Inhaled Antibiotics in Non-CF

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Advantages

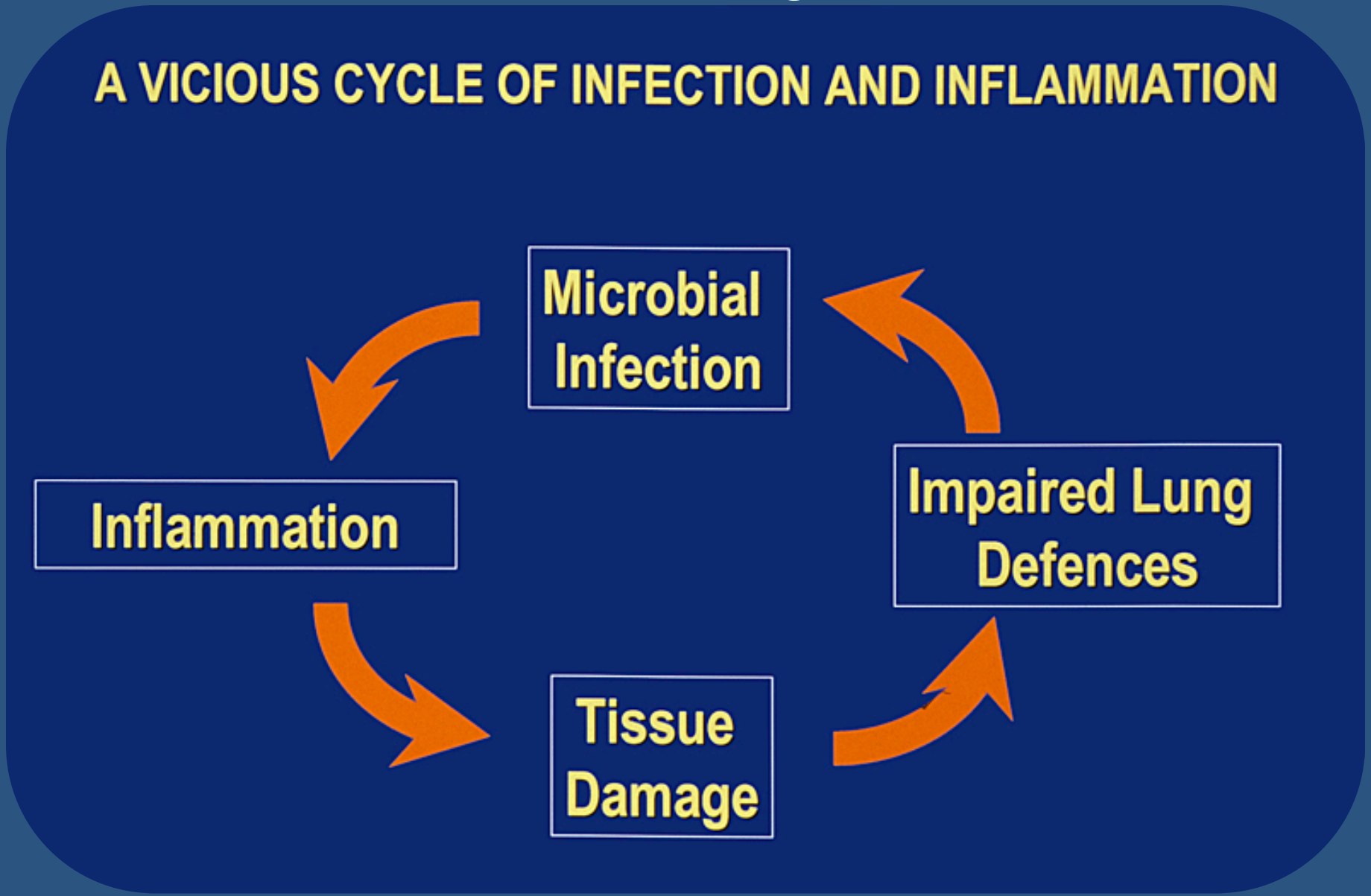
- Increased drug concentrations locally
- Reduced systemic adverse effects
- Home treatment

Role

- Prophylaxis / chronic management
- Eradication
- Acute Treatment

- Bronchiectasis
- Pneumonia

Chronic management



Nebulised colomycin studies

Study	Study design	N	Medications	Study time-frame	Outcome	Side effects
Steinfort 2007	Prospective, open-label	18 14 Bx	Nebulised colistin 30 mg in 2 ml od	Average 41 months 6/12 rv	**Three patients showed improved FEV_1** and increase in patient-reported quality of life	No resistance side effects
Dhar 2010	Retrospective, open-label	19 17 completed	Nebulised colistin 1–2 megaunits twice daily	Average 21.2 months 6/12 rv	**Significant decrease of PA** **↓ exacerbation frequency (7.8 to 2.7/year, *P*<0.001)**	No side effects

- Improvement in PFT, exacerbations, micro BUT small uncontrolled studies
- International multicentre RCT with primary endpoint time to next exacerbation will report soon.

Nebulised tobramycin studies

Study	N	Medications	Study time-frame	Outcome	Side effects
Barker 2000	74 37 tobramycin 37 placebo	Inhaled tobramycin 300 mg twice daily	4 weeks with 2-week washout	**↓Colonisation with PA in treatment arm (35% eradication at week 6),** possible subjective symptomatic improvement	↑ incidence of dyspnoea (32%), resistance 11%
Scheinberg 2005	41	Inhaled tobramycin 300 mg twice daily	Open label Three cycles of 2 weeks on/2 weeks off therapy	**Eradication of PA in 22% at week 12,** **QoL**	10% dropout resistance 7%
Drobnic 2005	30 20 completed 5 died	Inhaled tobramycin 300 mg twice daily	6 months, 1-month washout and crossover for 6 months	No change in exacerbation frequency or quality of life, **↓ number of hospitalisations in treatment arm**	No resistance; 10% bronchospasm
Orriols 1999	15	Ceftaz and tobra vs symptomatic Rx	Open label 12 month	**Significant ↓ hospital days and admissions** No change in FEV_1	1 pt withdrew bronchospasm

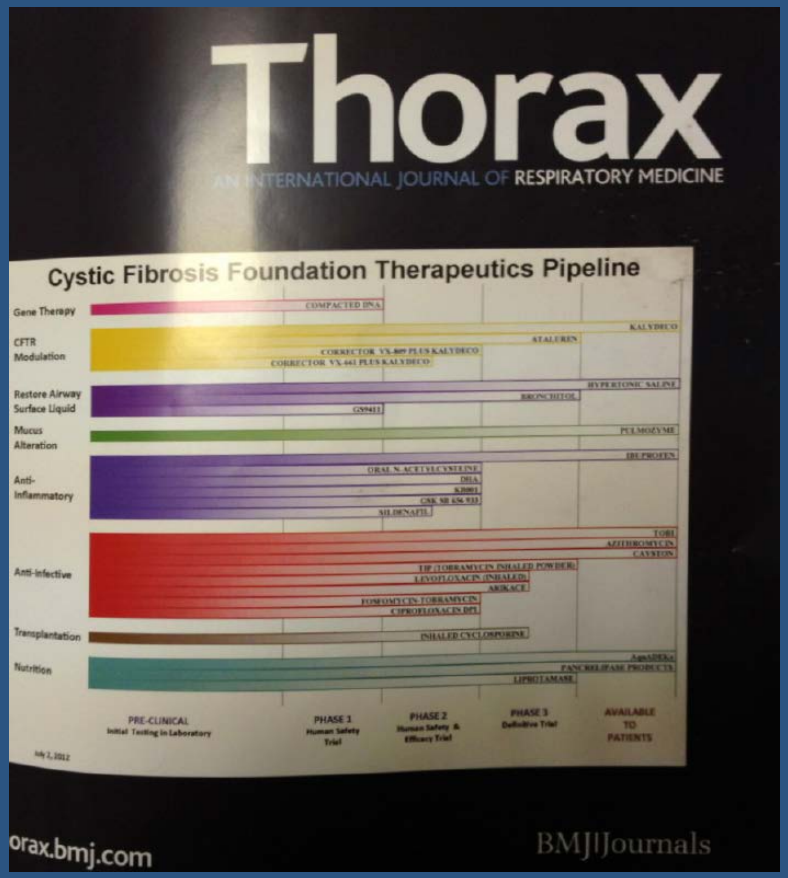
- Some ↓hospital, micro, but resistance and side effects

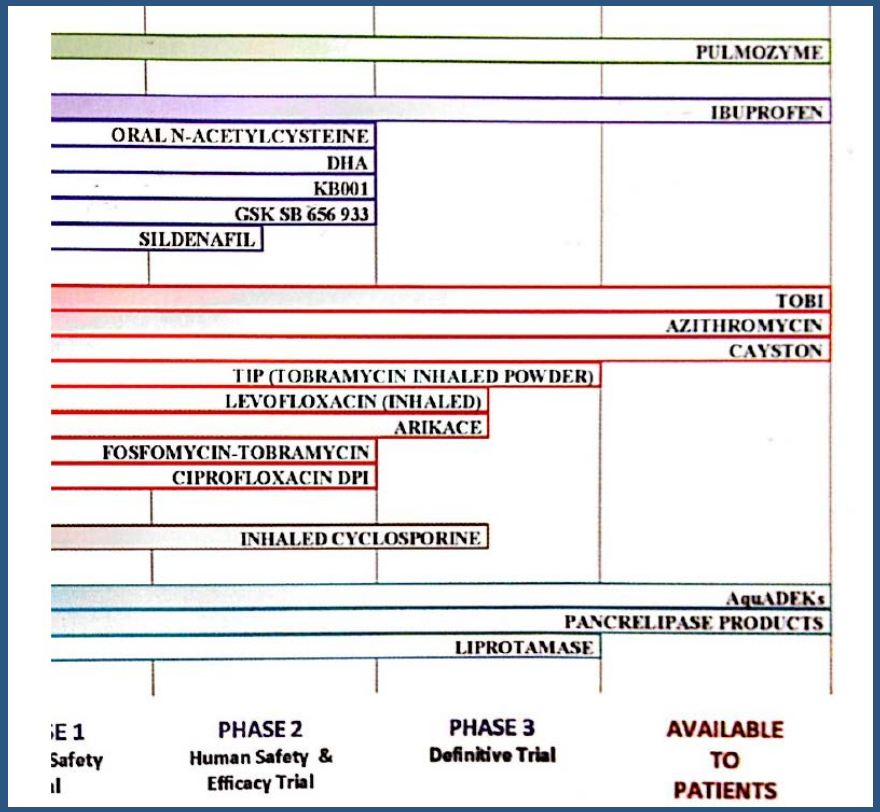
Nebulised gentamicin studies

Study	N	Medications	Study time-frame	Outcome	Side effects
Murray 2011	65	Neb Gent 80mg bd vs HTS	12 months, 3monthly rv	**Bacterial eradication: 31% *PSA*, 93% other pathogens** **↓ Sputum purulence (*P*≤0.02)** **↑ Exercise capacity (*P*=0.03)** **↓ Exacer 0 (0–1) cf 1.5 (1–2) (*P*<0.0001)** **Better quality of life: LCQ and SGRQ**	No resistance ↑ incidence of dyspnoea (32%), chest pain and wheezing in treatment arm

- Improved clinical and micro end points, but not sustained.

New formulations





New formulations

Therapy	Phase	N	Description	Result primary endpoint
Liposomal amikacin for Inhalation	II	61	Inhaled liposomal amikacin 280 mg or 560 mg once daily for 28 days	**Significant ↓ in PA density in the 560 mg arm *vs* placebo[1,2]**
Aztreonam for Inhalation Solution (AZLI) Phase III (AIR BX1 and AIRBX2 recruiting)	II	89	Nebulised aztreonam for inhalation solution 75 mg three times daily for 28 days	**Statistically and clinically significant improvement in respiratory symptoms.** **Significant ↓ of PA (>99%) and non-PA (98%) Gram-negative density[3]**
Dual Release Ciprofloxacin for Inhalation (DRCFI) ARD-3150 Phase III study in preparation	IIb	42	ARD-3150 and placebo once daily for 28 days then 28 days off treatment for three cycles	**Significant ↓ of PA density 4.2 log units *vs* 0.1 log units placebo (*P*=0.004)[4]** **Significant difference in median time to first exacerbation (DRCFI 134 days vs. placebo 56 days (P=0.046)[5]**
Ciprofloxacin DPI Phase III study in preparation	II	124	Ciprofloxacin DPI 32.5 mg or placebo twice daily for 28 days plus 2 months' follow-up	**Significant ↓ of total bacterial counts in ITT population 3.6 log units *vs* 0.3 log units placebo (*P*=0.001)[7]**

- Predominantly micro end points, but clinical endpoints needed.

Treatment - Eradication

- Pseudomonas
- No specific studies
- CF
  - Ciprofloxacin and nebulised colomycin 3/12 (16% vs 72% historical controls)
  - TOBI (ELITE)
  - Recent comparison cipro + TOBI / Colo

Treatment - Exacerbations

Study	N	Medications	Study time-frame	Outcome	Side effects
Bilton 2006	53 43 completed	Oral ciprofloxacin 750 mg plus inhaled tobramycin 300 mg or placebo bid	2 weeks followed by 1 week follow-up	**Significant ↓ of PA in sputum, 35% cf 19%** ↓ in FEV_1 while on tobramycin (*P*=NS)	50% on tobramycin developed wheeze compared with 15% on placebo

- microbiological but not clinical improvement

Pneumonia - VAP

Study	Study design	N	Medications	Outcome
Ioannidou 2007	Metaanalysis	5RCTs, 176pts	Tobra, gent, sisamycin	**Improved cure, no mortality effect**
Michalopoulos 2008	Prospective, open-label	60	Nebulised colistin 57received iv Rx	**83% bact and clinical response No control group**
Ghannam 2009	Retrospective	32 cancer and VAP	IV colistin/amino With Neb 16 Without Neb 16	**Increase complete resolution and micro eradication**
Korbila 2010	Retrospective	121	IV colistin With Neb 78 Without Neb 43	**Cure rate 79.5% cf 60.5%**
Kofteridis 2010	Retrospective	86	IV colistin With Neb 43 Without Neb 43	**No difference**
Korbila 2010	Retrospective	121	IV colistin With Neb 78 Without Neb 43	**Cure rate 79.5% cf 60.5%**
Lu 2011	Phase 2 RT	40	20 IV ceftaz/ami 20 Neb ceftaz/ami	**No difference in outcome, more resistance in IV group**

Treatment

- New formulations – Amikacin

- Not yet well supported by studies
- Some rationale for concurrent use in VAP

Others

- NTM – amikacin
- Pneumocystis – pentamidine
- Fungal infection - amphotericin
- Pneumonia prophylaxis
- Other chronic resp conditions

Challenges

- Evidence
  - Which patients
  - Optimal regimen and delivery
  - Regrowth after use
- Resistance
  - Patient
  - Community
- Bronchospasm
- Cost
- Burden

Conclusions

- Poor evidence
- Good rationale
- Established use in bronchiectasis
- Less so in VAP
- Increasing interest
- Increasing number of products, studies, trials