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

Oral Cipro/cefuroxime/ flagyl

Occasional hospitalizations
For IV antibiotics

Physiotherapy

Ventolin, aerovent, budesonide

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 (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
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, 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
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

1st infection

Negative sputum cultures

Repeated infections

Mucoid strain

Antibiotics

Recurrent infection

Chronic infection

Birth

Poorer prognosis
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
- Increased adherence
- Impaired antimicrobial activity
- Antibacterial proteins
- Impaired phagocytosis
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:

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

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, >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:
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**

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

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>Drobnic [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 + tobramyacin</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 ($I^2=51.0\%, p=0.070$)
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 bronchiectasis

- 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 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)

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 of 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!