



# BRONCHIECTASIS- WHERE ARE WE?

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# Plan

- Stable State

Aetiology

Treatable causes

Role of bacteria

Strategies

- Exacerbations

Viruses

When to give  
antibiotics

Role of IV antibiotics

# What is bronchiectasis?

## Symptoms and Pathology

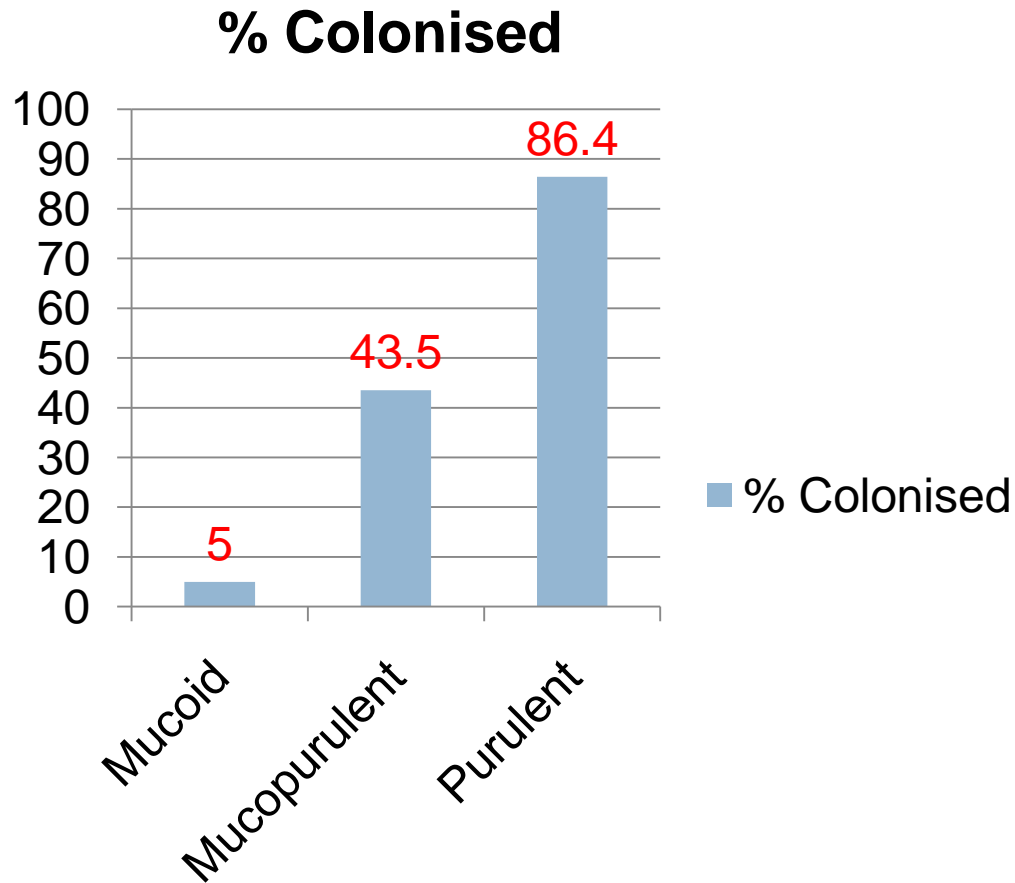
- ❑ Permanently inflamed and damaged airways
- ❑ Leads to chronic colonisation
- ❑ Leads to daily cough + sputum production
- ❑ Leads to recurrent chest infections



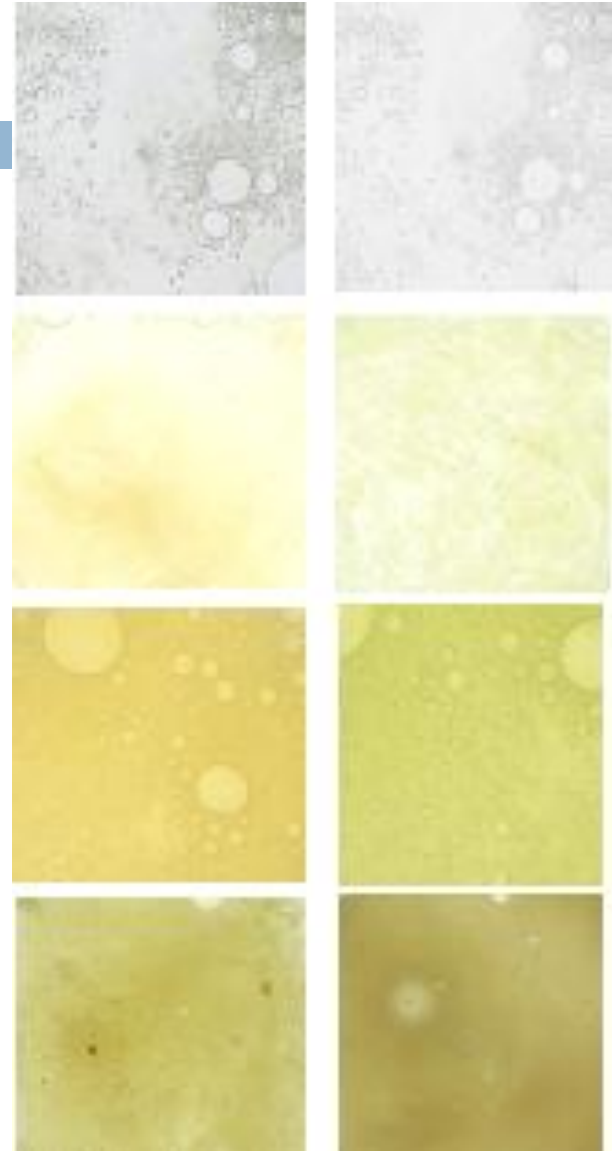
## SPECTRUM OF DISEASE

Characteristic	Mild	Moderate	Severe
<b>Sputum Colour</b>	Mucoid	Mucopurulent	Purulent
<b>24hr Sputum Volume</b>	<5mls		≥20mls
<b>Exacerbation Frequency</b>	<2/yr		≥3/yr.
<b>Exacerbation Severity</b>	Oral Ab Outpatient Tx		IV Ab Hospital admission
<b>Sputum bacteriology when stable</b>	MNF	MNF/ Pathogens (HI, SPn, MC, SA)	PA, Enteric Gram-ve, MRSA
<b>Affected lobes on CT scanning</b>	<3 Lobes		≥3
<b>Degree of bronchial dilatation</b>	Tubular	Varicose	Cystic

# Sputum purulence



N=141

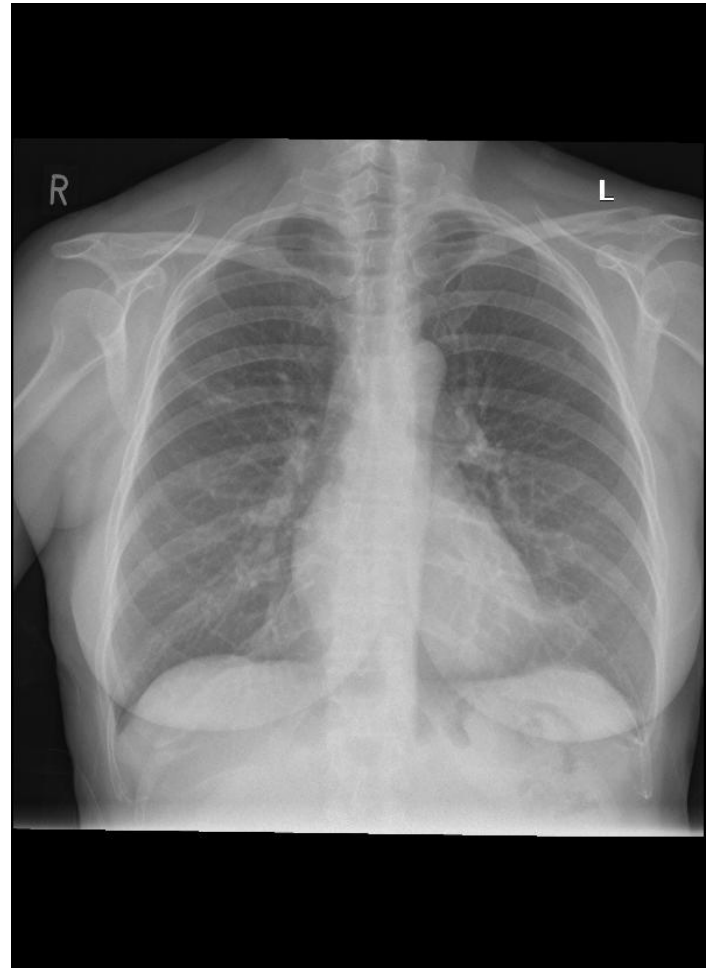


ERJ 2009;34:361-4

# Case

Oct 2008

- 51 female
- Cough, Thick Tenacious Sputum
- 6 exacs/yr
- PMH Asthma
- DH  
Seretide 250 2p bd  
Salbutamol prn  
Montelukast 10mg nocte  
Always well on steroids (6 courses past year)
- SH  
0 Pack Years
- Exam- Nil



# Case

- FEV<sub>1</sub> 2.0L                      64% P
  
- O<sub>2</sub> sats air                      98%
  
- Sputum microbiology
  - 01/09 MNF                      MP
  - 03/09 NTHI                      MP
  - 08/09 MNF                      MP
  - 12/09 NTHI                      MP
  - 03/10 MNF                      MP
  
- Eosinophils 1.1 (<0.4)  
  IgE 2000 kU/L (<250)

Apr  
2009

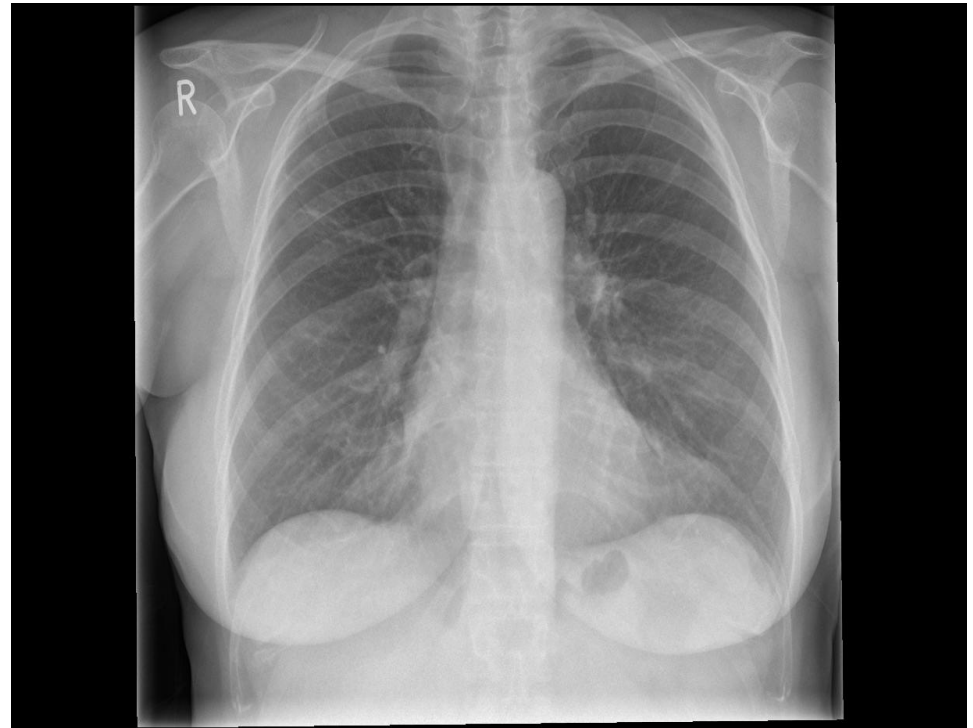




# What treatment did I give?

- A] DNase
- B] Omalizumab
- C] Oral steroids
- D] IV antibiotics

Feb 2010



Ref	N	INF	IMMUNE	CT	ABPA	CF	Ciliary	IBD	Aspiration	Cong	No cause
1995	123	42%	4%				4%				30%
2000	150	29%	8%	3%	7%	3%	2%	1%	4%	1%	53%
2003	100	33%	1%	6%	1%						41%

*Nicotra et al Chest 1995;108:955-61*

*Pasteur et al Am J Respir Crit Care Med 2000;162:1277-84*

*Kelly et al Eur J Intern Med 2003;14:488-92*

# Investigate treatable causes

- Exclude common variable immunodeficiency
- Exclude ABPA
- Exclude cystic fibrosis
- Why?
- These all have treatments that differ from standard management

# Case

- 61 male
- 6 exacs/yr
- PMH Hiatus Hernia
- DH  
Omeprazole 20mg od
- SH  
0 Pack Years
- Exam- BS in chest



# Case

- CXR Hiatus Hernia
- HRCT HH + very mild bilat LL Bx
- FEV<sub>1</sub> 2.9L                      88% P
- O<sub>2</sub> sats air                      98%
- Sputum microbiology
  - 01/09 MNF                      MP
  - 03/09 SPn                      MP
  - 08/09 PA  
                    MP
  - 12/09 M Catt                      MP
  - 03/10 MNF                      MP

Management?

- A] Erythromycin
- B] Increase PPI
- C] Metoclopramide
- D] Fundoplication
- E] Long term nebulised

# Case

- 51 female
- 6 exacs/yr
- PMH Nil
- DH  
Nil
- SH  
0 Pack Years
- Exam- Nil
- CXR RML + Ling changes
- HRCT Nodular Bx RML + Ling
- FEV<sub>1</sub> see below
- O<sub>2</sub> sats air 98%
- Sputum microbiology

01/09 MNF	MP	2.7L
03/09 MNF + MAC	MP	2.6L
08/09 MNF + MAC	MP	2.6L
12/09 MNF + MAC	MP	2.3L
03/10 MNF + MAC	MP	2.3L

# CT



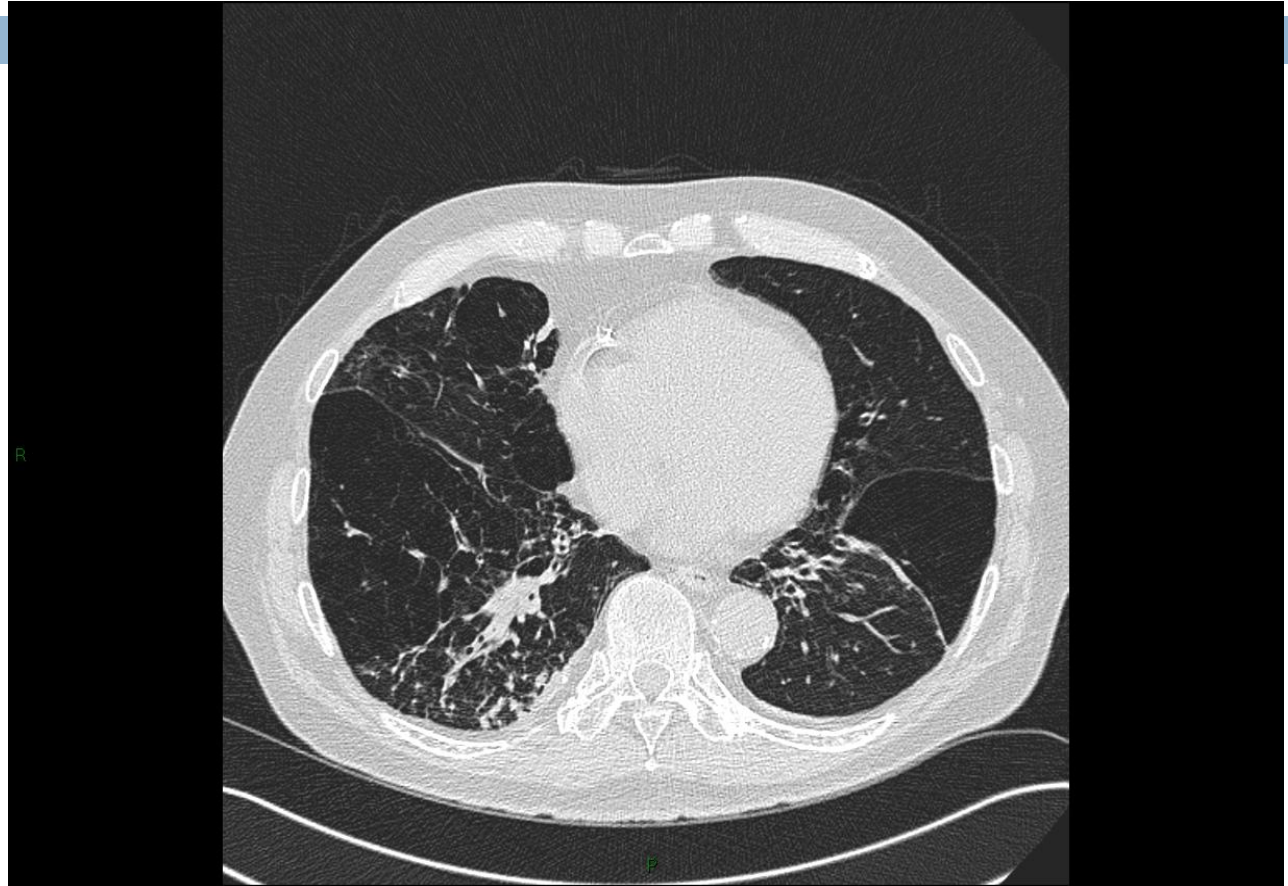
# Indications and Management

- Fibrocavitatory disease
- Nodular Bx with clinical deterioration
- What treatment?
- A] RE
- B] RECI
- C] RECipro
- D] RHZE
- D] IV amikacin + IV tigecycline + moxifloxacin + rifampicin



# Case

- 72 male
- 7 exacs/yr
- PMH COPD
- DH  
Tiotropium 18mcg od  
Seretide 250 2p bd  
Salbutamol prn
- SH  
60 pack years  
Current- 20cpd
- Exam- COPD  
+ bibasal insp. crackles



# Case

- CXR COPD
- HRCT Emphysema and bilat LL Bx
- FEV<sub>1</sub> 0.6L (28% Predicted)
- O<sub>2</sub> sats air 90%
- Sputum microbiology
  - 04/09 NTHI P
  - 08/09 NTHI P
  - 12/09 MNF MP
  - 04/10 M Catt MP

Severe COPD

Mild bilateral Bx

Excess Exacerbation History

Chronically colonised

Management?

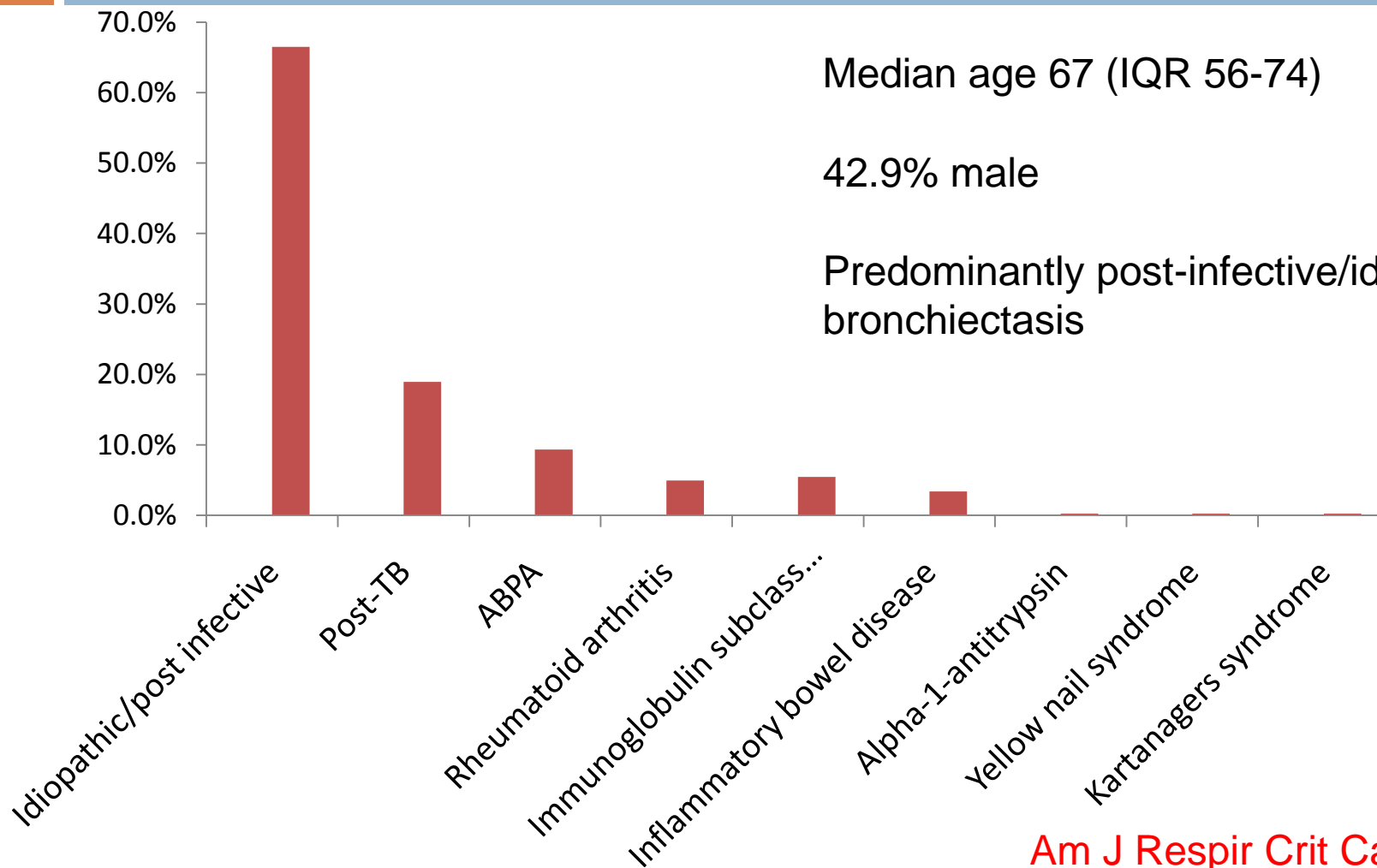
# Management

- A] Smoking Cessation Alone
- B] Smoking cessation + LT Oral Co-amoxiclav
- C] LT Oral Co-amoxiclav
- D] Smoking cessation and LT Nebulised Tobramycin

# Are bacteria important

- Related to severity of bronchiectasis
- MNF Mild disease
- PA, enteric gram-  
ves, MRSA in  
severe disease
- Is bacterial load  
important?

# Results- n=385



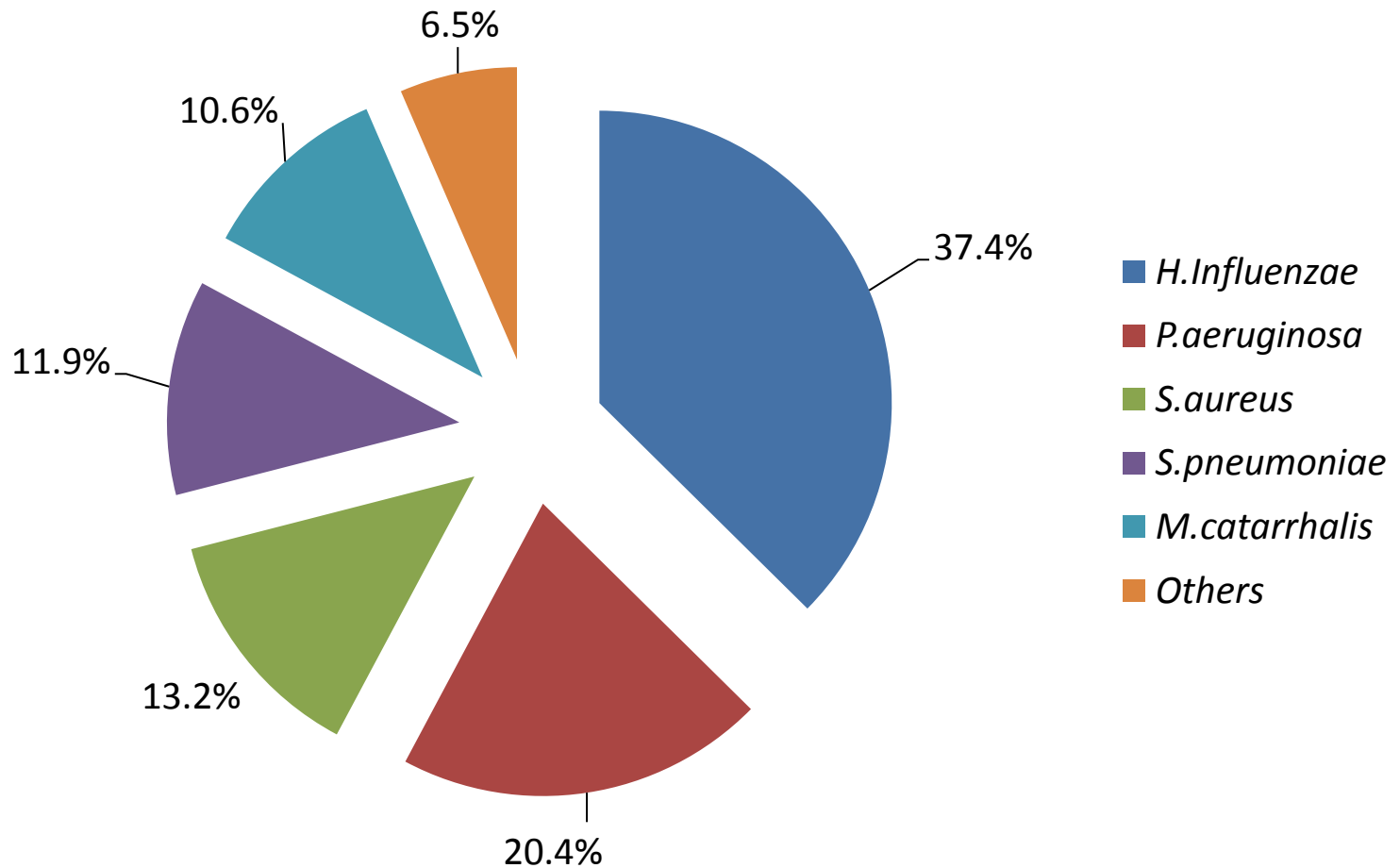
Median age 67 (IQR 56-74)


42.9% male

Predominantly post-infective/idiopathic bronchiectasis

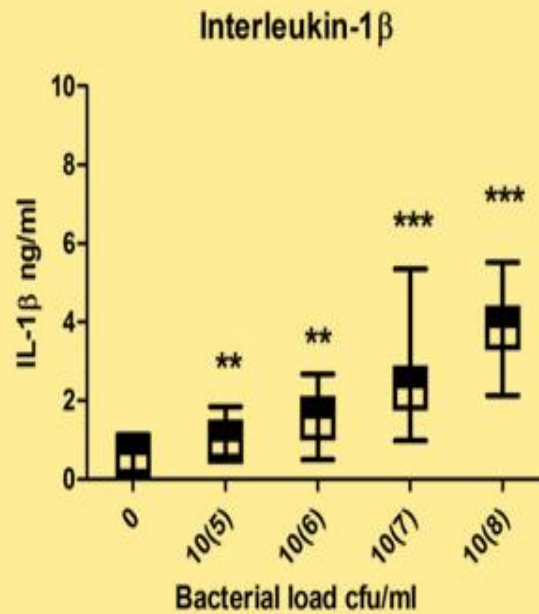
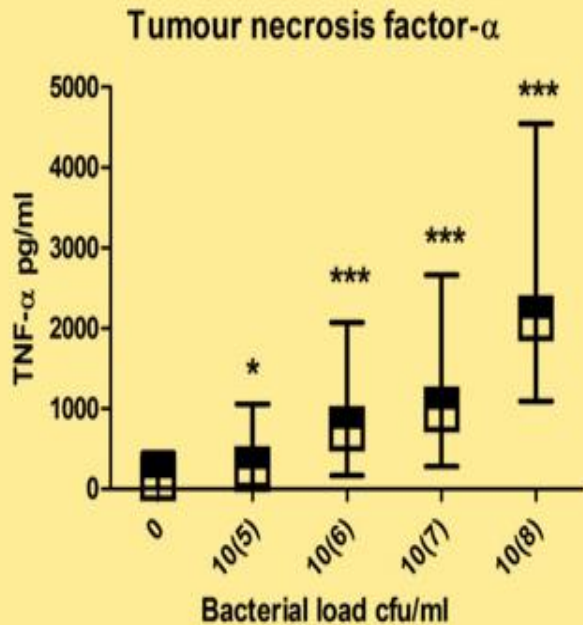
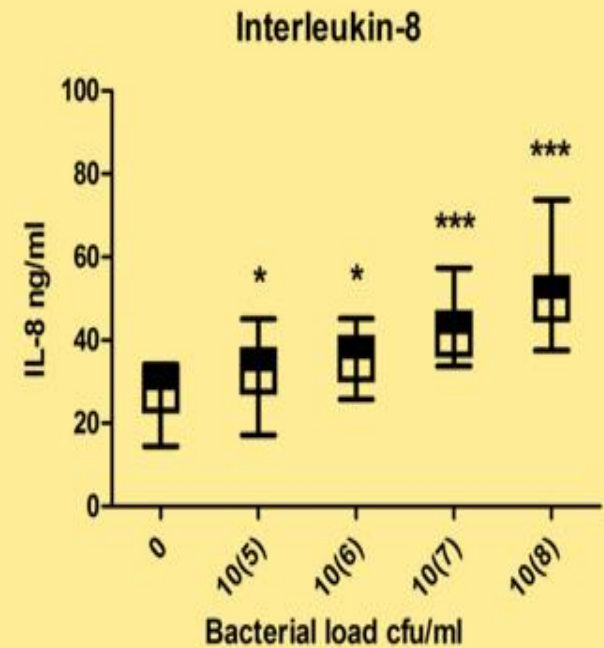
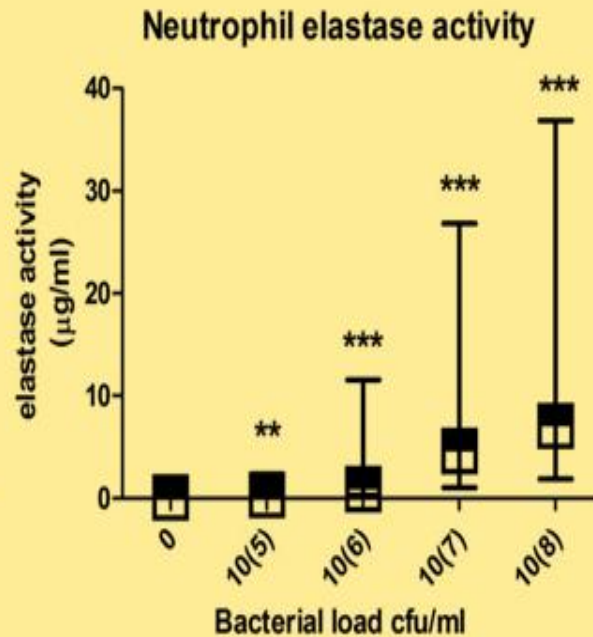
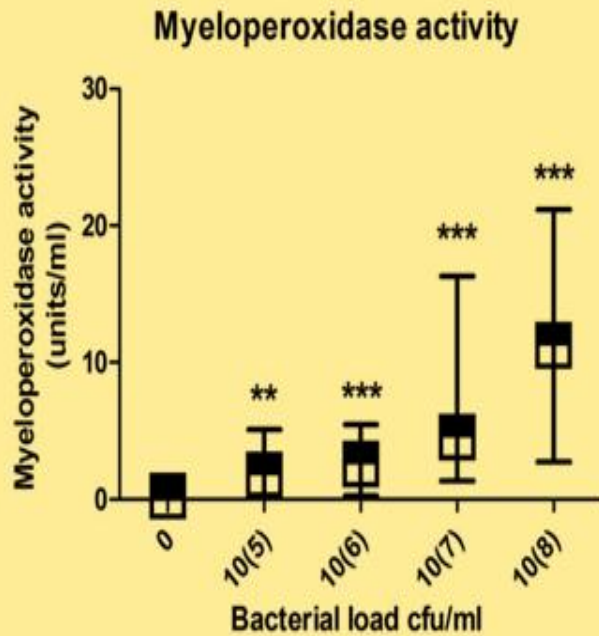
# Microbiology

Pathogenic microorganisms were isolated in 77.9% of patients





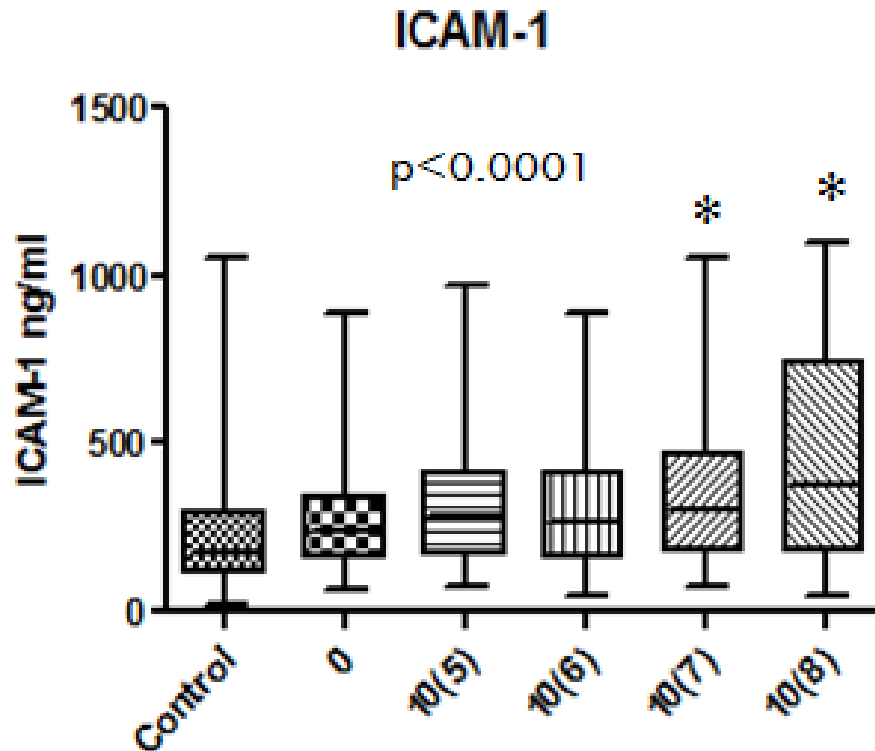
**Q1- Does bacterial load correlate with  
markers  
of airway and systemic inflammation?**



**Bacterial  
load  
drives  
neutrophil  
airways  
inflammation**



# Bacterial load correlates with systemic markers of neutrophil recruitment

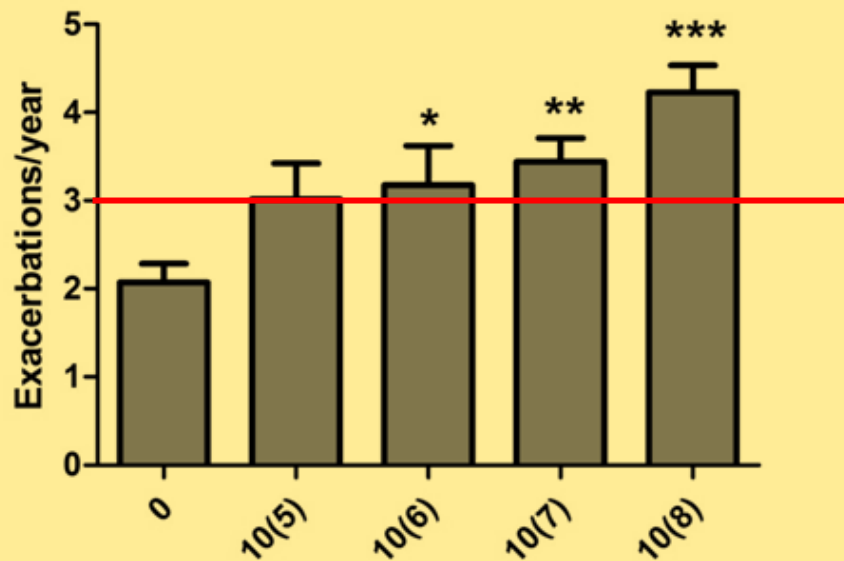


Bacterial load drives neutrophil recruitment

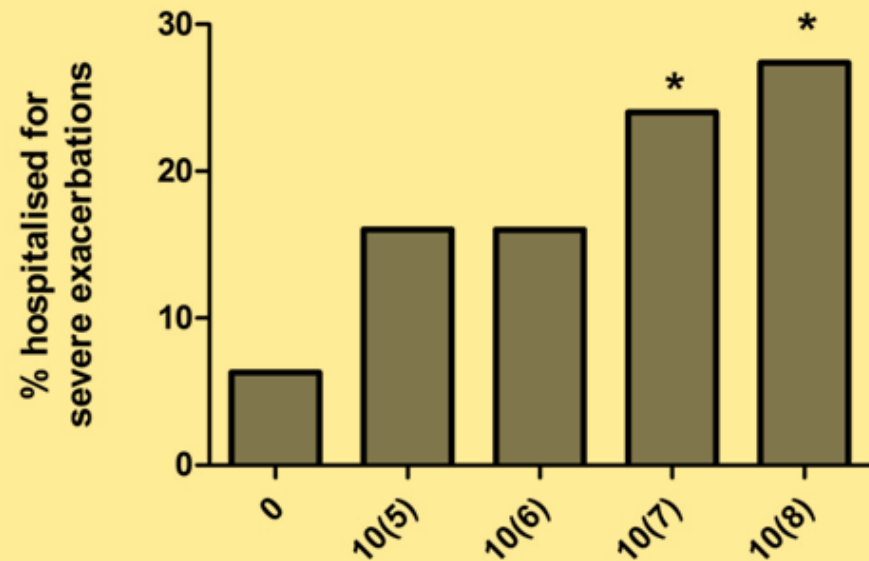


**Q2- What is the clinical relevance?**

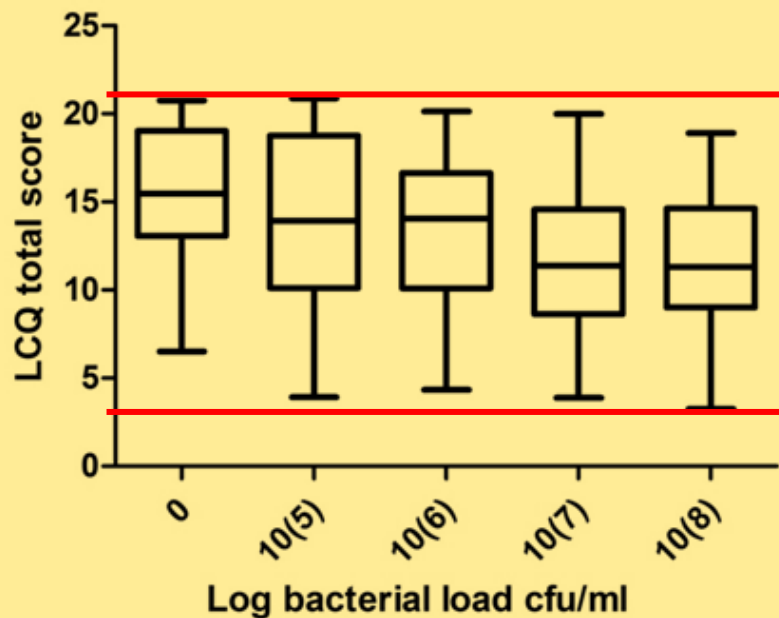
### Outpatient exacerbations



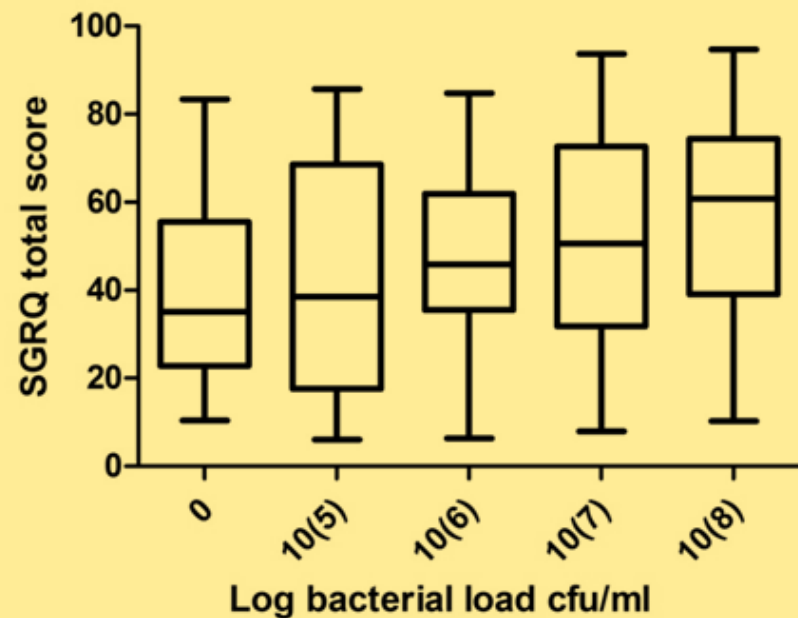
### Unscheduled Hospital Admissions




### Leicester Cough Questionnaire

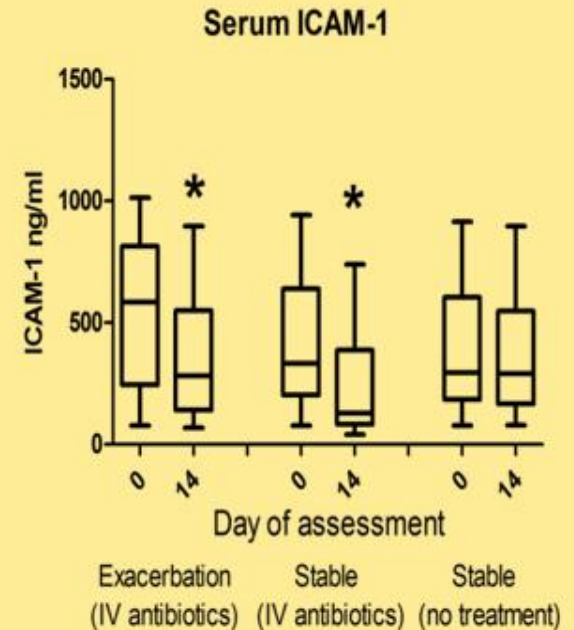
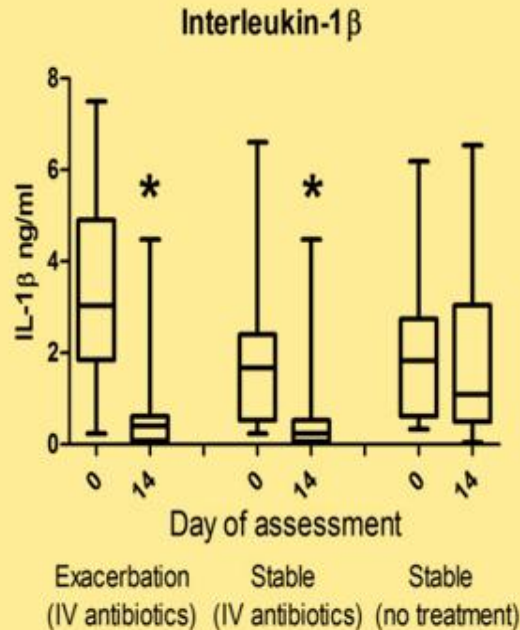
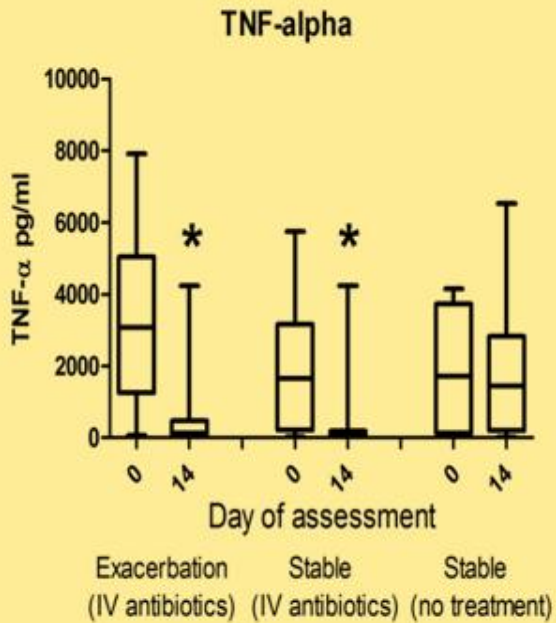
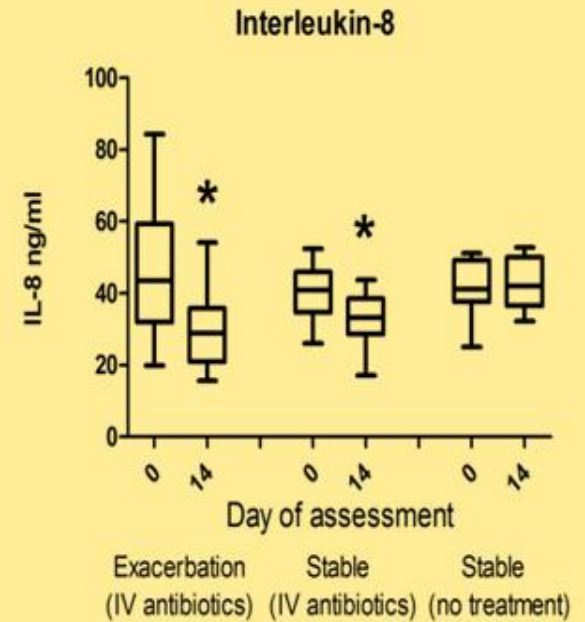
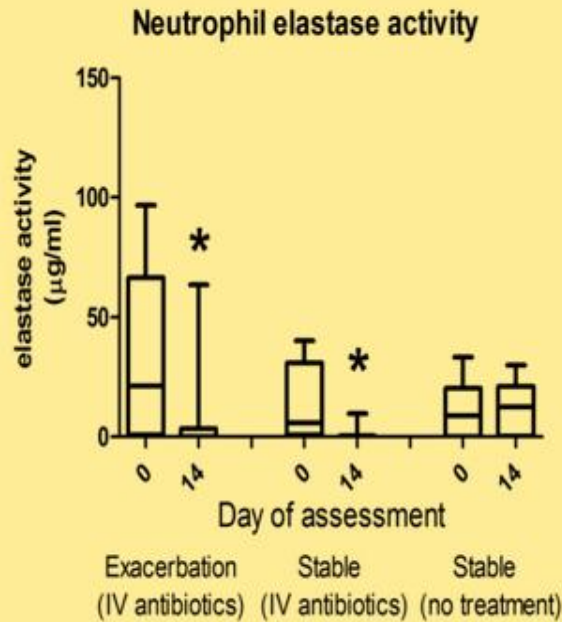
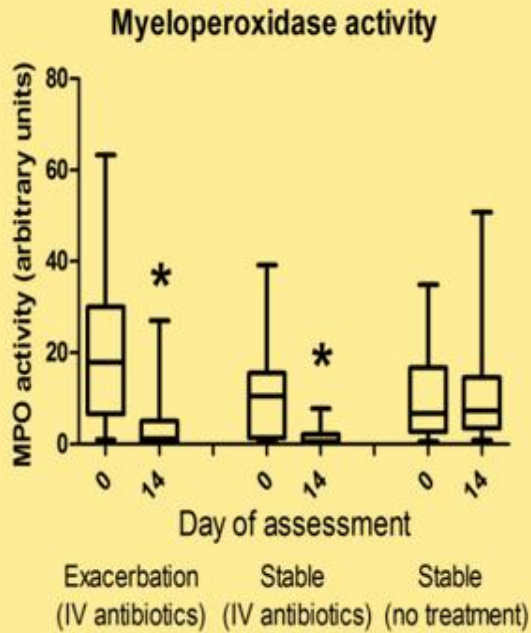


### St. Georges Respiratory Questionnaire





**Q3- Does antibiotic therapy reduce markers  
of  
airway inflammation?**



34

15

11

# Role of long term oral antibiotics- Randomised trials

				Exacerbations	Exacerbations
MRC 1957	122	Oral Penicillin 2G vs. Oral Tetracycline 2G vs. 2G Lactose	1 year 2 days per week	None recorded	↓ days confined to bed ↓ Less days off work
Currie et al 1990	38	3G bd oral amoxicillin vs. Placebo	32 weeks	24% had PA	↓ severe exacerbations but no effect on frequency
Tsang et al 1999	21	Oral Erythromycin 500mg BD vs. Placebo	8 weeks	76% PA 14% HI 5% KPn 5% E Coli	No effect

# Role of long term oral antibiotics- Randomised trials

## Bacteriology

## Exacerbations

<p><b>Lancet</b> <b>2012</b> <b>380</b> <b>660-667</b></p>	<p>122</p>	<p>Azithromycin Vs. Placebo</p>	<p>6m</p>	<p>30% HI 11% PA 3% MC 3% SA 1% SP</p>	<p>Exacerbations (0.59/patient in Azi Gp. Vs. 1.57/pt in placebo gp) at 6m.  (1.58/patient in Azi Gp. Vs. 2.73/pt in placebo gp) at 12m.  Median time to exacerbation 239 vs. 185 days (-5.17 vs. -1.92)</p>
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- Azithromycin 500mg M,W, Fr

- Entry criteria: 1 exac in last 1y

- Three primary endpoints: Exacs, FEV<sub>1</sub>, SGRQ

- Baseline FEV<sub>1</sub> 67% predicted

- 3.34-3.93 Exacerbations/year

- No change in FEV<sub>1</sub> or SGRQ

- Decreased serum WCC and CRP but no effect on sputum differential cell ct.

# EMBRACE study

- No effect on bacterial clearance
- No bacterial load measured
- 4% developed SPn resistance
- More GI side effects
  - 27% vs. 13% (diarrhoea 18%, nausea or vomiting 13%, epigastric discomfort 7% and constipation 3%)
  - No audiometry carried out

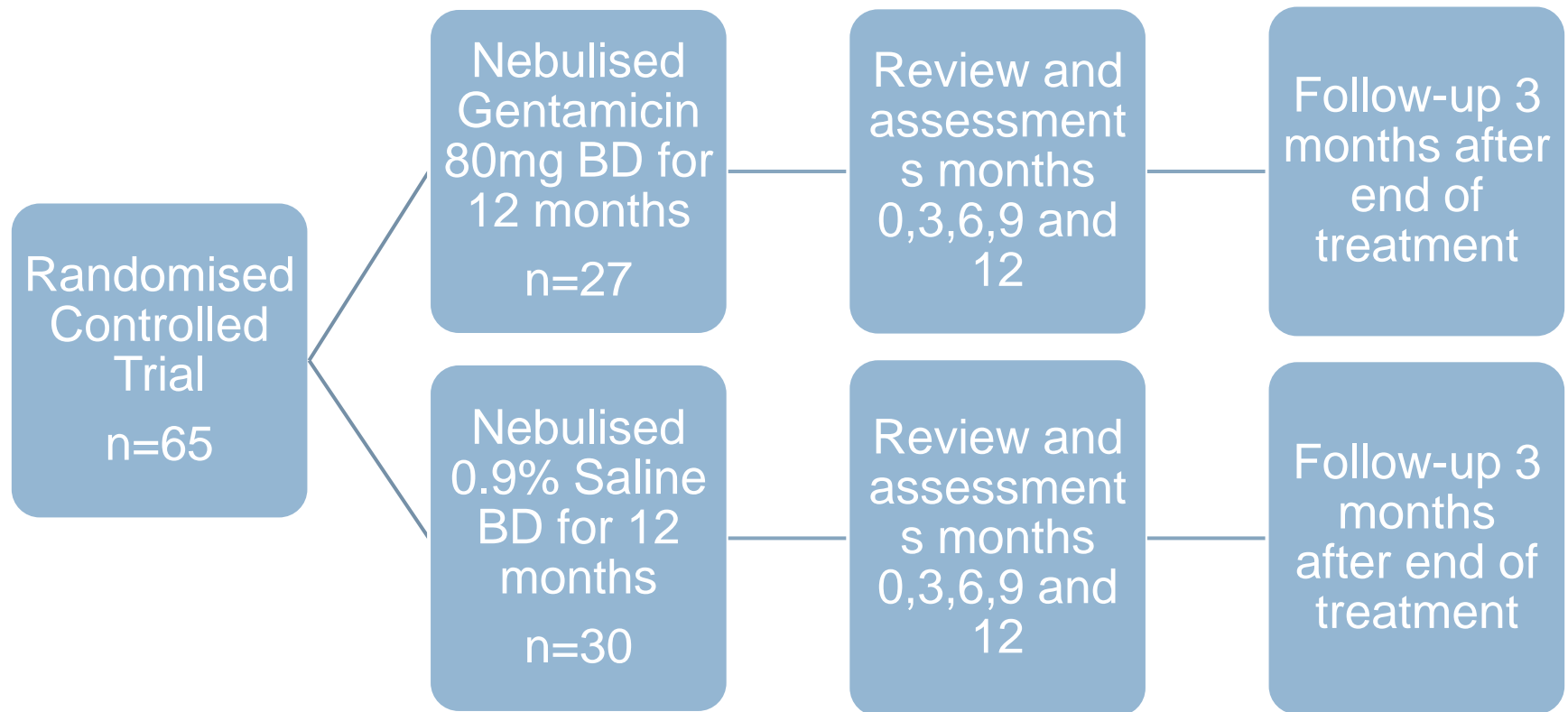


# Role of long term nebulised antibiotics- Randomised trials in PA

## Exacerbations

Barker et al 2000	74	Nebulised Tobramycin 300mg BD vs. Placebo	4 weeks on Tx	100% PA	No Effect
Drobnic et al 2005	30	Nebulised Tobramycin 300mg BD vs. Placebo	6 months	100% PA	↓ number and days of hospital admission  No differences in number of exacerbations
Orriols et al 1999	15	Nebulised Ceftazidime plus Tobramycin vs. symptomatic treatment	1 year	100% PA	↓ no. hospital admissions + ↓ no. days in hospital

# Role of nebulised Gentamicin: a randomised controlled trial

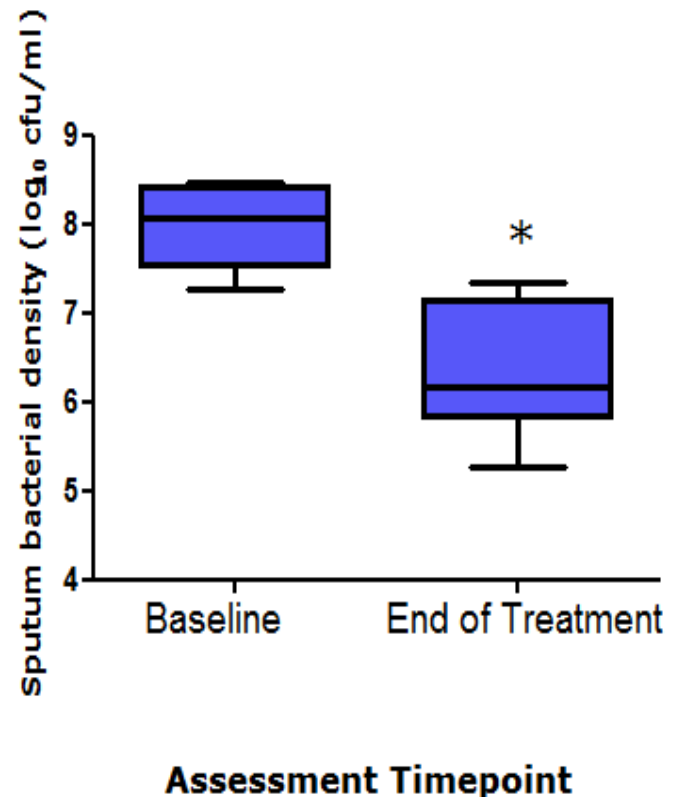


# Sputum Bacteriology

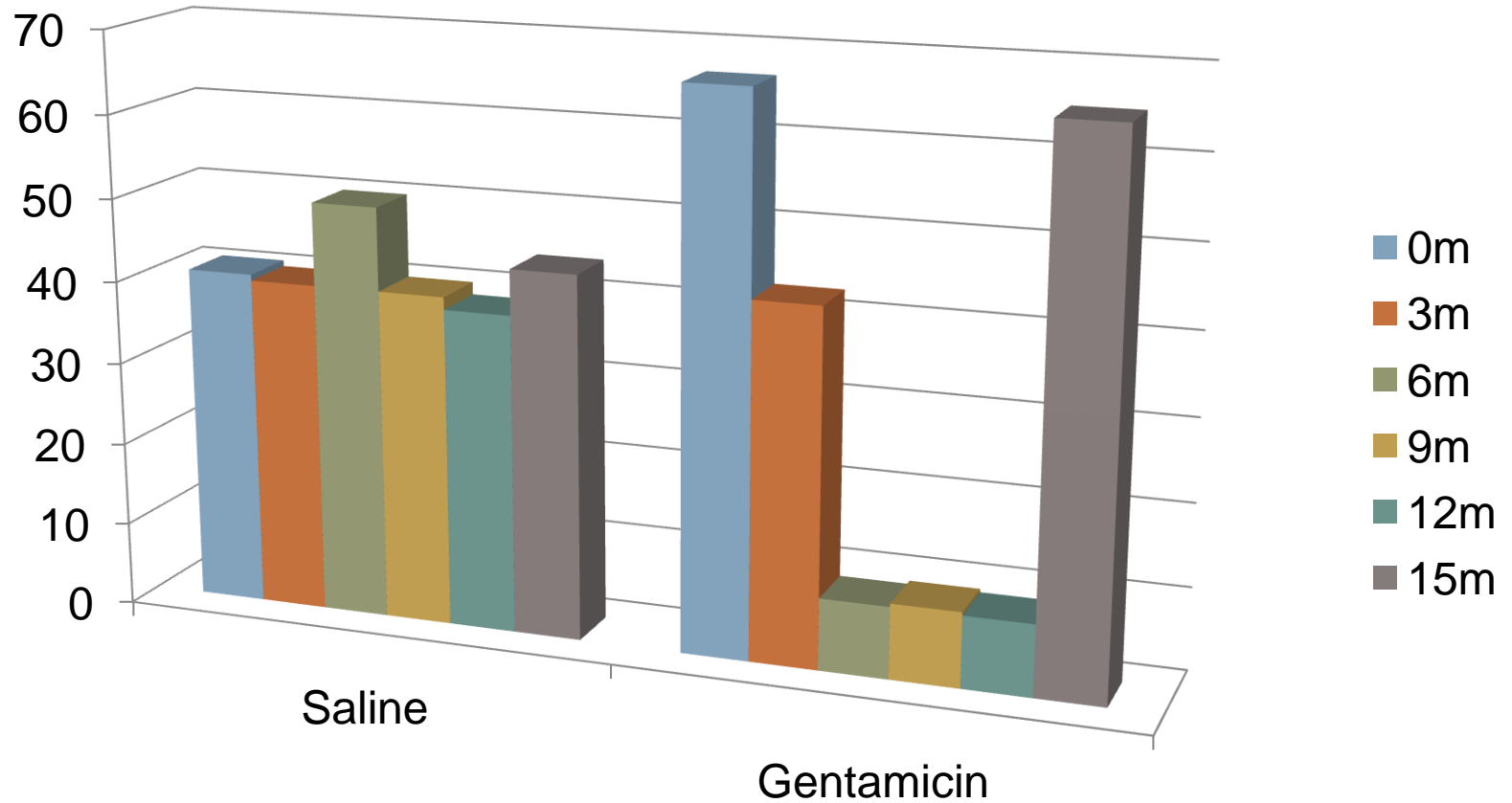
## Gentamicin Group:

- 30.8% of those colonised with *Pseudomonas aeruginosa* achieved eradication.
- 92.8% of those colonised with pathogenic organisms other than *Pseudomonas aeruginosa* achieved eradication.

Change bacterial load in patients not eradicated



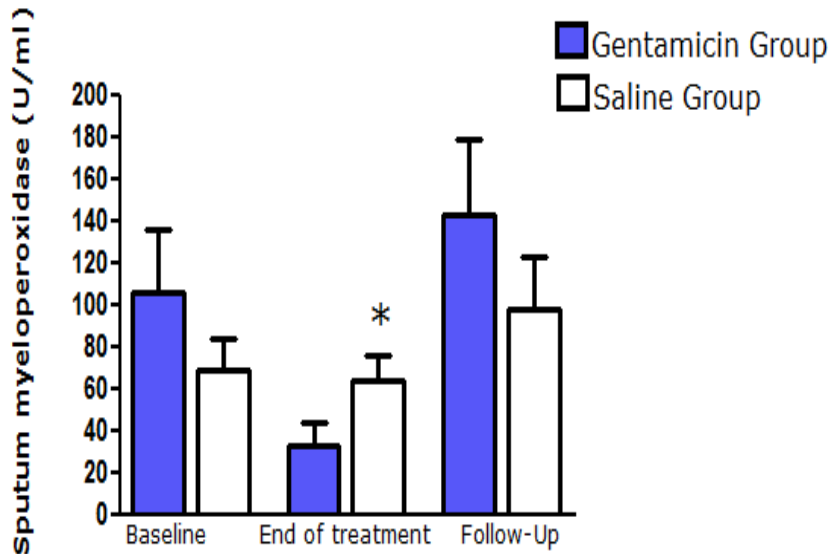
# % Purulent sputum



# Inflammation

## □ Airways Inflammation

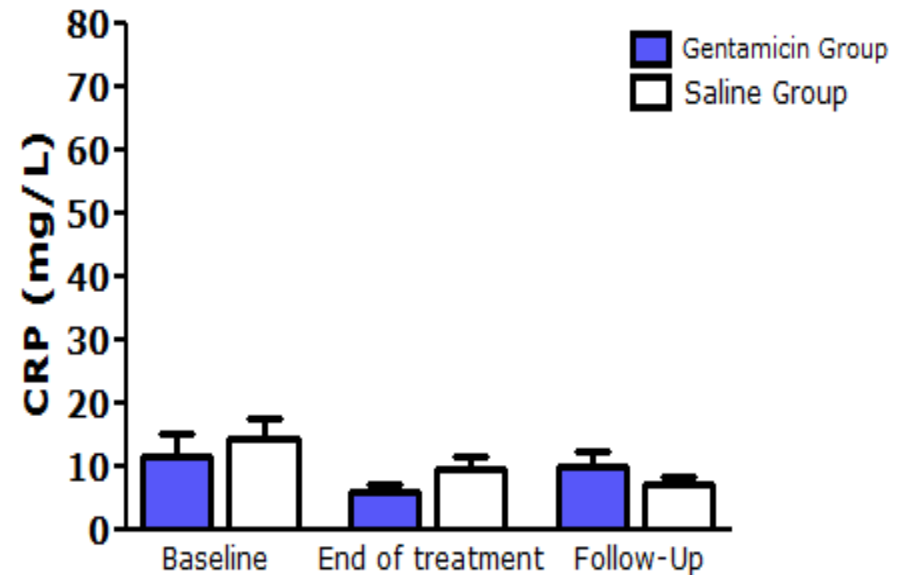
### Effect on Sputum Myeloperoxidase



Assessment Timepoint

## □ Systemic Inflammation

### Effect on CRP



Assessment Timepoint

	Gentamicin n=27		Saline n=30	
Time point (months)	0	12	0	12
IL-8 ng/ml	38.4 (34.8-44.1)	33.2 (25.0-37.5)*#	39.1 (37.8-46.8)	42.9 (36.1-48.5)
TNF- $\alpha$ pg/ml	1346 (485.1-3581)	485.4 (115.1-1286)*#	1281 (374.9-2874)	1421 (290-3074)
IL-1 $\beta$ ng/ml	2.2 (0.96-4.0)	0.99 (0.46-2.2)*#	2.1 (0.59-3.4)	2.0 (0.68-3.0)
ICAM-1 ng/ml	304.7 (190.9-463.8)	245.3 (167.4-359.4)*#	278.8 (163.2-459.7)	318.7 (177-458.3)
E-selectin ng/ml	72.7 (50.7-91.7)	54.4 (36.5-77.1)*	65.6 (45.1-80.1)	63.1 (47.2-80.8)
VCAM-1 ng/ml	671.2 (473.4-869)	591.5 (362.7-836.6)	671.6 (399.1-878.7)	642 (447.1-862)
% positive microbiology	100%	33.3%*#	100%	96.7%

# Role of long term nebulised antibiotics- Randomised trials in PA + Other Pathogens

Murray et al 2011	67; 57 finished study	Nebulised Gent 80mg bd vs. 0.9% saline	1 year	40-48% PA Other PPMs	Reduced exacerbations and increased time to first exacerbation
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## Exacerbations

Gent 33% vs. Saline 80%  
Gent 0(0-1) vs. Saline 1.5(1-2)  
Gent 120d (87-162) vs. Saline 61.5d (20-7-122.7)

# Other clinical endpoints

- Increased ETT 95m
- Increased frequency of improved HRQOL
- LCQ 81% vs. 20%
- SGRQ 82.5% vs. 19.2%
  
- No effect 24hr volume, FEV<sub>1</sub>, FVC, FEF25/75
- 21.9% (7 of 32 patients) reported bronchospasm and received adjunctive nebulised  $\beta_2$  agonist treatment.
- Despite this, two patients required withdrawal from the study (one at month 3 and one at month 6)
  
- Treatment needs to be continuous for its ongoing efficacy.



# Other therapies



# ICS?

Author	Journal	Type of study	Treatment	Number	Results
Tsang et al	Thorax 2005 60:239	Randomised	Fluticasone 500mcg bd vs. Placebo 12/12	86	↓ 24hr sp. vol °Δ sp. Purulence °Δ PFT °Δ Exacs Better in PA patients but small nos.
Martinez- Garcia et al	Resp Med 2006 100:1623	Randomised	Fluticasone 250mcg bd vs. 500mcg bd vs. Placebo 6/12	93	500mcg BD ↓ cough+sputum ↓ breathless ↑ SGRQ (5U) °Δ micro °Δ PFT °Δ Exacs
Kapur et al	Cochrane 2009 Jan 21;CD0009 96	Cochrane review of RCTs		303	Insufficient evidence

# Other therapies

## Oral Tx

- Leukotriene B4 inhibitors – no randomised trials
- Elastase inhibitors- phase 2 trials ongoing
- Statins- ongoing RIE- will be reported next year

## Inhaled Tx

- Inhaled mannitol improved mucociliary clearance  
Daviskas et al *Am J Respir Crit Care Med* 1999;159:1843  
Daviskas et al *Chest* 2001;119:414  
Daviskas et al *Respirology* 2005;10:46

Multicentred studies ongoing and results awaited

- DNase harmful  
Cochrane review 2000

# Saline

Author	Journal	Type of study	Treatment	Number	Results
Kellett et al	Resp Med 2011 105:1831	Randomised 3m crossover study  Single blinded	0.9% Saline vs. 7% Saline for 1yr.	28	<ul style="list-style-type: none"><li>•HS improvement %FEV<sub>1</sub>, SGRQ better + reduced antibiotic use</li><li>•No data on microbiology or other therapies</li></ul>
Nicolson et al	Resp Med 2012 106:661	Randomised	0.9% Saline vs. 6% Saline for 1yr.	40	<ul style="list-style-type: none"><li>•FEV<sub>1</sub> slightly better (20ml IS vs.90 ml)</li><li>•Improvement in HRQOL</li><li>•55-60% colonisation reduced to 15%</li></ul> <p>No difference between groups</p>

Conflicting results- further studies are needed

# Case

- 74 year old man with known bronchiectasis presents to GP feeling unwell with 2/7 history of cough, myalgia, headaches and fevers.
- No change in sputum volume or purulence

Is this an exacerbation requiring antibiotics?

- Vote for antibiotics

# Case

- 69 year old lady with known tubular bronchiectasis RLL presents feeling less well for 5 days and there is increased sputum volume and purulence
- Investigations?
- Is this an exacerbation requiring antibiotics?

# BTS Guidelines-

## Thorax- 2010 Jul;65 Suppl 1:i1-58.

- Antibiotics recommended if deteriorating symptoms + change of sputum volume + purulence
- Prior to antibiotics being commenced send sputum C+S
- Empirical Abs based on previous microbiology.
- Treat 14 days but there is a lack of RCTs
- Di Bilton + colleagues
- Chest 2006;130(5):1503
- UK+US study in PA
- 14/7 ciprofloxacin 750mg bd +/- inh tobramycin 300mg bd
- No change in clinical outcomes at days 14 or 21
- Increased wheeze with tobramycin 50% vs. 15%

# Case- Known case attending GP

## GP

- 61 male
- 5 exacs/yr
- PMH Bx
- DH  
Omeprazole 20mg od  
Fluticasone 500mcg bd  
Salbutamol prn
- SH  
0 Pack Years
- Exam- Bilateral coarse inspir crackles





# Case

□ FEV<sub>1</sub> 1.9L                      61% P

□ O<sub>2</sub> sats air                      94%

□ Sputum microbiology

01/10 PA    P

03/10 NTHI + Mcatt                              P

08/10 PA    P

12/10 PA    P

03/11 PA    MP

Management?

Went to GP with a further chest infection

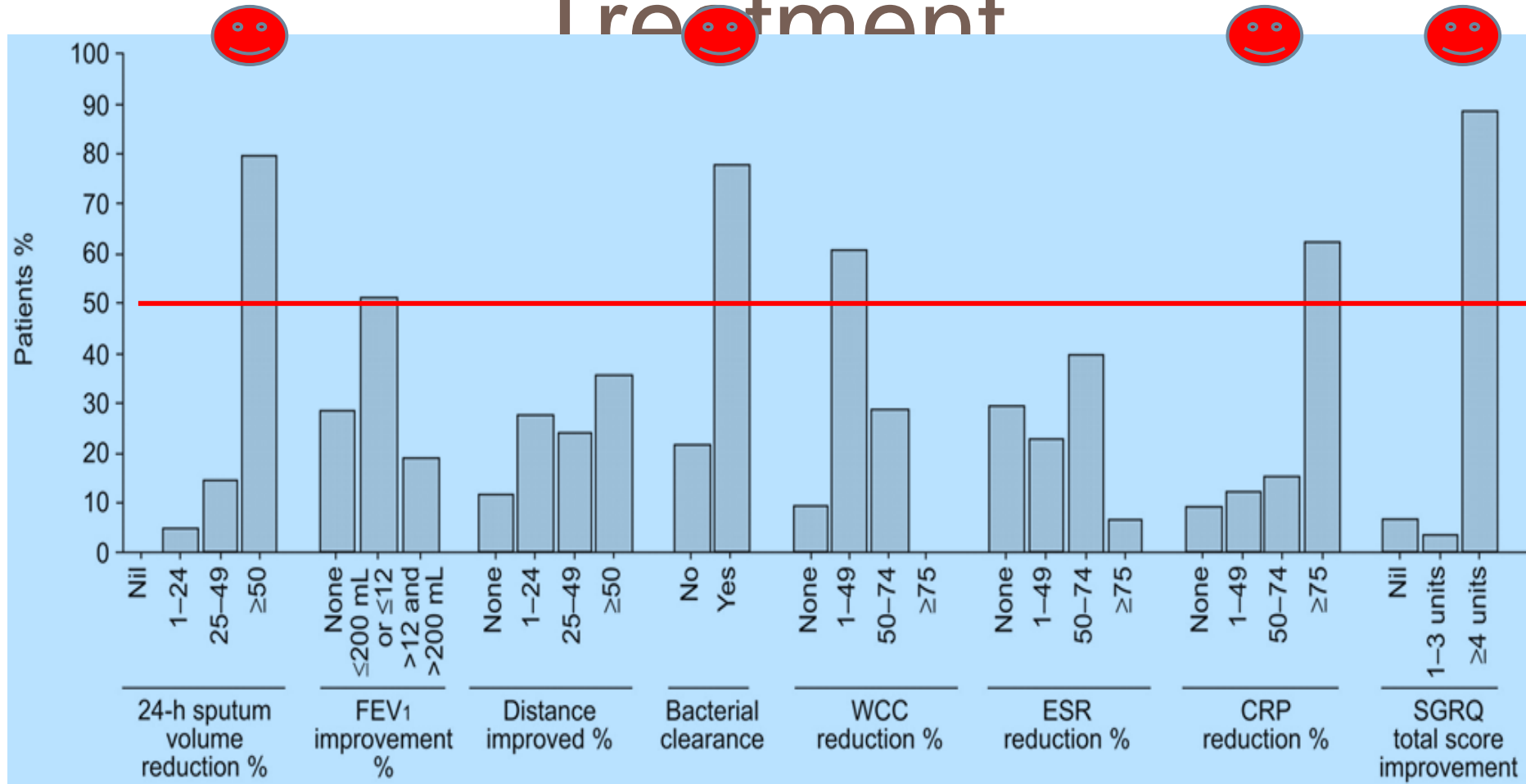
GP Gave Ciproxin 500mg bd for 14d but patient still felt ill. **What action?**

# IV Antibiotics

- Dual agents to reduce drug resistance
  - Ceftazidime+ Ciproxin/Gentamicin
  - Tazocin + Ciproxin/Gentamicin
  - Meropenum + Ciproxin/Gentamicin
  - Meropenum + Colomycin
  - Aztreonam + Colomycin
- **In Vitro Resistance does it matter?**
  - Yes  
Risk of lack of response if given in vivo
  - Risk of polymicrobial resistance
  - ?  
Often patients respond even when in vitro resistance- try and assess response

**How do you assess treatment response?**

# Assessing Response to Treatment



- Few evidence based endpoints
- Studies to date use various markers
- Sputum colour + volume; Sputum bacterial clearance; CRP; SGRQ were the best markers

# Case

- 45 year old lady
- Bilateral cystic bx
- FEV<sub>1</sub> 63% predicted
- Chronically colonised with PA resistant to Cipro + Tazocin
- 8 Chest infections in the past year
- On Seretide 500 1 accule bd
- Salbutamol prn
- Neb Colomycin
- What action?

# Treatments strategy

- Ensure complying with treatment
- Ensure complying with chest physiotherapy
- 8 Weekly IV Antibiotics
- May make patients feel better and more control of the Bx

# Acknowledgements

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- James Chalmers
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