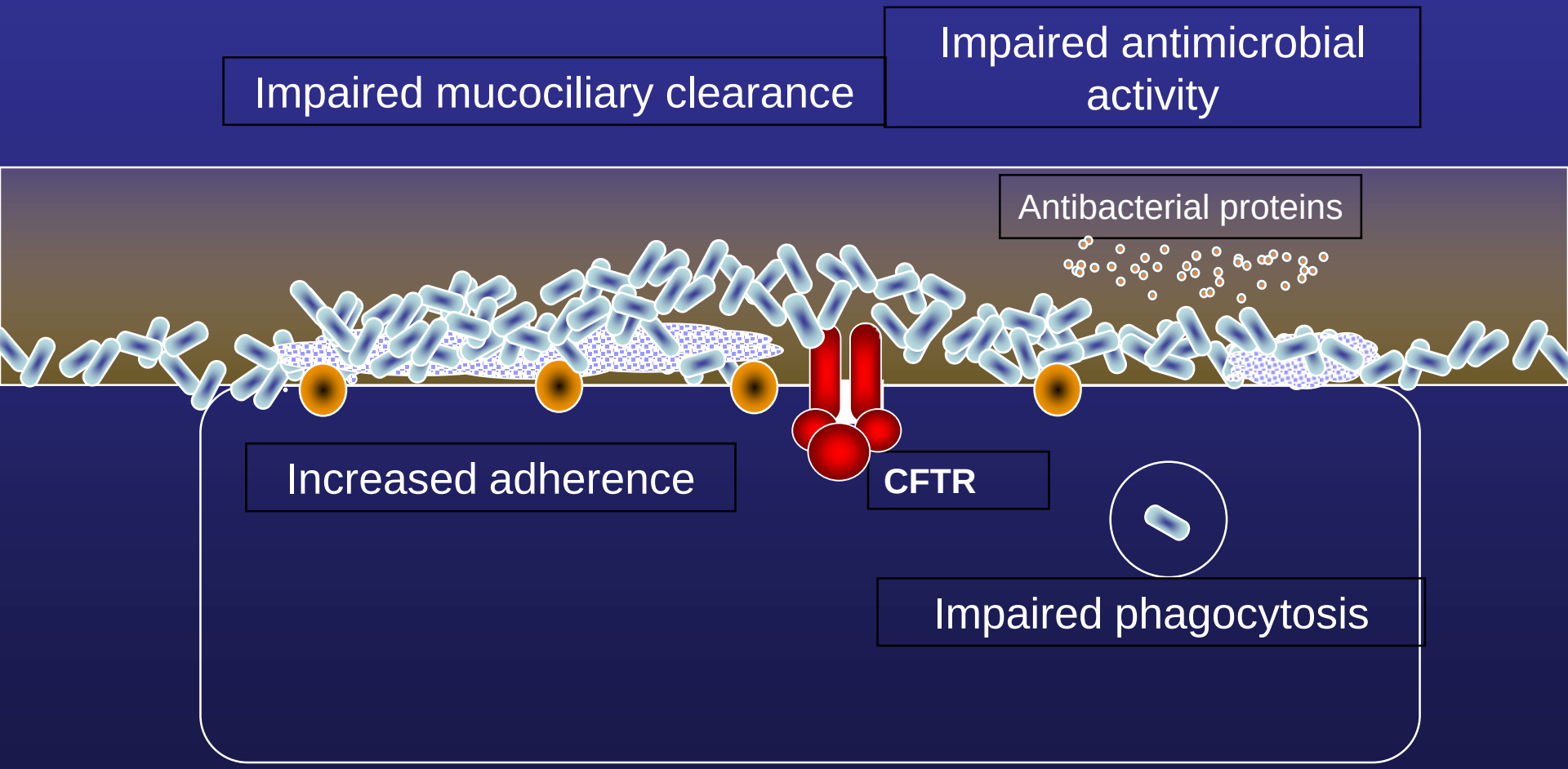




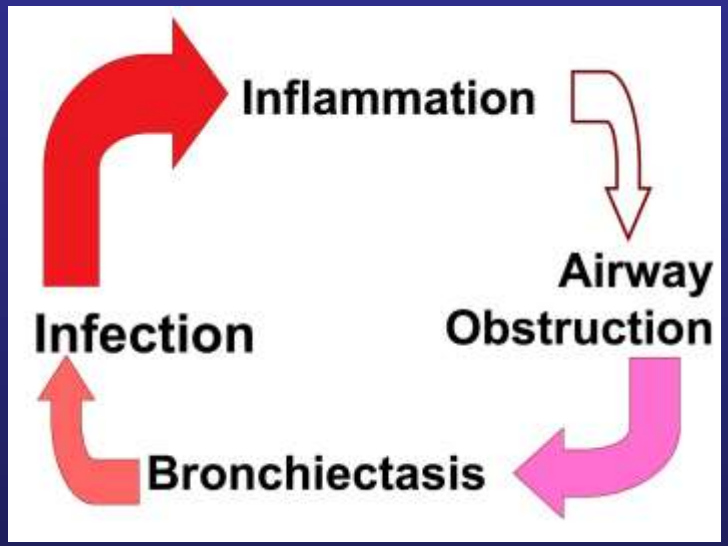
Evolutionary Role for Biofilms?

A mechanism for anchoring to a solid surface and facilitating *persistence* in a turbulent aqueous environment

Mechanisms of Colonization



Vicious cycle



impaired mucociliary clearance →

chronic infection and colonization →

inflammatory response that persists even

after infection has been controlled →

progressive small airways obstruction

Markers of inflammation:

	CF	Non-CF
n	23	8
IL-8 pg/ml, Median (range)	834 (81-6920)	1809 (150-48550)
NE , ng/ml Median (range)	171 (30-3005)	229 (0-7030)
% neutrophils Median (range)	64.5 (4.5-87)	46 (0.5-94)

Mussaffi et al, CHEST, 2008

Dysregulation of both innate and adaptive immunity

- A complex series of inter-related events leading to
- increased airway pro-inflammatory cytokines (e.g. TNF-α, IL-1 and IL-8),
- neutrophil recruitment and migration.

Antibiotics for bronchiectasis: British Thoracic Society guidelines, 2010

- Cornerstone of treatment for
  - Acute exacerbations
  - Prophylaxis to prevent exacerbations
- Sputum cultures are important
- Colonization / chronic infection = same microorganism, $\geq$ 3 cultures >1 mth apart over 6mth
- *H. influenza* and *S. Pneumonia* are common
- *S. aureus* and *P. aeruginosa* if present must be addressed

Antibiotics for bronchiectasis (British Guidelines, 2010)

For acute exacerbations with *P. aeruginosa*:

- 10-14d p.o.

Give IV if :

- no response to p.o. or
- sensitive only to IV antibiotics
- Suggested protocol to eradicate PA:

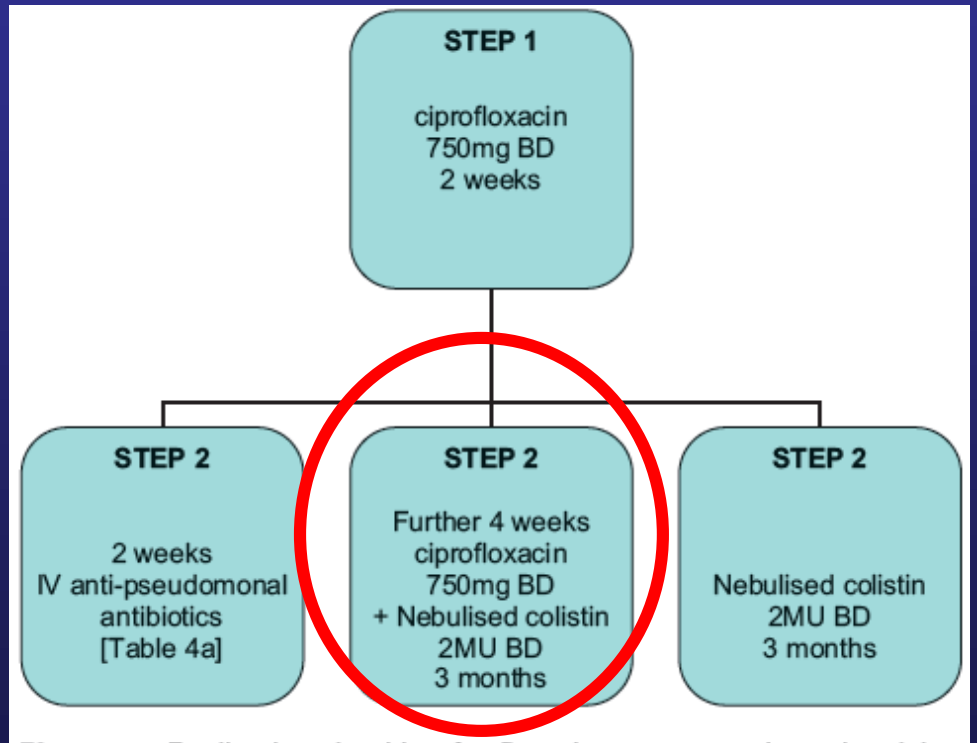


Figure 4 Eradication algorithm for *Pseudomonas aeruginosa* in adults. Attempt to eradicate with a 2-week course of oral ciprofloxacin (step 1). If step 1 fails, further regimens may be considered (step 2).

Long term nebulized antibiotics in non CF bronchiectasis British Guidelines 2010

Patients with chronic PA: ↑ admissions, ↓ QOL and may have accelerated ↓ FEV1

Aim:

- improve symptoms
- reduce exacerbations
- deliver high dose directly to airway, little systemic toxicity

↓ bacterial burden, disrupt vicious cycle infection- inflammation

- choice of antibiotic guided by sensitivities
- Need further studies….

Inhaled antibiotics for non-CF bronchiectases

- Previously: extrapolation from evidence in CF
- Recently: several large randomized trials in Bx
- Phase 3 trials for colistin, aztreonam

Inhaled antibiotics for stable non CF bronchiectasis. ERJ review. Brodt AM, June 2014

- Meta-analysis of RCT including Cochrane airways group register
- 12 RCT in 1264 adults (5 unpublished)
  - 8 RCT in 590 adults were used
- Inhaled amikacin, aztreonam ciprofloxacin, gentamicin, colistin or tobramycin for 4w – 12mth

Inhaled antibiotics for stable non CF bronchiectasis. ERJ review. Brodt AM, June 2014

- ↓ sputum bacterial load -2.65 log10 CFU/g
- Eradicated bacteria : risk ratio 4.2, 95% CI 1.66-10.64
- ↓ exacerbations: risk ratio 0.72, 95% CI 0.55-0.94

- Emerging resistance: 7.8% vs 3.5% in controls (NS)

Effect on reduction of PA sputum load

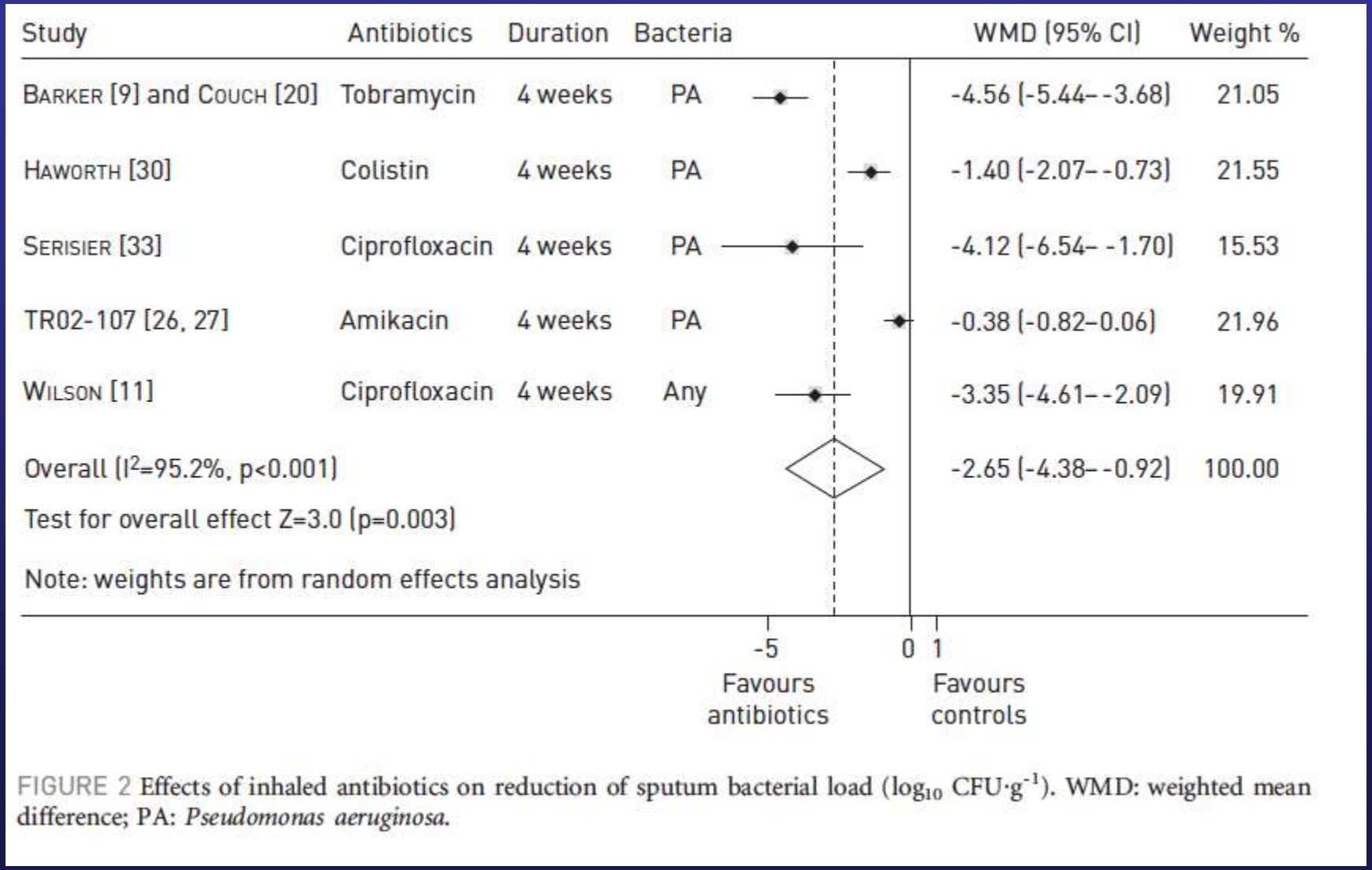


FIGURE 2 Effects of inhaled antibiotics on reduction of sputum bacterial load (log_{10} CFU·g^{-1}). WMD: weighted mean difference; PA: *Pseudomonas aeruginosa*.

Inhaled antibiotics and PA eradication

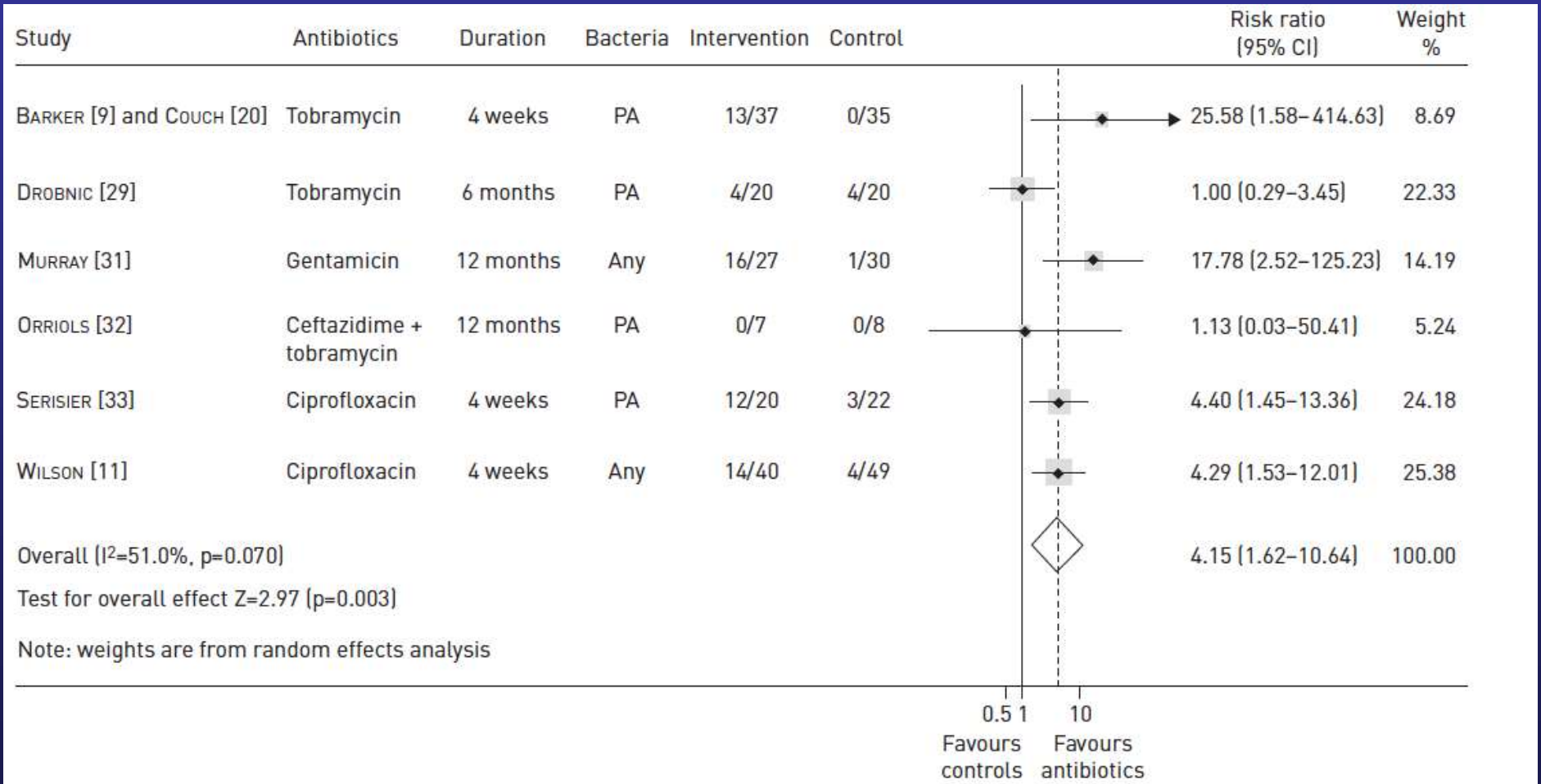


FIGURE 3 Effects of inhaled antibiotics on bacterial eradication from sputum. PA: *Pseudomonas aeruginosa*.

Inhaled antibiotics for stable non CF bronchiectasis. ERJ review. Brodt AM, June 2014

Concluded:

“Inhaled antibiotics may provide an effective suppressive therapy with acceptable safety profile in adults with stable non CF bronchiectasis and chronic bronchial infection”

Nebulized antibiotics for bronchiectases

- Tobramycin shown to be effective
  - reduce PA colony density;
  - improve symptoms;
  - decrease hospitalizations and LOS;
  - variable rates of prolonged eradication
- Recurrence of PA on withdrawal – almost universal

Inhaled Gentamicin in non CF bronchiectasis. Murray MP. Am J Resp Crit Care Med 2011

- RPCT, n= 65, gentamicin 80mg bid for 12mth
- Reduced sputum bacterial density
- 30.8% eradication PA, 92.8% for other pathogens; less sputum purulence ($p<0.0001$)
- Fewer exacerbations: 0 vs 1.5; increased time to 1st exacerbation: 120 vs 61.5d, $p=0.02$
- Improved LCQ and StGeorge Resp Q ($p<0.004$)
- No difference in lung function
- No resistance developed
- At follow up all returned to baseline. Needs to be continuous

Inhaled dual release inhaled liposomal ciprofloxacin for non-CF bronchiectasis.

Bilton D, Thorax 2013

- Phase II, 24w, ANZ multicenter RDBPCT; N=42 adults with ≥2 exacerbations in past yr and Cipro-sensitive PA
- Cipro qd for 3, 28d on/off cycles over 6m
- Primary outcome: bacterial density dropped 4.2 log10 vs -0.08, p=0.002, at 28d
- Secondary outcomes: well tolerated; Time to 1st exacerbation 134 vs 58d (p=0.06)

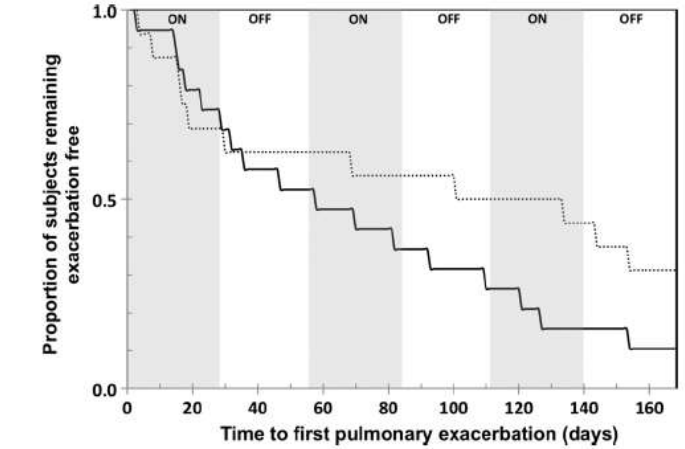
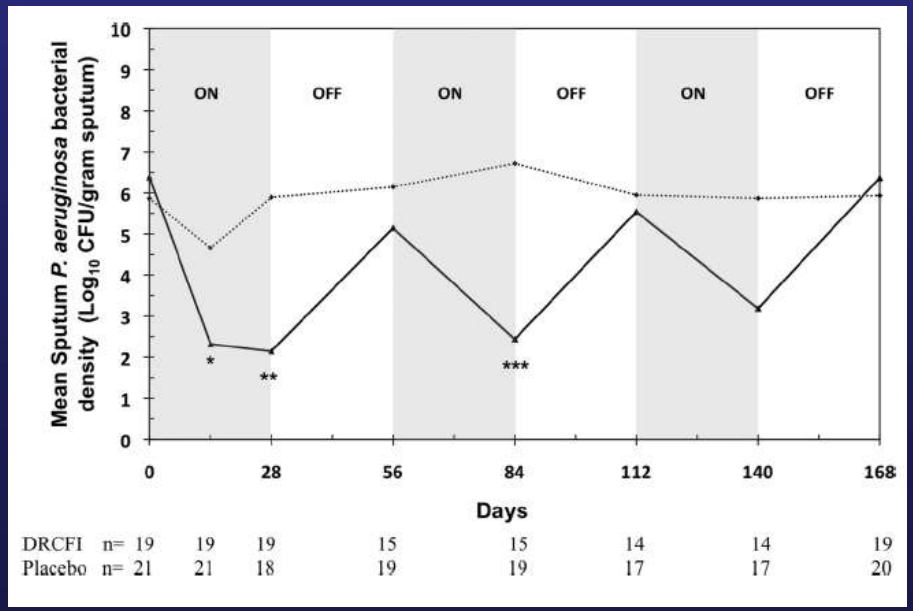
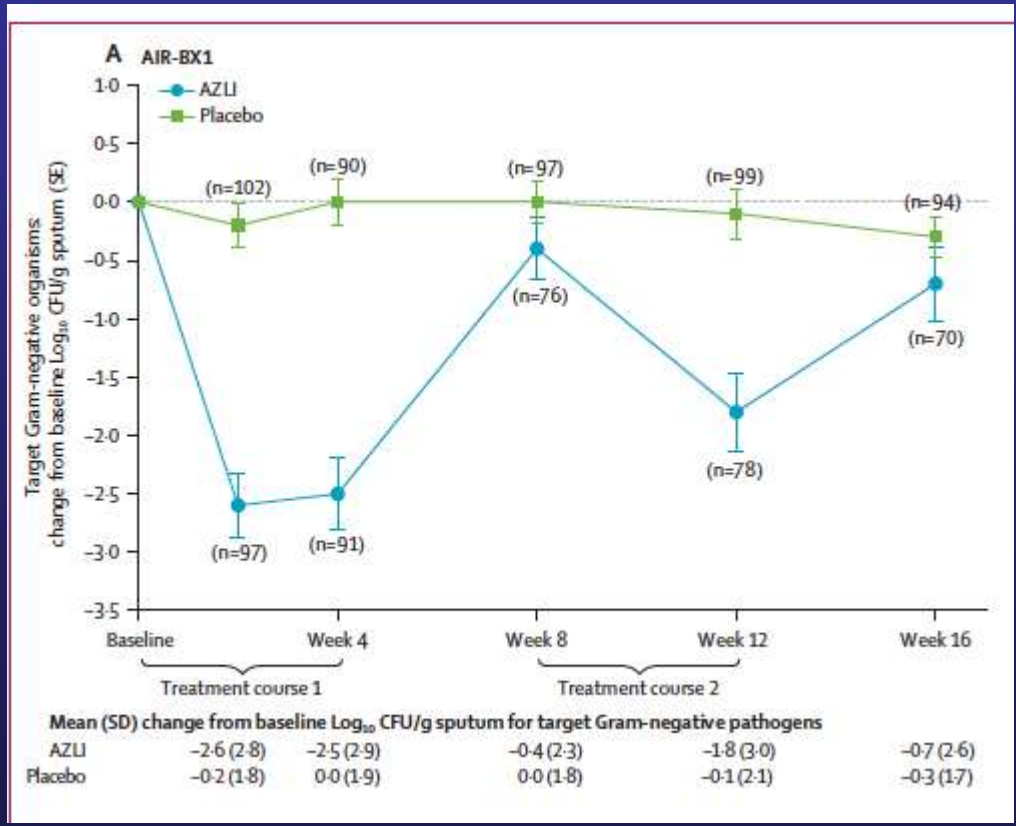


Figure 3 Kaplan–Meier curves comparing DRCFI and placebo groups for time to first pulmonary exacerbation in the modified intention to treat (mITT) population. (Dotted line represents DRCFI, solid line represents placebo; median 134 vs 58 days, p=0.057 mITT, p=0.046 per protocol, by log-rank test; DRCFI, dual release ciprofloxacin for inhalation.)



AIR-Bx trials, Gilead. Inh aztreonam 75mg tid via eflow, Lancet Resp Sep 2014, Barker AF

- Multicenter multinational, RDBPCT
- 2 on/off cycles of 28 days vs placebo
- BX1, n=266 (134 Az); BX2, n= 274 (136 Az);
- Bacterial load decreased BUT
- Primary outcome: change in QOL-B to day 28
- Secondary outcome: change in QOL-B to day 84; time to 1st exacerbation
- Not significant.
- Increased adverse events



Why did the aztreonam study fail when it succeeded in CF

"Bronchiectasis, losing the battle but winning the war". JD Chalmers. Lancet Resp. Sep 2014 editorial

- QOL –Bx RSS: is this the best outcome ?
- Very mixed population (1/3 had COPD in aztreonam group and only 19% in placebo gp)
- Different gram negative bacteria
- Range of patient severity
- Underpowered to detect frequency of exacerbations – too short; 1/3 of patients had no exacerbations previous year

Colistin RCT for non cf bronchiectases

- N=140 ,RPCT, colistin 1 million IU BD for 6mth using I-neb,

- PA bacterial density ↓
- Well tolerated
- QOL improvement
- Just failed to meet primary end point: time to next exacerbation, (placebo group had less exacerbations than expected; underpowered)

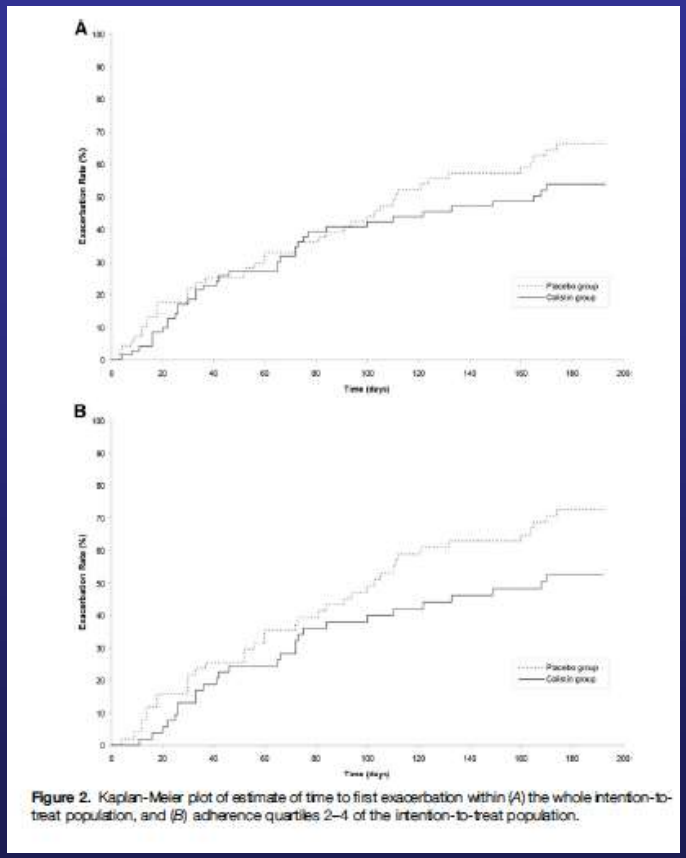


Figure 2. Kaplan-Meier plot of estimate of time to first exacerbation within (*A*) the whole intention-to-treat population, and (*B*) adherence quartiles 2–4 of the intention-to-treat population.

Haworth CS et al Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection.
Am J Respir Crit Care Med 2014

Nebulized colistin for non cf bronchiectasis. Déjà vu all over again?

Matersky and O'Donnell,Editorial AJRCCM 2014

- Can't slavishly following CF care models
- Heterogeneity of population
- Optimal endpoints ?
- Bacterial density does not necessarily reflect clinical e.g. symptoms; exacerbations
- Lack of basic and translational research in NCFB
- No animal model

Causes for optimism

- Increasing recognition fo the worldwide scope of the problem
- More publications recently
- Guidelines for evaluation and care
- New delivery devices for less toxicity

Lessons learned for future studies

- Define the phenotype
- Target more severe, most likely to benefit (recent: bronchiectasis severity index)
- COPD related bronchiectasis needs better definition and characterisation
- Need international registries e.g COPD foundation's bronchiectasis research registry in the USA
- ERS's EMBARC registry

Finally…

- Bronchiectasis is not cystic fibrosis
- Dnase, effective in CF, caused increased exacerbations and drop in FEV1 in bronchiectasis
- TOBI failed because of toxicity
- May need different antibiotic doses

- What about children??

Speaking practically..

- clinicians should personalize care,
- combining antibiotics with different therapies and including airway clearance

תודה רבה!