Therapies for Non-CF Bronchiectasis: Where is the Evidence?

Mark L. Metersky, MD, FCCP, FACP
Director, Center for Bronchiectasis Care
Professor, and Interim Chief, Division of Pulmonary, Critical Care and Sleep Medicine
University of Connecticut School of Medicine

Disclosures

- Consultant
  - Insmed
  - Aradigm
- Clinical Trial Investigator
  - Aradigm
  - Insmed

Question

How many therapies are currently FDA approved for the treatment of non-CF bronchiectasis?

1. 0
2. 1-2
3. 3-5
4. More than 5

Answer

How many therapies are FDA approved for the treatment of non-CF bronchiectasis?

1. **0**
2. 1-2
3. 3-5
4. More than 5

Summary

- There are no current therapies for non-CF bronchiectasis
- Questions?

Issues to consider

- Bronchiectasis is not Cystic Fibrosis
- What works for CF may not work for bronchiectasis
- Our highest quality data for therapies we frequently use in non-CF bronchiectasis comes from CF studies

Issues to consider

- We don’t know what outcomes to measure in bronchiectasis
  - Therapies that we think have benefit usually don’t improve FEV1 in this disease
  - Frequency of exacerbations is a tough endpoint for unfunded studies
  - QOL may be one of the most important endpoints
  - FDA has not generally accepted QOL as the primary outcome

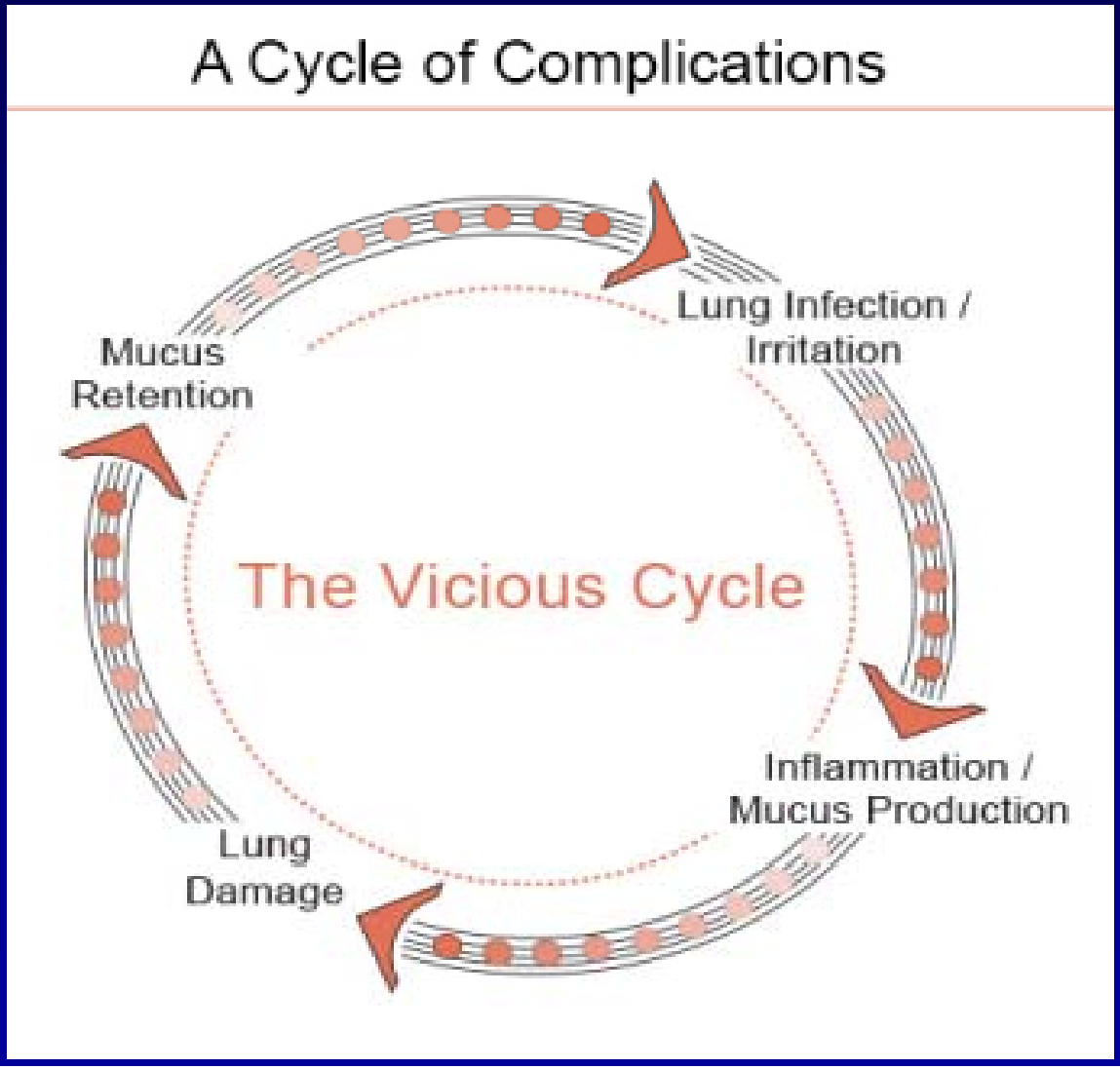
BE registry 2011

Therapies	800 patients
Inhaled bronchodilator	498 (62%)
Airway clearance	383 (48%)
Inhaled steroids	336 (42%)
Macrolides	239 (30%)
Mucolytic	178 (22%)
Oral steroids	111 (14%)
oxygen	82 (10%)

Treatment

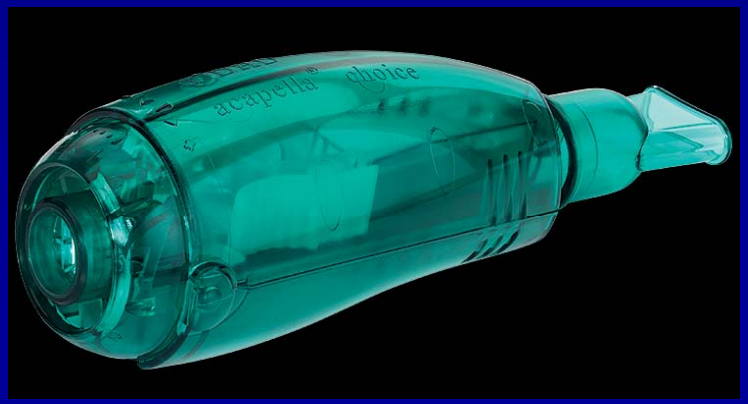
- Mucus clearance regimens
- Mucoactive agents
- Anti-inflammatory agents
  - Macrolides
  - Inhaled Corticosteroids
- Inhaled Antibiotics

Mucus clearance-Vicious cycle hypothesis



Mucus clearance

- Chest physical therapy
- Devices
  - Positive pressure/vibratory
    - Acapella
    - Aerobika
    - Flutter
  - High Frequency Chest Wall Oscillation



Airway clearance devices

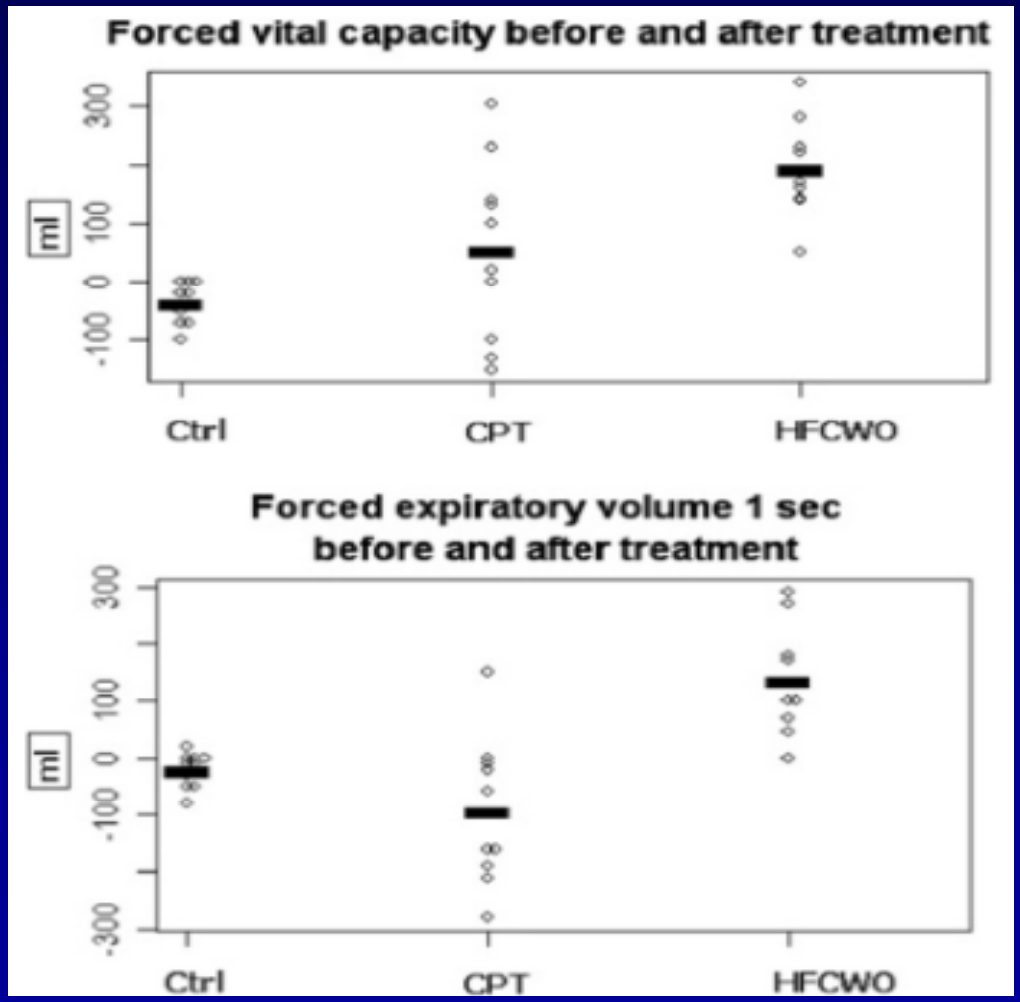
- Cochrane review
  - 7 studies, total of 105 patients
    - Only 2 studies 6 months or greater
  - Conclusions
    - They are safe
    - HFCWO may improve lung function short term
    - The devices probably increase volume of mucus clearance
    - May improved perceived ease of mucus clearance
    - No evidence of effect on exacerbations or long term prognosis

HFCWO vs PEP/vibratory

- If we assume that some method of airway clearance is important, this is probably the most important question, given cost and treatment burden
  - Limited data
  - In a 2 week crossover pediatric study, improved spirometry, no difference between HFCWO and traditional chest physiotherapy

Gokdemir, Pediatr Pulmonol, 2014

3-Way HFCWO study
Changes in lung function after 15 days of therapy



Nicolini, BMC Pulmonary Medicine, 2013

Mucoactive agents

- Theory is that by decreasing viscosity of the mucus, can be cleared more easily
  - Decreased inflammation
  - Improved quality of life
- It works for CF

Mucoactive agents

- Mucolytics
  - Dnase
- Hyperosmolar agents
  - Mannitol
  - Hypertonic saline

rhDNase in non-CF bronchiectasis

Table 3—*Pulmonary Exacerbations: Rates and Risk*

	Placebo Rate	rhDNase Rate	Relative Risk	95% CI
PDEs	0.56	0.66	1.17	0.85, 1.65
NPDEs	0.14	0.29	2.01	1.15, 3.50
PDEs and NPDEs	0.71	0.95	1.35	1.01, 1.79

O'Donnell, Chest, 1998

Hyperosmolar Agents

- Hypertonic saline (7%)
- Mannitol

Hypertonic Saline

- One small study, blinded to NS vs HS
- Cross over design
- Four single day interventions
  - Active cycle breathing (ACB)
  - Nebulised terbutaline, ACB
  - Nebulised terbutaline, then NS, then ACB
  - Nebulised terbutaline, then 7% saline, then ACB

Hypertonic Saline

- HS associated with
  - Increased mucus clearance
  - Improved subjective ease in expectoration
  - Decreased sputum viscosity
  - Marginal improvement in FEV1

Kellett, Resp Med, 2005

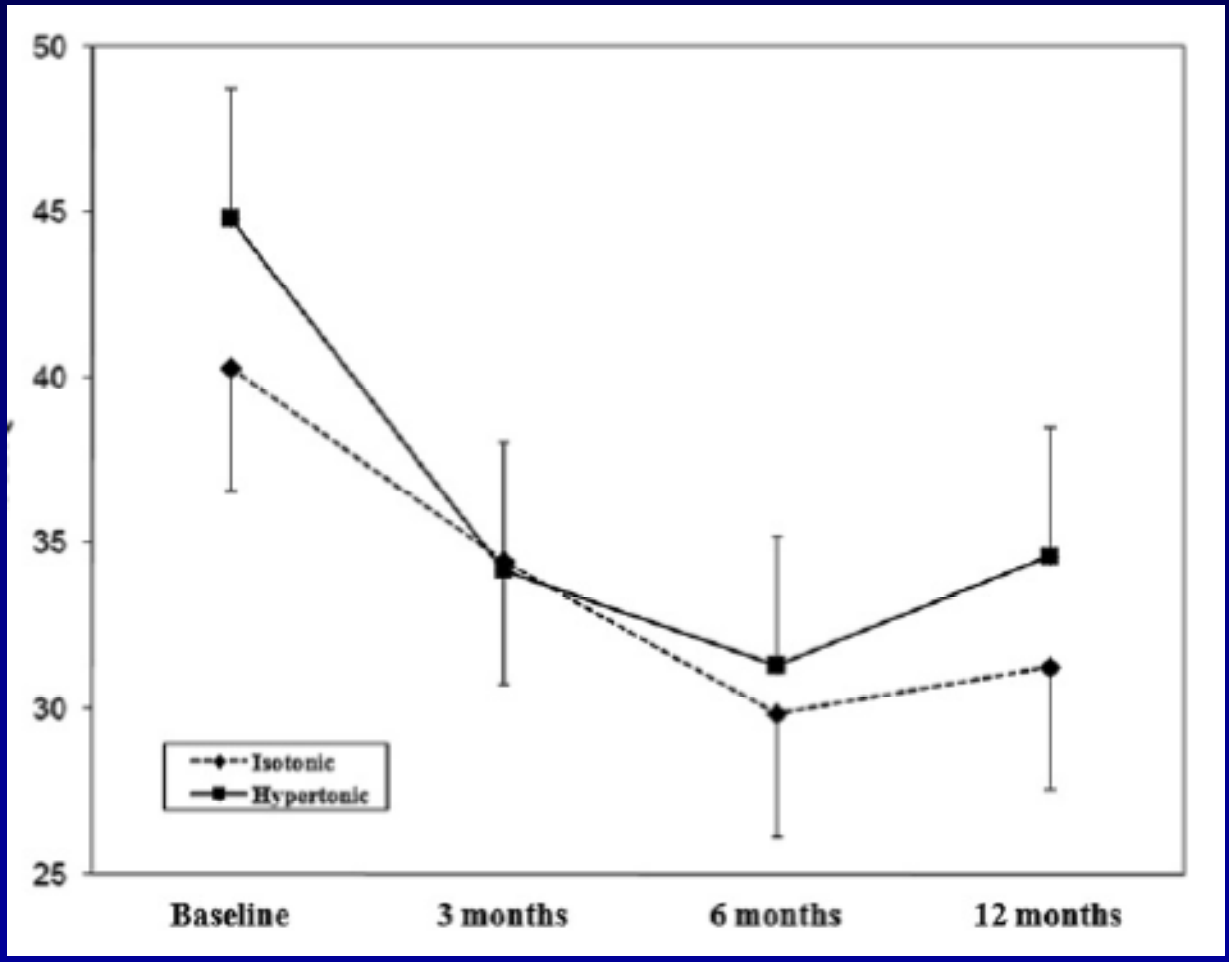
Table 2 Number of exacerbations over 12 months.

	IS (0.9%)	HTS (6%)	*p* value
Exacerbations	1.0 (0–4)	3.0 (0–6)	0.24
Exacerbations requiring antibiotics	0.5 (0–3)	1.0 (0–2.5)	0.99
Exacerbation days	2.0 (0–26)	12.0 (1–26)	0.57
Exacerbation days requiring antibiotics	1.0 (0–19.5)	2.0 (0–7)	0.77

Data are median (IQR). IS: isotonic saline, HTS: hypertonic saline. *p* value for comparison of isotonic saline and hypertonic saline over 12 months.

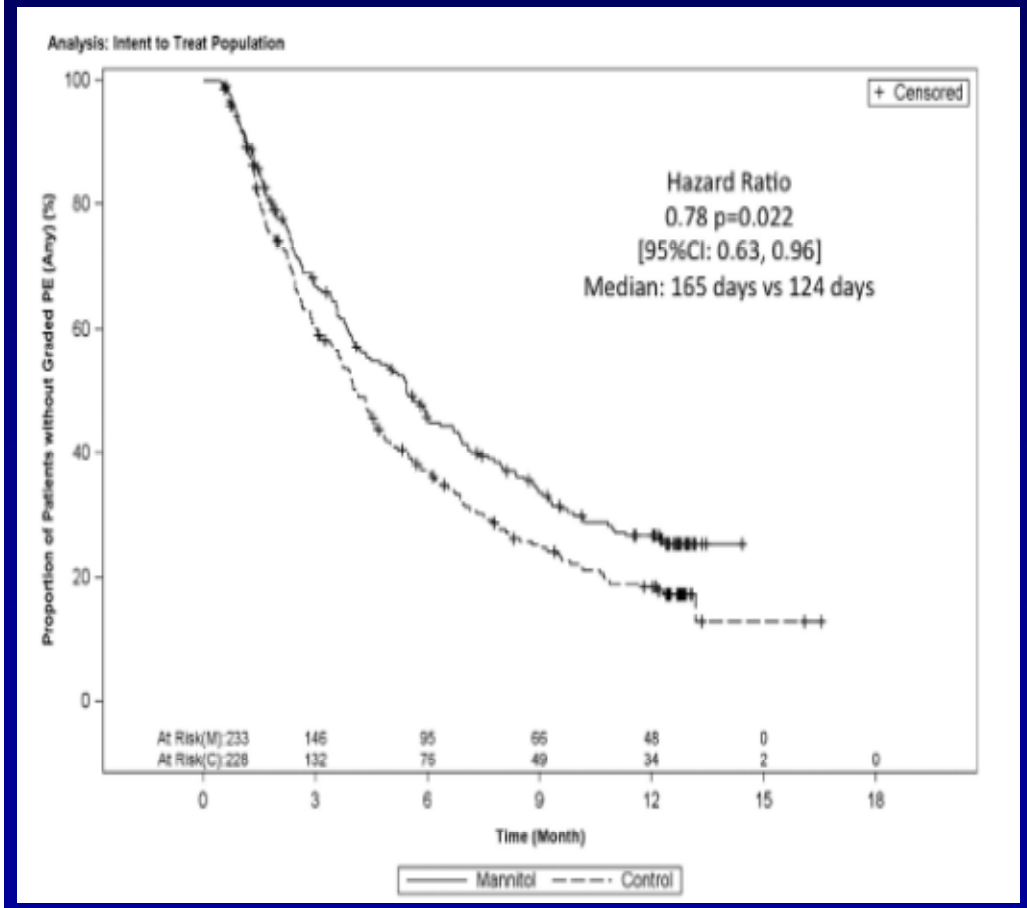
Nicolson, Respir Med, 2012

SGRQ


50
45
40
35
30
25
Isotonic
Hypertonic
Baseline
3 months
6 months
12 months

Inhaled Mannitol

Time to exacerbation reduced



Annual exacerbation rate not reduced

SGRQ improved more than control

Antibiotic days reduced (26 vs 20 days)

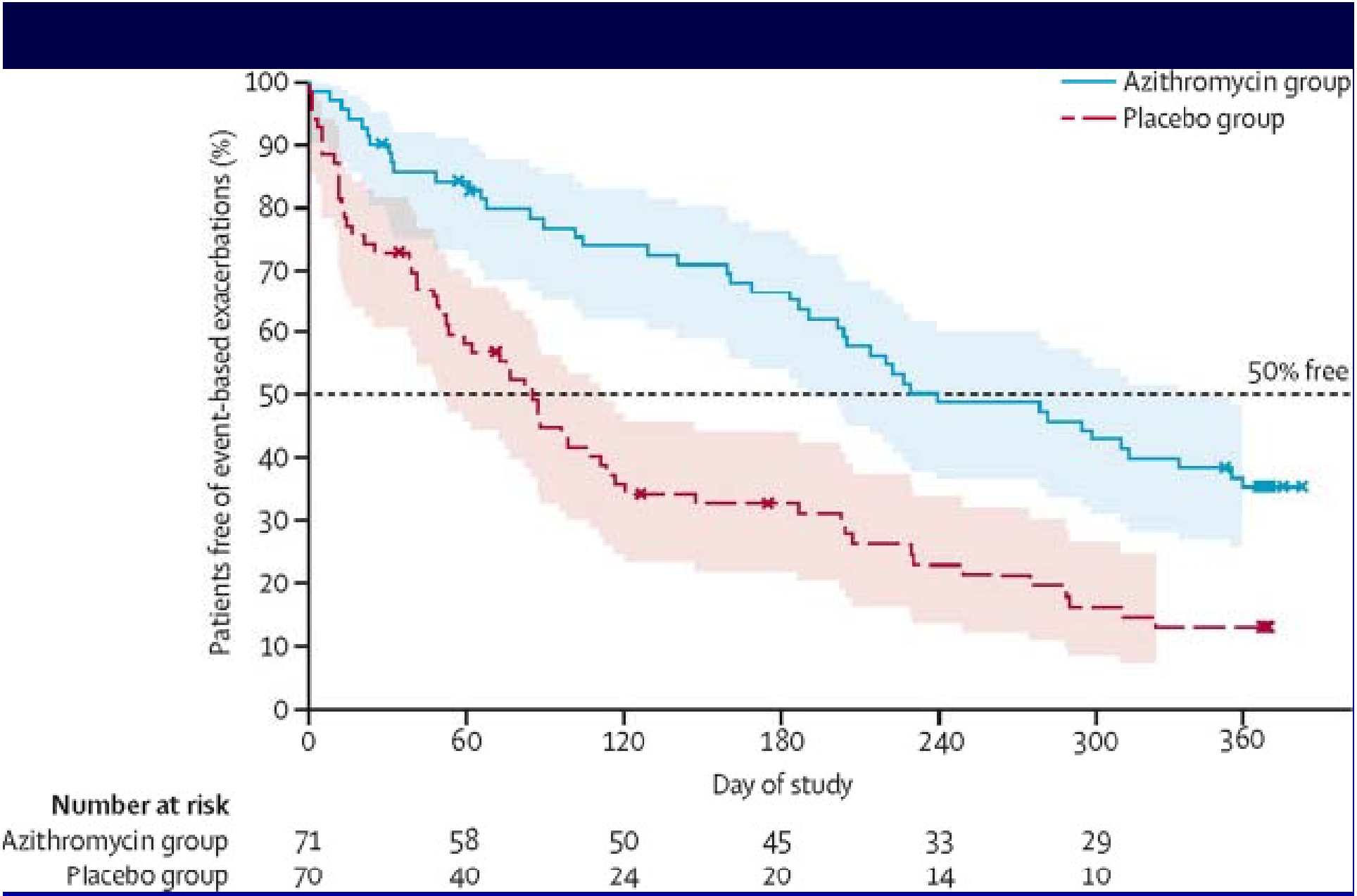
Bilton, Thorax, 2014

Anti-Inflammatory Therapy

- Macrolides
- Inhaled corticosteroids

Why macrolides?

- Effect on pathogens?
  - Inhibit exotoxin production
  - Inhibit quorum sensing
  - Inhibit bio-film production
- Direct immunomodulatory/anti-inflammatory effects
  - Decreased neutrophil recruitment
  - Decreased mucus secretion
  - Decreased cytokine production



Wong, Lancet, 2012

Macrolide effect on SGRQ

Study or Subgroup	Macrolides Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Altenburg 2013	-6.09	13	43	-2.06	9.3	40	19.0%	-4.03 (-8.87 to 0.81)
de Diego 2013	-7.9	3.1	16	4.1	3.8	14	22.6%	-12.00 (-14.50 to -9.50)
Liu 2012	-14	9	24	-10	9.06	22	18.3%	-4.00 (-9.22 to 1.22)
Serisier 2013	-3.9	10	59	-1.3	14.5	58	19.5%	-2.60 (-7.12 to 1.92)
Wong 2012	-5.17	12	71	-1.92	12	70	20.5%	-3.25 (-7.21 to 0.71)
Total (95% CI)			213			204	100.0%	-5.39 (-9.89 to -0.88)

Heterogeneity: $Tau^2 = 21.70$; $Chi^2 = 24.99$, $df = 4$ ($P < 0.0001$); $I^2 = 84\%$

Test for overall effect: $Z = 2.34$ ($P = 0.02$)

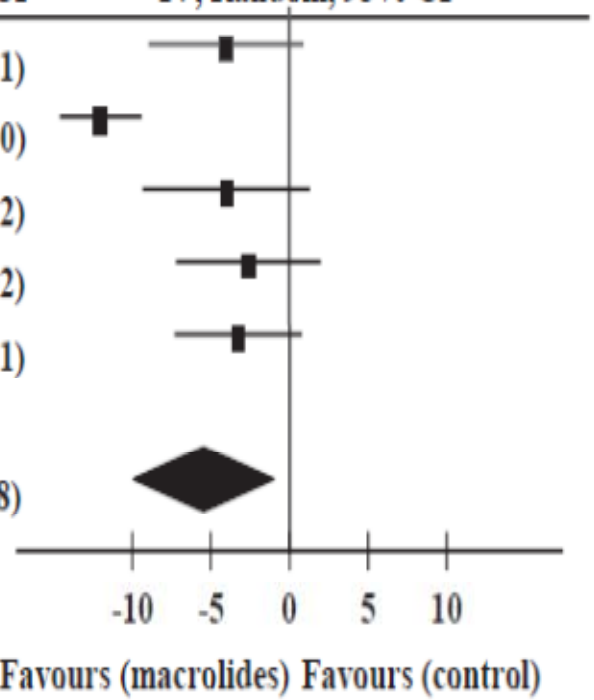


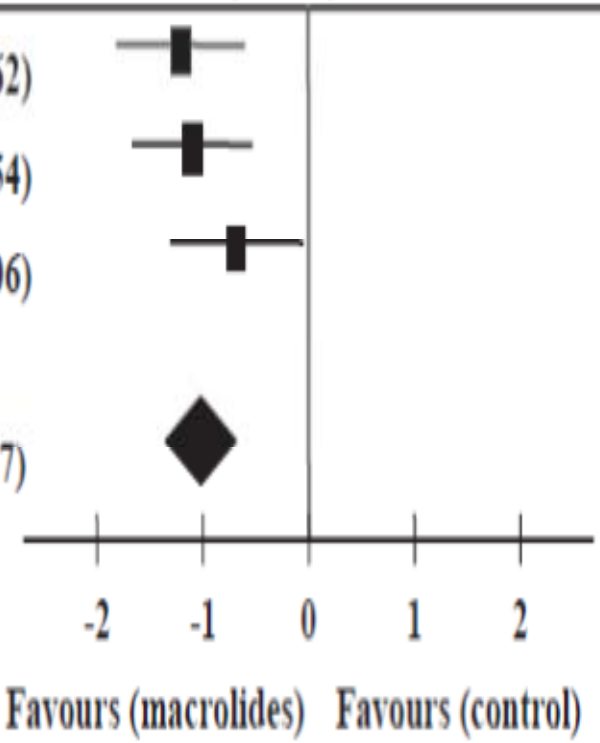
Figure 3 Forest plots showing a significant reduction in the St George's Respiratory Questionnaire total scores in the macrolides group compared with control group. CI, confidence interval; IV, inverse variance; SD, standard deviation.

Macrolide effect on exacerbations

Study or Subgroup	Macrolides Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Altenburg 2013	0.84	1.1	43	2.05	1.6	40	32.4%	-1.21 (-1.80 to -0.62)
de Diego 2013	0.1	0.6	16	1.2	0.9	14	37.2%	-1.10 (-1.66 to -0.54)
Serisier 2013	1.29	1.38	59	1.97	1.96	58	30.3%	-0.68 (-1.30 to -0.06)
Total (95% CI)			118			112	100.0%	-1.01 (-1.35 to -0.67)

Heterogeneity: $Chi^2 = 1.64$, $df = 2$ ($P = 0.44$); $I^2 = 0\%$

Test for overall effect: $Z = 5.83$ ($P < 0.00001$)



Wu, Respirology, 2014

Potential Complications of Chronic MacrolideTherapy

- Macrolide resistant NTM
  - Must rule out NTM/ *M. avium* complex infection
  - Macrolide resistant *M. avium* complex extremely difficult to treat, with low cure rates
- Antibiotic resistance
  - Oral Streptococci
  - Probably not often clinically significant
- Shift of microbiome towards GNs/Pseudomonas

Potential Roles for Inhaled corticosteroids

- Diminish progressive airway damage caused by chronic inflammation
- Decrease mucus hypersecretion
- Treat bronchial hyper-responsivenes

Inhaled corticosteroids

Randomized, blinded trial of inhaled fluticasone

Subjects:	24 patients, 50% female
Intervention:	Fluticasone 500 ug BID vs placebo for 4 weeks
Endpoints:	Spirometry, sputum volume, bacterial density, inflammatory mediators

Tsang, AJRCCM, 1998

Results

No improvement in FEV1 or PEFR

No improvement in 24 hour sputum volume or in sputum bacterial density

Improved sputum leukocyte density

Improved IL-1β, IL-8, LTB4

Quality of life not measured

Obviously not designed to assess affect on lung function loss

The NEW ENGLAND JOURNAL of MEDICINE

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Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

Peter M.A. Calverley, M.D., Julie A. Anderson, M.A., Bartolome Celli, M.D., Gary T. Ferguson, M.D., Christine Jenkins, M.D., Paul W. Jones, M.D., Julie C. Yates, B.S., and Jørgen Vestbo, M.D., for the TORCH investigators*

There was no difference in the incidence of ocular or bone side effects. The probability of having pneumonia reported as an adverse event was higher among patients receiving medications containing fluticasone propionate (19.6% in the combination-therapy group and 18.3% in the fluticasone group) than in the placebo group (12.3%, $P<0.001$ for comparisons between these treatments and placebo).

BE registry 2011

Chronic Antibiotic Therapies	800 patients
Aerosol antibiotic	94 (12%)
Rotating oral antibiotic	62 (8%)
Continuous po antibiotic	235 (29%)

Prolonged antibiotics

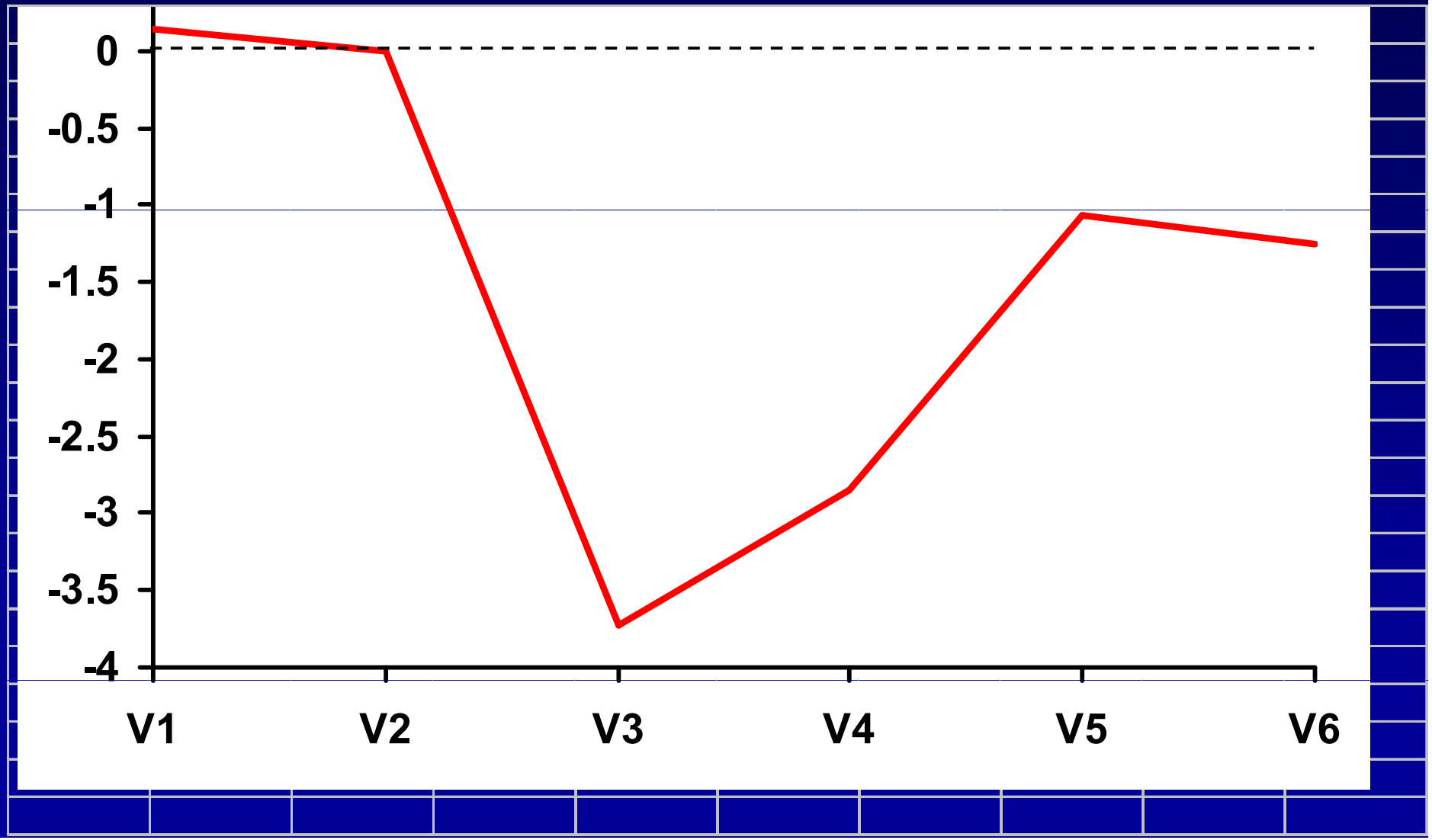
- Cochrane meta-analysis
- 9 studies
- Significant heterogeneity in treatment
  - 4 weeks-1 year
  - Inhaled and oral
  - Tobramycin, B-lactam, macrolide
- Significant heterogeneity in measured outcomes

Prolonged antibiotics

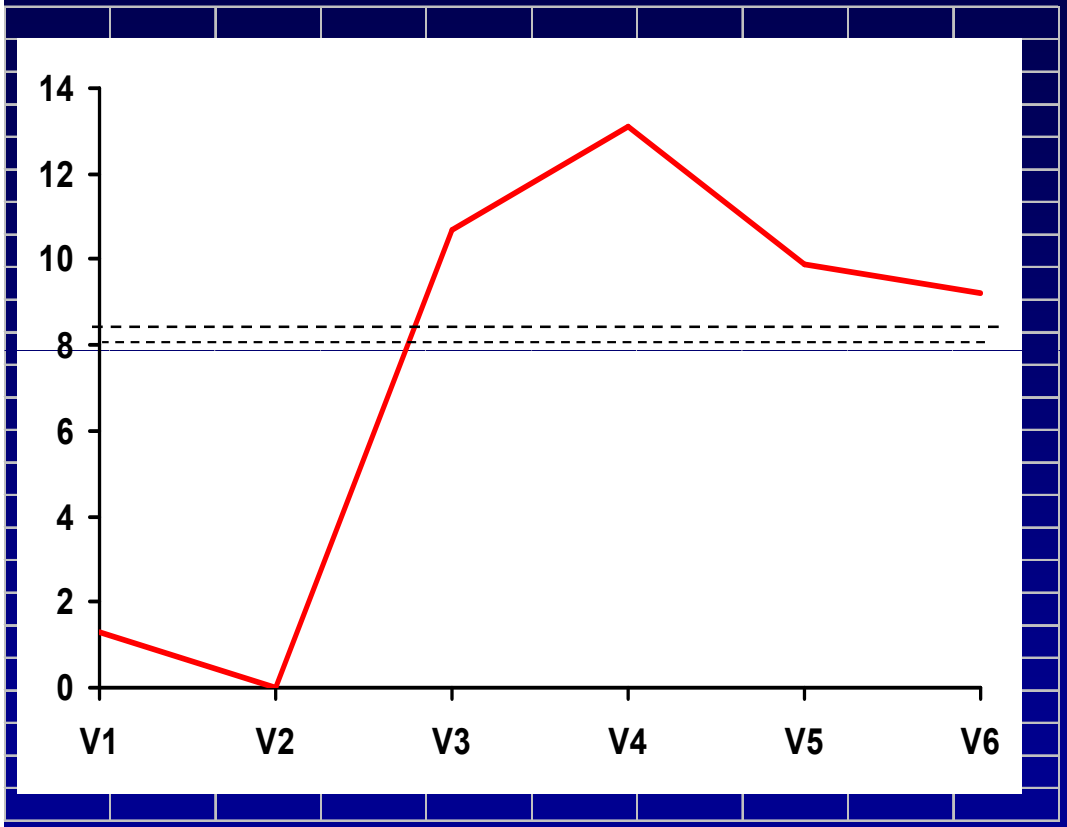
- Conclusion
  - Small benefit in symptoms
  - No benefit in frequency of exacerbation
  - Development of resistance not an obvious concern

Davis, Cochrane Database, 2011

Aerosolized aztreonam
Log_{10} CFUs of *P. aeruginosa*



Change in QOL-B Respiratory Domain



Response at Day 28 (n = 83)

Improved	**61 (73.5%)**
Stable	**6 (7.2%)**
Worsened	**16 (19.3%)**

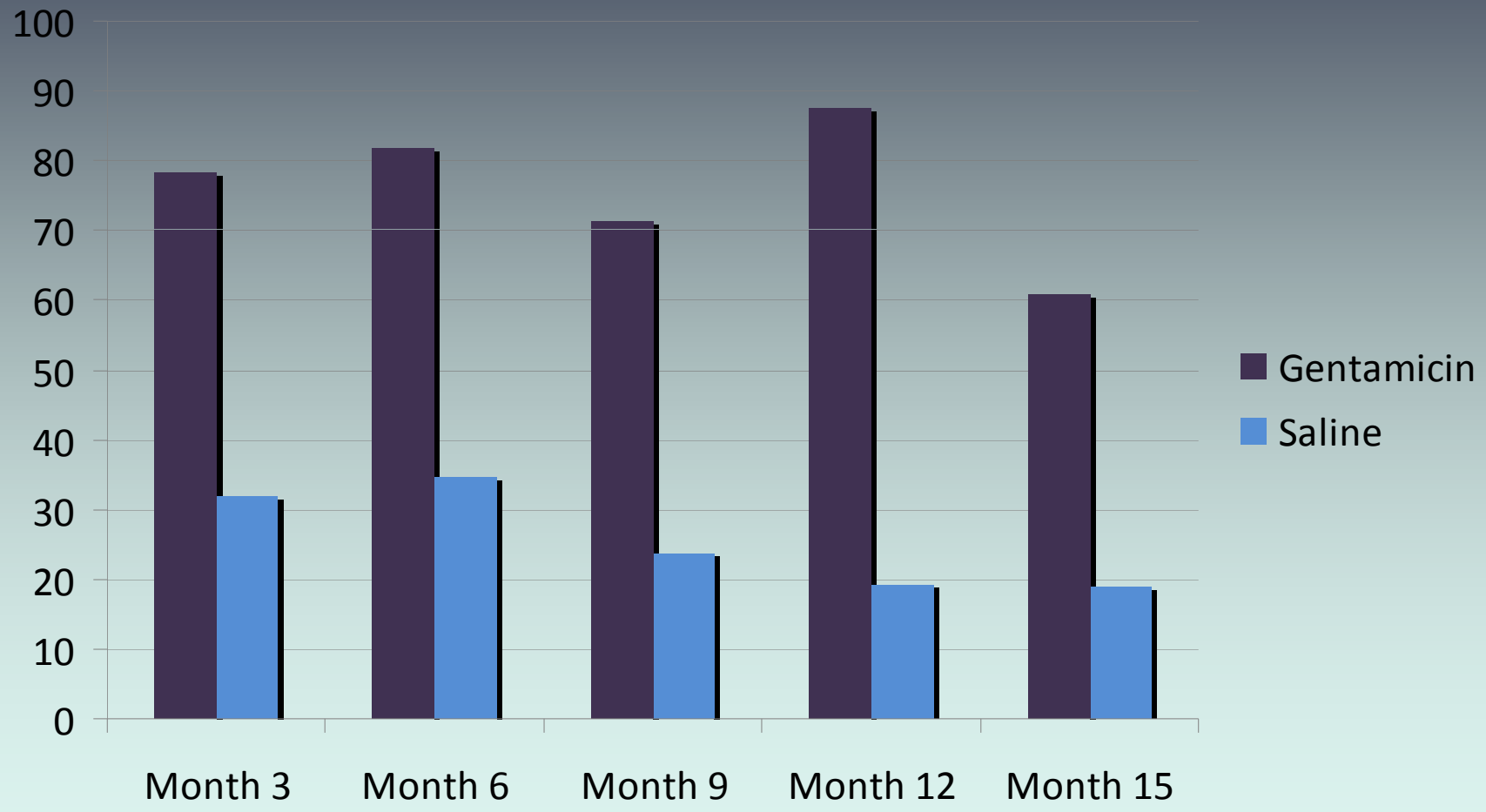
Barker et al, AJRCCM, 2010

Phase 3

- Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomized double-blind, placebo-controlled phase 3 trials
  - No clinically significant benefit
  - Increased treatment-related adverse events and discontinuations in aztreonam group

Lancet Respir Med, 2014

Open label gentamicin
% of patients improved SGRQ ≥4



Murray, Am J Respir Crit Care Med, 2011

Double-blind RCT of inhaled Colistin

- Patients with bronchiectasis and chronic Pseudomonas aeruginosa infection
  - Failed to reach primary endpoint (exacerbation rate), although significant decrease in the most compliant patients
  - Clinically significant improvement in SGRQ

Haworth, AJRCCM, 2014

Inhaled antibiotic trials

- Inhaled ciprofloxacin/liposomal ciprofloxacin
- Two Phase III studies for patients with *P. aeruginosa*
  - In only one was there a statistically significant increase in time to first exacerbation, or frequency of exacerbations
- Not approved by FDA in January, 2018

Dry powder Cipro

- Phase III studies
- 14 day and 28 day regimens
- Again, conflicting results with a positive and a negative result (positive for 14 days)
- Small increase in resistance noted
  - A potentially big problem for quinolones
    - The only oral Rx for Pseudomonas
- Turned down by FDA

Inhaled Antibiotics

- There is no doubt that some patients benefit
- “Life-changing”
- “Grandma, you’re not coughing today
  - Not placebo effect

Inhaled antibiotics

- We do not know which are the right patients to treat
- We do not know the proper way to administer
  - 14 on/off
  - 28 on/off
  - Continuously
- We don’t know how long to administer

Summary

- We were in the golden age of bronchiectasis treatment investigation
  - May be over, with little to show for it
- Macrolides appear to be effective
- We think mucus clearance is important
  - Don’t ask for evidence
- Role of inhaled antibiotics for long term control remains to be seen