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The management of bronchiectasis in Europe

Data from the European Bronchiectasis Registry

James Chalmers
University of Dundee, UK

Presenter disclosures

Clinical Trials

AstraZeneca, Aradigm corporation, Bayer Healthcare, GSK

Research Grant Support

Wellcome Trust, Chief Scientist Office, Medical Research Council, AstraZeneca, EU Innovative Medicines Initiative, European Respiratory Society, Tenovus Scotland, Bayer Healthcare, Aradigm Corporation, Griffols, Pfizer inc

Consultancy

Bayer Healthcare, Griffols, AstraZeneca, Basilea, Napp

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Why do we need a European Bronchiectasis registry?

- To answer key questions about the epidemiology of bronchiectasis
- A series of unsuccessful clinical trials suggests the need for better outcome measures and greater research co-ordination
- To contribute to the generation of evidence-based recommendations on the management of patients with BE
- To encourage young investigators to become involved in this emerging field
- To disseminate knowledge and communicate results at international conferences and in peer reviewed publications

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What is the EMBARC?

- European Bronchiectasis Registry
- ERS Bronchiectasis task force – European BE guidelines due 2016
- European Bronchiectasis patient advisory group
- ERS clinical research collaboration
- European Bronchiectasis Clinical Trials Network

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S.I.M.e.R.
SOCIETÀ ITALIANA di MEDICINA RESPIRATORIA

BRONCHIECTASIS RESEARCH REGISTRY
A COPD FOUNDATION INITIATIVE

ecfs

PROGNOSIS

ELF EUROPEAN LUNG FOUNDATION

BRONCH-UK
The National Bronchiectasis Network

LUNGFOUNDATION AUSTRALIA
"When you can't breathe... nothing else matters"™

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Challenges in forming a European registry

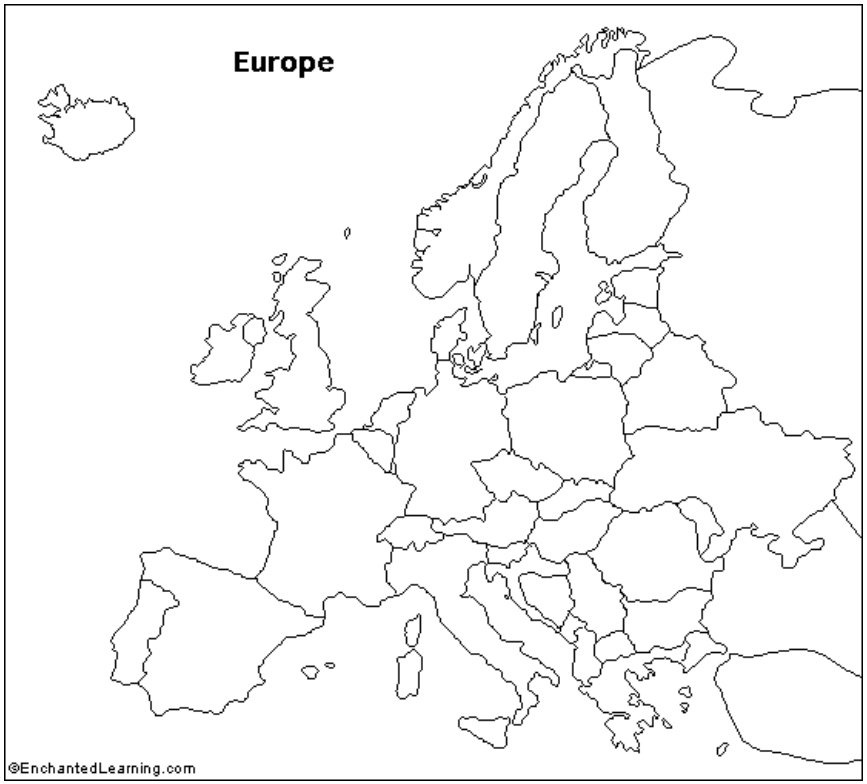
ecfs

Variable definitions

Inclusion/exclusion criteria

Variable quality control

Huge cost of administering registries in every country



Solution:
Alignment of data fields and definitions at set-up

Single data collection platform

Shared administrative set-up= sustainability

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Login

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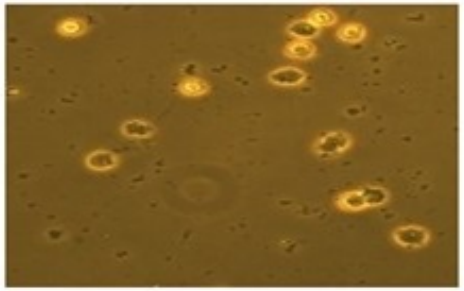

Sharing expertise and research protocols around Europe. Help to build a wider network and grow clinical research capacity for bronchiectasis in Europe.

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research idea and expertise. Central to this project is the creation of the European Bronchiectasis Registry, a collaboration open to all investigators around Europe caring for patients with bronchiectasis.

Latest News

Support Healthy Lungs for Life at ERS 2015

Sep 14 2015 8:39 PM

At Congress, the Healthy Lungs for Life campaign will launch its new theme: Take the Active Option. We think this campaign offers a great opportunity to raise awareness of the role of physical ...

Read More

The EMBARC registry receives funding from EU Innovative Medicines Initiative

Sep 7 2015 2:28 PM

EMBARC is contributing to a €50 million

Latest Research

Secreted mucins and airway bacterial colonization in non-CF bronchiectasis.

Sibila O, Suarez-Cuartin G, Rodrigo-Troyano A, Fardon TC, Finch S, Mateus EF, Garcia-Bellmunt L, Castillo D, Vidal S, Sanchez-Reus F, Restrepo MI, Chalmers JD / Respirology. 2015 Jul 14. doi: 10.1111/resp.12595. [Epub ahead of print]

Non-cystic fibrosis bronchiectasis: clinical presentation, diagnosis and treatment, illustrated by data from a Dutch Teaching Hospital.

Altenburg J, Wortel K, van der Werf TS, Boersma WG. / Neth J Med. 2015 May;73(4):147-54.

Join EMBARC

EMBARC is an open group and free to join.

For more information contact info@bronchiectasis.eu

Sign up at the registration page

Follow EMBARC on Facebook!

Talk to us on Twitter!

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Welcome, editor.

Summary:

Completed Sections: 2
Incomplete Sections: 5

Not all sections are completed: you cannot submit the case

Demographic information updated succesfully.

Embarc Database CRF Case J2071

Back to list

Basic case information	Complete
Co-morbidities - Demographics and Background	Complete
Bronchiectasis background information	Draft
Aetiology and laboratory testing	Draft
Microbiology	Draft
Radiology	Draft
Respiratory Treatments	Draft
Additional information	

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Registry study design

- Prospective observational study
- Patient consent and enrolment as baseline
- Follow-up annually for up to 5 years

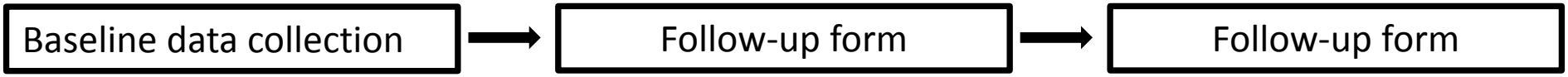
Support

Central administrative office/help desk

Project management

Support for statistics and dissemination

Compensation to sites for enrolment



Recruitment started February 2015

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Participants from 40 countries

232 registered centres

TARGET:

- **1000 patients by April 2016**
- **10,000 patients by March 2020**

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The first results of the EMBARC Bronchiectasis registry

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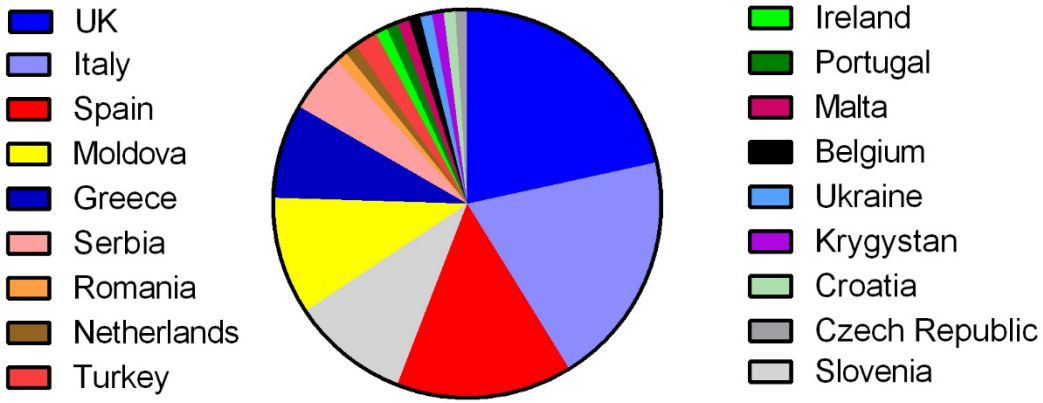
Results at 23/9/15

1283 patients enrolled



Demographics

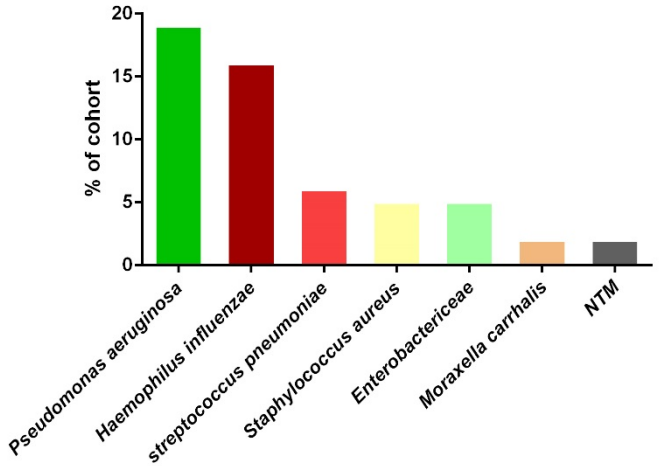
57% female

Average age= 61 years

Most common aetiology- post-infective= 35%

Never smoked =60.3%

Ex smoker= 28.7%



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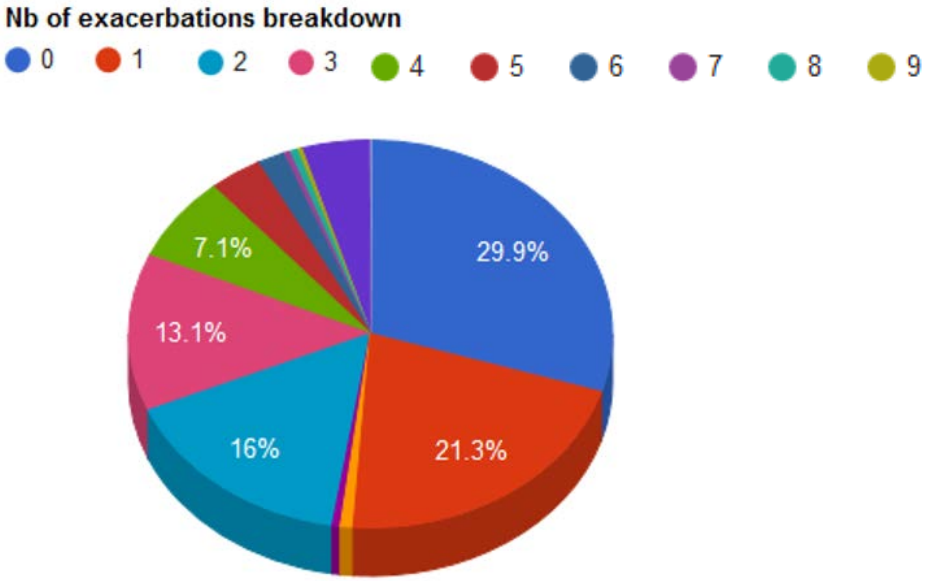
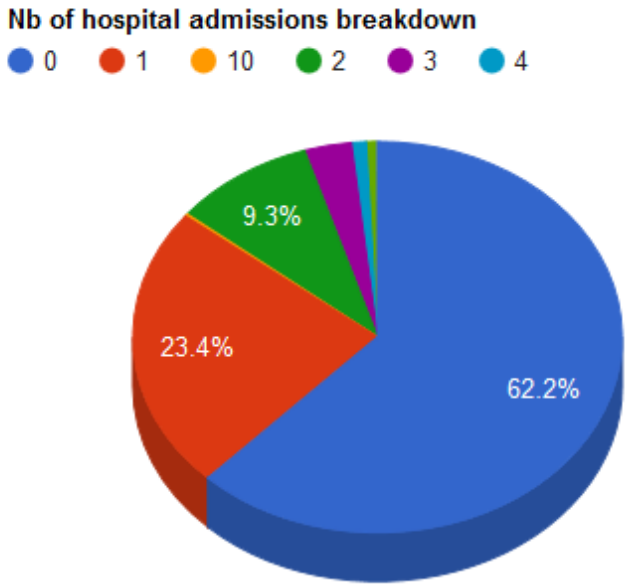
Disease impact- exacerbations

Outpatient exacerbations



Severe exacerbations



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Bronchiectasis severity index

Bronchiectasis Severity Index

Predicting Mortality and Exacerbation Rates in Non-CF Bronchiectasis

HOME

Online Calculation Tool

Enter your patient's information below to calculate the Bronchiectasis Severity Index.

UNIVERSITY OF DUNDEE

Age
< 50

BMI
< 18.5

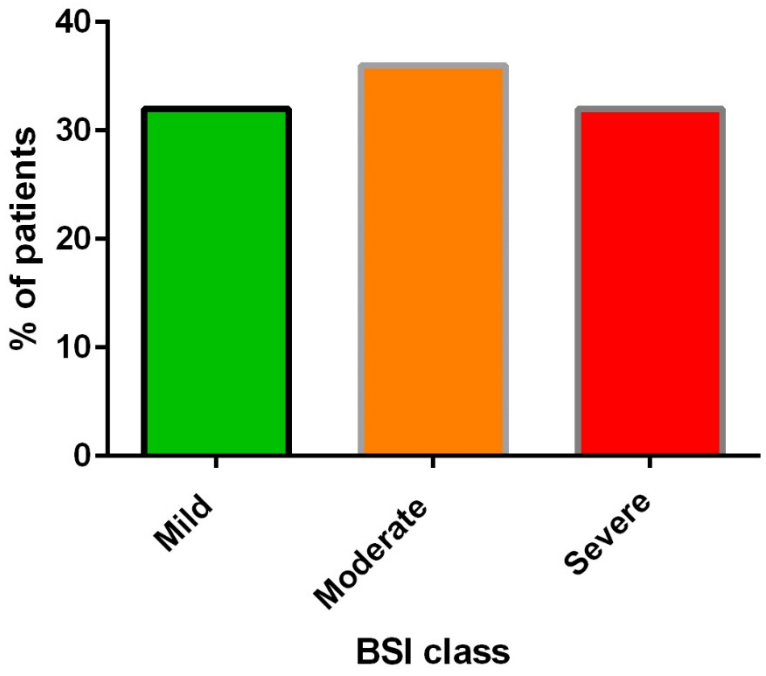
% FEV1 Predicted
> 80%

Previous Hospital Admission
No
Has the patient been hospitalised with a severe exacerbation in the past 2 years?

Number of exacerbations in previous year
0

MRC Breathlessness Score
1 - 3
MRC Breathlessness Score
1 - Not troubled by breathlessness except on strenuous exercise
2 - Short of breath when hurrying or walking up a slight hill
3 - Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4 - Stops due to breathlessness after walking 100m
5 - House bound due to breathlessness, or breathless on dressing or undressing.

Pseudomonas Colonisation
No
Chronic colonisation is defined by the isolation of pseudomonas aeriginosa in sputum culture on 2 or more occasions, at least 3 months apart in a 1 year period



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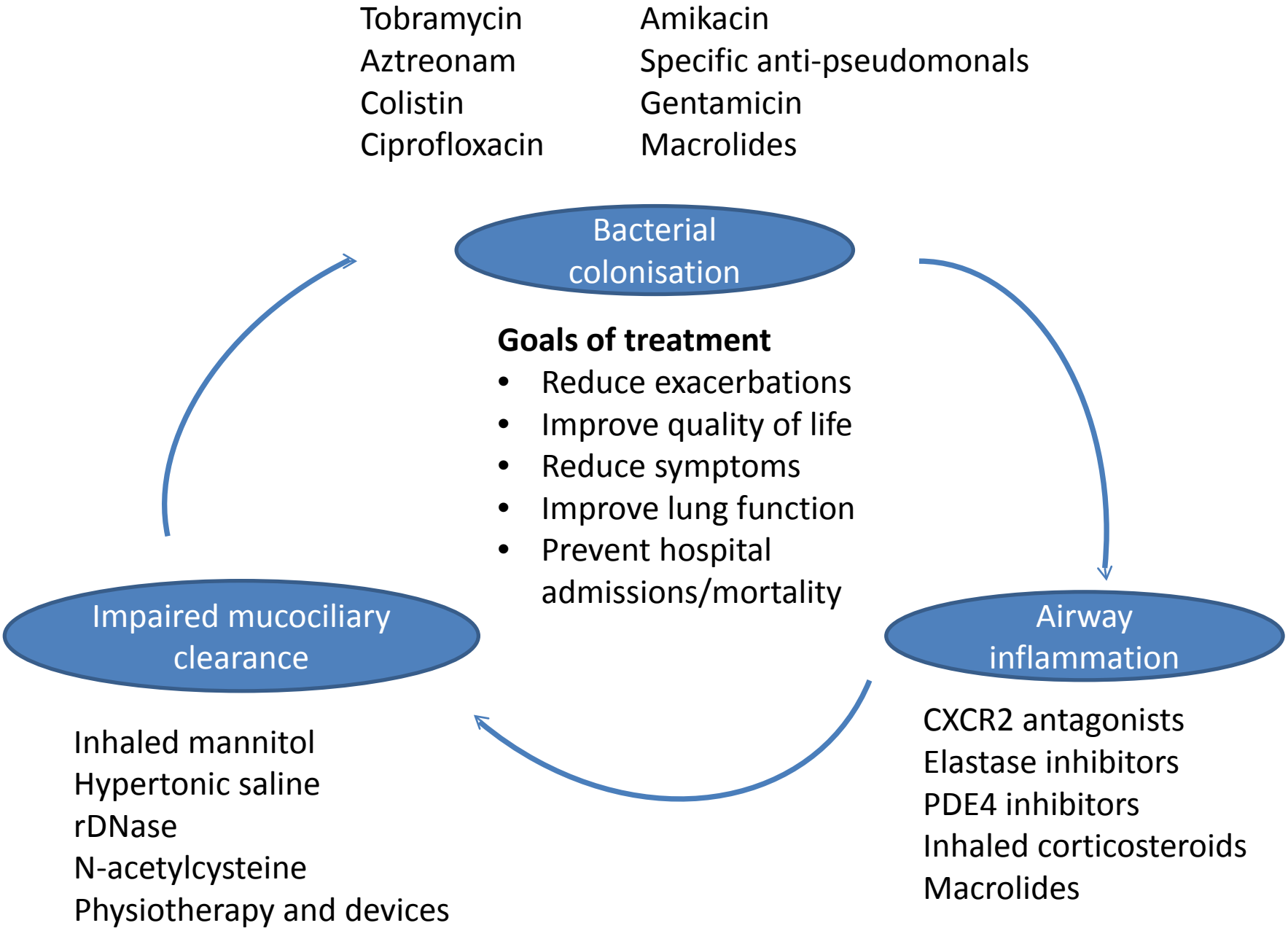
How are patients with bronchiectasis treated in Europe?


Tobramycin
Aztreonam
Colistin
Ciprofloxacin
Amikacin
Specific anti-pseudomonals
Gentamicin
Macrolides
Bacterial colonisation
Goals of treatment
• Reduce exacerbations
• Improve quality of life
• Reduce symptoms
• Improve lung function
• Prevent hospital admissions/mortality
Airway inflammation
CXCR2 antagonists
Elastase inhibitors
PDE4 inhibitors
Inhaled corticosteroids
Macrolides
Impaired mucociliary clearance
Inhaled mannitol
Hypertonic saline
rDNase
N-acetylcysteine
Physiotherapy and devices

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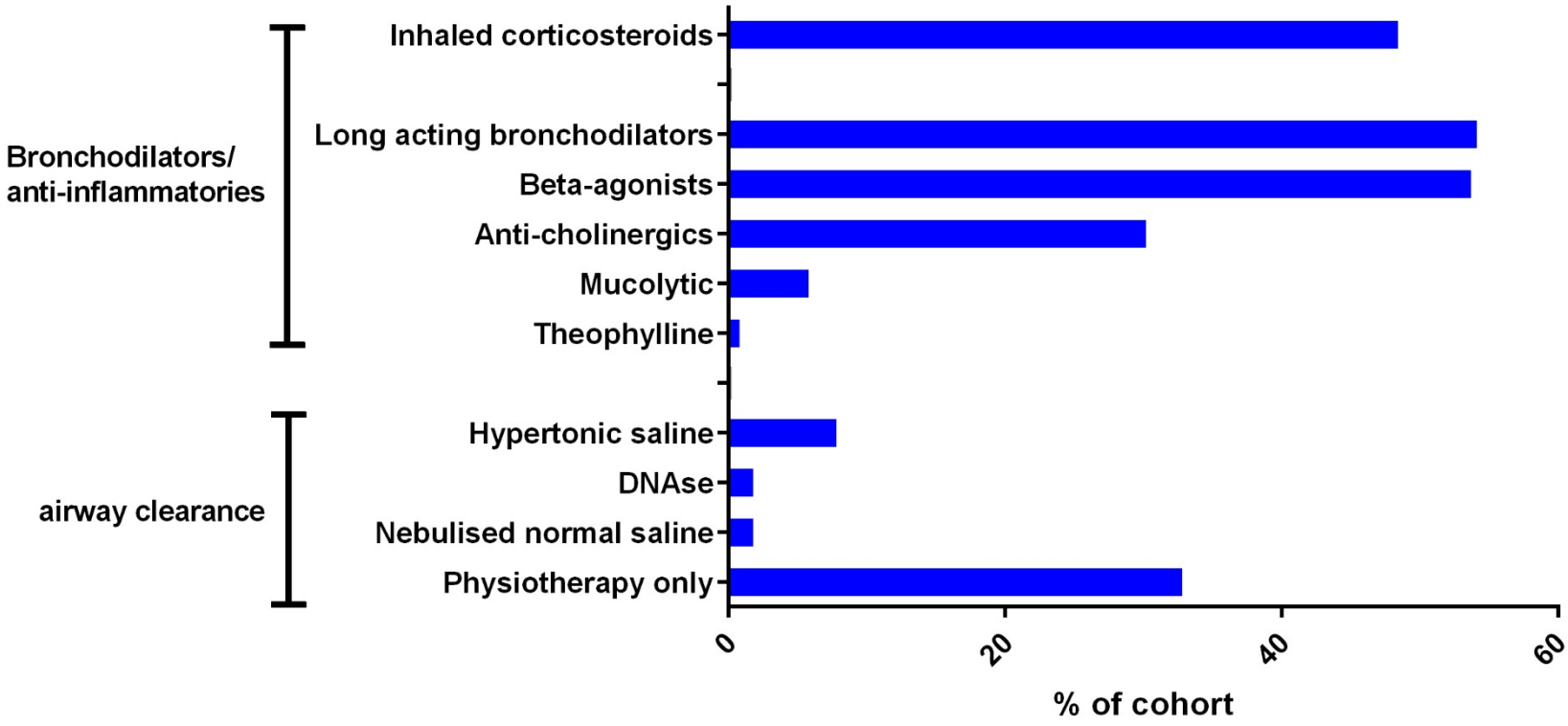
Inhaled and mucoactive therapies



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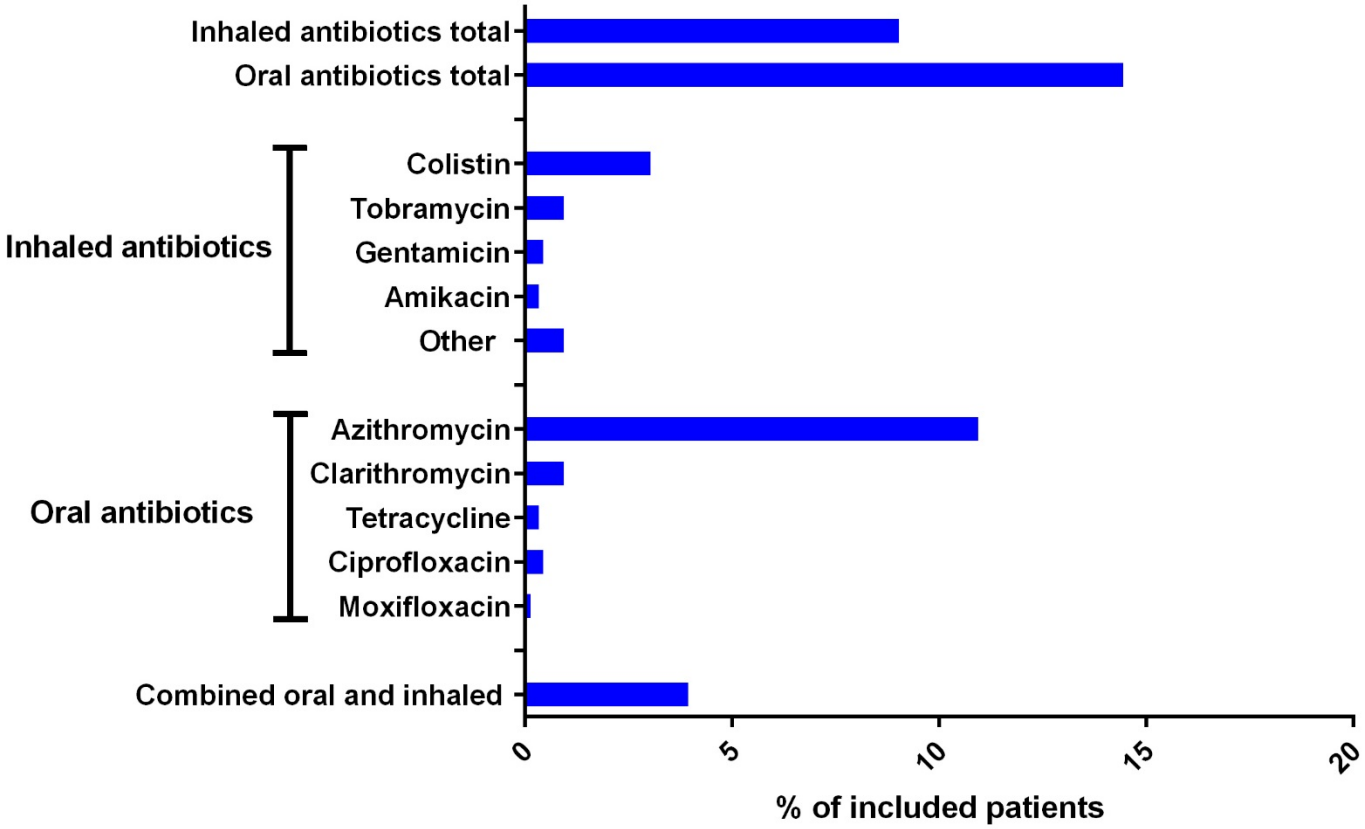
Antibiotic therapies



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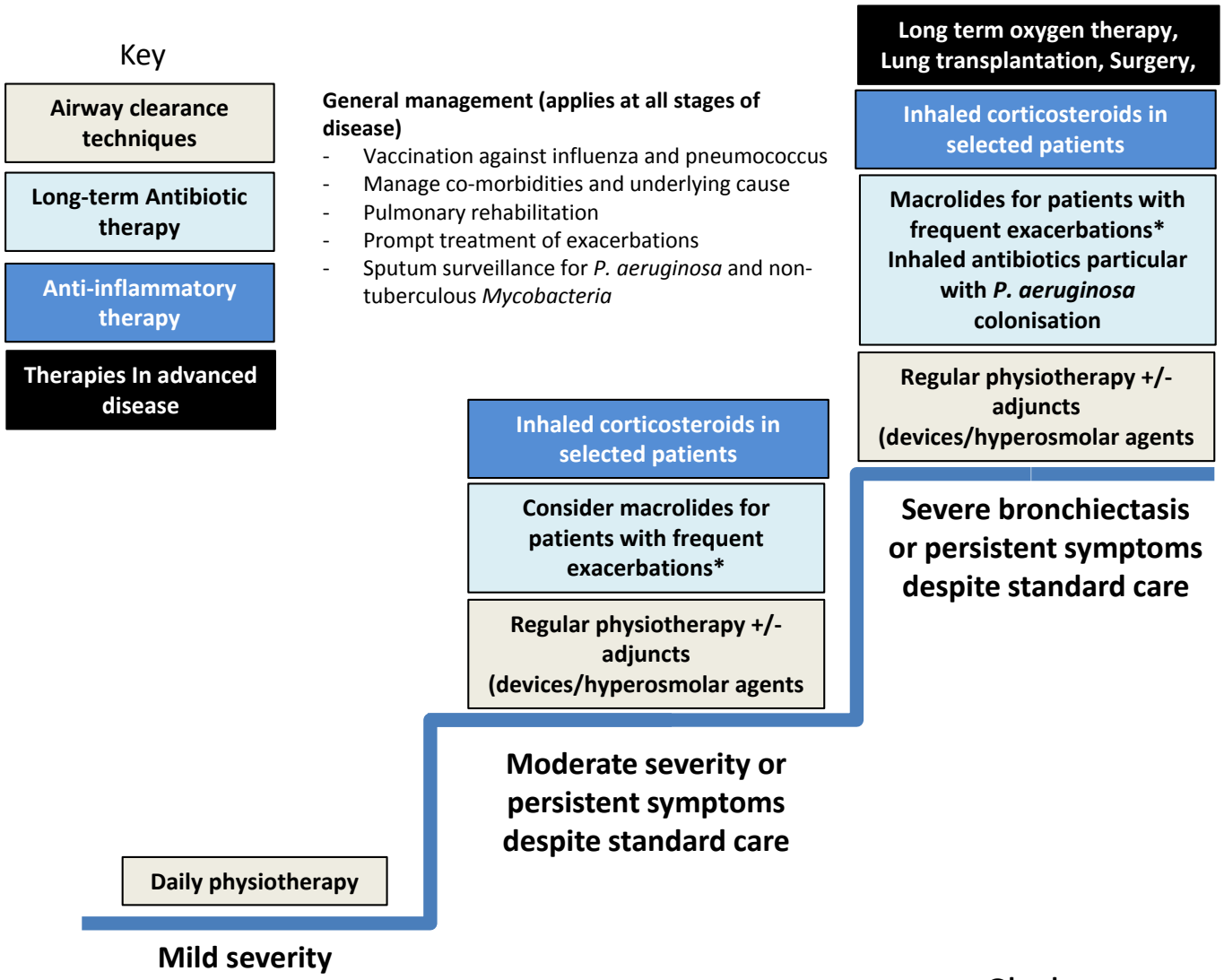

Chalmers et al, ERJ 2015

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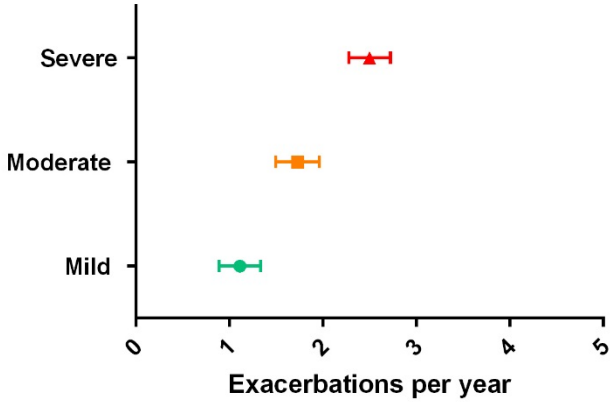
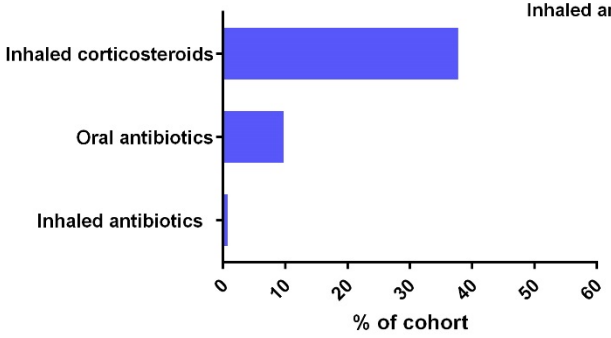
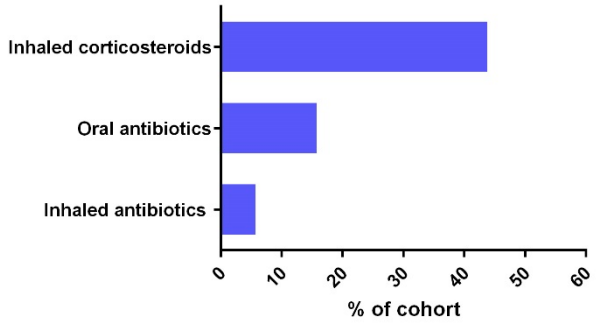
BSI score

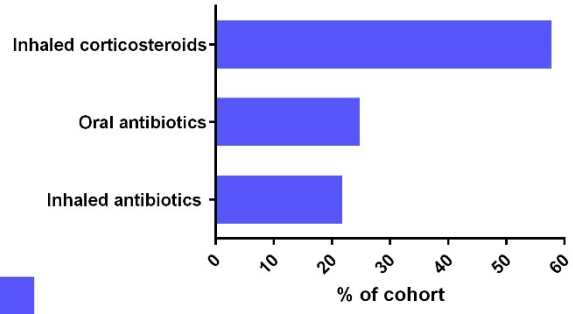




Mild severity



Moderate severity or persistent symptoms despite standard care



Severe bronchiectasis or persistent symptoms despite standard care

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Pseudomonas aeruginosa is a key pathogen

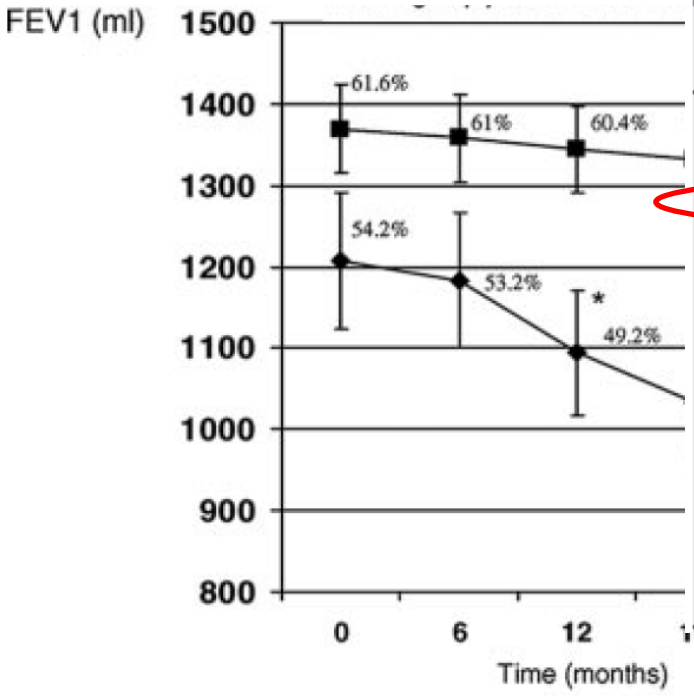

TABLE 3 Multivariate Cox proportional hazard stepwise analysis

Parameters	RR (95% CI)#	p-value
Age	1.10 (1.06–1.15)	<0.0005
PSA	3.61 (1.35–9.62)	0.010
Male sex	3.42 (1.34–8.77)	0.010
LF criteria % pred		
RV/TLC	1.03 (1.01–1.04)	<0.0005
TLC	0.95 (0.93–0.98)	<0.0005
Kco	0.96 (0.94–0.98)	<0.0005
Health-related quality of life questionnaire scores		
SGRQ activities	1.05 (1.02–1.08)	<0.0005

Martinez-Garcia Chest 2007, Loebinger et al, ERJ 2009

Comprehensive analysis of *P. aeruginosa* impact

Data from 4 published/unpublished cohorts in the European registry project

Systematic review of all published BE data

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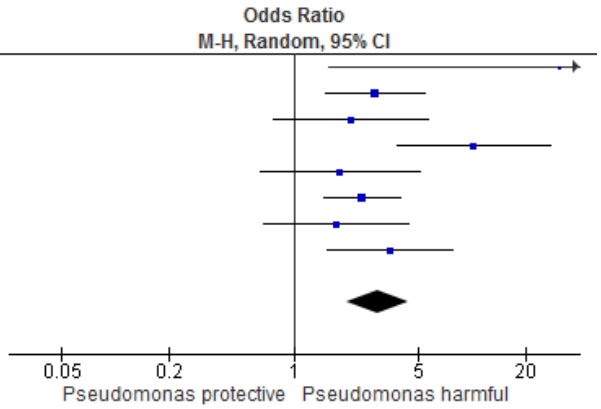
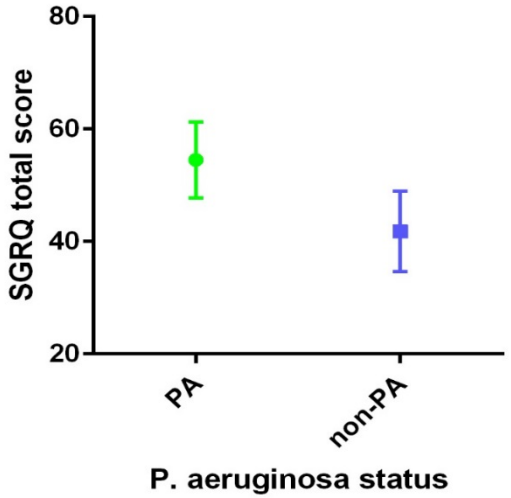
Study or Subgroup	Pseudomonas Events	Pseudomonas Total	Non-Pseudomonas Events	Non-Pseudomonas Total	Weight	Odds Ratio M-H, Random, 95% CI
Aliberti 2014	3	39	0	162	1.7%	31.16 [1.58, 616.55]
Chalmers 2014	15	70	47	538	17.9%	2.85 [1.50, 5.43]
Chalmers 2015	6	44	17	242	11.0%	2.09 [0.77, 5.64]
Goeminne 2014	10	20	20	225	11.0%	10.25 [3.81, 27.57]
Loebinger 2009	8	20	19	71	10.3%	1.82 [0.65, 5.15]
Martinez-Garcia 2014	38	126	41	271	21.8%	2.42 [1.46, 4.01]
McDonnell 2014	9	47	13	108	12.0%	1.73 [0.68, 4.38]
McDonnell 2015	13	34	27	178	14.3%	3.46 [1.55, 7.73]
Total (95% CI)		**400**		**1795**	**100.0%**	**2.95 [1.98, 4.40]**
Total events	102		184			

Heterogeneity: Tau² = 0.13; Chi² = 11.72, df = 7 (P = 0.11); I² = 40%

Test for overall effect: Z = 5.29 (P < 0.00001)



- Mortality increased by 3x
- Hospital admissions 7 x increased risk
- Average of 1 additional exacerbation per patient per year
- 15% lower FEV1 % predicted
- 18.2 points difference on the SGRQ quality of life score



Finch et al, *Ann Am Thoracic Soc.* 2015 in press.

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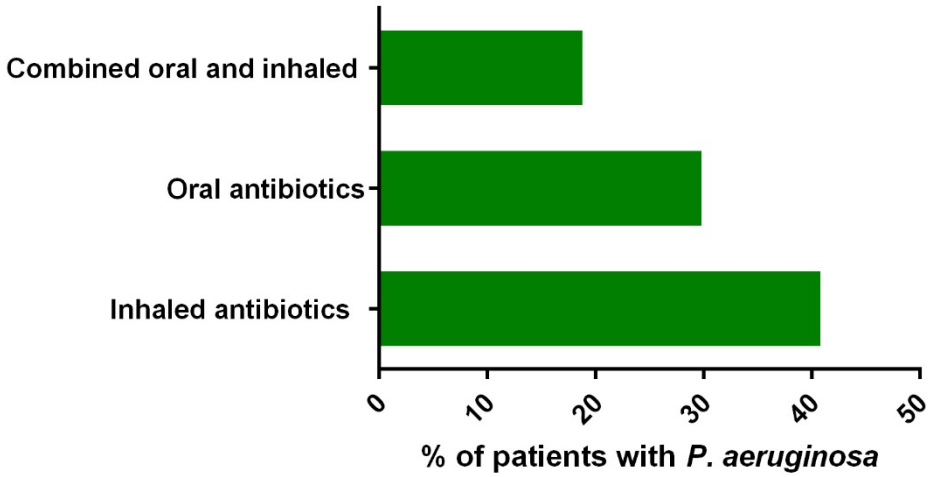
Treatment of *P. aeruginosa*



290 patients reported at least one isolation of *P. aeruginosa*

66% had at least one attempt at eradication

Successful in 62% (defined as PA clear for at least 2 years)

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How is this impacted by COPD?

COPDGene®
COPD Genetic Epidemiology

N=3636
Bronchiectasis
20.8%- associated with more exacerbations, worse FEV_1

Single centre studies
- 50-60% of patients with moderate to severe COPD
- More bacterial colonisation
- More *P. aeruginosa*
- Independent predictor of death

ECLIPSE

N=2164
Bronchiectasis
5% GOLD III, 7% GOLD IV

Stewart et al, AJRCCM 2012
Agusti et al, Respir Res 2012
Martinez et al AJRCCM 2013
Getheral et al COPD 2014

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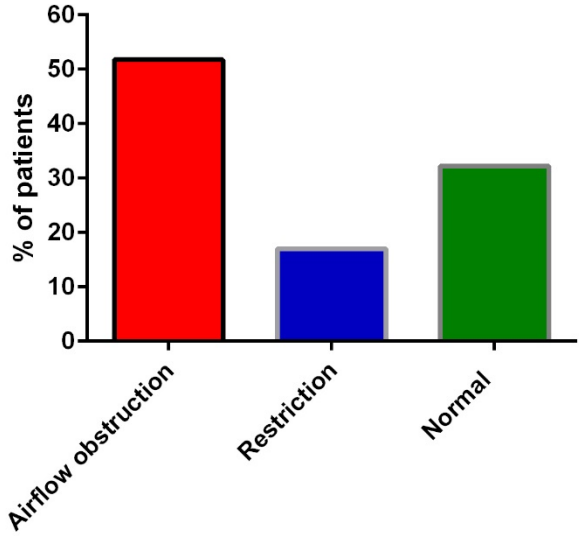
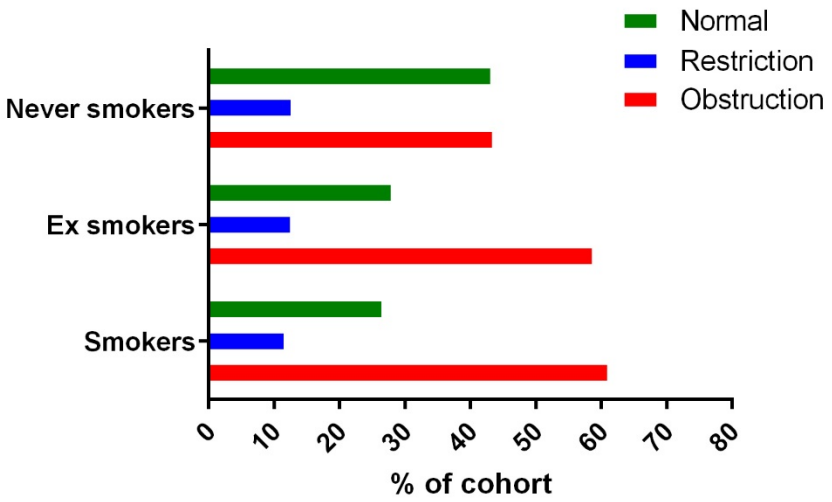
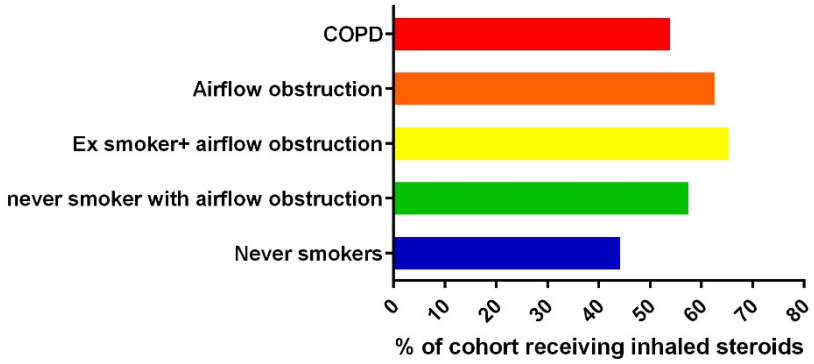
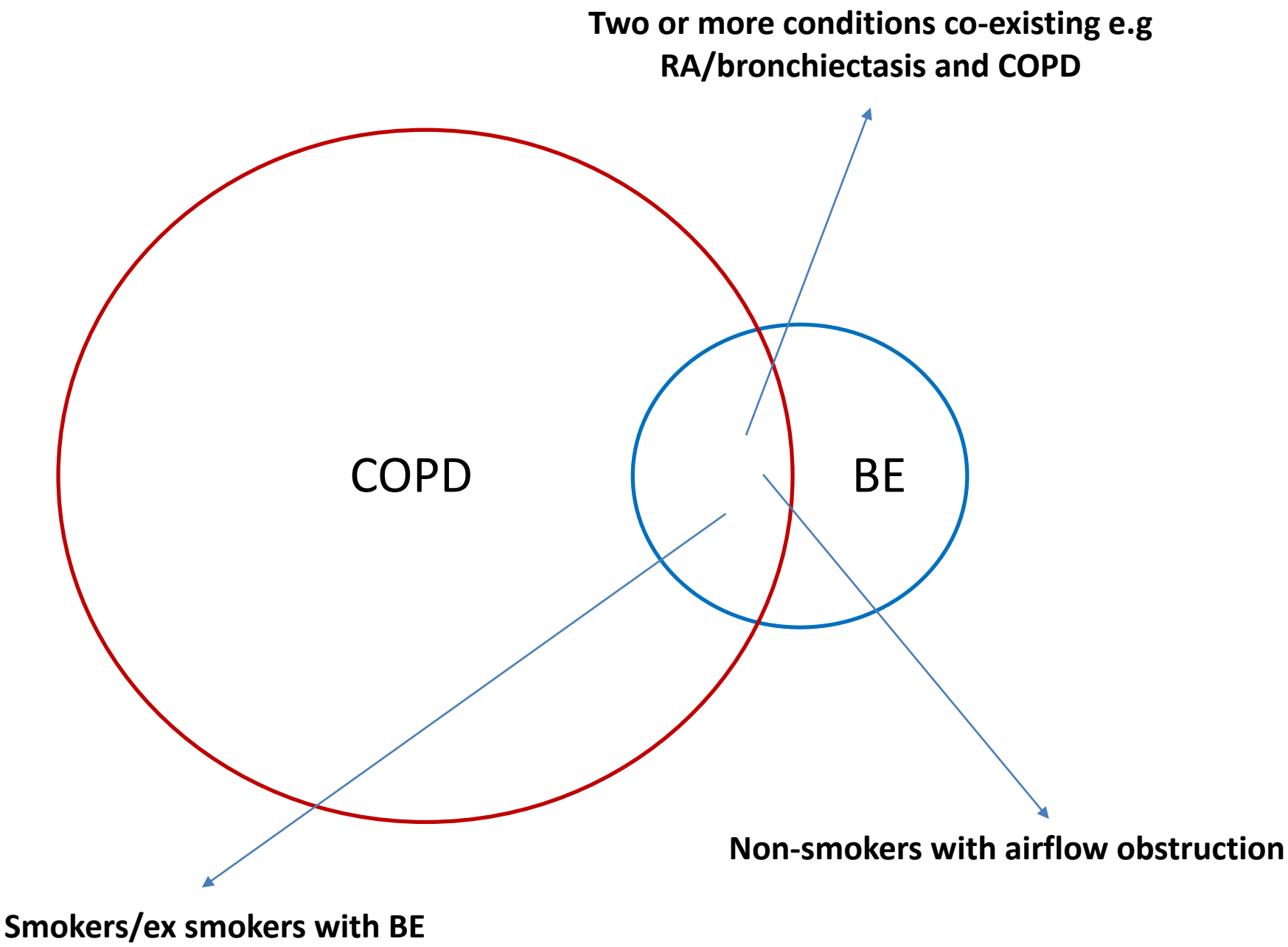
How is this impacted by COPD?

8.1% reported to have COPD








Two or more conditions co-existing e.g
RA/bronchiectasis and COPD
COPD
BE
Non-smokers with airflow obstruction
Smokers/ex smokers with BE

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Evidence gap

- Inhaled corticosteroids
- Recombinant DNAse
- Bronchodilators

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BRONCHIECTASIS

Inhaled fluticasone in bronchiectasis: a 12 month study

K W Tsang, K C Tan, P L Ho, G C Ooi, J C Ho, J Mak, G L Tipoe, C Ko, C Yan, W K Lam, M Chan-Yeung

Thorax 2005;**60**:239–243. doi: 10.1136/thx.2002.003236

Largest trial= 43 patients in each arm. Small improvement in sputum volume. No improvement in exacerbations or lung function.

Inhaled steroids for bronchiectasis (Review)

Kapur N, Bell S, Kolbe J, Chang AB

THE COCHRANE COLLABORATION®

No clinical benefits in long term and in placebo controlled studies.

Limited data (6 trials, 303 patients)

Should be limited to patients with overlapping COPD and asthma and not used routinely in bronchiectasis

Tsang et al Thorax 2005, BTS guidelines 2010

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Treatment of Idiopathic Bronchiectasis With Aerosolized Recombinant Human DNase I*

Anne E. O'Donnell, MD, FCCP; Alan F. Barker, MD, FCCP; Jonathan S. Ilowite, MD, FCCP; and Robert B. Fick, MD; for the rhDNase Study Group[†]

349 patients randomized (173 DNAse, 176 placebo)

30% vs 19% *P. aeruginosa* colonisation

Results

Reduced FEV1 with DNAse (-3.6% vs --1.7%, p<0.05)

Increase in exacerbations RR 1.35 (1.01-1.79)

British Thoracic Society Guidelines 2010-
Grade A recommendation <u>against</u> DNAse

O'Donnell et al, Chest 1998

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Inhaled bronchodilators

Long-acting beta2-agonists for bronchiectasis (Review)

Sheikh A, Nolan D, Greenstone M

THE COCHRANE COLLABORATION®

Anticholinergic therapy for bronchiectasis (Review)

Lasserson TJ, Holt K, Evans DJ, Milan SJ, Greenstone M

THE COCHRANE COLLABORATION®

No valid randomized controlled trials identified

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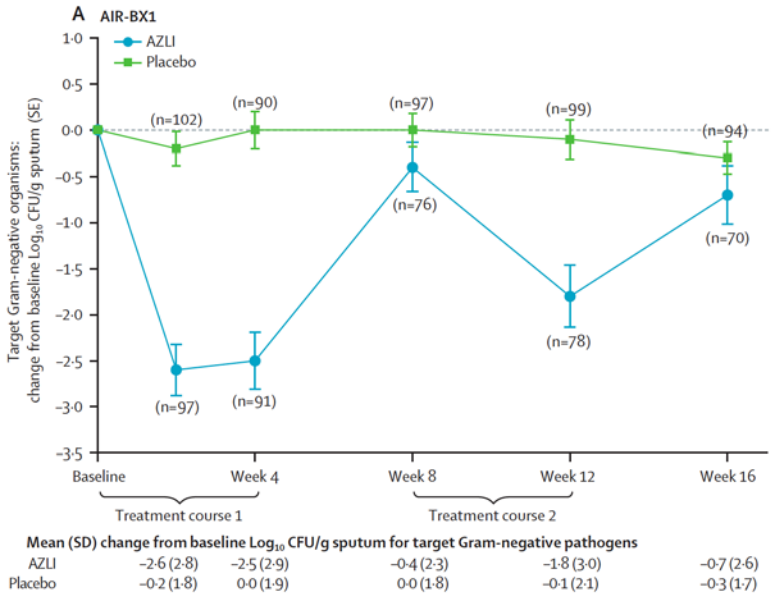
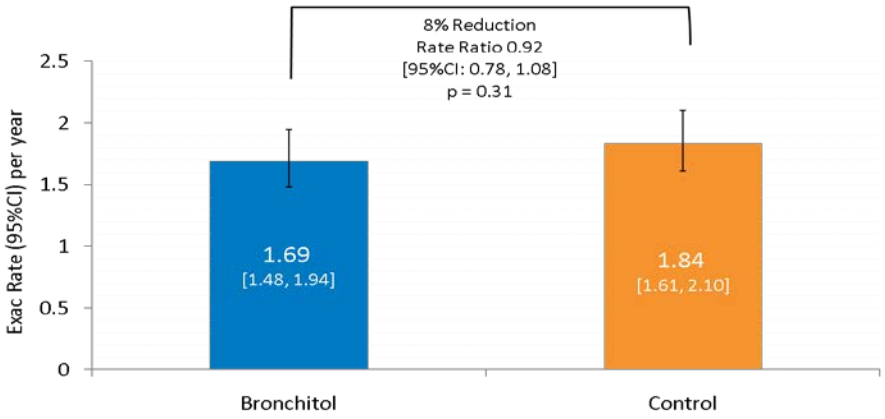
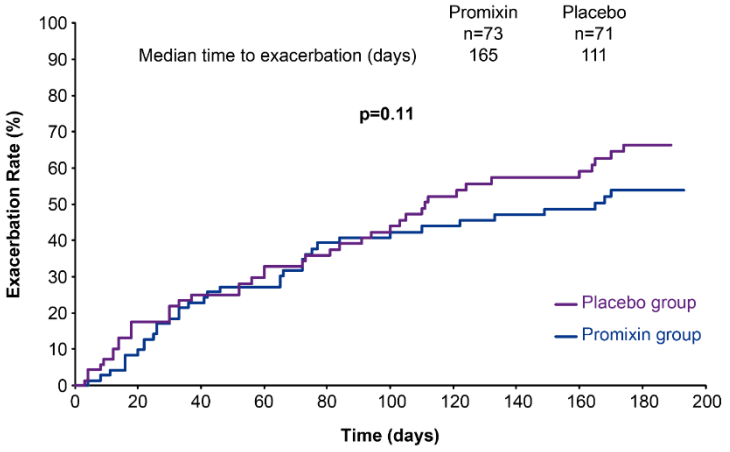
Working towards better evidence

- Bronchiectasis trials are challenging
- Recruitment
- Feasibility
- Endpoints







Barker et al, 2014, Haworth et al 2014.

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How can EMBARC help with trials?

- Feasibility- identification of patients and sites
- End-point validation
- Obtain funding from EU and national sources
- Patient input into trials through the ELF patient advisory group
- Identification of research priorities
- Standardisation of procedures and end-points.
- Identification of subgroups and phenotypes

EMBARC

The European Bronchiectasis Registry

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EMBARC promotes awareness and clinical excellence in bronchiectasis care through educational events, courses and online resources.

EMBARC is a pan-European network committed to promoting clinical research and education in bronchiectasis, through sharing of protocols, research idea and expertise. Central to this project is the creation of the European Bronchiectasis Registry, a collaboration open to all investigators around Europe caring for patients with bronchiectasis.

Latest News

Call for participation- the Bronchiectasis research roadmap

Jul 9 2014 1:03 PM

The European Bronchiectasis Network (EMBARC) seeks to promote clinical research in bronchiectasis and to build research capacity in Europe. A key task in this will be identifying the areas of …

Latest Research

Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial.

Mandal P, Chalmers JD, Graham C, Harley C, Sidhu MK, Doherty C, Govan JW, Sethi T, Davidson DJ, Rossi AG, Hill AT / Lancet Respir Med. 2014 Mar 24. pii: S2213-2600(14)70050-5. doi: 10.1016/S2213-2600(14)70050-5

Join EMBARC

EMBARC is an open group and free to join.

For more information contact info@bronchiectasis.eu

Sign up at the registration page

Follow EMBARC on Facebook!

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Data access

Sites have unrestricted access to their own data for analysis.

Analysis to the full dataset is open to anyone – apply online at www.bronchiectasis.eu

Applications to use the data are screened by the registry scientific committee Members

- Anthony De Soyza (UK)
- Felix Ringshausen (Germany)
- Stefano Aliberti (Italy)
- Charlie Haworth (UK)
- Pieter Goeminne (Belgium)
- Marlene Murris (France)
- Montserrat Vendrell (Spain)
- Wim Boersma (Netherlands)

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Why bronchiectasis research?

- Common
- Disabling
- Neglected
- Tractable

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Summary

- The first data from the European Bronchiectasis registry suggest *P. aeruginosa* and *H. influenzae* are the most common pathogens
- The treatment burden in *P. aeruginosa* infection is high and prognosis is poor, suggesting a key unmet need.
- The most frequently used therapies are inhaled corticosteroids and bronchodilators, for which we lack robust evidence.
- The majority of bronchiectasis patients, therefore, are managed with therapies for which there is no evidence.

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The future

- Recruit 10,000 patients from across Europe with high quality data and consistent follow-up
- Disseminate and publish epidemiological data that can increase knowledge of bronchiectasis and lead to improvements in care
- Make a registry that is sustainable beyond the life of the project
- Inform high quality randomized controlled trials, providing the evidence base for current and future therapies.

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Come and visit us in the World Village (desk 1)