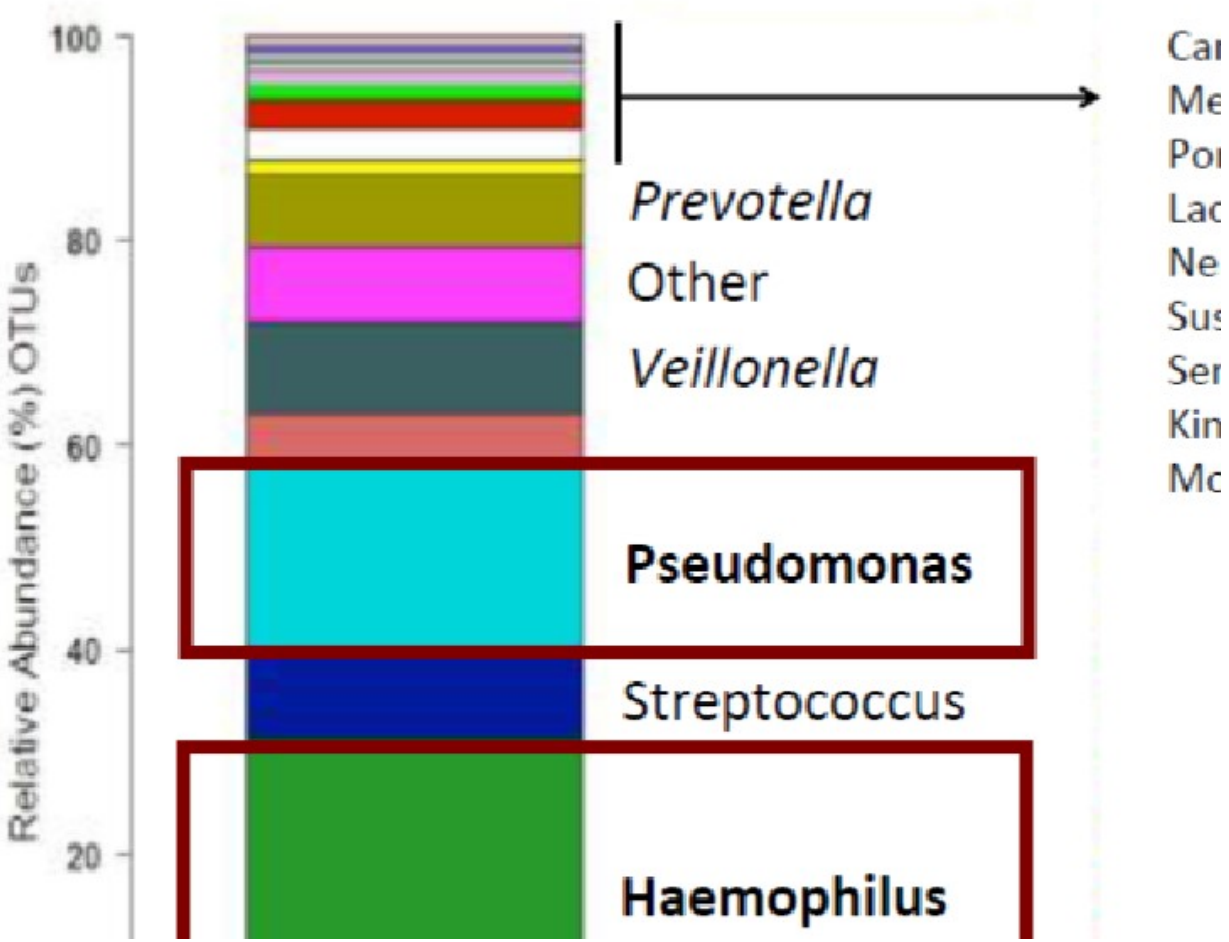
Phénotypes/endotypes et bronchiectasies (hors mucoviscidose)



Dr B. Camara - Praticien Hospitalier

Centre de Ressources et de Compétences pour la Mucoviscidose (CRCM Adultes)

Service de Pneumologie - Physiologie

Pôle Thorax et Vaisseaux

CHU Grenoble Alpes

BCamara@chu-grenoble.fr

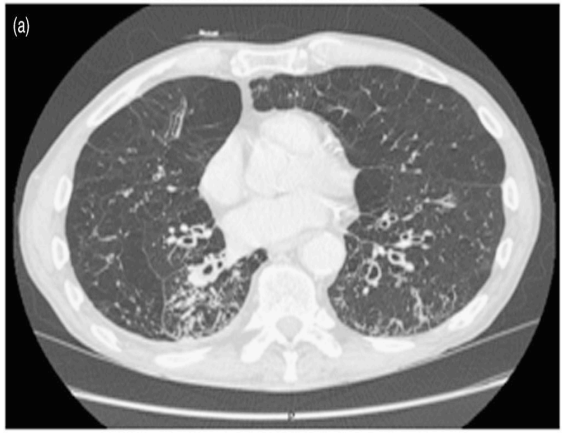
Colloque Médical du Jeudi – Le 08 Novembre 2018

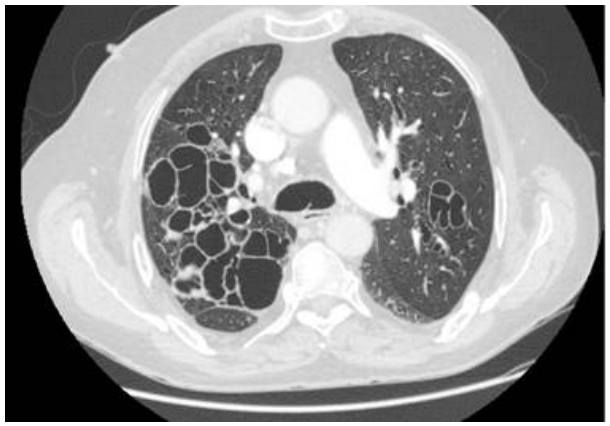
Dilatations des bronches

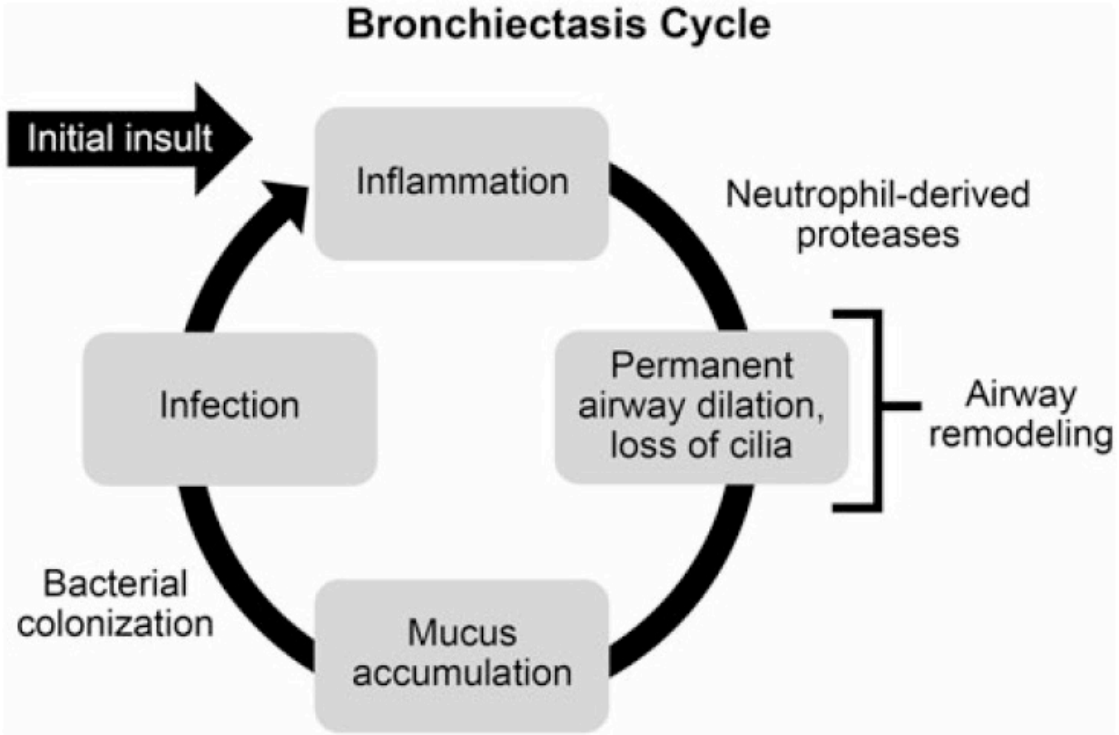
La dilatation des bronches ou bronchiectasie est maladie respiratoire chronique définie par la presence :

syndrome clinique fait de toux, production bronchique associé ou pas à des infections respiratoires récurrentes

dilatation bronchique permanente à l'imagerie (***scanner thoracique +++)***

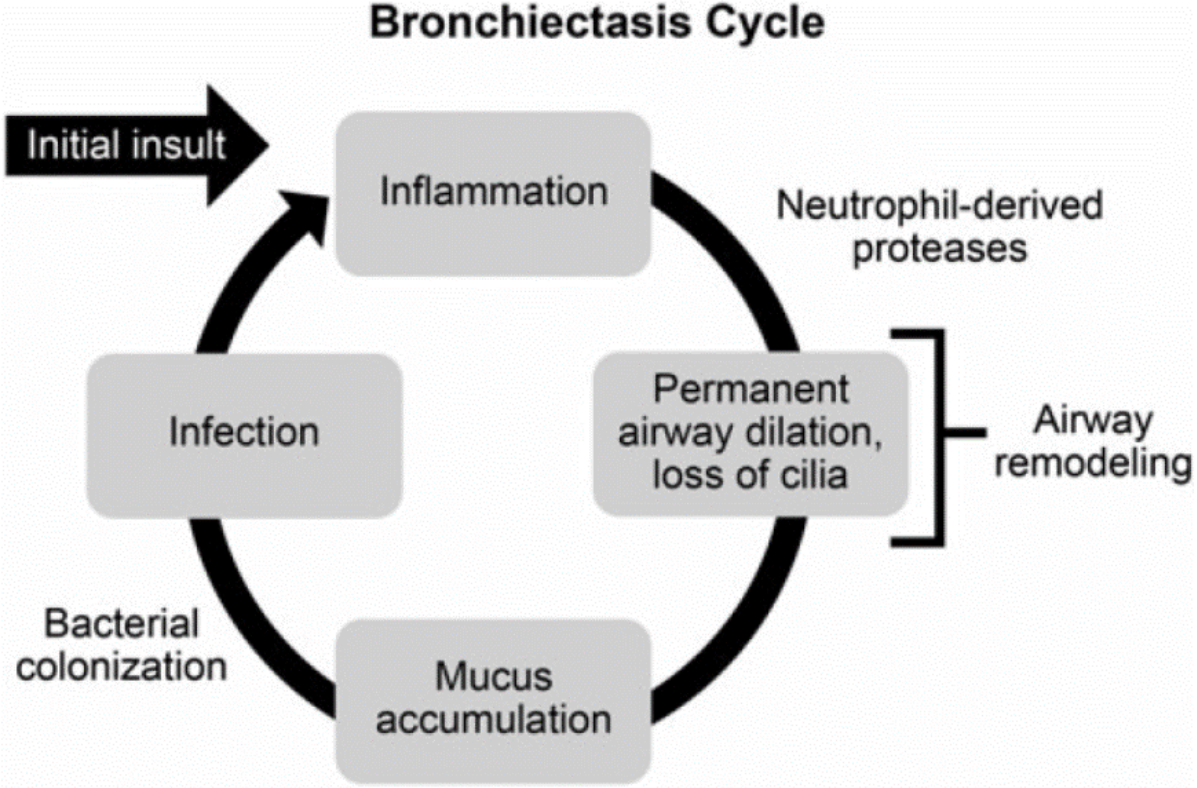






The "vicious circle" of bronchiectasis originally described by Cole. Cole PJ, Eur J Respir Dis Suppl. 1986

Physiopathologie



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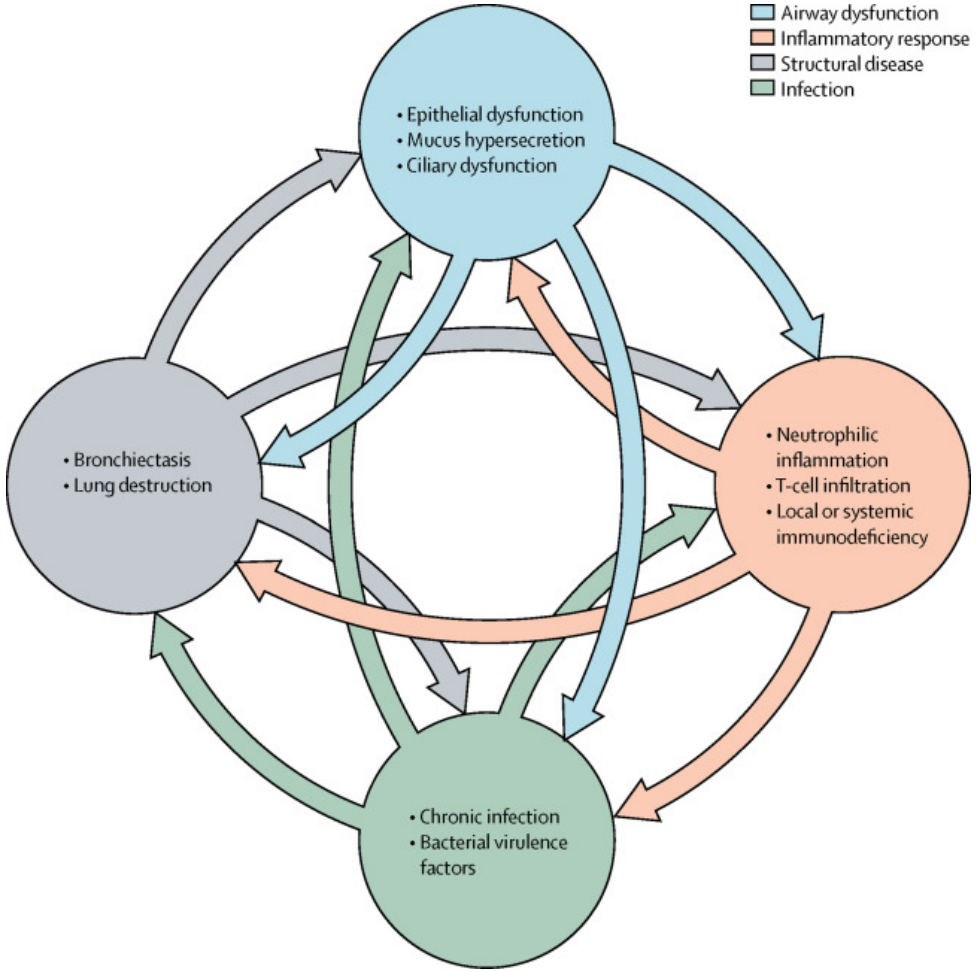

Flume, Chalmers & Olivier. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet. 2018 Sep 8;392(10150):880-890.

Pourquoi faut-il « phénotyper » les patients ?

Phenotype : comme un ensemble de caractéristiques observables d'un individu résultant de l'interaction de sa nature (génétique) et de l'environnement

[1] Han et al. Am J Respir Crit Care Med 2010 ; [2] Chalmers. Journal of Chronic Obstructive Pulmonary Disease 2017 ; [3] Wang et al. Eur Respir J 2016

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Patients BPCO [1] : phenotype définit par un ou une combinaison d'attributs de la maladie qui décrivent les différences entre les individus atteints de BPCO en relation avec des résultats cliniquement significatifs (symptômes, exacerbations, réponse au traitement, taux de progression de la maladie ou décès)⇢ applicable à d'autres entités…

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En termes pratiques [2] : aspects du patient qui influencent la prise de décision clinique (surveillance étroite à cause d'un mauvais pronostic) ou, peut-être plus important comment un patient devrait être traité en se basant sur une réponse spécifique à une thérapie

Autres exemple parlant [3] : BPCO avec antécédents d'exacerbations plus susceptible d'être un exacerbateur à l'avenir et peut donc être classé comme un phénotype exacerbateur même si les patients peuvent exacerber pour plusieurs raisons (inflammation éosinophile ou neutrophile, immunodéficience, comorbidité, susceptibilité génétique ou microbienne, dysbiose…

[1] Han et al. Am J Respir Crit Care Med 2010 ; [2] Chalmers. Journal of Chronic Obstructive Pulmonary Disease 2017 ; [3] Wang et al. Eur Respir J 2016

Endotypes, phénotypes et dilatation des bronches

- ***Phénotypes*** émergeant : ***Imagerie***, ***microbiologie***, ***étiologie***, ***comorbidités***, ***pronostic***, ***clustering multidimentionnel***, ***inflammation***…
- Le but de la stratification des maladies est de définir les ***endotypes***
- ***Endotypes*** : sous-types d'une condition définie par un mécanisme fonctionnel et physiopathologique distinct.
- En pratique pour la dilatations des bronches
  - *Physiopathologie encore mal comprise*
  - *Endotypes non précis*
  - *impossible de baser les décisions de traitement sur les endotypes*
  - *Biologie sous-jacente essentiel*

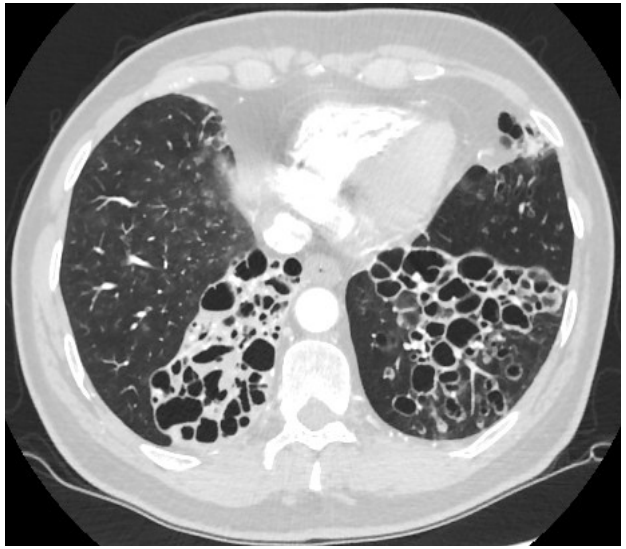
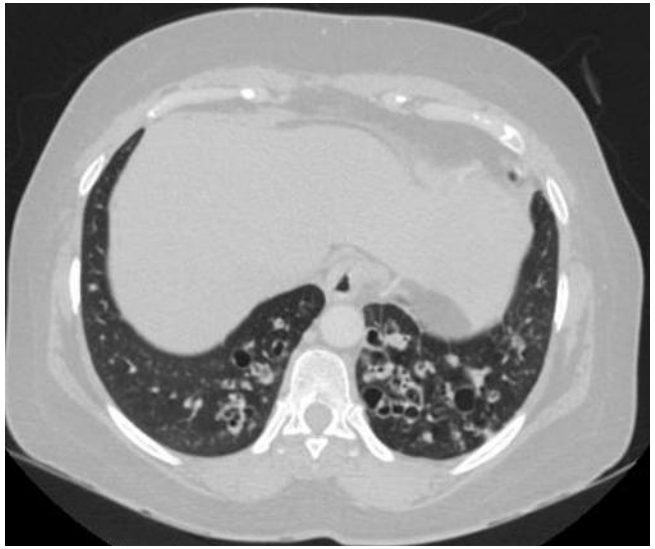
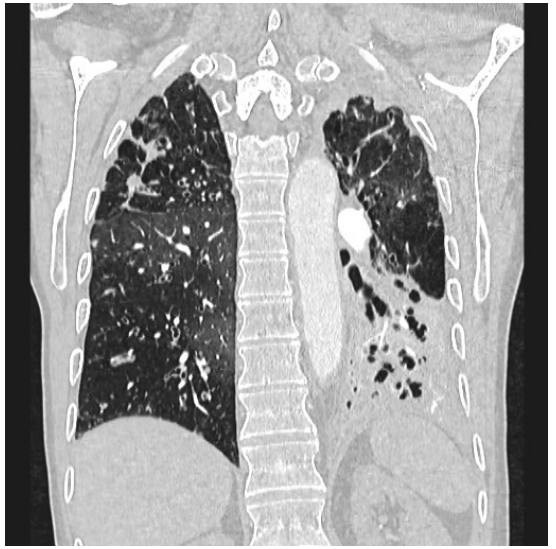
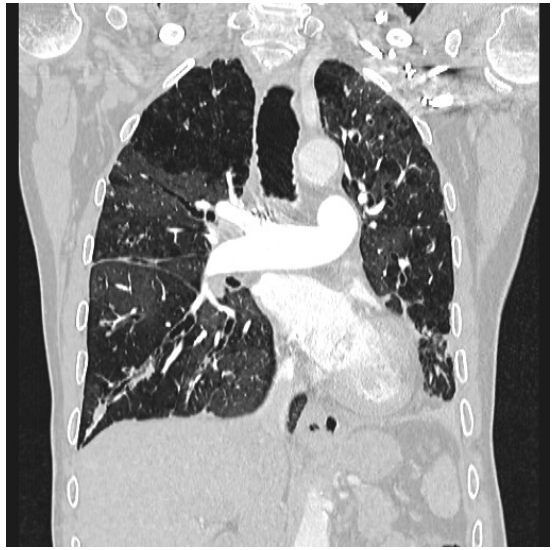
Imagerie des dilatations des bronches

Aspects radiologiques, ***hétérogènes***

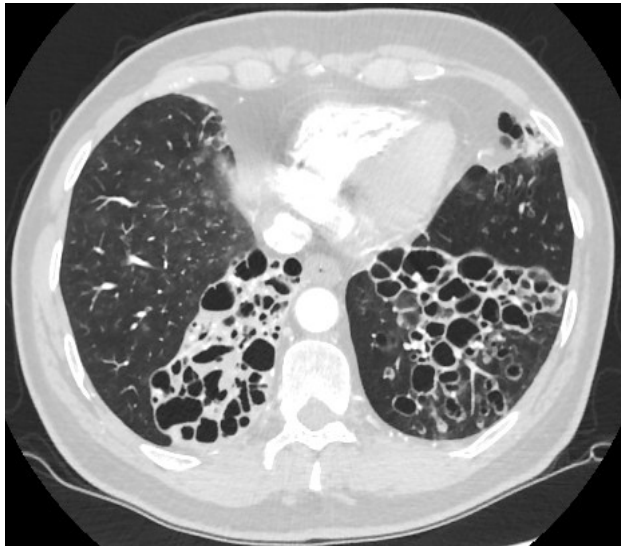
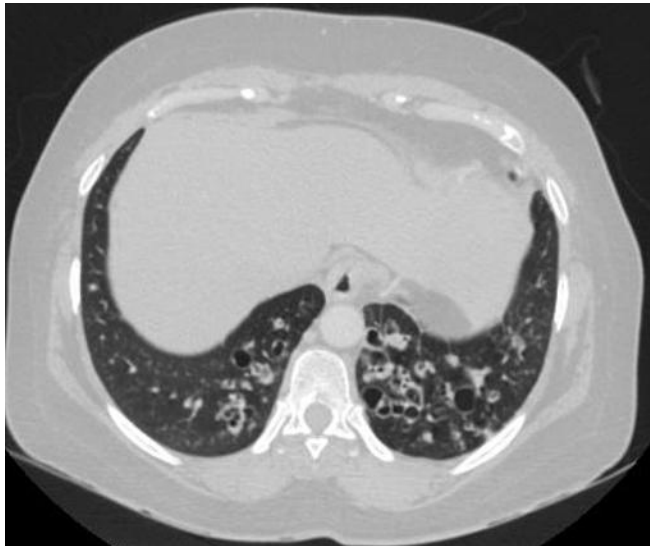
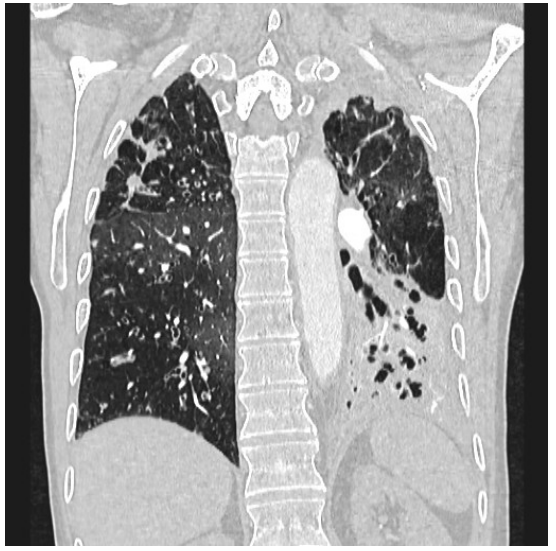
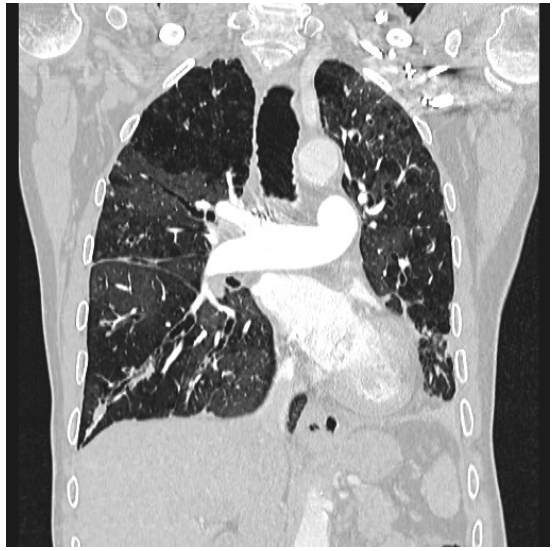
Correlée avec : étiologie, symptômes, exacerbations [1] et décés

[1] *Chalmers et al. The Bronchiectasis Severity Index. Am J Respir Crit Care Med 2014*
[2] *Loebinger et al. Mortality in bronchiectasis. Eur Respir J 2009*

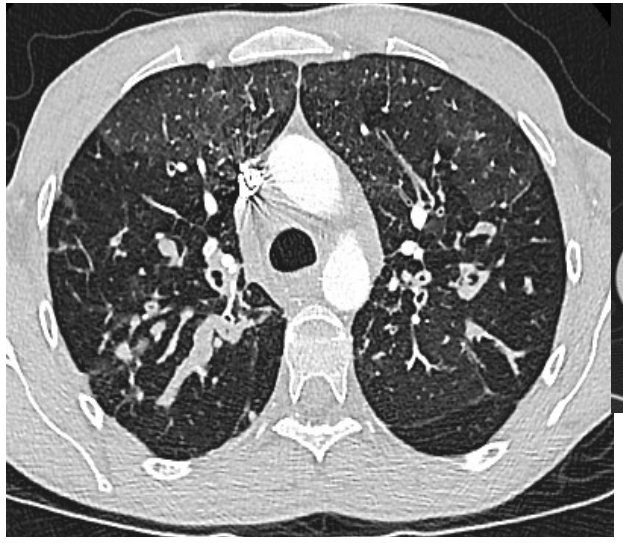
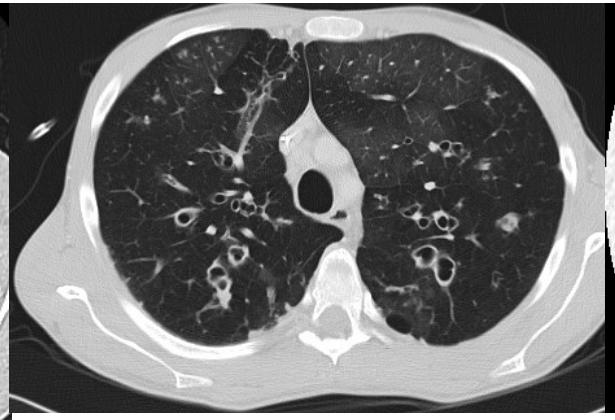
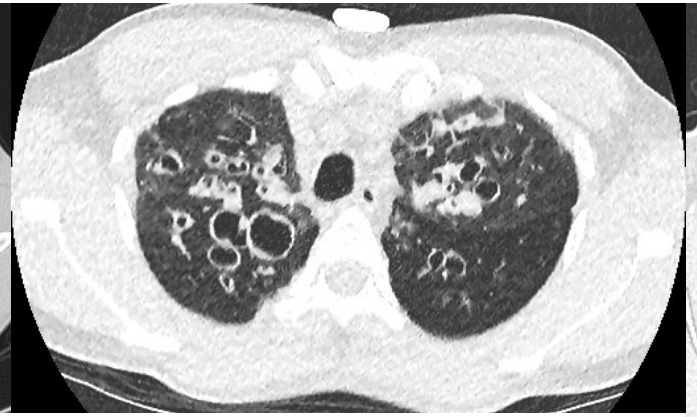
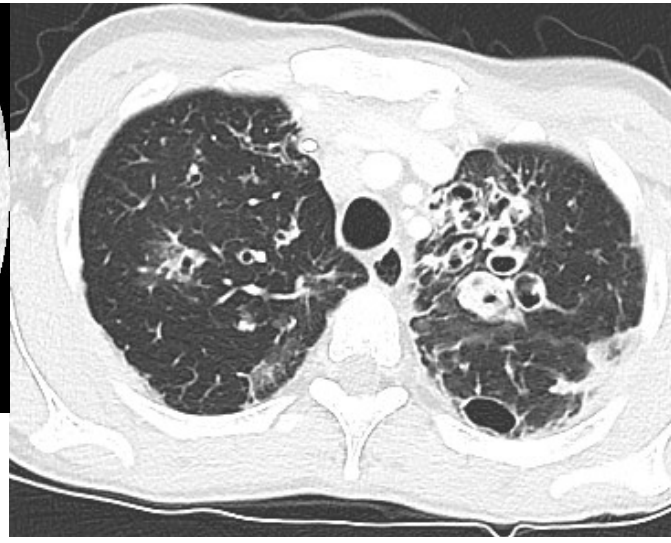
Localisation basales

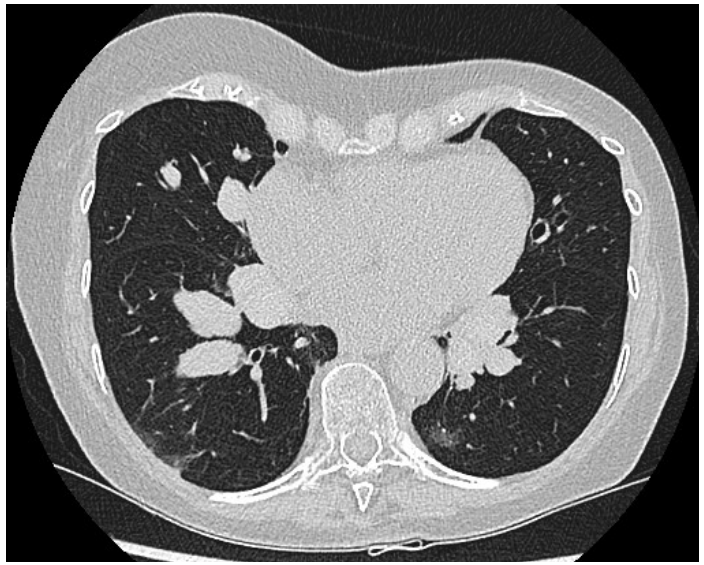
Localisation basales

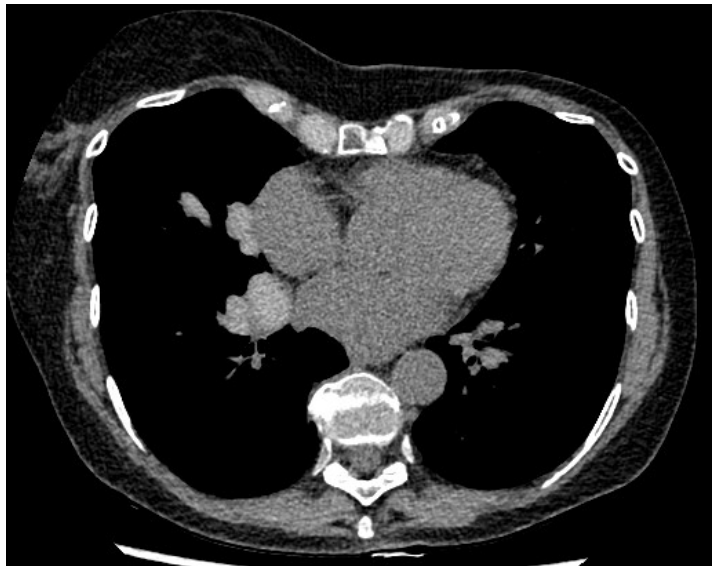





Localisation aux sommets

Localisation centrales





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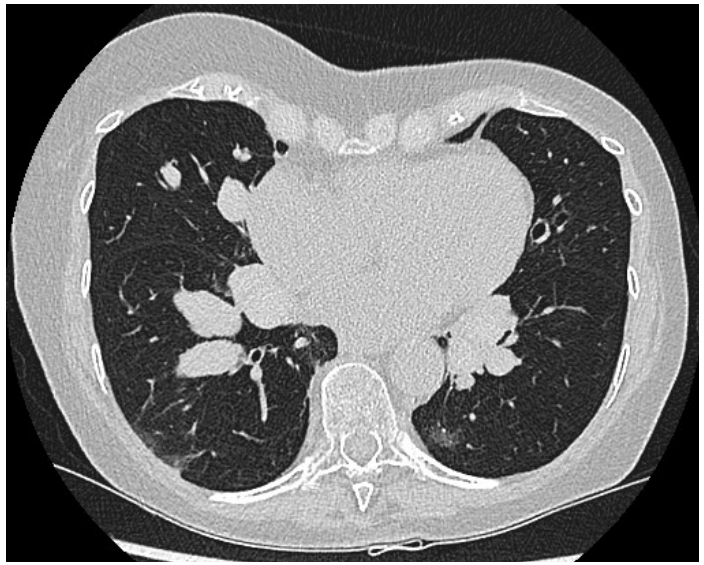
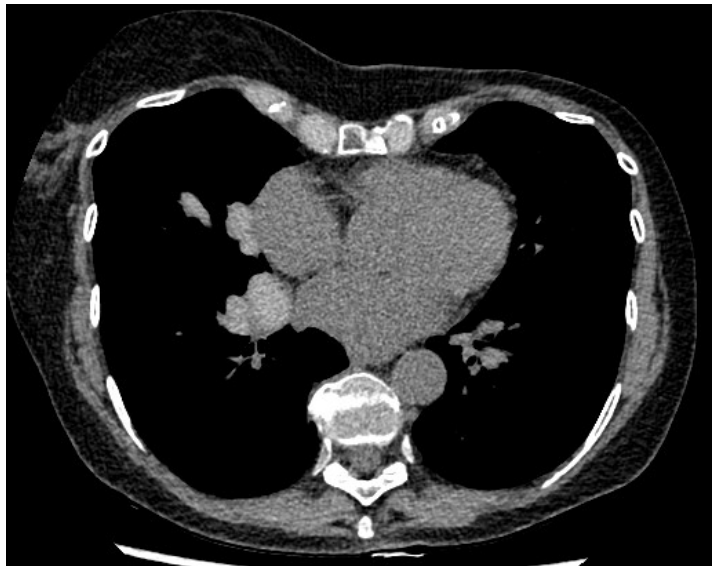
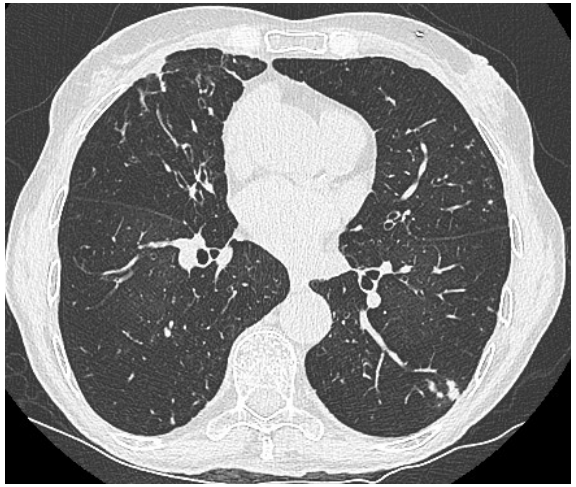
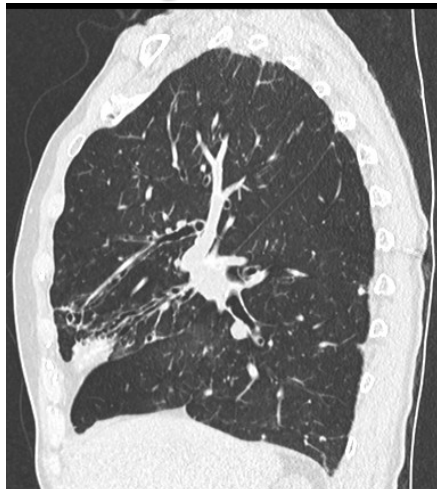
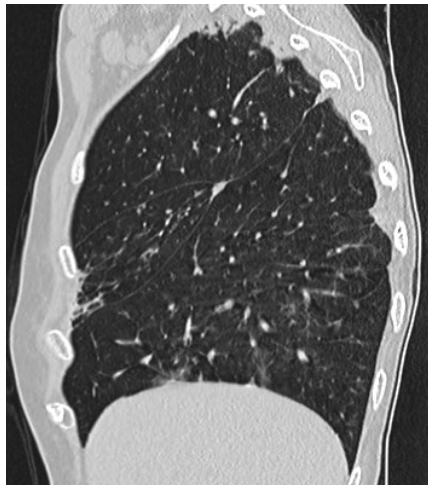




Lobes moyens







Imagerie des dilatations des bronches

Aspects radiologiques, ***hétérogènes***

Correlée avec : étiologie, symptômes, exacerbations [1] et décés

- ***Lobes inferieurs***
  - *Phénotype le plus frequent caracteristique des formes idiopathiques, associées à la BPCO, causes infectieuses et pathologies d'aspiration*
- ***Lobes moyens***
  - *mycobactérie atypiques*, dyskinésie cyliaire primitive
- ***Lobes supérieurs***
  - *Exclure absolument une mucoviscidose +++*
- ***Régions centrales***
  - *Phenotype le moins frequent devant évoquer une ABPA ou un syndrome de Mounier-Kuhn*

[1] *Chalmers et al. The Bronchiectasis Severity Index. Am J Respir Crit Care Med 2014*
[2] *Loebinger et al. Mortality in bronchiectasis. Eur Respir J 2009*

Impact de la microbiologie sur les phénotypes ?

Distribution of Major Pathogens from Sputum and Bronchoalveolar Lavage Fluid in Patients with Noncystic Fibrosis Bronchiectasis: A Systematic Review

Table 3: Weighted mean isolation rates according to the culture technique used in the studies

Pathogens	Sputum	BALF alone or BALF and sputum	*P*
Haemophilus influenzae	*n* = 19	*n* = 12	
Isolation rate (95% *CI*)	0.29 (0.23–0.36)	0.37 (0.29–0.44)	0.172
Pseudomonas aeruginosa	*n* = 19	*n* = 9	
Isolation rate (95% *CI*)	0.28 (0.21–0.34)	0.08 (0.05–0.11)	0.004
Streptococcus pneumoniae	*n* = 14	*n* = 12	
Isolation rate (95% *CI*)	0.11 (0.07–0.14)	0.14 (0.09–0.19)	0.205
Staphylococcus aureus	*n* = 10	*n* = 8	
Isolation rate (95% *CI*)	0.12 (0.07–0.16)	0.05 (0.03–0.06)	0.093
Moxarella catarrhalis	*n* = 13	*n* = 8	
Isolation rate (95% *CI*)	0.08 (0.05–0.11)	0.10 (0.05–0.15)	0.473

P values comparing the pathogen isolation rate for studies that used sputum with studies that used BALF or BALF and sputum, calculated by nonparametric test. BALF: Bronchoalveolar lavage fluid; *n*: Numbers of studies; *CI*: Confidence interval.

Distribution of Major Pathogens from Sputum and Bronchoalveolar Lavage Fluid in Patients with Noncystic Fibrosis Bronchiectasis: A Systematic Review

Xu et al CMJ 2015

Méta-analyse 1996 à 2014

- ***Bronchiectasies non mucoviscidose (bnm)***
- n = 3073 patients
- cultures positives = 65% (2358)

Hétérogénéité

- Conditions prélèvements
- Antibiothérapies…

- H. Influenzae : 29 à 37 %
- P. Aeruginosa : 08 à 28 %
- S. pneumoniae: 11 à 14 %
- S. Aureus : 05 à 12 %
- M. Catarrhalis : 08 à 10 %

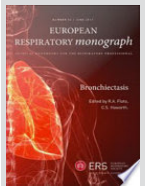
Pas de données virales ou fongiques

Pas de données sur Co-isolement

Impact de la microbiologie sur les phénotypes ?

Microbiology of non-CF bronchiectasis

Country	Subjects n	Sample	Age yrs	Stable or at exacerbation	*Haemophilus influenzae*	*Pseudomonas aeruginosa*	*Streptococcus pneumoniae*	*Moraxella catarrhalis*	*Staphylococcus aureus*
Ireland	92	Sputum	<18	ND	50 (46)	8 (9)	34 (37)	9 (10)	14 (15)
Thailand	50	Sputum	58 (30–85)	ND	7 (14)	10 (20)	3 (6)	2 (4)	
Spain	75	PSB	58 (16–76)	Stable	24 (32)	12 (16)	6 (8)	3 (4)	2 (3)
USA	123	Sputum	57.2 ± 16.7	ND	37 (30)	38 (31)	13 (11)	3 (2)	9 (7)
Australia	89	Sputum	57 ± 14	Stable	42 (47)	11 (12)	6 (7)	7 (8)	3 (4)
UK	150	Sputum		ND	52 (35)	46 (31)	20 (13)	30 (20)	21 (14)
UK	143	Sputum	60.6 (16–90)	ND	75 (52)	62 (43)	42 (30)	39 (27)	39 (27)
				Colonised subgroup¶	47 (33)	47 (33)	13 (9)	9 (6)	15 (10)

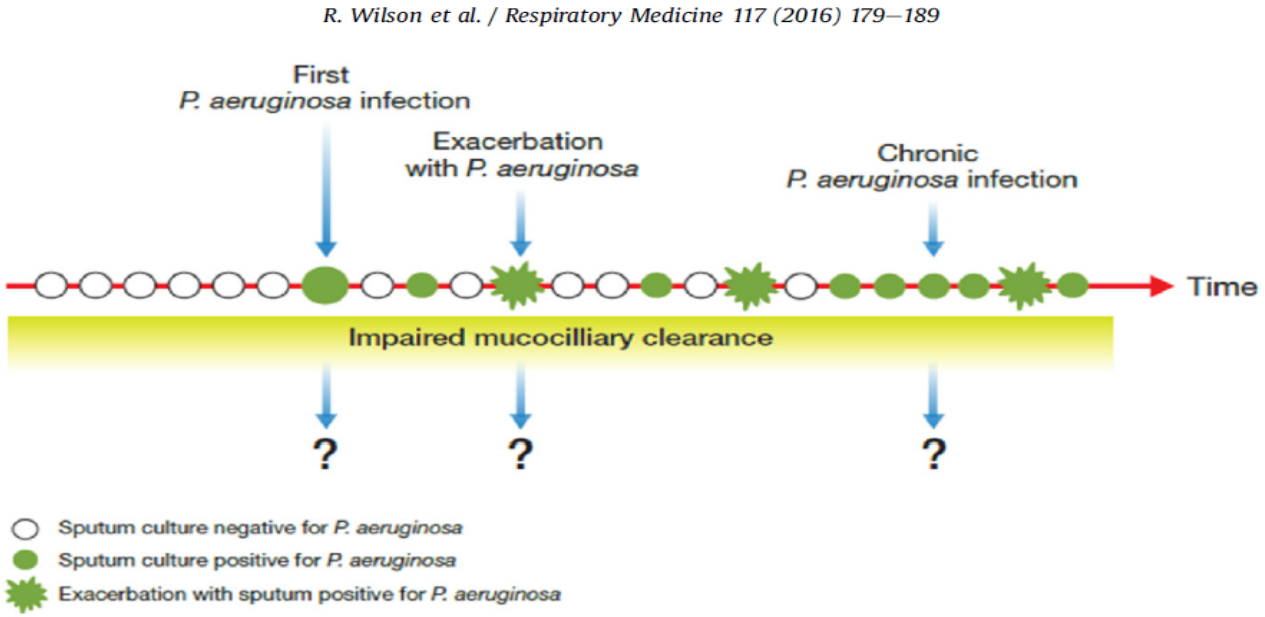


Bronchiectasis: European Respiratory Monograph - R.A. Floto & C.S. Haworth

Foweraker and Wat, ER Monograph 2011

Impact de la microbiologie sur les phénotypes ?

- Microbiologie = élement majeur pour phénotyper les patients
- La presence/absence de bactérie, le type de bactérie influence la symptomatologie des patients, les exacerbations et constitue un facteur indépendant associé à la mortalité
- Impact de la coloniasation à Pseudomonas Aeruginosa et effet sur la mortalité

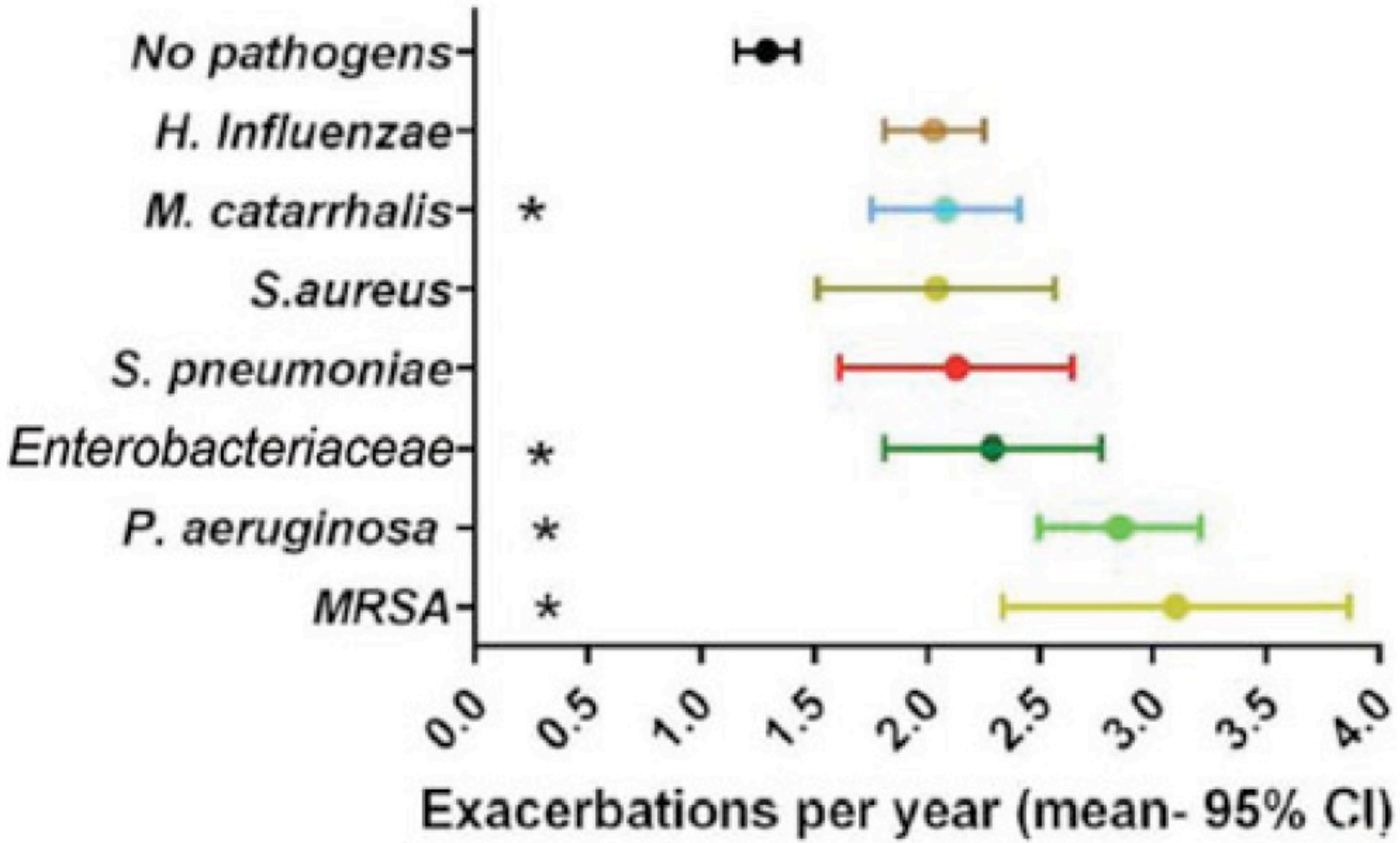


Intervention points in managing P. aeruginosa respiratory infection in patients with non-cystic fibrosis bronchiectasis

Finch et al. comprehensive analysis of the impact of pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc 2015

Wilson et al. Respiratory Medicine (2016). Adapted with permission from figure by Dr. Patrick Flume

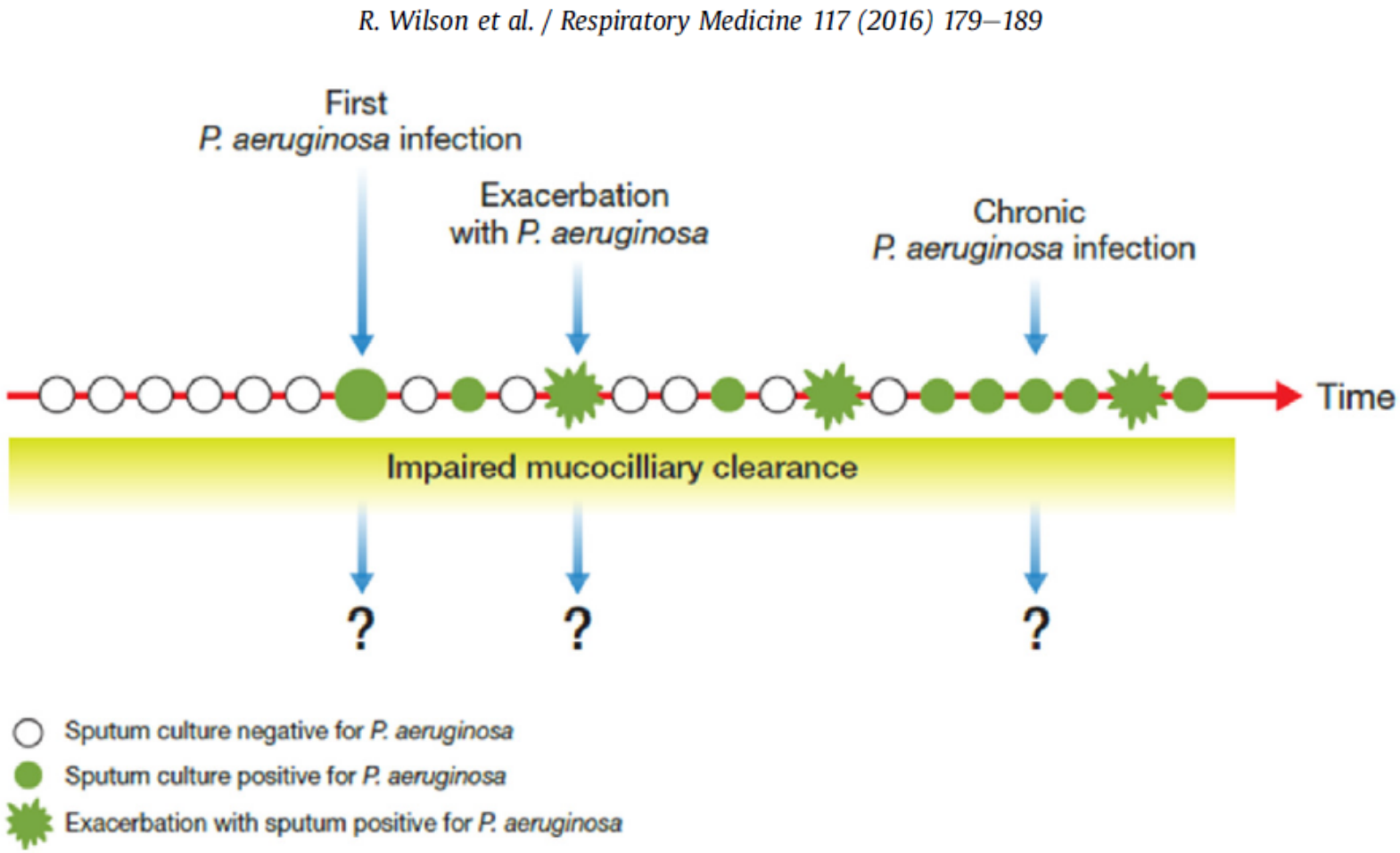
Impact de la microbiologie sur les phénotypes ?



Impact of microbiology on annual exacerbation frequency in bronchiectasis

Chalmers et al. Am J Respir Crit Care Med 2014

Impact de la microbiologie sur les phénotypes ?



Intervention points in managing P. aeruginosa respiratory infection in patients with non-cystic fibrosis bronchiectasis

Wilson et al. Respiratory Medicine (2016). Adapted with permission from figure by Dr. Patrick Flume

ORIGINAL RESEARCH

A Comprehensive Analysis of the Impact of *Pseudomonas aeruginosa* Colonization on Prognosis in Adult Bronchiectasis

Simon Finch[1], Melissa J. McDonnell[2], Hani Abo-Leyah[1], Stefano Aliberti[3], and James D. Chalmers[1]

[1]Tayside Respiratory Research Group, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom; [2]Department of Respiratory Medicine, Galway University Hospitals, Galway, Ireland; and [3]Department of Health Science, University of Milan-Bicocca, Pneumology Clinic, San Gerardo Hospital, Monza, Italy

Abstract

Rationale: Eradication and suppression of *Pseudomonas aeruginosa* is a key priority in national guidelines for bronchiectasis and is a major focus of drug development and clinical trials. An accurate estimation of the clinical impact of *P. aeruginosa* in bronchiectasis is therefore essential.

Methods: Data derived from 21 observational cohort studies comparing patients with *P. aeruginosa* colonization with those without it were pooled by random effects meta-analysis. Data were collected for key longitudinal clinical outcomes of mortality, hospital admissions, exacerbations, and lung function decline, along with cross-sectional outcomes such as quality of life.

Measurements and Main Results: In the aggregate, the included studies comprised 3,683 patients. *P. aeruginosa* was associated with a highly significant and consistent increase in all markers of disease severity, including mortality (odds ratio [OR], 2.95; 95% confidence interval [CI], 1.98–4.40; $P < 0.0001$), hospital admissions (OR, 6.57; 95% CI, 3.19–13.51; $P < 0.0001$), and exacerbations (mean difference, 0.97/yr; 95% CI, 0.64–1.30; $P < 0.0001$). The patients with *P. aeruginosa* also had worse quality of life on the basis of their St. George's Respiratory Questionnaire results (mean difference, 18.2 points; 95% CI, 14.7–21.8; $P < 0.0001$). Large differences in lung function and radiological severity were also observed. The definitions of colonization were inconsistent among the studies, but the findings were robust regardless of the definition used.

Conclusion: *P. aeruginosa* is associated with an approximately threefold increased risk of death and an increase in hospital admissions and exacerbations in adult bronchiectasis.

Keywords: bacteria; bronchiectasis; exacerbations; mortality; severity

Impact de la microbiologie sur les phénotypes ?

Table 1. Outcomes in bronchiectasis patients with versus without *Pseudomonas aeruginosa* colonisation: meta-analysis of 21 observational cohort studies comprising 3683 patients.

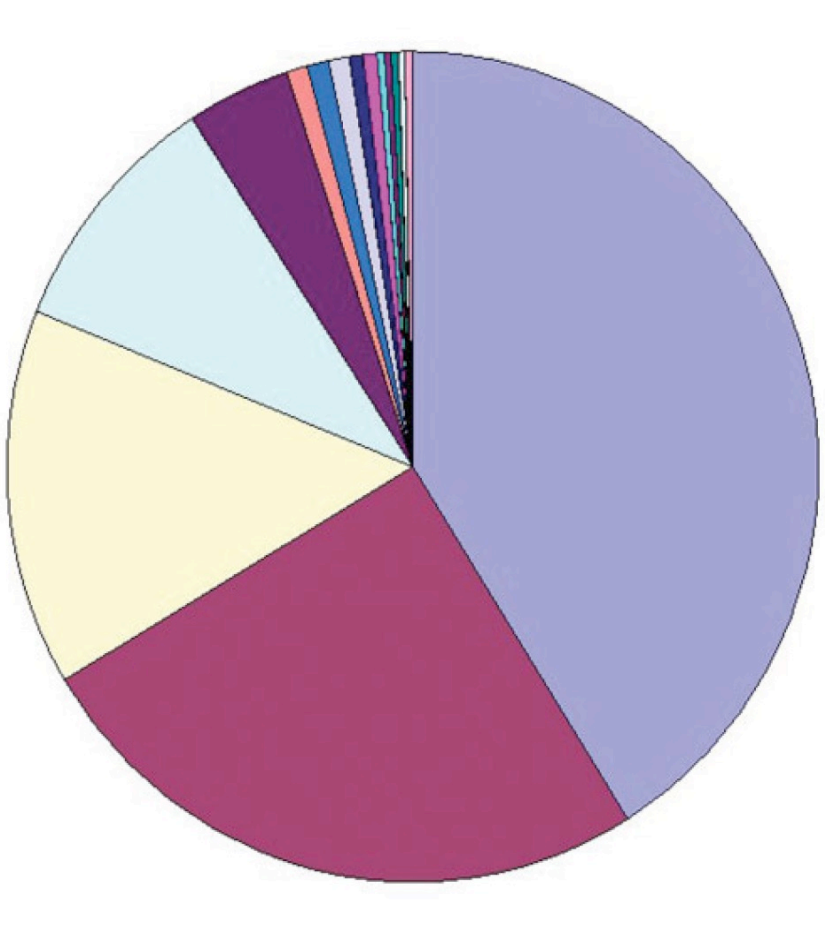
Outcome	Odds ratio	95% CI	*p*-value
Mortality	2.95	1.98—4.40	$p < 0.0001$
Hospital admissions	6.57	3.19—13.51	$p < 0.0001$
Outcome	Mean difference	95% CI	*p*-value
Exacerbations	0.97/year	0.64—1.30	$p < 0.0001$
Quality of life†	18.2 points	14.7—21.8	$p < 0.0001$

Constructed using data from (16).
†Assessed by the St George's Respiratory Questionnaire.

Finch et al. comprehensive analysis of the impact of pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc 2015
Chalmers. Journal of Chronic Obstructive Pulmonary Disease 2017

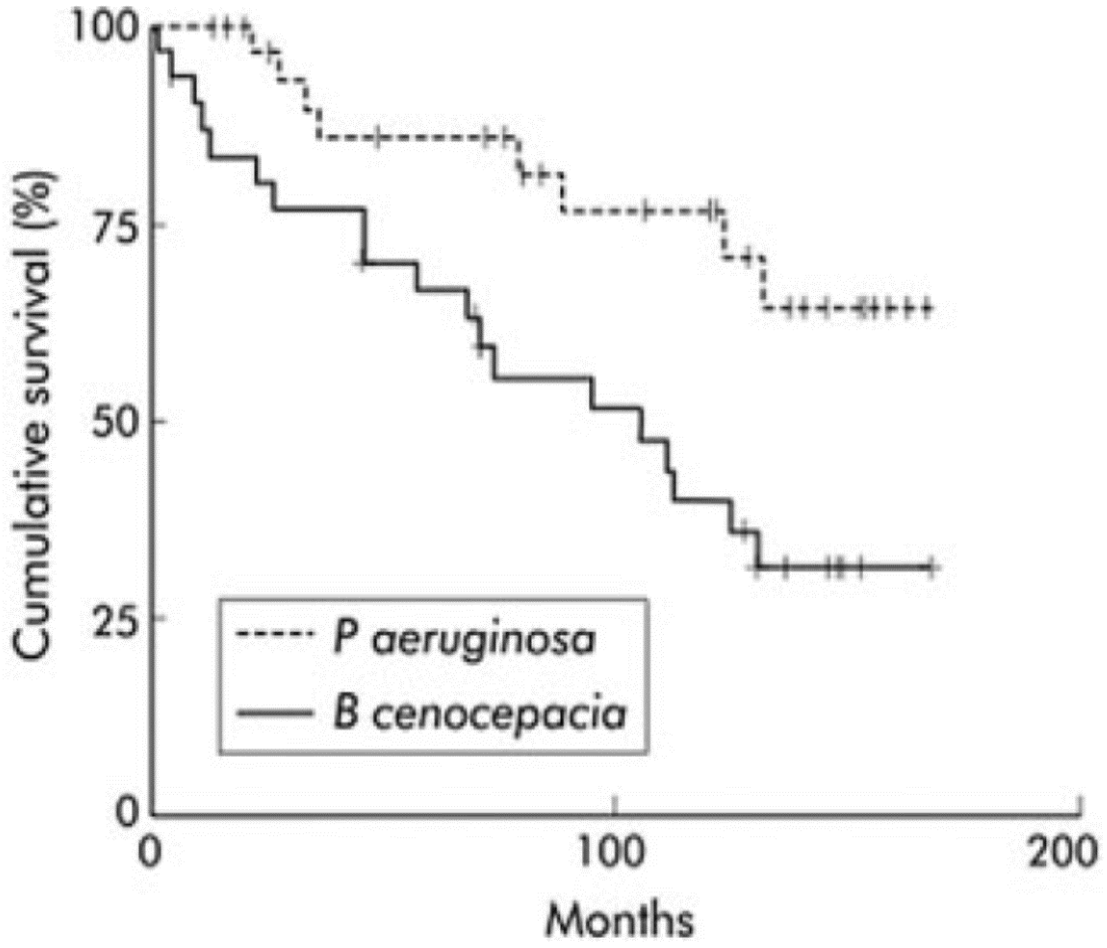
Impact de la microbiologie sur les phénotypes ?

The Microbiome and Emerging Pathogens in Cystic Fibrosis and Non–Cystic Fibrosis Bronchiectasis



Pie chart showing the microbial diversity in the sputum of an adult with cystic fibrosis.

Burkholderia, Stenotrophomonas, Achromobacter, Ralstonia
Pandoraea, Nontuberculousmycobacteria, Fungal species...



Green Semin Respir Crit Care Med 2015

Microbiome

Impact de la microbiologie sur les phénotypes ?

Risk factors for multidrug-resistant pathogens in bronchiectasis exacerbations

- Etude observationelle prospective
- Patients en premières exacerbation
- Recherche de BMR

- Objectif : facteurs des risques associés aux excacerbation et BMR

- 233 exacerbations, microorganismes pour 159 episodes.

- MBR 20.1% épisodes:
  - P aeruginosa (48.5%)
  - SAMR (18.2%)
  - BLSE (6.1%)

Menéndez et al. BMC Infectious Diseases 2017

Table 2 Microorganisms isolated in exacerbations

Microorganism Isolated	Total No. 241 (100)
Pseudomonas aeruginosa	51 (21.16)
[a]MDR *Pseudomonas aeruginosa*	16 (6.64)
Methicillin susceptible *Staphylococcus aureus*	11 (4.56)
Methicillin resistant *Staphylococcus aureus*	6 (2.49)
Acinetobacter sp	3 (1.24)
Moraxella catarrhalis	7 (2.9)
Stenotrophomonas maltophilia	4 (1.66)
Enterobacteriaceae	12 (4.98)
Escherichia coli	5 (2.07)
Proteus spp	3 (1.24)
Klebsiella pneumonia	3 (1.24)
Serratia spp	1 (0.41)
Haemophilus influenzae	27 (11.2)
Streptococcus pneumoniae	25 (10.37)
Achromobacter xylosoxidans	5 (2.07)
Mycoplasma pneumoniae	6 (2.49)
Chlamydia pneumoniae	1 (0.41)
Atypical mycobacteria	4 (1.66)
Aspergillus spp	12 (4.98)
Candida spp	15 (6.22)
Virus	25 (10.37)
Coronavirus	1 (0.41)
Metapneumovirus	4 (1.65)
Rhinovirus	10 (4.14)
Influenza A	3 (1.24)
Influenza B	2 (0.82)
Parainfluenza 3	2 (0.82)
Respiratory Syncytial virus	3 (1.24)
Others	11 (4.56)

Impact de la microbiologie sur les phénotypes ?

Risk factors for multidrug-resistant pathogens in bronchiectasis exacerbations

Table 4 Multivariate analysis to predict Multidrug-resistant pathogens

	Multidrug-Resistant Microorganisms		
	OR[a]	95% CI[b]	*p*
Age	1.03	0.97-1.09	0.393
Male	0.77	0.25–2.41	0.656
Arterial hypertension	0.83	0.27–2.62	0.756
Congestive heart failure	1.60	0.40–6.45	0.511
COPD	1.51	0.45–5.03	0.500
Renal disease	7.60	1.92–30.09	0.004
Age-adjusted Charlson >5	0.64	0.19–2.16	0.469
Chronic *Pseudomonas aeruginosa* infection	0.41	0.11–1.55	0.189
Prior multidrug-resistant microorganism isolation	5.58	2.02–15.46	0.001
Inhaled/Nebulized antibiotic	1.93	0.57–6.47	0.288
Chronic oxygen therapy	1.90	0.57–6.32	0.297
Hospitalization last year	3.88	1.37–11.02	0.011
Severe FACED	0.72	0.22–2.29	0.573
Severe BSI	1.58	0.42–5.95	0.501

[a]OR: Odds ratio
[b]CI: Confidence interval

Menéndez et al. BMC Infectious Diseases 2017

Etiologie des dilatations des bronches – Registre EMBARC

- **EMBARC : European Multicentre Bronchectasis Audit and Research Collaboration**
- Un registre européen soutenu par l'ERS, initié en 2015
- Constitué de registres nationaux autonomes
- Concernant les bronchectasies ***HORS mucoviscidose***
- Alimenté par de nombreux cliniciens provenant de différents horizons
- Financement industriel
- Promoteur: Université de Dundee;
- Investigateur coordonnateur: Dr James Chalmers
- **Le rationnel : t**rès peu de données sur bronchectasies non muco en termes d'épidémiologie, diagnostic et prise en charge
- **Objectifs : m**ieux comprendre et prendre en charge les DDB non mucoviscidose

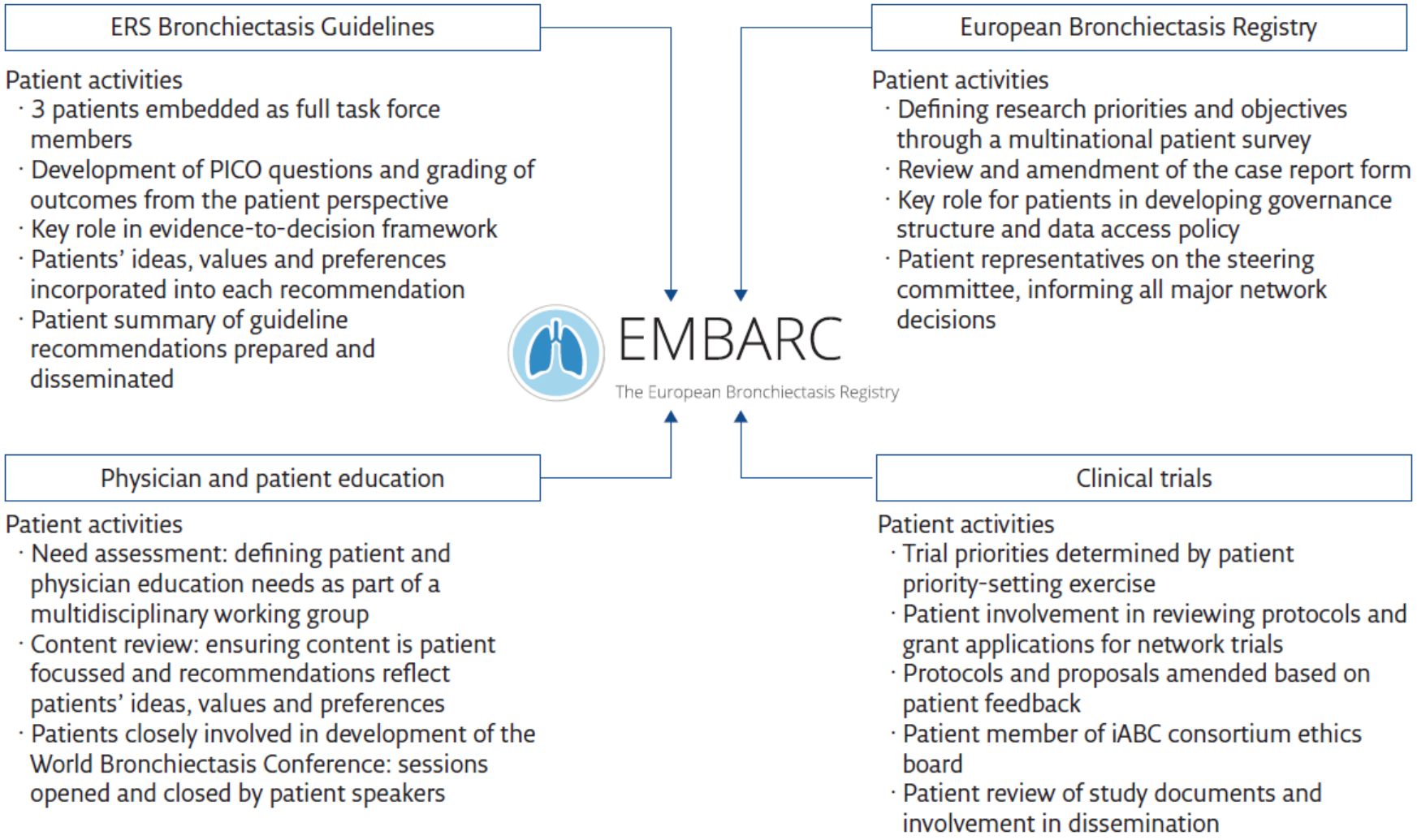
ERS EUROPEAN RESPIRATORY SOCIETY every breath counts

The EMBARC European Bronchiectasis Registry: protocol for an international observational study. ERJ 2016

GREPI Groupe pour la Recherche et l'Enseignement en Pneumo-Infectiologie

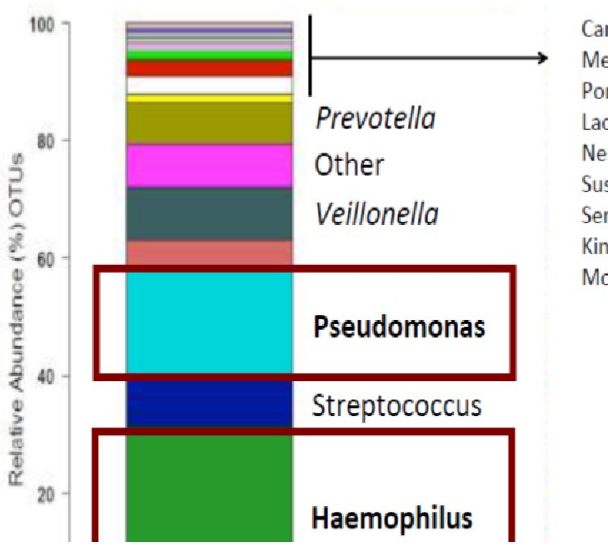
Etiologie des dilatations des bronches – Registre EMBARC

Patient involvement in the EMBARC project



Patient participation in ERS guidelines and research projects: the EMBARC experience. al Breathe 2017

Etiologie des dilatations des bronches – Registre EMBARC



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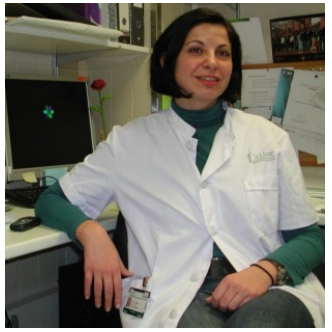

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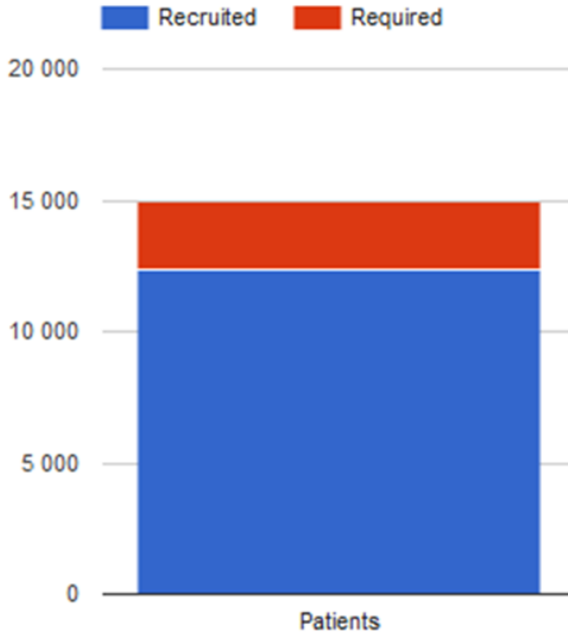


Nombre total de patients restant à inclure dans EMBARC au 26-10-2018

Nombre total de patients inclus dans EMBARC au 26-10-2018 12376

Etiologie des dilatations des bronches – Registre EMBARC

EMBARC France

- **Registre autonome**
  - Basé sur un CRF commun
  - soutenu SPLF-GREPI
  - Validation CCTIRS-CNIL
  - Un conseil scientifique
- **Objectifs** :
  - Registre représentatif de l'ensemble des bronchectasies diagnostiquées en France
  - Contribuer à la recherche clinique dans ce domaine
  - De favoriser les liens et les travaux académiques avec les autres groupes de travail du GREPI et de la SPLF d'autres société savantes
  - De mettre en place une bio-banque permettant de projeter des études phénotypiques et immunologiques ultérieures ?

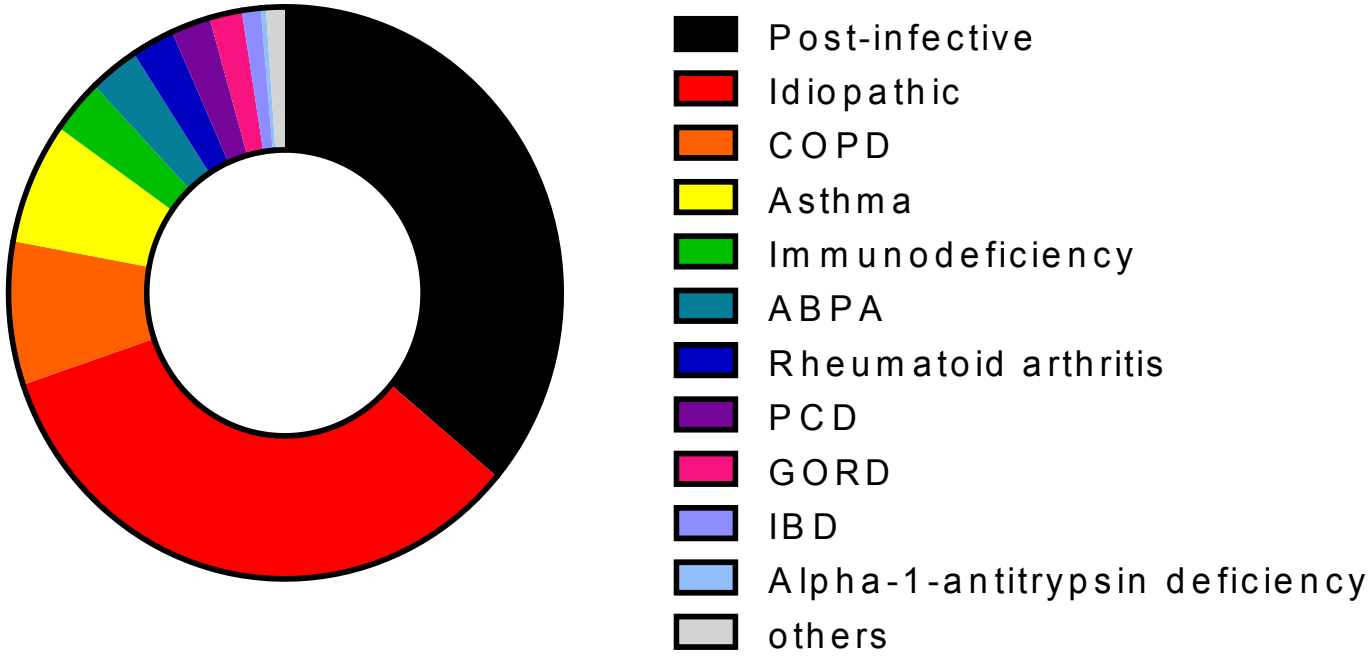
EMBARC France
Dr Marlène Murris-Espin
Service de Pneumologie
CRCM adulte
HU de Toulouse
24 chemin de Pouvourville
31059 Toulouse Cédex 09

Au 26 octobre 2018 : 428 patients inclus en France/ > 12.000 patients !!!

Etiologies et conditions pathologiques associées aux DDB

Table 1. Possible causes and associated comorbid conditions of non-cystic fibrosis bronchiectasis

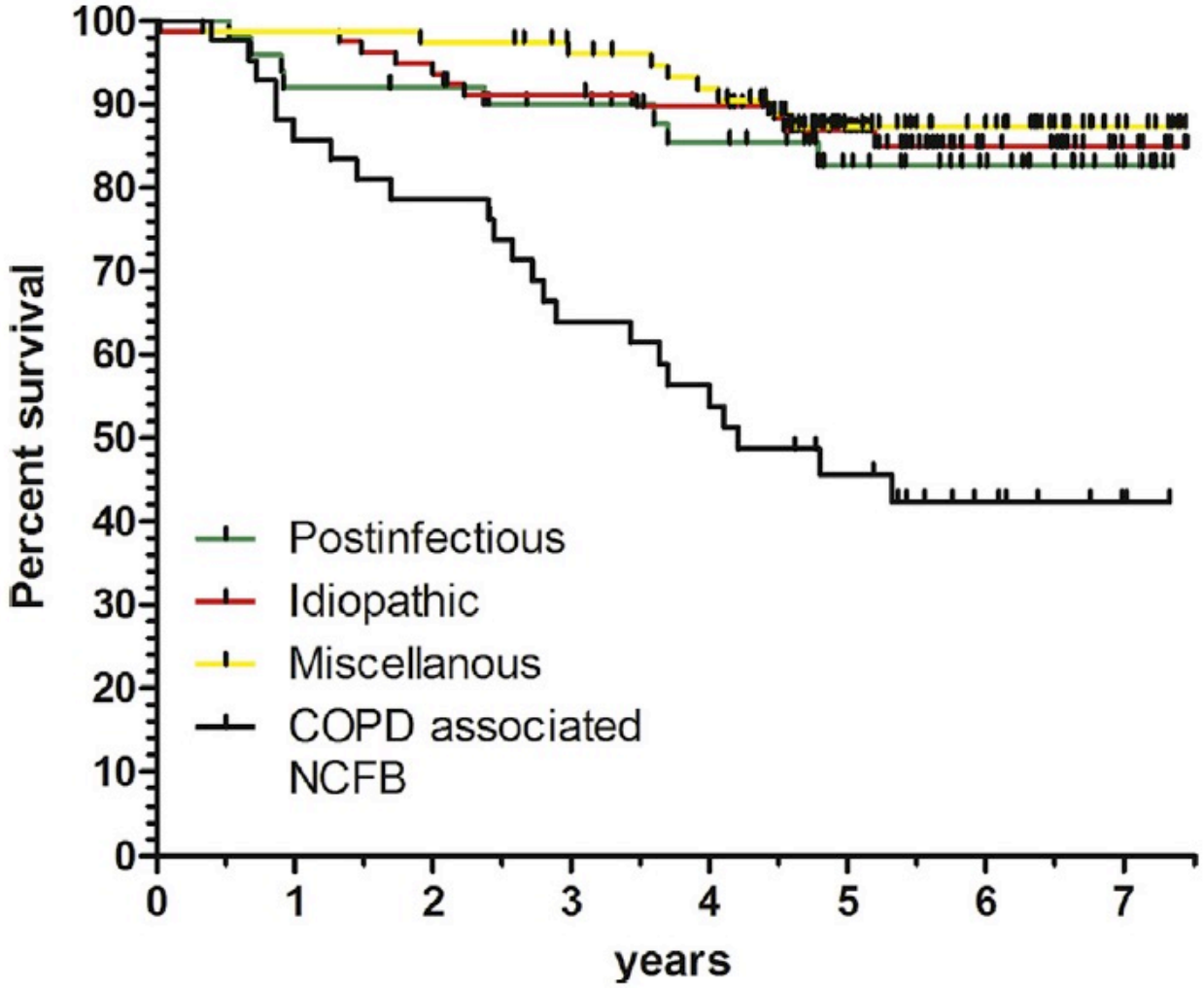
Causes	Frequency (%)
Primary cause	
Undetermined (idiopathic bronchiectasis)	30–53
Previous infection–bacterial or viral	33–42
Aspiration/inhalation injury	2–4
Congenital defect of large airway (e.g., Mounier-Kuhn syndrome)	<1
Immune deficiency (hypogammaglobulinaemia)	1–8
Primary ciliary dyskinesia	1–17
Connective tissue disease/rheumatoid arthritis/ Sjögren's syndrome/systemic sclerosis	3–6
Cause or comorbid condition	
COPD[a]	4–69
Asthma[a]	17.5–43.0
Allergic bronchopulmonary aspergillosis (associated with asthma)	1–7
Inflammatory bowel disease	1–2
Non-tuberculosis mycobacterial infection	0.7–34.0



Raising awareness of bronchiectasis in primary care. Primary Care Respiratory Medicine 2017

Etiologies et conditions pathologiques associées aux DDB

Mortality in non-cystic fibrosis bronchiectasis: A prospective cohort analysis



Goeminne et al. Respiratory Medecine 2014

Des scores pronostiques pour phénotyper les patients?

- BPCO : score ayant contribué à la comprehension de l'hétérogénité de la maladie
  - L'index de BODE (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity)
  - Classification de GOLD (Global initiative for chronic Obstructive Lung Disease)
- Dilatations des bronches :
  - The Bronchiectasis Severity Index : sévérité de la maladie, facteurs independent de risque de mortalité, exercerbations, hospitalisations et qualité de vie
  - The FACED Score : système de scoring pour prédire la mortalité chez les patients suivis pour dilatations des bronches

Chalmers et al. The Bronchiectasis Severity Index. Am J Respir Crit Care Med 2014
Martínez-García et al. Multidimensional approach to noncystic fibrosis bronchiectasis: the FACED score. Eur Respir J 2014

The Bronchiectasis Severity Index score

Severity Marker	HR (95% CI) for Hospital Admissions during Follow-up	HR (95% CI) for Mortality	Score Points
Age, yr			
<50	1.0 (reference)	1.0 (reference)	0
50–69	1.38 (0.73–2.56)	2.21 (0.28–17.5)	2
70–79	1.50 (0.79–2.82)	8.57 (1.15–63.63)	4
Colonization with other organisms			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.66 (1.12–2.44)	1.10 (0.54–2.24)	1
Radiological severity: ⩾3 lobes involved or cystic bronchiectasis			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.48 (1.02–2.15)	1.05 (0.57–1.94)	1

0- 4 Mild Bronchiectasis

1 year outcomes: 0 – 2.8 % mortality rate, 0 – 3.4 % hospitalisation rate

4 year outcomes: 0 – 5.3 % mortality rate, 0 – 9.2 % hospitalisation rate

5 – 8 Moderate Bronchiectasis

1 year outcomes: 0.8 – 4.8 % mortality rate, 1.0 – 7.2 % hospitalisation rate

4 year outcomes: 4 % – 11.3 % mortality rate, 9.9 – 19.4 % hospitalisation rate

9 + Severe Bronchiectasis

1 year outcomes: 7.6 % – 10.5 % mortality rate, 16.7 – 52.6 % hospitalisation rate

4 year outcomes: 9.9 – 29.2 % mortality, 41.2 – 80.4 % hospitalisation rate

The FACED Score

F – FEV1 (> 50% = 0 points, ≤ 50% = 2 points)

A – Age (≤ 70 years = 0 points, > 70 years = 2 points)

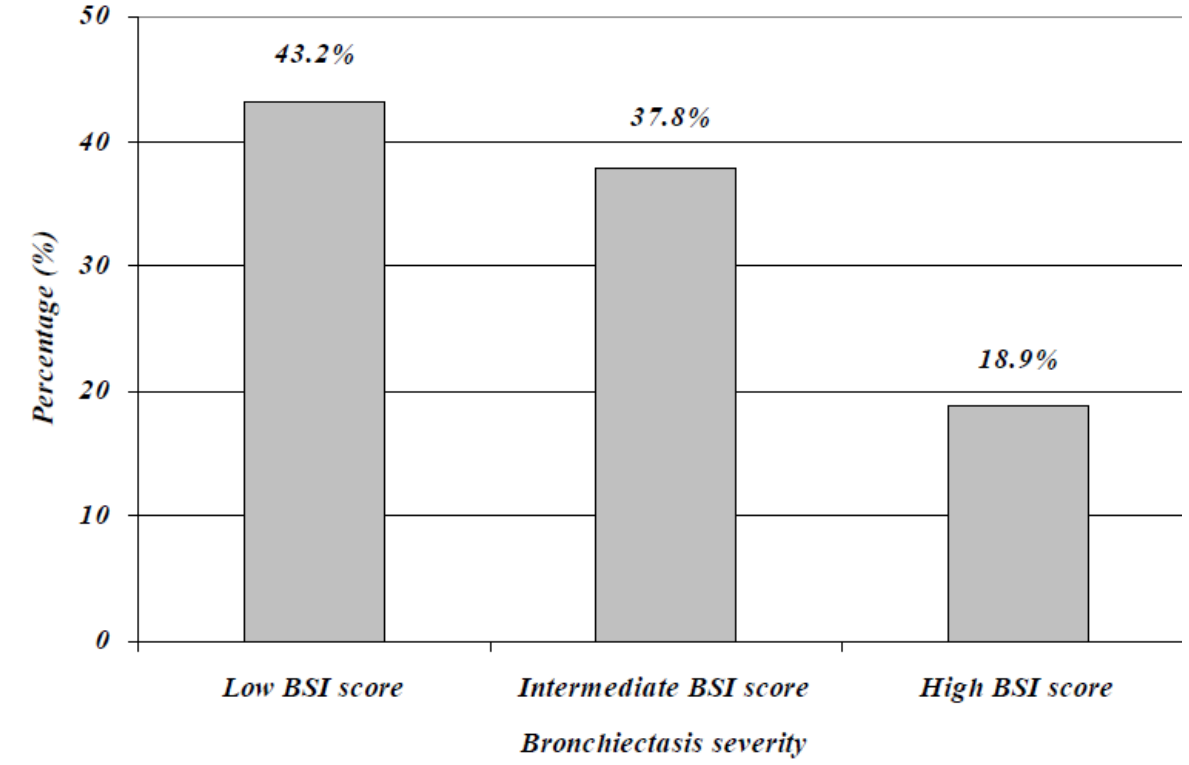
C – Chronic colonisation (no Pseudomonas = 0 points, presence of Pseudomonas = 1 point)

E – Extension (< 2 lobes affected = 0 points, ≥ 2 lobes affected= 1 point)

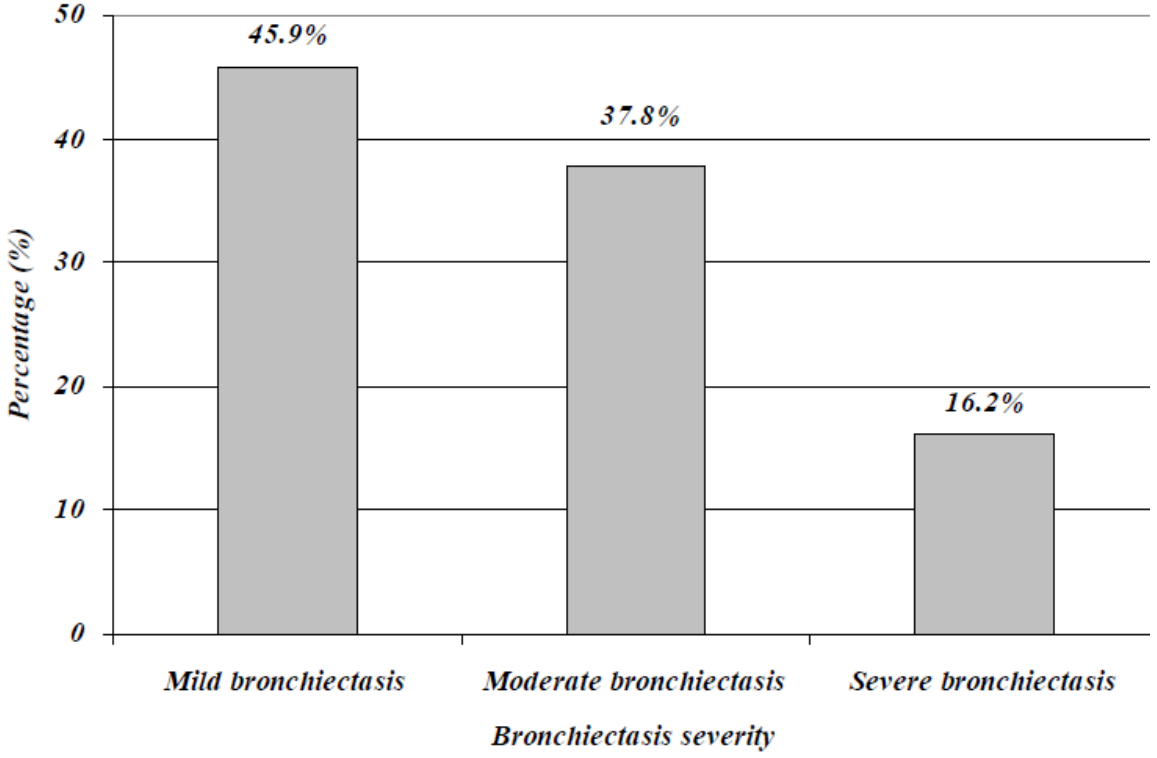
D – Dyspnoea (no dyspnoea = 0 points, ≥ 2 on Medical Research Council scale = 1 point)

0-2 points	Mild bronchiectasis
3-4 points	Moderate bronchiectasis
5-7 points	Severe bronchiectasis

Assessment of the Non-Cystic Fibrosis Bronchiectasis Severity: The FACED Score vs the Bronchiectasis Severity Index



Bronchiectasis Severity



FACED Score

Clinical phenotypes in adult patients with bronchiectasis

ORIGINAL ARTICLE
BRONCHIECTASIS

Clinical phenotypes in adult patients with bronchiectasis

Stefano Aliberti[1], Sara Lonni[1], Simone Dore[2], Melissa J. McDonnell[3], Pieter C. Goeminne[4,5], Katerina Dimakou[6], Thomas C. Fardon[7], Robert Rutherford[3], Alberto Pesci[1], Marcos I. Restrepo[8], Giovanni Sotgiu[2] and James D. Chalmers[7]

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Severe Pseudomonas infection (16%)
Other chronic infections (Haemophilus) (24%)
Daily sputum production without colonisation (33%)
Dry bronchiectasis (27%)

Phynotypes

Albertini et al. ERJ 2016

Clinical phenotypes in adult patients with bronchiectasis

TABLE 5 Patient characteristics and quality of life in the validation cohort according to the four clusters

	Cluster 1: "*Pseudomonas*"	Cluster 2: "Other chronic infection"	Cluster 3: "Daily sputum"	Cluster 4: "Dry bronchiectasis"	Overall p-value
Demographics and comorbidities					
Age years	70 (62–72)	66 (57–74)	65 (55–72)	63 (55–75)	0.7
Male	14 (46.6)	10 (33.3)	13 (43.3)	11 (36.7)	0.7
BMI $kg \cdot m^{-2}$	24 (21–26)	26 (22–30)	25 (24–30)	26 (22–30)	0.8
Smoker/ex-smoker	9 (30)	8 (27)	9 (30)	4 (13.3)	0.4
CCI >1	11 (37)	10 (33)	8 (27)	12 (40)	0.7
Disease severity					
BSI score	12 (9–15)	8 (5–11)	6 (3–9)	6 (4–8)	0.0001
Radiological status					
Reiff score	6 (3–10)	3 (2–6)	2 (2–5)	3 (2–4)	<0.0001
Clinical status					
Daily cough	30 (100)	28 (93)	30 (100)	19 (64)	<0.0001
Daily sputum	29 (97)	27 (90)	30 (100)	0 (0)	<0.0001
Prior history of haemoptysis	8 (27)	4 (13)	3 (10)	0 (0)	0.02
MRC breathlessness scale	3 (2–5)	3 (2–4)	1 (1–2)	1 (1–2)	<0.0001
Exacerbations in the previous year	2 (1–5)	2 (0–2)	1 (0–1)	1 (0–2)	<0.0001
At least one hospitalisation in the previous year	20 (66.7)	15 (50)	5 (16.6)	3 (10.0)	<0.0001
Functional status					
FEV_1 % predicted	51 (35–76)	61 (49–81)	83 (65–97)	93 (59–99)	<0.0001
Microbiology					
Chronic infection with *Pseudomonas aeruginosa*	30 (100)	0	0	0	<0.0001
Chronic infection with other pathogens	0	30 (100)	0	0	<0.0001
Quality of life					
SGRQ	58.3 (38.6–70.3)	44.3 (31.8–51.9)	33.3 (25.6–37.1)	36.6 (20–49.0)	<0.0001
Leicester Cough Questionnaire	10 (9–16)	13 (10–17)	16 (14–19)	13.2 (11.0–19.0)	0.004

Data are presented as median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; CCI: Charlson Comorbidity Index; BSI: Bronchiectasis Severity Index; MRC: Medical Research Council; FEV_1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire.

Albertini et al. ERJ 2016

Clinical phenotypes in adult patients with bronchiectasis

TABLE 4 Quality of life and longitudinal outcomes in the four clusters

	Cluster 1: "*Pseudomonas*"	Cluster 2: "Other chronic infection"	Cluster 3: "Daily sputum"	Cluster 4: "Dry bronchiectasis"	Overall p-value
Patients	179 (100)	273 (100)	373 (100)	307 (100)	
Quality of life					
SGRQ	58 (34–72)	43 (27–61)	39 (27–55)	29 (12–40)	<0.001
Outcomes					
Exacerbations during 1-year follow-up	2 (1–3)	2 (1–2)	1 (0–2)	1 (0–2)	0.0001
At least one hospitalisation during 1-year follow-up	67 (42)	41 (16)	56 (16)	42 (14)	<0.0001
Mortality during 1-year follow-up	9 (5.1)	4 (1.5)	13 (3.6)	14 (4.9)	0.12
Mortality during 3-year follow-up	26 (17)	19 (7.6)	24 (8.2)	23 (11)	0.02

Data are presented as n (%) or median (interquartile range), unless otherwise stated. SGRQ: St George's Respiratory Questionnaire.

Albertini et al. ERJ 2016

Cluster Analysis Approach in Bronchiectasis

ORIGINAL RESEARCH

The Multiple Faces of Non–Cystic Fibrosis Bronchiectasis

A Cluster Analysis Approach

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Phenotypes :

- *Young women with mild disease;*
- *Overweight elderly women with mild bronchiectasis;*
- *Elderly men, severe disease, chronic infection (P. aeruginosa), airflow obstruction and exacerbations*
- *Elderly patients with 'severe' disease but infrequent exacerbations.*

Cluster Analysis Approach in Bronchiectasis

Table 3. Characteristics of the four clinical phenotypes

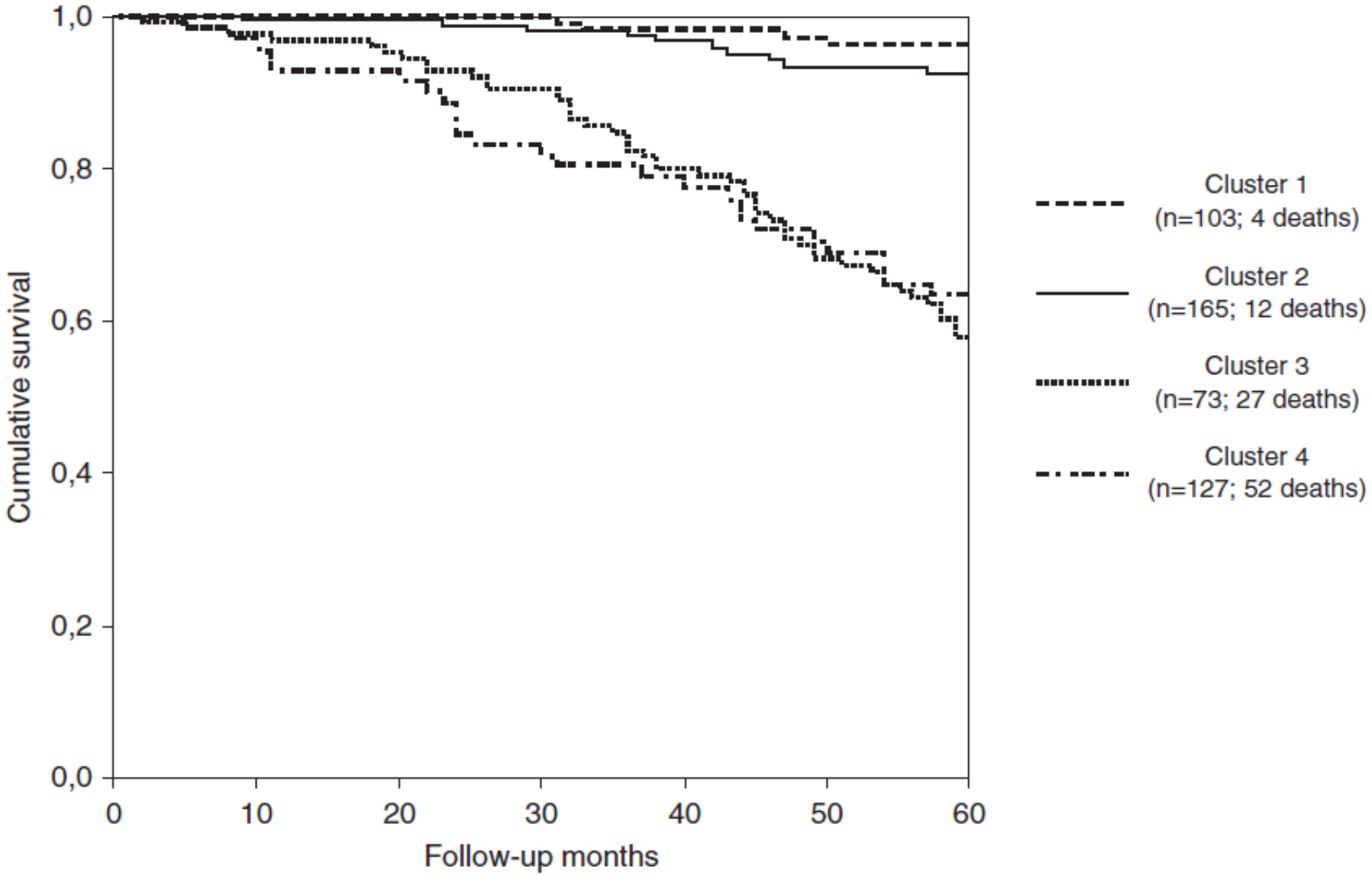
	Phenotype 1 (*n* = *103* [22%])	Phenotype 2 (*n* = *165* [35.2%])	Phenotype 3 (*n* = *73* [15.6%])	Phenotype 4 (*n* = *127* [27.1%])
Age, yr	41.9 (15.3)	67.1 (10.1)	70.8 (9)	70.3 (9.6)
Sex, % males	21 (20.4%)	58 (35.2%)	60 (82.2%)	59 (46.5%)
Dyspnea based on mMRC scale	0.42 (0.67)	1.38 (0.9)	2.29 (1.1)	2.16 (1.1)
Body mass index, kg/m^2	21.8 (3.4)	28.7 (3.6)	24.4 (4.2)	26.5 (4.16)
FEV_1, % predicted	79 (21.6)	71.6 (20.4)	51.1 (19.8)	46.8 (18.4)
FVC, % predicted	83.3 (18.8)	82.8 (18.5)	64.9 (16.8)	66.4 (20)
Number of exacerbations in previous yr	1.5 (1.6)	1.55 (1.5)	5.1 (2.67)	1.5 (1.4)

Table 4. Causes of death in the four clinical phenotypes found

	Phenotype 1: Young/Mild (*n* = *103*)	Phenotype 2: Elderly/Mild (*n* = *165*)	Phenotype 3: Elderly/ Severe/Exacerbator (*n* = *73*)	Phenotype 4: Elderly/ Severe/Nonexacerbator (*n* = *127*)
Death	4 (3.9%)	12 (7.6%)	27 (37%)	52 (40.4%)
Respiratory causes	2 (50%)	7 (58.3%)	21 (77.8%)	18 (34.5%)
Nonrespiratory causes	2 (50%)	5 (41.7%)	6 (22.2%)	34 (65.5%)
Cardiovascular death	0	2 (16.7%)	4 (14.8%)	15 (28.8%)
Neoplasm	1 (2%)	2 (16.7%)	2 (7.4%)	8 (15.4%)
Other	1 (2%)	1 (8.4%)	0	11 (21.1%)

The percentages refer to the total number of deaths.

Cluster Analysis Approach in Bronchiectasis



Bronchiectasis phenotypes with distinct clinical characteristics

INT J TUBERC LUNG DIS 20(3):402–410

http://dx.doi.org/10.5588/ijtld.15.0500

Unsupervised learning technique identifies bronchiectasis phenotypes with distinct clinical characteristics

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Phenotypes

Mild and idiopathic bronchiectasis in young patients

Severe patients with post-infective bronchiectasis and P. aeruginosa

Late onset severe idiopathic bronchiectasis

Elderly patients with moderate disease

Bronchiectasis phenotypes with distinct clinical characteristics

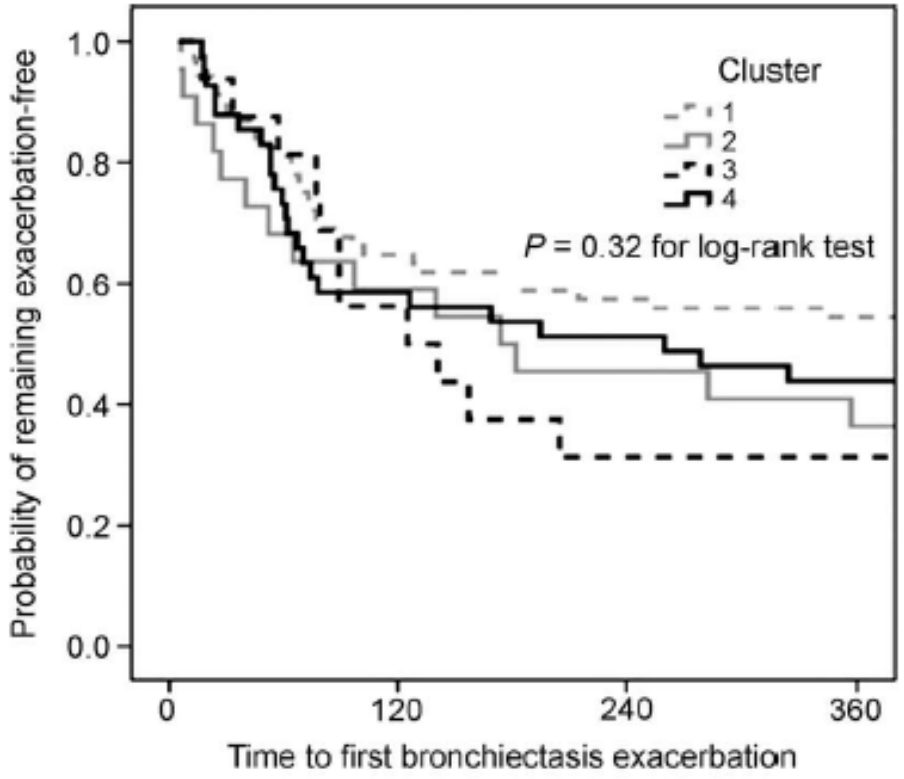
Table 1 Clinical characteristics of the different clusters

Parameters	All patients *n* (%)	Cluster 1 *n* (%)	Cluster 2 *n* (%)	Cluster 3 *n* (%)	Cluster 4 *n* (%)	*P* value*
Patients, *n*	148	69	22	16	41	—
Age, years, mean ± SD	44.5 ± 13.8	40.6 ± 13.0	41.1 ± 12.7	50.0 ± 16.4	50.9 ± 12.0	<0.01†
Females	92 (62.2)	41 (59.4)	16 (72.7)	9 (56.3)	26 (63.4)	0.68
Highest level of education						0.06
Primary school or lower	44 (29.7)	19 (27.5)	9 (40.9)	5 (32.1)	11 (26.8)	—
Junior and senior middle school	37 (25.0)	21 (30.4)	2 (9.1)	0	14 (34.2)	—
College or higher	67 (45.4)	29 (42.0)	11 (50.0)	11 (68.8)	16 (39.0)	—
BMI, kg/m^2, mean ± SD	20.4 ± 3.1	20.7 ± 3.0	19.8 ± 3.7	19.7 ± 2.4	20.7 ± 3.1	0.48
BMI <18.5 kg/m^2	36 (24.3)	21 (30.4)	5 (22.7)	4 (25.0)	6 (14.6)	0.07
Age at bronchiectasis onset, years	30.6 ± 16.7	32.2 ± 14.6	21.3 ± 14.8	31.3 ± 18.4	32.5 ± 19.1	0.04†
Symptom onset >10 years previously	21 (14.2)	3 (4.3)	9 (40.9)	2 (12.5)	7 (17.1)	<0.01†
Duration of bronchiectasis, years, median [IQR]	3.0 [9.0]	2.0 [6.0]	8.0 [13.0]	2.5[5.0]	4.0 [9.0]	<0.01†
Ever experienced haemoptysis	94 (63.5)	38 (55.1)	18 (81.8)	10 (62.5)	28 (68.3)	0.13
Bronchiectatic lobes, *n*, median [IQR]	4.0 [2.0]	3.0 [2.0]	5.0 [2.0]	6.0 [1.0]	4.0 [2.0]	<0.01†
HRCT total score, median [IQR]	7.0 [5.0]	5.0 [4.0]	10.5[6.0]	13.5[6.0]	7.0 [5.0]	<0.01†
BSI, median [IQR]	6.0 [7.0]	4.0 [5.0]	8.0 [5.0]	11.0 [5.0]	6.0 [5.0]	<0.01†
Patients with severe bronchiectasis‡	137 (92.6)	61 (88.4)	22 (100)	16 (100)	38 (92.7)	0.26
Never smokers	131 (88.5)	60 (87.0)	22 (100)	14 (87.5)	35 (85.4)	0.63
FVC% predicted, mean ± SD	78.5 ± 20.3	86.7 ± 13.9	62.0 ± 18.8	53.4 ± 14.4	83.5 ± 19.6	<0.01†
FEV_1% predicted, mean ± SD	70.3 ± 23.8	80.7 ± 16.4	49.2 ± 19.8	39.3 ± 12.1	76.2 ± 22.7	<0.01†
FEV_1/FVC%, mean ± SD	73.0 ± 12.9	77.4 ± 10.2	65.8 ± 16.0	61.2 ± 12.7	74.0 ± 11.3	<0.01†
D_LCO% predicted, mean ± SD	89.2 ± 17.4	94.5 ± 13.3	78.5 ± 19.0	74.6 ± 18.4	91.8 ± 17.0	<0.01†
Baseline sputum bacteriology						<0.01†
Pseudomonas aeruginosa	44 (29.7)	9 (13.0)	13 (59.1)	12 (75.0)	10 (24.4)	—
Other pathogenic organisms	43 (29.1)	21 (30.5)	6 (27.3)	3 (18.8)	13 (31.7)	—
Commensals	61 (41.2)	39 (56.5)	3 (13.6)	1 (6.2)	18 (43.9)	—
Sputum bacterial colonisation						<0.01†
Pseudomonas aeruginosa	39 (26.3)	9 (13.1)	13 (59.1)	10 (62.5)	7 (17.1)	—
Other pathogenic organisms	10 (6.8)	5 (7.2)	2 (9.1)	0 (0.0)	3 (7.3)	—
None	99 (66.9)	55 (79.7)	7 (31.8)	6 (37.5)	31 (75.6)	—

* Comparison of parameters among clusters 1–4.
† Statistically significant.
‡ BSI ⩾9.
SD = standard deviation; BMI = body mass index; IQR = interquartile range; HRCT = high-resolution computed tomography; BSI = Bronchiectasis Severity Index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; D_LCO = diffusing capacity or transfer factor of the lung for carbon monoxide.

Bronchiectasis phenotypes with distinct clinical characteristics

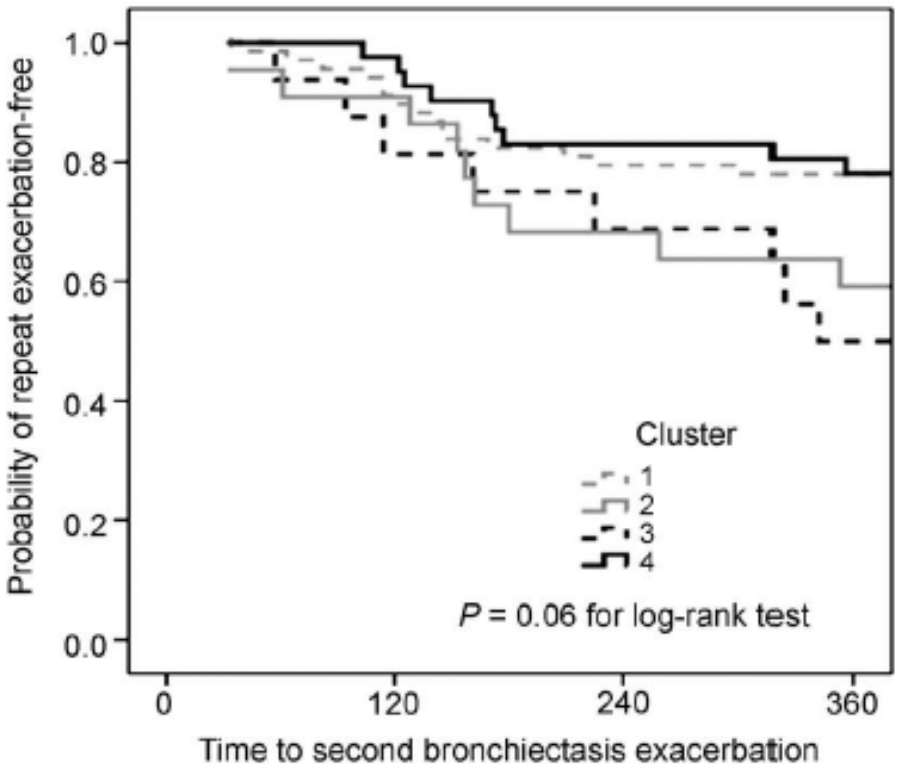
A



Number of patients at risk

Cluster 1	69	46	39	35
Cluster 2	22	13	10	8
Cluster 3	16	9	5	5
Cluster 4	41	24	21	18

B



Number of patients at risk

Cluster 1	69	61	54	53
Cluster 2	22	20	15	13
Cluster 3	16	13	11	8
Cluster 4	41	40	34	32

European Respiratory Society guidelines for the management of adult bronchiectasis

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 # strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances.

TABLE 1 Understanding the recommendations made in this document

Target group	Strong recommendations#	Conditional (weak) recommendations
Patients	All or almost all informed people would choose the recommended choice for or against an intervention.	Most informed people would choose the recommended course of action, but a substantial number would not.
Clinicians	Most patients should receive the recommended course of action.	Recognise that different choices will be appropriate for different patients. Clinicians and other healthcare providers need to devote more time to the process of shared decision making by which they ensure that the informed choice reflects individual values and preferences; decision aids and shared decision making are particularly useful.
Policy makers	The recommendation can be adopted as a policy in most situations.	Policy making will require substantial debate and involvement of many stakeholders.

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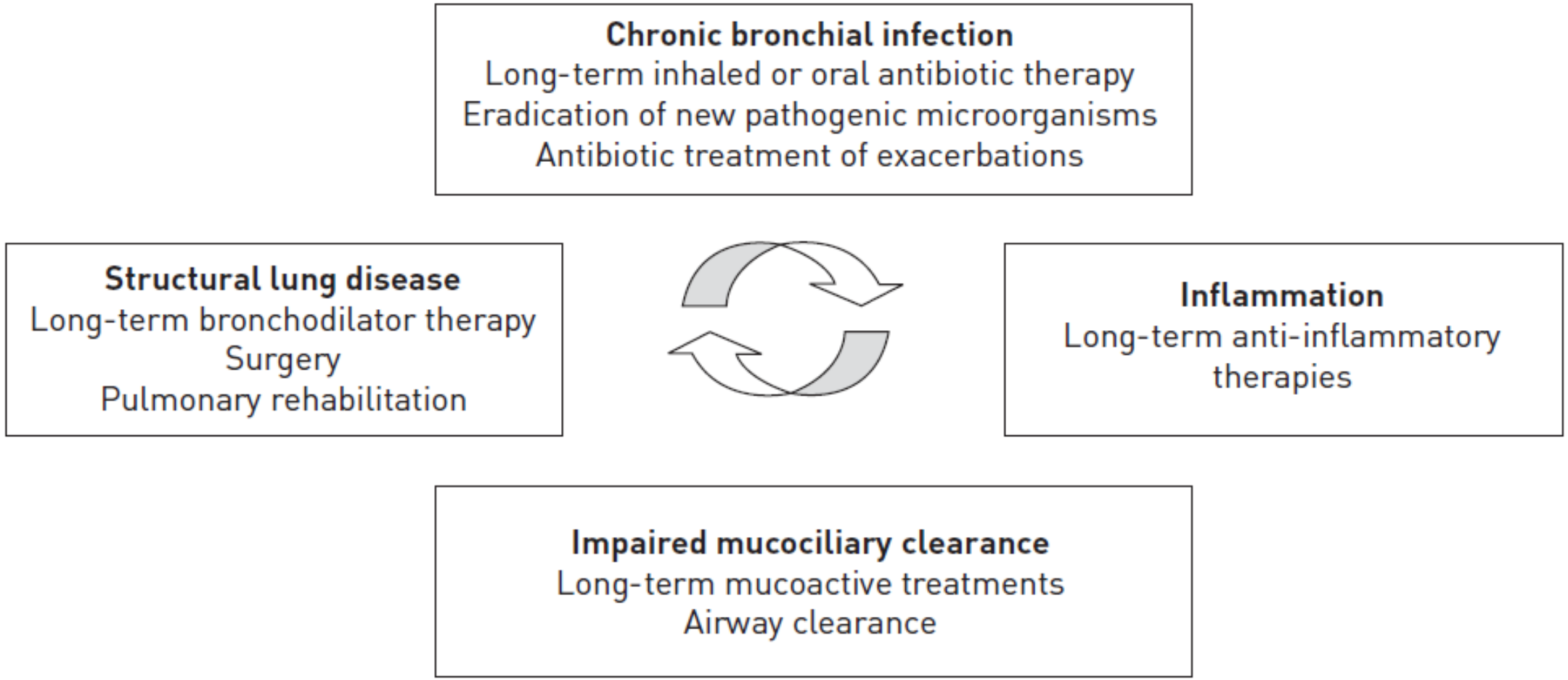
Treatments for bronchiectasis considered in this guideline according to the vicious cycle concept of bronchiectasis.



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Methods of guideline panel : ERS/EMBARC recommendations

- The guideline panel held four face-to-face meetings, beginning in 01-2015.
- The most relevant clinical questions on the management of bronchiectasis in adults (for both clinicians and patients) were debated.
- Nine clinical questions were formulated using the **PICO** format : **P**atients, **I**ntervention, **C**omparison, **O**utcomes
- Systematic reviews were conducted to answer these specific questions,
- 09-2016 : final guideline recommendations were discussed and agreed.
- Aims : reduce exacerbations, reduce symptoms, improve quality of life and reduce the risk of future complications such as lung function decline and severe exacerbations.

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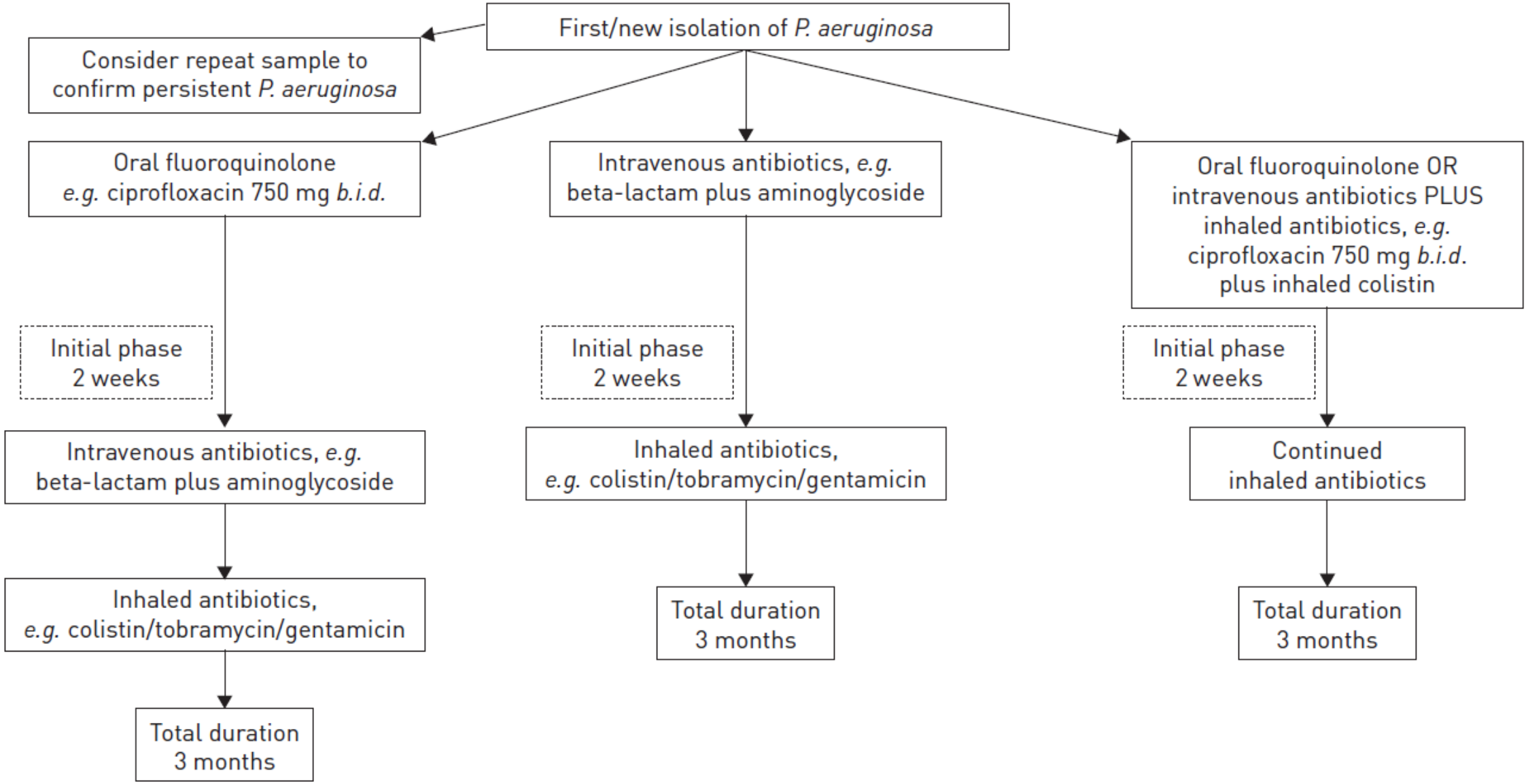
ERS/EMBARC recommendations

Bilan étiologique minimal	NFS, dosage Ig G, A et M, Recherche d'une ABPA ECBC à faire en routine systématiquement Présentation évocatrice ou une évolution rapide ou sévère rechercher: mycobactérie, mucoviscidose ou de dyskinésie ciliaire primitive, bilan immunologique complet, dosage de l'alpha-1-anti-trypsine.
Traitement des exacerbations	Antibiothérapie adaptée au tableau clinique et à la documentation microbiologique antérieure. Durée : 14 jours (absence de preuve ++)
Eradication / primo-colonisation	Seulement *P. aeruginosa* (niveau de preuve faible++)
Place des anti-inflammatoires	- Corticoïdes inhalés : N (sauf Asthme ou de BPCO si nécessaire) - Statines : NON
Place des bronchodilatateurs	- Dyspnée, (recommandation faible) - Avant les séances de kinésithérapie ou antibiotiques inhalés. - BPCO ou asthme associé

ERS/EMBARC recommendations

Place des antibiotiques au long cours	≥ 3 exacerbations année n-1 - Antibiotiques inhalés : infection par *P. aeruginosa*. - Macrolides : patients non infectés par *P. aeruginosa*, - Tétracyclines, amoxicilline : si macrolides contre-indiqués
Place des traitements muco-actifs	Dérivés de la cystéine, mannitol, serum salé iso- ou hypertonique : en cas de difficultés à expectorer et d'un faible niveau de qualité de vie. Pas d'indication pour les aerosols de DNase.
Place de la chirurgie thoracique	DDB localisée, ↗ exacerbations / traitement médical optimal Hémoptysie massive et/ou réfractaire ou inaccessible à l'artério-embolisation
Place de la kinésithérapie et de la réhabilitation respiratoire ?	- Kinésithérapie respiratoire : avec apprentissage de l'auto-drainage +++ - Réhabilitation respiratoire : forte recommandation et niveau de preuve

ERS/EMBARC recommendations



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ERS/EMBARC recommendations

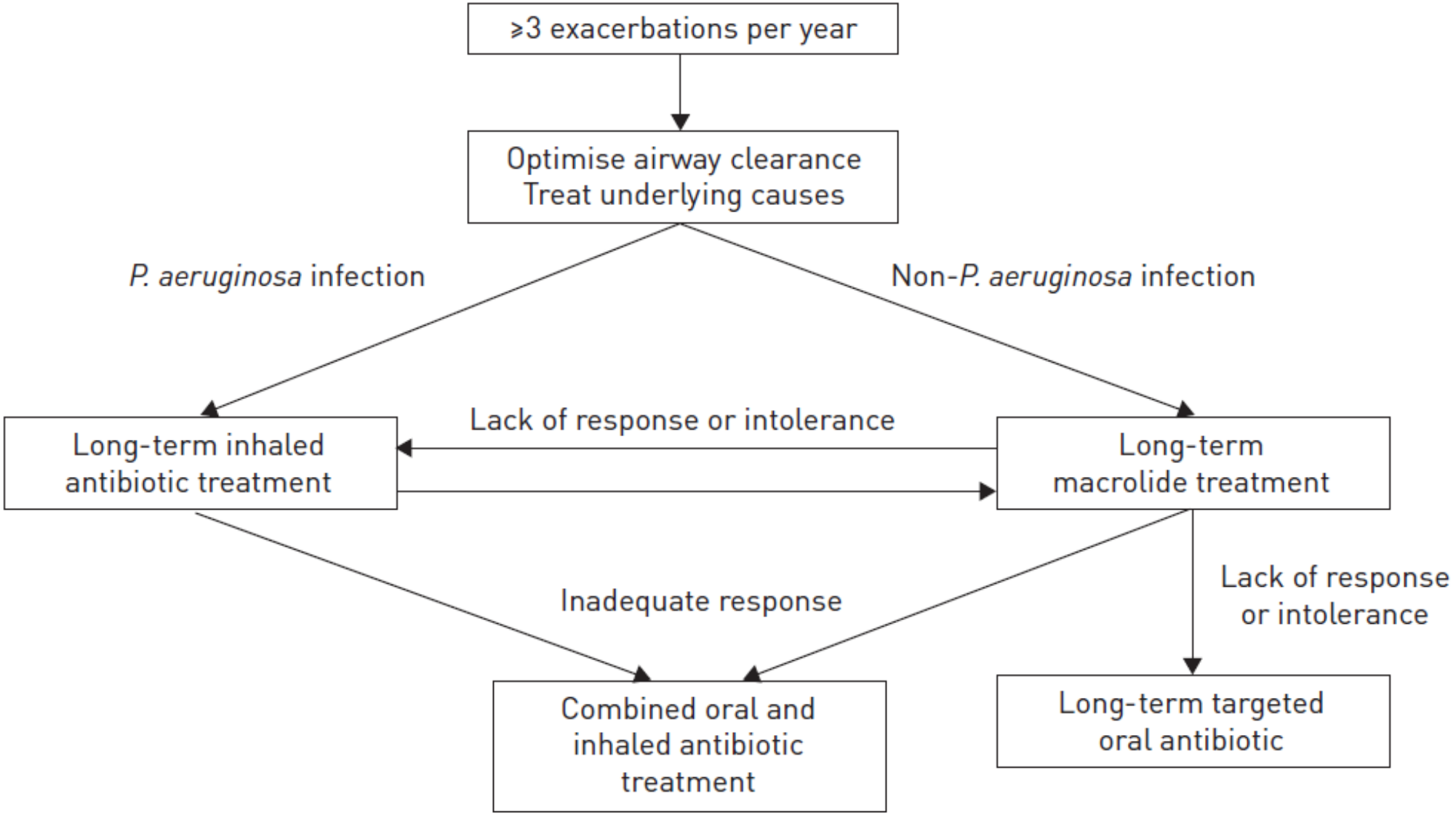

FIGURE 4 Summary of recommendations for long-term antibiotic treatment.

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Quand référer le patient à un centre tertiaire?

- Progression de la maladie vers une forme modérée à sévère
  - Symptômes
  - l'aggravation
  - scores pronostic comme BSI ou FACED
- Présence de Pseudomonas Aeruginosa ou mycobactérie atypique
- Dégradation de la fonction respiratoire
- Aspergillose bronchopulmonaire allergique
- Décision sur un traitement prophylactique

Raising awareness of bronchiectasis in primary care: overview of diagnosis and management strategies in adults. Primary Care Respiratory Medicine 2017

Conclusion

- Physiopathologie encore floue
- Recherche clinique / domaine en développement
- Phénotypes objectivant une grande hétérogénéité
  - gravité de la maladie / présentation
  - probabilité de réponse au traitement / pronostic
- Long délais diagnostique / sous-diagnostic fréquent
- Perspectives
  - Nouvelles thérapies et traitement personalisés
  - Attention à la résistance aux antibiotiques !
  - Registres, réseaux, collaboration, microbiome