INHALED ANTIBIOTICS THERAPY
IN NON-CF LUNG DISEASE

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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, 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*
• 18 months inhaled colistin
  \(1 \times 10^6\) units x2/day

Oral Cipro/cefuroxime/ flagyl

Occasional hospitalizations
For IV antibiotics

Physiotherapy

Ventolin, aerovent, budes

2011
No longer oxygen dependent

Gag returned

Still vocal cord paralysis

Still on intermittent Cipro
And inhaled colistin
- thus avoids hospitalization

Chronic lung disease
Case 2

- Diagnosed in infancy with pseudohypoaldosteronism type 1 (ENaC, epithelial sodium channel 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

Life threatening hyperkalemia

Treatment:
Kexalate

IV antibiotics
Then maintained on:

Inhaled colistin

Oral ciprofloxacin
Physiotherapy
Hypertonic saline inh aerovent
Chronic lung disease

Inhaled colistin for 20 months

And later, intermittent
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 (≤ 2 months)
Age range: 0.7-33y
Diagnoses, n=29

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

impaired mucociliary clearance →
chronic infection and colonization →
inflammatory response that persists even after infection has been controlled →
progressive small airways obstruction
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

• 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

• \textit{H. influenza} and \textit{S. Pneumonia} are common

• \textit{S. aureus} and \textit{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 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....
Development chronic Pseudomonas aeruginosa lung infection

- Birth
- First infection
- Negative sputum cultures
- Repeated infections
- Recurrent infection
- Chronic infection
- Antibiotics
- Mucoid strain
- Poorer prognosis
Infection

P. aeruginosa
6,264,403 bp
Evolutionary Role for Biofilms?

A mechanism for anchoring to a solid surface and facilitating persistence in a turbulent aqueous environment.
Mechanisms of Colonization

- Impaired mucociliary clearance
- Impaired antimicrobial activity
- Antibacterial proteins
- Increased adherence
- CFTR
- Impaired phagocytosis
The Inflammatory Response in CF

Elastase
MPO

pmn

IL-8

IL-8

IL-6

macrophage

TNF-

IL-8

IL-1β

respiratory epithelium
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
- Bronchospasm in 10% (controls 2.3%) but same withdrawal rate due to adverse events
- Emerging resistance: 7.8% vs 3.5% in controls (NS)
Effect on reduction of PA sputum load

![Graph showing the effect of various antibiotics on the reduction of PA sputum load.](image)

**Study** | **Antibiotics** | **Duration** | **Bacteria** | **WMD [95% CI]** | **Weight %**
---|---|---|---|---|---
Barker [9] and Couch [20] | Tobramycin | 4 weeks | PA | -4.56 (-5.44--3.68) | 21.05
Haworth [30] | Colistin | 4 weeks | PA | -1.40 (-2.07--0.73) | 21.55
Serisier [33] | Ciprofloxacin | 4 weeks | PA | -4.12 (-6.54--1.70) | 15.53
TR02-107 [26, 27] | Amikacin | 4 weeks | PA | -0.38 (-0.82--0.06) | 21.96

Overall ($I^2=95.2\%, p<0.001$)
Test for overall effect $Z=3.0\ (p=0.003)$

Note: weights are from random effects analysis

**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

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibiotics</th>
<th>Duration</th>
<th>Bacteria</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk ratio [95% CI]</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DROBINC [29]</td>
<td>Tobramycin</td>
<td>6 months</td>
<td>PA</td>
<td>4/20</td>
<td>4/20</td>
<td>1.00 [0.29–3.45]</td>
<td>22.33</td>
</tr>
<tr>
<td>ORRIOLS [32]</td>
<td>Ceftazidime + tobramycin</td>
<td>12 months</td>
<td>PA</td>
<td>0/7</td>
<td>0/8</td>
<td>1.13 [0.03–50.41]</td>
<td>5.24</td>
</tr>
</tbody>
</table>

Overall (I²=51.0%, p=0.070)

Test for overall effect Z=2.97 (p=0.003)

Note: weights are from random effects analysis

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

- 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)
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 within 21d of anti PA exacerbation Rx using I-neb, breath activated vibrating mesh with adherence download.
- PA bacterial density ↓
- Well tolerated
- QOL improvement
- Just failed to meet primary endpoint: time to next exacerbation, (placebo group had less exacerbations than expected; underpowered)
Nebulized colistin for non cf bronchiectasis. Déjà vu all over again?  
Matersky and O’Donnell, Editorial AJRCCM 2014

• There are no drugs approved by the FDA for non CF bronchiectasis. In contrast to CF where several agents improve survival, QOL and exacerbations

• We can’t just extrapolate BUT…
Suggested causes of failure:

- Slavishly following CF care models not applicable to NCFB
- Heterogeneity of population
- Optimal endpoints not found yet
- Bacterial density does not necessarily reflect clinical outcome e.g. symptoms; exacerbations
- Lack of basic and translational research in NCFB
- No animal model
Causes for optimism

• Increasing recognition for 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

- Need high quality phenotype to identify populations that can benefit and tolerate inhaled antibiotics
- Probably best to 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
Speaking practically..

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