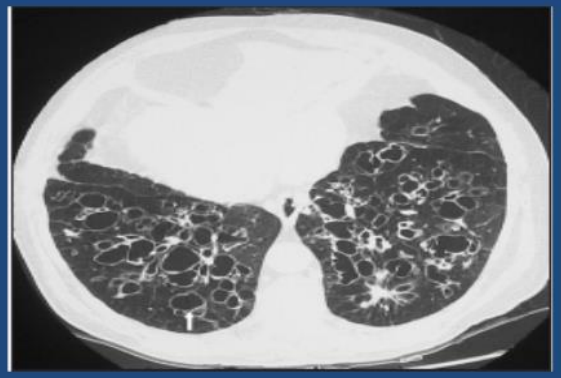
PSEUDOMONAS AND BURKHOLDERIA INFECTIONS IN NON-CF BRONCHIECTASIS.

John R W Govan
Professor Emeritus
University of Edinburgh

john.r.w.govan@ed.ac.uk

Reclaiming the name ‘bronchiectasis’

Chalmers & Elborn (Thorax March 2015)



- **Bronchiectasis** is defined as abnormal, usually permanent dilation of the bronchi associated with pulmonary infection and inflammation.
- It is a feature of a range of clinical disorders.
- Major cause of morbidity and NHS costs (~ £26 M per annum)
- The use of the term ‘non-cystic fibrosis’ bronchiectasis is relatively recent (1992) and stems from the surge in CF lung research following discovery of the CF gene in 1989. It should be discontinued.

CF versus non-CF Bronchectasis

- CF bronchiectasis benefits from extensive research and evidence-based therapies.
- Defined genetic basis (CFTR mutations) with impaired mucocilary clearance, early lung infection and progessive non-reversible loss of lung function.
- Onset of non NCFBr is less clear, reversible and has multiple causes.
- Significant number of CF therapies have failed or not been investigated in NCFBr.

Burkholderia cepacia complex

- Rhizosphere habitat
- Biopesticide
- Bioremediant
- Biocontaminant
- Plant, human, animal, pathogen
- Transmissible
- Virtually untreatable

Microbial pathogens in bronchiectasis

- *Haemophilus influenzae**
- *Pseudomonas aeruginosa*****
- *Streptococcus pneumoniae*
- *Staphylocccus aureus*
- *Moraxella catarrhalis*
- *Nontuberculous mycobacteria*
- *Aspergillus*
- *Respiratory viruses*

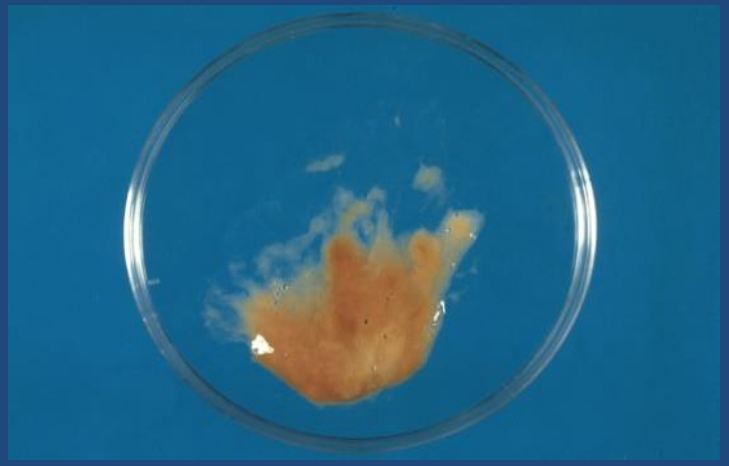
Note:

*Culture density of >10^6 *CFU/ml*

**Link with advanced disease

Influenced by:

- Specimen (sputum, BAL)
- Stable or exacerbation
- Culture or non-culture

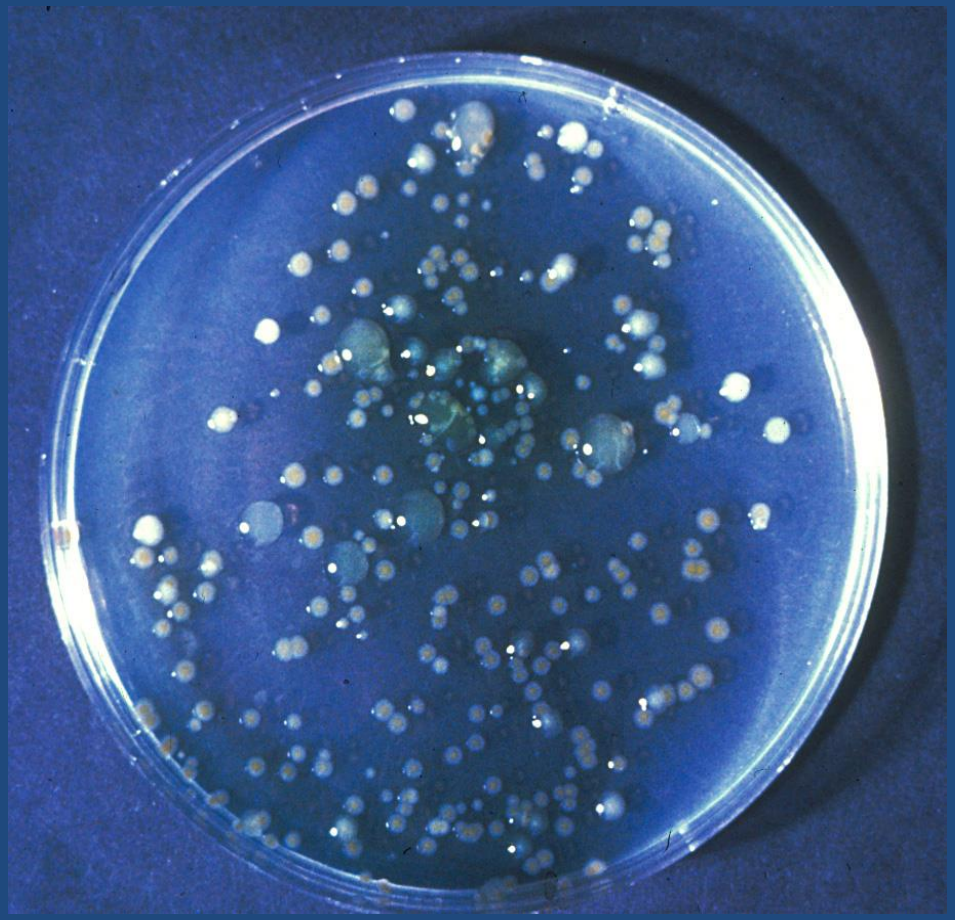


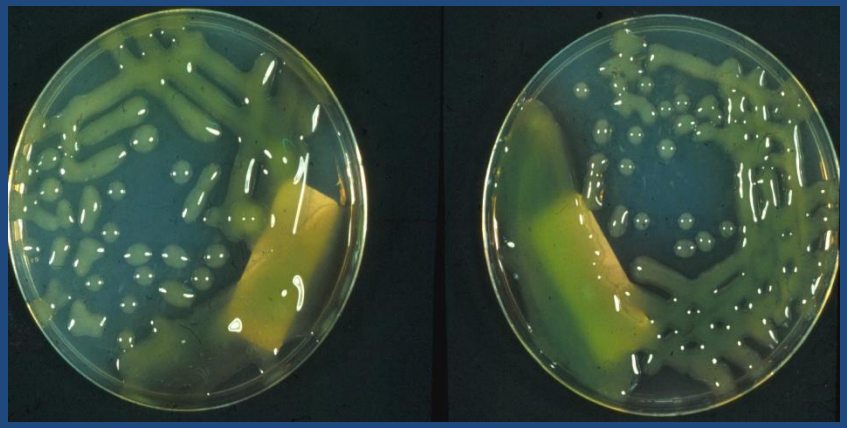
Polymicrobial airway communities in NCFBr

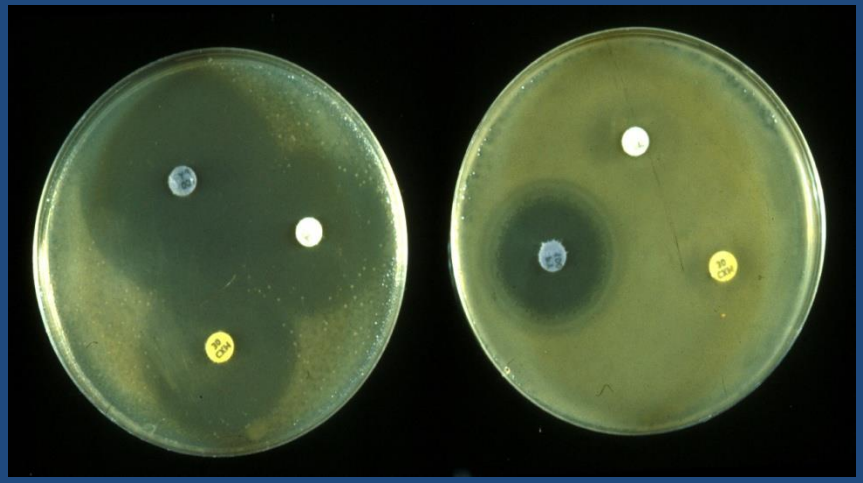
Purcell et al. BMC Microbiology 2014; 14: 130

- Sputum culture (blood agar and chocolate blood agar plus bacitracin) and 16S rRNA gene amplicon pyrosequencing.
- Pyrosequencing showed more microbial diversity than indicated by culture.
- Lower airways are dominated by three taxa *Pasteurellaceae,* Streptococcacea and *Pseudomonadaceae*
- Different bacteria taxa can be associated with different clinical states.
- Culture of *Pseudomonas* and *Haemophilus* correlate with loss in the diversity of the microbiome, and poorer outcome.

Mucoid Pseudomonas aeruginosa



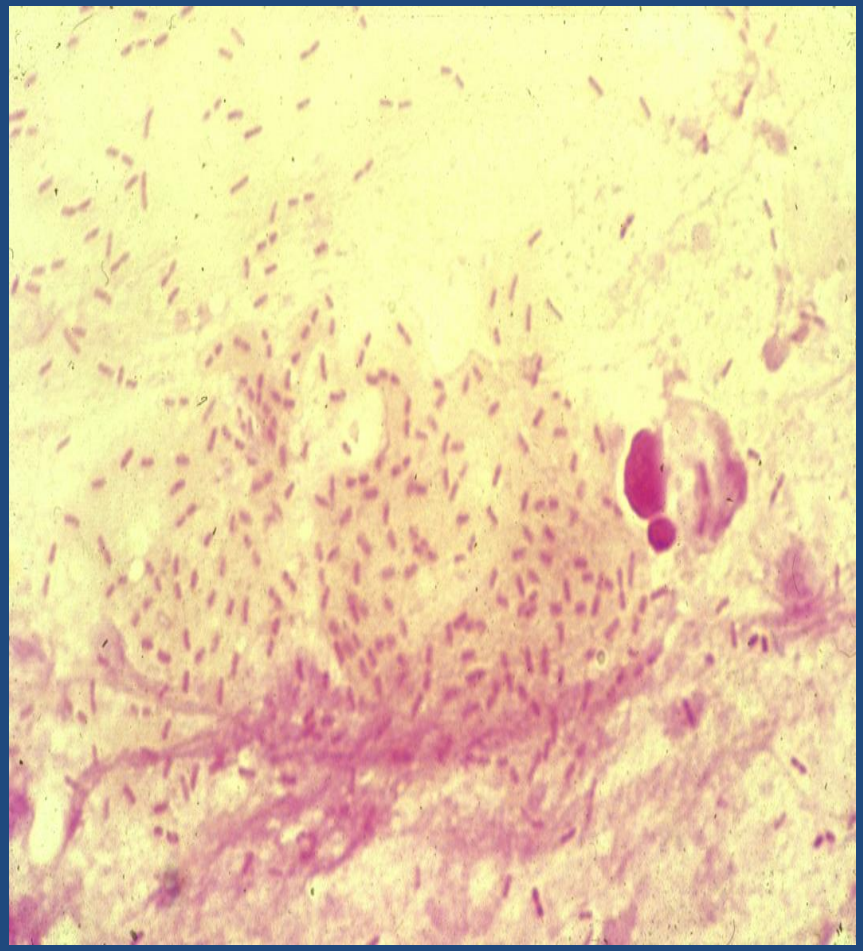




Mucoid Pseudomonas & Bronchiectasis

Adaptation, Quorum sensing, hypermutation & inflammation

- Microbial biofilms/gels



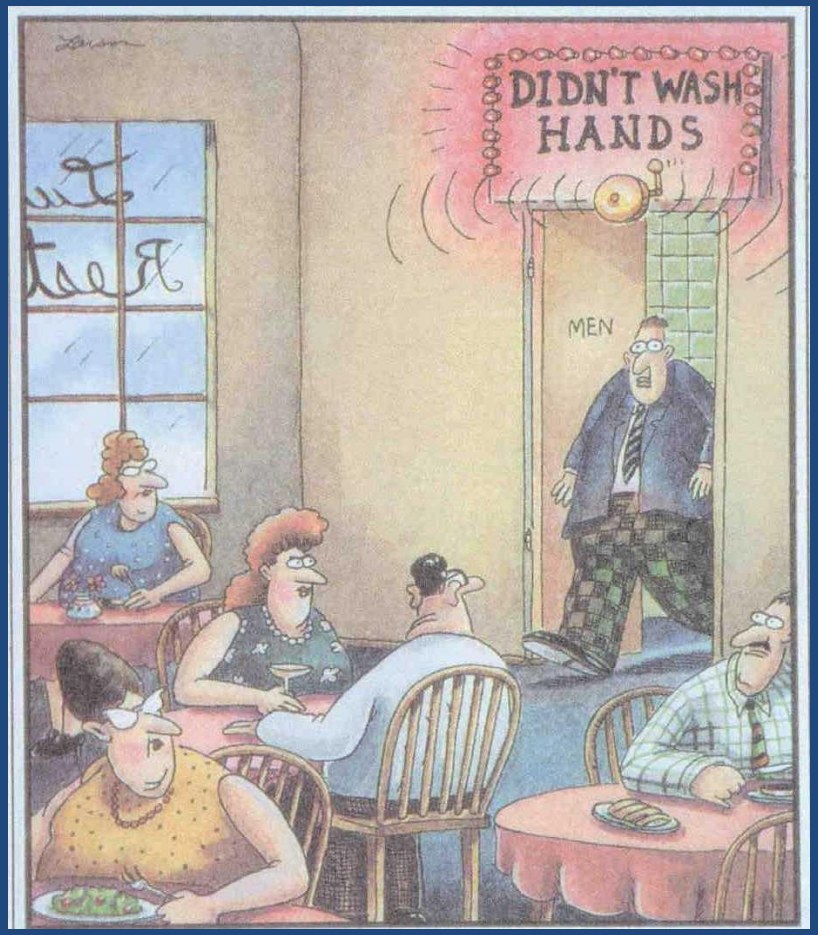
- Frustrated neutrophils

Antipseudomonal therapy in bronchiectasis

Murray et al. AJRCCM 2010: Sidhu et al Expert Opin Pharmacother 2014, NIHR Project 2015

- Early eradication on first culture. NCFBr?
- Macrolides (azithromycin) as immunomodulators
- Oral and IV therapy for pulmonary exacerbations
- Nebulised therapy to reduce bacterial density and exacerbations. Includes “dry powder” formulations
- Resistance revisited!

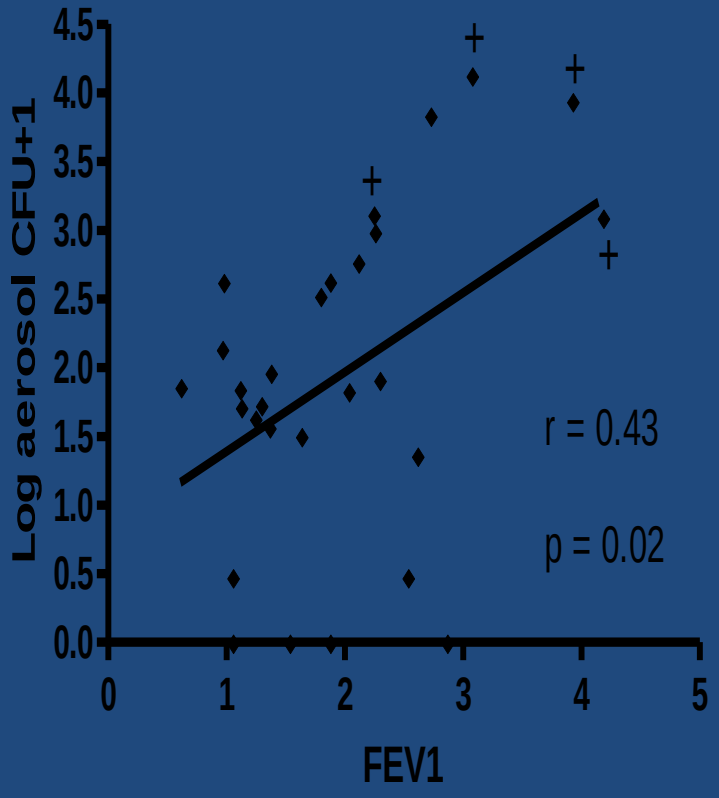
Infection control and Hygiene



- Is cross-infection an issue in bronchiectasis clinics?
- If so, what degree of infection control is feasible?
- Handwashing is not enough?

Airborne dispersal of Pseudomonas
Is one metre far enough?

Jones *et al* 2003; Panagae *et al* 2005; Festini *et al* 2010: Wainwright *et al* 2009; Knibbs et al 2014



Cross-infection in NCFBr?

De Soyza et al Eur Resp J 2014; 43: 900-903

- 36 patients attending Newcastle clinic
- Isolates genotyped Array/Tube and VNTR.
- 2 patients harboured same *P. aeruginosa*
- Longitudinal isolates similar in 9/10 patients
- Distribution suggested environmental acquisition

- Caveats: Single centre and *P. aeruginosa* only

Summary
More questions than answers

- When and why do patients “acquire” NCFBr?
- Do interactions and changes in microbial diversity trigger pulmonary exacerbations.
- Is cross-infection an issue? Are CF-like guidelines feasible?
- Culture and culture-independent microbiology are complementary

Summary
Challenges of non-CF bronchiectasis

- To break the cycle of chronic colonization and infection, secondary inflammation and lung injury.

- Need for well-designed multicentre antibiotic trials including:

1. Optimum aerosol delivery and length of treatment.
2. Immunosuppressive role for oral macrolides.
3. Value of subjugate markers of pulmonary infection (e.g. CRP)
4. Targeted therapy against species within the microbial “zoo”