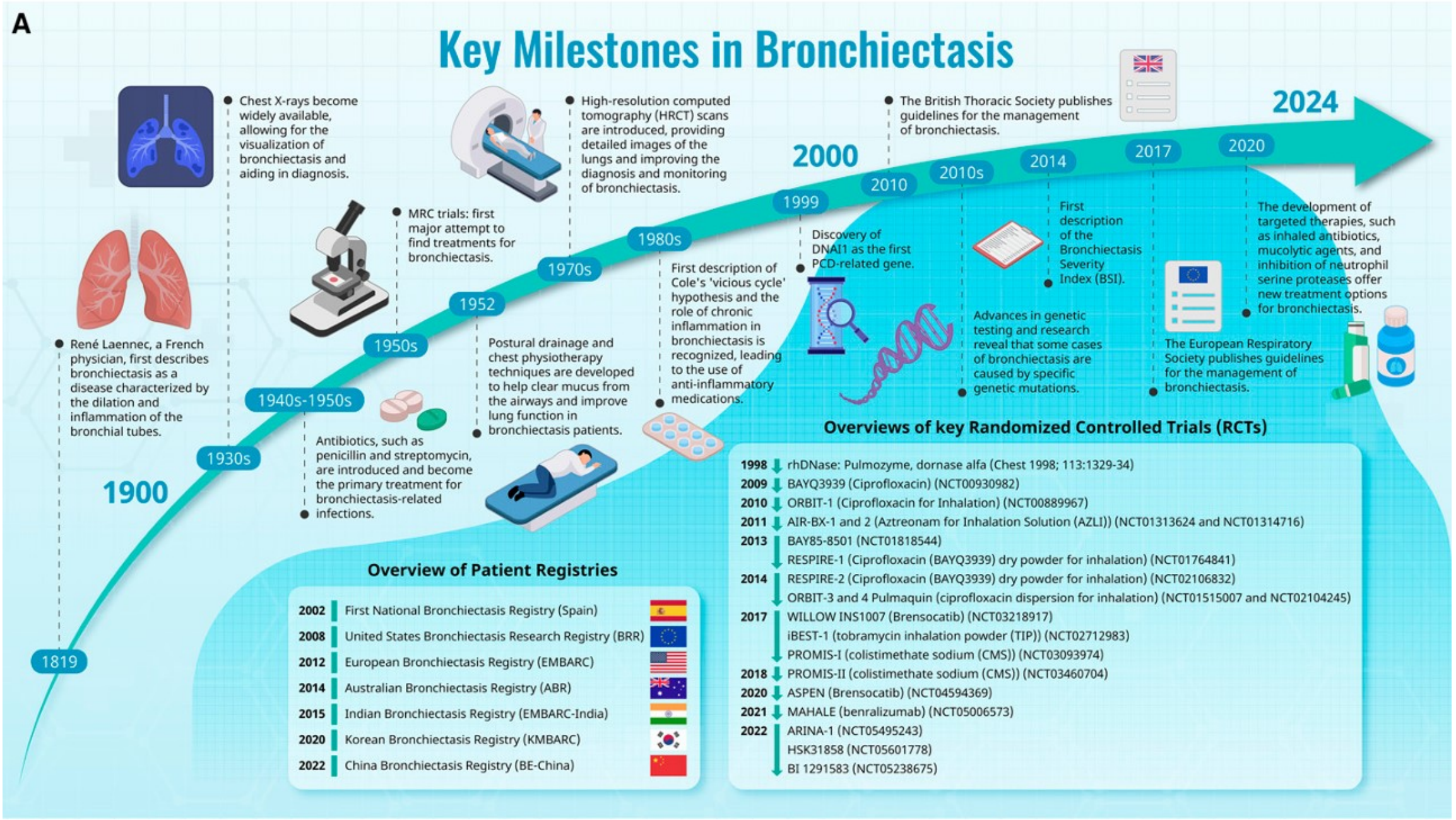
What's new in bronchiectasis?

Assoc. Prof. Dr. Özlem Erçen Diken

Health Sciences University, Adana Faculty of Medicine,

Adana City Training and Research Hospital, Department of Pulmonology, Adana, Turkey



Chotirmall SH, Chalmers JD. The Precision Medicine Era of Bronchiectasis. Am J Respir Crit Care Med. 2024 Jul 1;210(1):24-34.

Unclear Aspects

- The fundamental origins, mechanisms, and natural history of bronchiectasis remain poorly understood.
- The “reversibility” of radiographic bronchiectasis during acute infection is widely accepted.
- How this translates to(at least) some adults remain uncertain, as does the clinical occurrence of **“traction bronchiectasis”** in relation to other respiratory diseases, including chronic obstructive pulmonary disease (COPD) and interstitial lung disease.
- It is now established that **early-life events** predispose to the adult onset of asthma and/or COPD, and it is similarly likely that early-life events may relate to the development of bronchiectasis in at least some form.

Unclear Aspects
Are there different forms of bronchiectasis?
Which, if any, are reversible?
Do some have early-life origins?

Challenge of the inherent heterogeneity

- There is no typical patient with bronchiectasis, and no two patients are the same.
- **Underlying this is the multitude of different etiologies (where identifiable), with up to half of all cases considered idiopathic.**
- There remain no licensed treatments for bronchiectasis, and many interventions used lack evidence.
- Although matters are improving through clinical trials, therapeutic development is undermined by **disease heterogeneity,** a lack of experimental models, and an urgent need for a better, more fundamental understanding of pathogenesis.

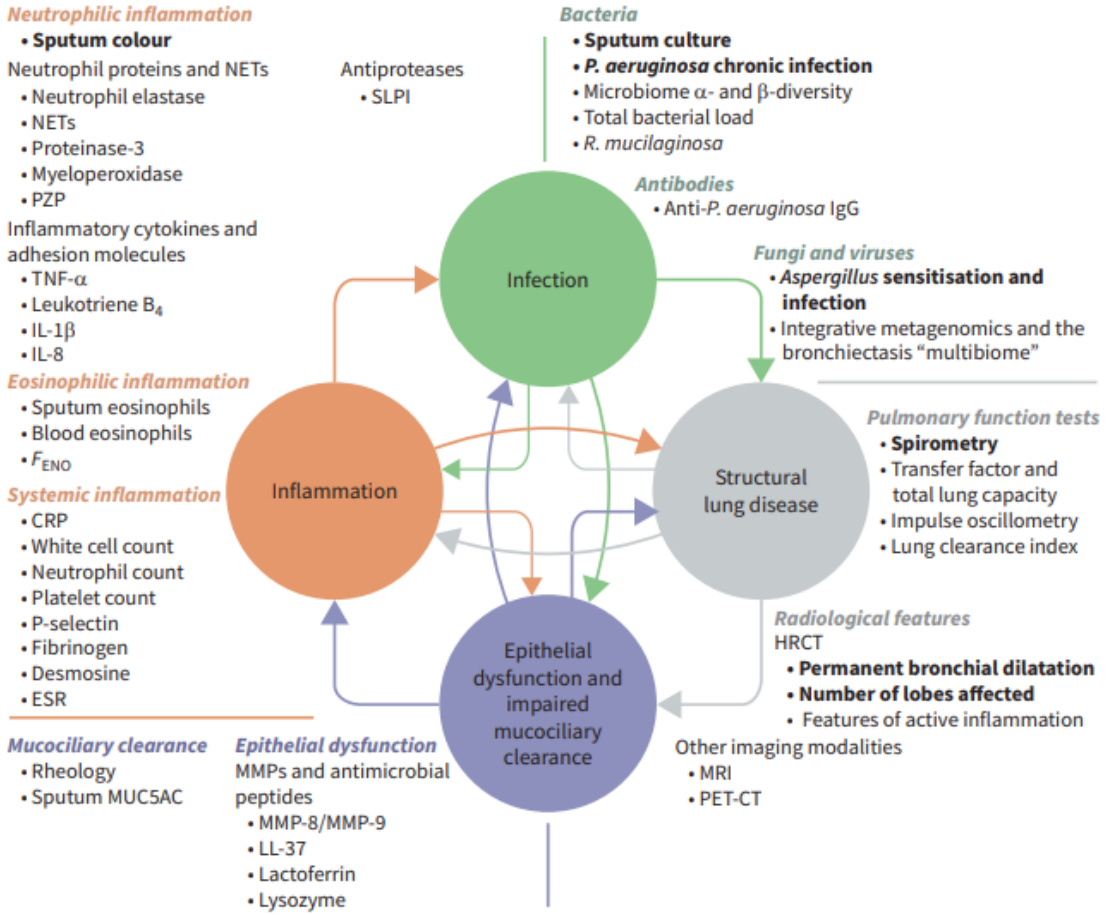


FIGURE 1 Established and exploratory biomarkers related to each aspect of the bronchiectasis vicious vortex: inflammation, infection, epithelial dysfunction and impaired mucociliary clearance, and structural lung damage. Established biomarkers are shown in bold. NETs: neutrophil extracellular traps; PZP: pregnancy zone protein; SLPI: secretory leukocyte protease inhibitor; TNF: tumour necrosis factor; IL: interleukin; F_{ENO}: exhaled nitric oxide fraction; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP: matrix metalloproteinase; *P. aeruginosa*: *Pseudomonas aeruginosa*; *R. mucilaginosa*: *Rothia mucilaginosa*; HRCT: high-resolution computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography; CT: computed tomography. Reproduced and modified from [5] with permission. Figure created with biorender.com.

Chang AB, et al. European Respiratory Society guidelinesforthemanagementofchildrenandadolescentswithbronchiectasis.EurRespirJ2021

A Decade of Advances in Bronchiectasis Education, Research, and Clinical Care

- We have observed exponential growth in the quantity and quality of bronchiectasis education, research, and clinical care.
- Despite the advances and promise, many clinical trials **have failed to reach** their primary endpoints.
- **The lack of available "evidence-based" treatments and the failure of bronchiectasis clinical trials** are intimately linked to **disease heterogeneity**, whether clinical, radiological, microbiological, or immunological.
- Selection of the **right patients for the right intervention** at the right time is central to appropriately addressing this challenge, one that necessitates fresh approaches to understanding, stratifying, and classifying bronchiectasis to optimally measure "treatment response."

A Decade of Advances in Bronchiectasis Education, Research, and Clinical Care

- No single variable encompasses the severity of bronchiectasis in individual cases, and therefore multidimensional approaches have been established, including the **bronchiectasis severity index**, **FACED and E-FACED** scores, which incorporate clinical, radiological, microbiological, and functional assessment.
- This poses challenges when interpreting translation to treatment efficacy.

A Decade of Advances in Bronchiectasis Education, Research, and Clinical Care

FACED
FEV1
Age
The presence of **C**hronic colonization by Pseudomonas aeruginosa
Radiological extension [number of pulmonary lobes affected]
Dyspnea

Table 5 Variables involved in calculating severity in the FACED score

	Factor and points for scoring system	
FEV_1% predicted	<50 (2 points)	≥50 (0 points)
Age (years)	≤70 (0 points)	>70 (2 points)
Colonisation by *P. aeruginosa*	No (0 points)	Yes (1 point)
Radiological extension of bronchiectasis	1–2 lobes (0 points)	>2 lobes (1 point)
Modified MRC dyspnoea scale	1–2 (0 points)	III-IV (1 point)

0–2 Points=mild disease; 3–4=moderate disease; 5–7=severe disease.

Hill AT, et al. Thorax 2019;74(Suppl 1):1–69.

A Decade of Advances in Bronchiectasis Education, Research, and Clinical Care

E-FACED
FEV1
Age
The presence of **C**hronic colonization by Pseudomonas aeruginosa
Radiological extension [number of pulmonary lobes affected]
Dyspnea
Severity of **E**xacerbations

The Bronchiectasis Severity Index (BSI)

Table 4 Variables involved in calculating the severity score in the Bronchiectasis severity index

	Factor and points for scoring system			
Age (years)	<50 (0 points)	50–69 (2 points)	70–79 (4 points)	>80 (6 points)
BMI (Kg/m^2)	<18.5 (2 points)	18.5–25 (0 points)	26–30 (0 points)	>30 (0 points)
FEV_1% predicted	>80 (0 points)	50–80 (1 point)	30–49 (2 points)	<30 (3 points)
Hospital admission within last 2 years	No (0 points)		Yes (5 points)	
Number of exacerbations in previous 12 months	0 (0 points)	1–2 (0 points)	≥3 (2 points)	
MRC breathlessness score	1–3 (0 points)	4 (2 points)	5 (3 points)	
P. aeruginosa colonisation	No (0 points)		Yes (3 points)	
Colonisation with other organisms	No (0 points)		Yes (1 point)	
Radiological severity	<3 lobes affected (0 points)	≥3 lobes or cystic bronchiectasis in any lobe (1 point)		

0-4 Points=mild disease; 5–8=moderate disease; 9 and over=severe disease.

Hill AT, et al. Thorax 2019;74(Suppl 1):1–69.

A Decade of Advances in Bronchiectasis Education, Research, and Clinical Care

- Identifying responders to specific interventions (i.e., mucoactive, antibiotic, or antiinflammatory) remains challenging, as those experiencing symptomatic amelioration may show no change in exacerbation frequency or severity or vice versa.

- **Those with smoking histories are less likely to demonstrate "responsiveness," exposing the relevance of coexisting smoking related lung diseases such as COPD.**

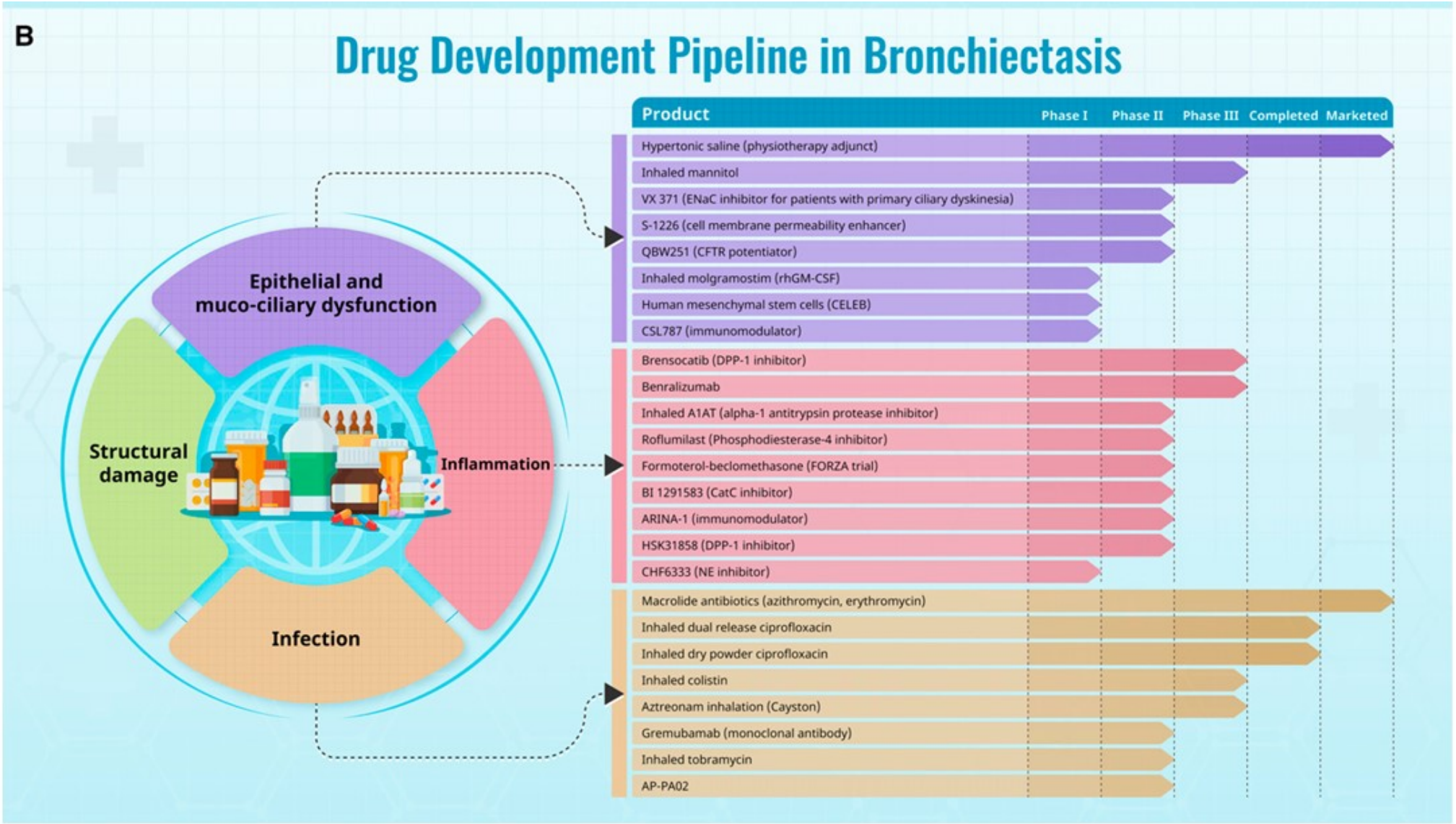


Figure 1. (*A*) Timeline summary of the key milestones in bronchiectasis, including patient registries and clinical trials. (*B*) Drug development pipeline (not comprehensive) in bronchiectasis categorized by the different aspects of the "vicious vortex" model of pathogenesis. A1AT = alpha-1 antitrypsin; CatC = cathepsin C; CFTR = cystic fibrosis transmembrane conductance regulator; DNAI1 = dynein axonemal intermediate chain 1; DPP-1 = dipeptidyl peptidase-1; EMBARC = European Multicentre Bronchiectasis Audit and Research Collaboration; ENaC = epithelial sodium channel; MRC = Medical Research Council; NE = neutrophil elastase; PCD = primary ciliary dyskinesia.

Chotirmall SH, Chalmers JD. The Precision Medicine Era of Bronchiectasis. Am J Respir Crit Care Med. 2024 Jul 1;210(1):24-34.

Bronchiectasis as a Syndrome Rather Than a Disease: Targetable and Treatable Traits

- Different therapies for different patients at different disease time points may be necessary to achieve optimal clinical outcomes in patients with bronchiectasis, an approach aided by **“targeting treatable traits”**

- In the RCT assessing **inhaled mannitol**, which showed **no exacerbation effect** (the primary endpoint) but on post hoc analysis revealed that **highly symptomatic patients** (by St. George’s Respiratory Questionnaire) significantly benefited.

Bronchiectasis as a Syndrome Rather Than a Disease: Targetable and Treatable Traits

- As each patient with bronchiectasis demonstrates multiple treatable traits, several are **not considered by solely assessing the vicious vortex**, for instance, **airflow obstruction** (including coexisting asthma or COPD) occurs in significant numbers and is associated with breathlessness, **targetable with bronchodilators.**

Bronchiectasis as a Syndrome Rather Than a Disease: Targetable and Treatable Traits

“chicken and egg” scenario

specific interventions at specific time points

Considering extrapulmonary comorbidities

As most patients with bronchiectasis have on average **three such “traits”**

- **Low body mass index,**
- **Gastroesophageal reflux disease,**
- **Rhinosinusitis,**
- **Depression,**
- **Anxiety,**
- **Cardiovascular disease.**

“ A syndrome rather than a disease”

Treatable traits approach

Redefining Bronchiectasis by Advanced Endophenotyping

- Leveraging a **treatable traits approach** to resolve **heterogeneity** in bronchiectasis is logical

- The adoption of **endophenotyping** in other respiratory diseases, including asthma and COPD, has provided a deeper **understanding of disease traits and targets** and driven **focused therapy.**

Clinical phenotyping

Clinical phenotyping
Chronic Pseudomonas infection
Dry bronchiectasis
Frequent exacerbator

Extension of clinical phenotyping	
Radiological pattern	Cylindrical, varicose, or cystic
Underlying etiology	Immunodeficiency subtypes
Disease overlap	Asthma, COPD or allergic bronchopulmonary aspergillosis (ABPA), and primary ciliary dyskinesia (PCD)–related bronchiectasis.

Molecular endotyping

- Molecular endotyping, assessing disease through **underlying pathobiological mechanisms and/or treatment response**, should be **combined with phenotyping** for a holistic view.

neutrophilic/neutrophil extracellular traps

eosinophilic/type 2 airway inflammation

Endophenotyping in bronchiectasis is key to driving the implementation of precision medicine and resolving its long-standing heterogeneity.

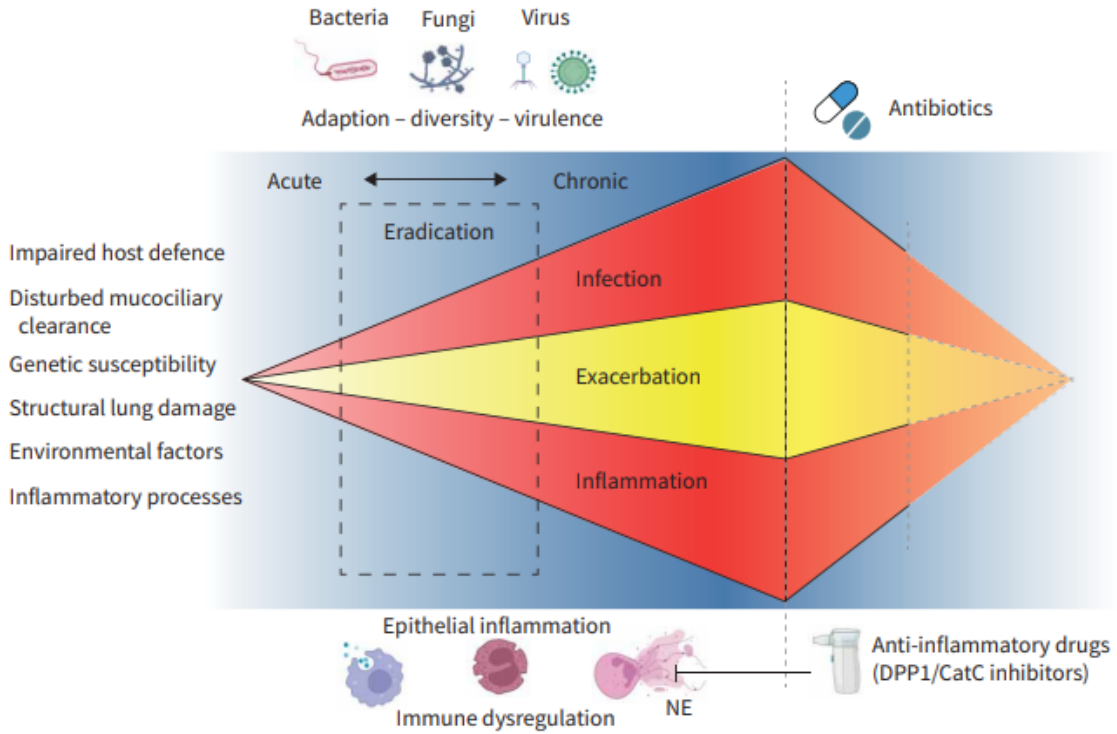


FIGURE 1 Overview of bronchiectasis pathogenesis. A complex interaction between infection and inflammation results in a self-perpetuating cycle initially triggered by various conditions (indicated on the left). This cycle is primarily driven by bacterial infections, with growing evidence of significant contributions from viruses and fungi. The progression from acute to chronic infection hinges on factors such as pathogen virulence, adaptability and the selective pressures within the host environment. Identifying the exact stage of infection (acute or chronic) is crucial, as it influences the effectiveness of eradication efforts (broken rectangle). Central to this process is an excessive (usually neutrophilic) inflammatory response that leads to further tissue damage and impairs mucociliary clearance. This infection-driven inflammation can increase the likelihood of acute exacerbations. Therapeutic strategies aim to mitigate both infection and inflammation. This is achieved through conventional antibiotics and newer pharmacological interventions targeting neutrophilic inflammation, such as dipeptidyl peptidase 1 (DPP1)/cathepsin C (CatC) inhibitors. Despite these efforts, the structural lung damage and the conditions present at the onset of infection and inflammation preclude a reversal to the pre-disease state. Figure created with BioRender.com.

Mac Aogáin M, et al. Infection and the microbiome in bronchiectasis. Eur Respir Rev 2024; 33: 240038

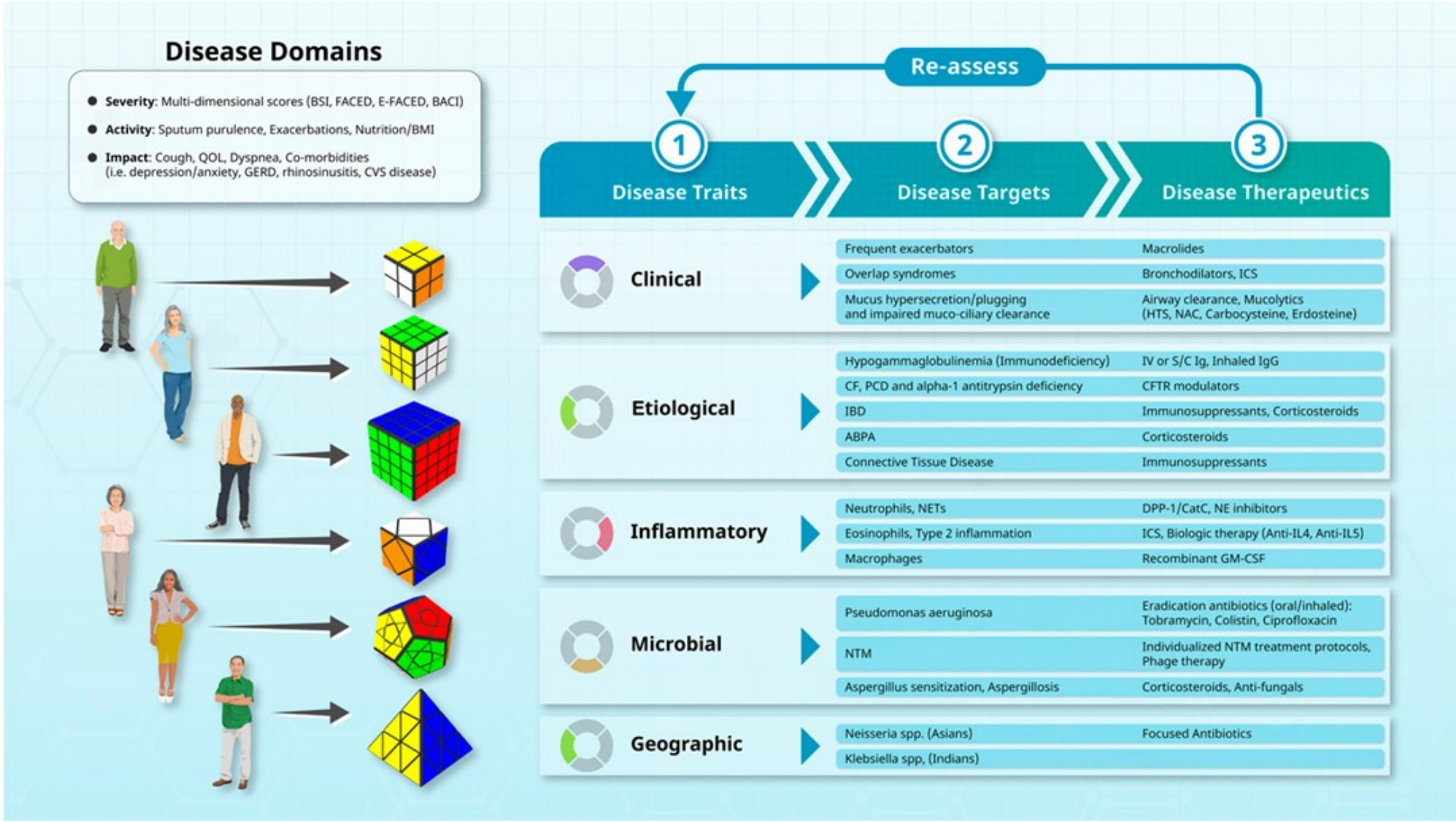
Rubik's cube

- Conceptually, if we consider each individual patient a single Rubik's cube, where a solved cube represents patients in a "stable" state

- A scrambled cube one in an "exacerbation,""active," or "progressed" diseased state

- Therefore, to achieve a solved cube, we must consider each cube holistically.

The various multiomics technologies
genomics
epigenomics
transcriptomics
metabolomics
lipidomics



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“precision medicine era” for bronchiectasis

“Precision medicine era” for bronchiectasis	
precision	**clinical**
	etiological
	inflammatory
	microbial
	and/or geographic

- **“inflammatory” rather than an “infective” disease.**
- This has parallels to other chronic respiratory disease states, such as asthma, COPD, and pulmonary fibrosis, whose therapeutic armory includes several effective antiinflammatory agents.

Recent phase II studies of **DPP-1/cathepsin C inhibition in bronchiectasis** have been completed or remain ongoing, and the field awaits the outcomes of phase III trials, which if successful will herald a paradigm shift for understanding bronchiectasis.

Clinical and Etiological Precision

- **Idiopathic** disease accounts for up to 70% of cases in studies and was reported in **38.1% of cases** in the recent report from **EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration).**
- **Postinfection-related bronchiectasis** (i.e., tuberculosis or pneumonia) is likely different from other forms, developing **over a longer time period and potentially attributable to yet unidentified underlying functional immune defects.**
- It is essential for precision medicine, however, to identify underlying causes with therapeutic implications, causes with specific treatments.

Clinical and Etiological Precision

It is essential for precision medicine, however, to identify underlying causes with therapeutic implications, causes with specific treatments.

- **Primary and secondary immunodeficiencies, which may benefit from immunoglobulin replacement**
- **ABPA, which may benefit from corticosteroids and/or antifungal treatments**
- **NTM infection, which may benefit from long-term combination antibiotic treatment**
- Inflammatory bowel disease–associated bronchiectasis is also reported to be highly corticosteroid responsive.
- COPD and connective tissue diseases such as rheumatoid arthritis are associated with significantly **increased mortality and hospitalization rates.** Knowledge that certain underlying causes are associated with worse outcomes should also inform more aggressive therapeutic strategies.

Clinical and Etiological Precision

Cystic fibrosis	**Onset of symptoms during childhood**
	Infertility
	Pancreatic insufficiency
	Other extrapulmonary features
	P. aeruginosa and Staphylococcus aureus infection are also more common

The availability of **highly effective modulator therapy** makes the identification of atypical presentations of cystic fibrosis essential as **treatment can be life changing.**

PCD

- PCD has both therapeutic and prognostic implications.
- The lack of effective mucociliary clearance in these patients requires **a more intensive approach to airway clearance** and **the use of mucoactive therapies**, as well as management of the upper airway disease, associated cardiac disease, and genetic counseling.
- Patients with PCD had a higher frequency of infection with pathogens including P. aeruginosa and worse clinical outcomes necessitating more intensive treatment and follow-up.
- Importantly, we do not find what we do not look for, and there is globally a lack of appropriate testing for underlying causes of bronchiectasis.
- In two studies from the United Kingdom, first in patients with severe bronchiectasis, whole genome sequencing identified PCD in 12% of patients tested, while genetic testing revealed the disease in **7% of a second cohort of patients with idiopathic bronchiectasis not suspected to have PCD .**

Clinical and Etiological Precision

- **Bronchiectasis is often cited in textbooks as an obstructive disorder, but like many textbook descriptions of disease, this is true in only a proportion of patients.**

- In a recent report from EMBARC of 16,963 patients from 28 countries, **obstructive spirometry was the most common pattern, but nearly one-third of individuals had normal spirometry**.

Clinical and Etiological Precision

- **Exacerbation frequency** is also heterogeneous among individuals, and the observation that patients at high risk of exacerbation tend to exacerbate frequently year on year has been described as the **frequent exacerbator phenotype.**
- Frequent exacerbators, usually defined by **three or more exacerbations per year,** are at higher risk of future hospitalization and mortality.
- Clinical management is therefore heavily influenced by clinical phenotype in terms of etiology, exacerbations, symptoms, comorbidities, and physiology and must be considered to achieve precision.

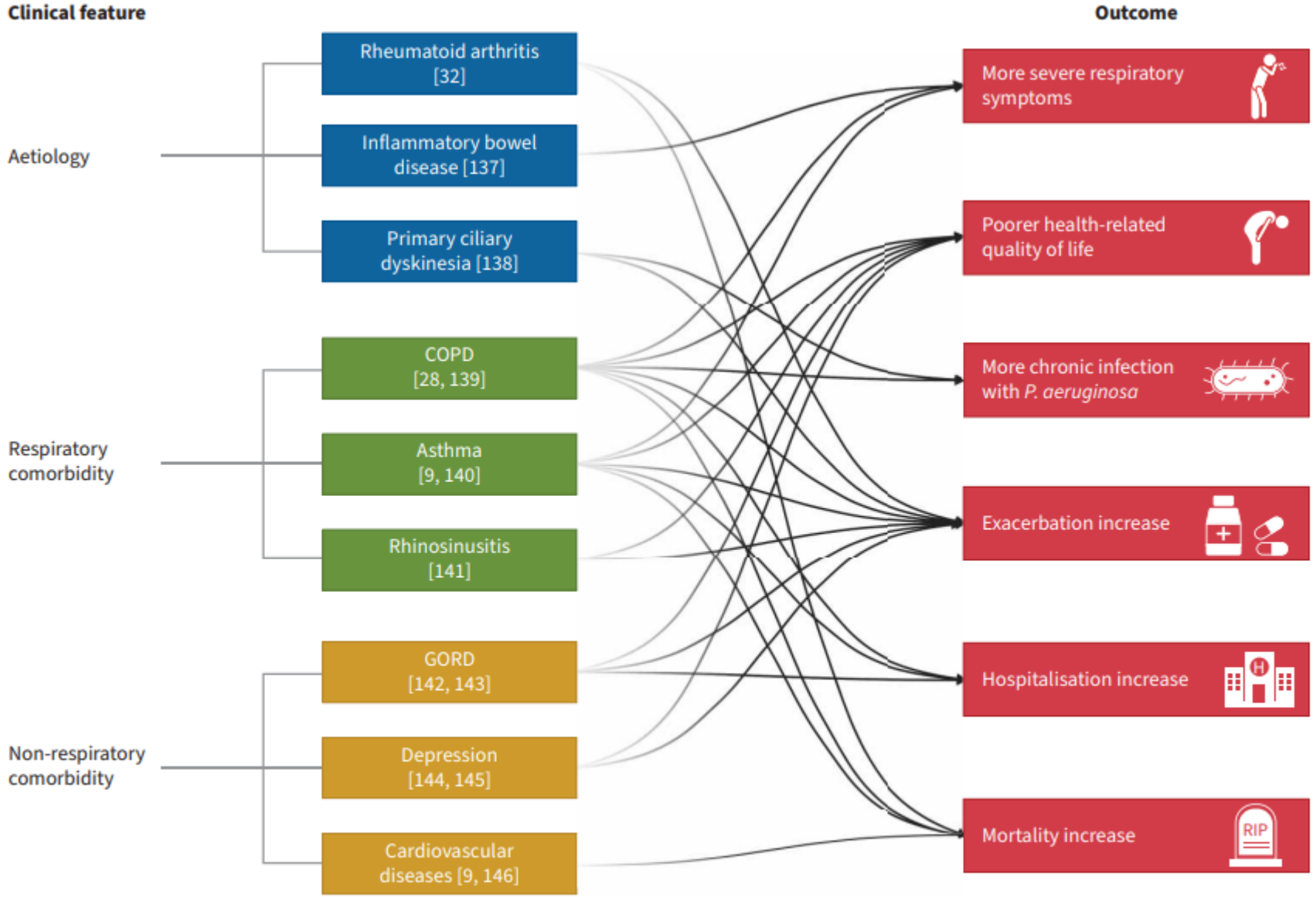


FIGURE 2 Clinical conditions associated with worse outcomes in patients with bronchiectasis. GORD: gastro-oesophageal reflux disease; *P. aeruginosa*: *Pseudomonas aeruginosa*.

Choi H, et al. Bronchiectasis management in adults: state of the art and future directions. Eur Respir J 2024; 63: 2400518

TABLE 1 Diagnosis and treatment of treatable aetiologies in bronchiectasis

Aetiology	Diagnosis	Treatment	Comments
NTM pulmonary disease [17, 18, 133, 134]	Sputum culture for mycobacteria Microbiological test results compatible with NTM pulmonary disease: 1) the same NTM species is isolated in ⩾2 sputum cultures, 2) isolated in ⩾1 bronchial wash or lavage or 3) biopsy with mycobacterial histopathological features plus positive culture for NTM (or ⩾1 sputum or bronchial washings that are culture positive for NTM)	Combination of antibiotics for 12 months after sputum culture conversion Decided based on clinical symptoms, progression of radiological signs and knowledge of the infecting NTM species	ERS 2017 and BTS 2019 guidelines recommend mycobacterial sputum cultures in patients with bronchiectasis ATS/ERS/ESCMID/IDSA 2020 clinical practice guidelines for the treatment of NTM pulmonary disease
ABPA [17, 18, 135]	Total serum IgE test *Aspergillus*-specific IgG test *Aspergillus*-specific IgE test (or skin prick tests for *Aspergillus*)	Systemic corticosteroids Antifungal agents	ERS 2017 and BTS 2019 guidelines recommend ABPA testing in all patients with bronchiectasis
Immunodeficiency [17, 18]	Serum IgA, IgM and IgG Serum IgG subclass Peripheral blood lymphocyte subpopulations (including T-, B- and NK-cells) Pneumococcal IgG to vaccine response	Immunoglobulin replacement	ERS 2017 and BTS 2019 guidelines recommend serum IgA, IgM and IgG testing in all patients with bronchiectasis BTS 2019 guideline recommends pneumococcal IgG to vaccine response
A1AT deficiency [17, 18, 136]	Serum A1AT A1AT genetic testing	Intravenous augmentation of A1AT in countries where this is available	BTS 2019 guideline recommends A1AT deficiency testing in patients with coexisting basal panacinar emphysema ERS 2017 guideline states the presence of basal emphysema or early-onset airflow obstruction could suggest the need to exclude A1AT deficiency Portuguese 2016 guideline recommends A1AT deficiency testing in all patients with bronchiectasis (estimated prevalence is 1:2191 in Portugal)

NTM: non-tuberculous mycobacterial; ERS: European Respiratory Society; BTS: British Thoracic Society; ATS: American Thoracic Society; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; IDSA: Infectious Diseases Society of America; ABPA: allergic bronchopulmonary aspergillosis; NK: natural killer; A1AT: α_1-antitrypsin.

Choi H, et al. Bronchiectasis management in adults: state of the art and future directions. Eur Respir J 2024; 63: 2400518

Microbial Precision

Microbial pathogen	RIBRON – Spain (n=1912)	KMBARC – Korea (n=598)	EMBARC – Europe (n=16963)	BRR – USA (n=1826)	EMBARC – India (n=2195)
P. aeruginosa (%)	40.4	11.0	25.1	33.0	13.7
H. influenzae (%)	18.9	1.5	23.6	8.0	0.5
M. catarrhalis (%)	5.4	0.5	5.4	1.0	1.0
Enterbacteriales (%)	5.3	3.9	15.9	–	9.8
Sta. aureus (%)	7.6	0.7	8.6	12.0	2.3
Str. pneumoniae (%)	5.1	–	8.5	3.0	0.8
Ste. maltophilia (%)	2.4	–	2.6	5.0	–
A. fumigatus (%)	0.7	–	3.2	19.0	–
Other/unknown	14.2	82.4	7.1	19.0	71.9

Mac Aogáin M, et al. Infection and the microbiome in bronchiectasis. Eur Respir Rev 2024; 33: 240038

TABLE 2 Summary of randomised controlled trials (RCTs) of inhaled antibiotics for bronchiectasis

Agent and study	Subjects (n)	Study design	Primary outcome	Duration	Study population	Main results	Safety
Ciprofloxacin DPI Wilson *et al.* (2013) [76]	A: 60 P: 64	Phase 2 double-blind RCT	Bacterial load	84 days (28-day treatment with follow-up)	⩾2 exacerbations in previous year; culture positive for target microorganisms	Mean difference in bacterial load −3.62 *versus* −0.27 $log_{10}CFU{\cdot}mL^{-1}$ (p<0.001); no significant differences in proportion of patients with exacerbations (36.7% *versus* 39.1%; p=0.6) and SGRQ (mean difference −3.56; p=0.059)	10% of patients developed resistance (MIC >4 $mg{\cdot}L^{-1}$) in the ciprofloxacin group; no difference in adverse events between groups
Ciprofloxacin DPI De Soyza *et al.* (2018) RESPIRE 1 [77]	14-day on/off A: 137 P: 68 28-day on/off A: 141 P: 70	Phase 3 double-blind RCT	Time to first exacerbation, frequency of exacerbations	12 months (14- or 28-day on/off-treatment cycles)	⩾2 exacerbation in previous year; culture positive for predefined microorganisms	14-day on/off cycle: significantly prolonged time to first exacerbation (median >336 *versus* 186 days; HR 0.53, 97.5% CI 0.36–0.80; p=0.0005); reduced frequency of exacerbation (IRR 0.61, 97.5% CI 0.40–0.91; p=0.0061); 28-day on/off cycle: no significant differences in primary end-points	No difference in adverse events between groups
Ciprofloxacin DPI Asakamit *et al.* (2018) RESPIRE 2 [78]	14-day on/off A: 176 P: 88 28-day on/off A: 171 P: 86	Phase 3 double-blind RCT	Time to first exacerbation, frequency of exacerbations	12 months (28-day on/off-treatment cycles)	⩾2 exacerbations in previous year; culture positive for predefined microorganisms	Missed primary end-point: prolonged time to first exacerbation (HR 0.87, 95% CI 0.62–1.21; p=0.40 in 14-day on/off and HR 0.71, 99% CI 0.39–1.27; p=0.051 in 28-day on/off) and reduced frequency of exacerbations (IRR 0.83, 95% CI 0.59–1.17; p=0.29 in 14-day on/off and IRR 0.55, 99% CI 0.30–1.02; p=0.001 in 28-day on/off)	No difference in adverse events between groups
Liposomal ciprofloxacin Serisier *et al.* (2013) ORBIT-2 [79]	A: 20 P: 20	Phase 2 double-blind RCT	Bacterial load after first 28-day treatment cycle with intervening 28-day off periods	24 weeks (three 28-day treatment cycles)	*P. aeruginosa*-colonised patients; ⩾2 exacerbations in previous 12 months	Reduction in *P. aeruginosa* bacterial load −4.2 *versus* −0.08 $log_{10}CFU{\cdot}mL^{-1}$ (p=0.002); reduced number of exacerbations in the active treatment group (OR 0.2, 95% CI 0.04–0.89; p=0.027)	No significant difference in MICs to ciprofloxacin at day 28; no increase in adverse events
Liposomal ciprofloxacin Haworth *et al.* (2019) ORBIT-3 and ORBIT-4 [80]	ORBIT-3 A: 183 P: 95 ORBIT-4 A: 206 P: 98	Phase 3 double-blind RCT	Time to first exacerbation	48 weeks (six 28-day on/off-treatment cycles)	⩾2 exacerbations in previous year; chronic *P. aeruginosa* infection	Median time to first exacerbation: 230 *versus* 158 days (HR 0.72, 95% CI 0.53–0.97; p=0.032) in ORBIT-4; 214 *versus* 136 days (HR 0.99, 95% CI 0.71–1.38; p=0.97) in ORBIT-3; and 222 *versus* 157 days (HR 0.82, 95% CI 0.65–1.02; p=0.074) in a pooled analysis of both trials	No difference in adverse events between groups
Aztreonam Barker *et al.* (2014) AIR-BX1 and AIR-BX2 [81]	AIR-BX1 A: 134 P: 132 AIR-BX2 A: 136 P: 138	Two phase 3 double-blind RCTs	QOL-B score at week 4	Two 28-day treatment courses with alternating 28 days off treatment	Positive sputum for *P. aeruginosa* or other Gram-negative organisms (excluding *H. influenzae*); FEV_1 >20% predicted; chronic sputum production	No difference in QOL-B at week 4 (mean difference 0.8, 95% CI −3.1–4.7; p=0.7 in AIR-BX1 and 4.6, 95% CI 1.1–8.2; p=0.011 in AIR-BX2); no difference in QOL-B in both studies at week 12 (p=0.56 in both studies); no difference in time to first exacerbation	Adverse events leading to discontinuation: AIR-BX1 22% *versus* 6%; AIR-BX2 10% *versus* 5%

Choi H, et al. Bronchiectasis management in adults: state of the art and future directions. Eur Respir J 2024; 63: 2400518

TABLE 2 Continued

Agent and study	Subjects (n)	Study design	Primary outcome	Duration	Study population	Main results	Safety
Tobramycin Barker *et al.* (2000) [82]	A: 37 P: 37	Phase 2 double-blind RCT	*P. aeruginosa* bacterial load at week 4	6 weeks (28-day treatment)	*P. aeruginosa*-colonised patients	Significant reduction in *P. aeruginosa* load (mean difference 4.56 $log_{10}CFU{\cdot}mL^{-1}$; p<0.01); 13/37 cleared *P. aeruginosa* from sputum; no significant change in FEV_1 (p=0.41)	Increased dyspnoea, chest pain and wheezing; new resistance to tobramycin in 4/36
Tobramycin Guan *et al.* (2022) TORNASOL [83]	A: 167 P: 172	Phase 3 double-blind RCT	*P. aeruginosa* bacterial load and QOL-B Respiratory symptoms score on day 29	16 weeks (two cycles of 28 days on/off treatment)	⩾1 exacerbations in previous 2 years; chronic *P. aeruginosa* infection	*P. aeruginosa* bacterial load mean difference 1.74 $log_{10}CFU{\cdot}mL^{-1}$ (p<0.001); QOL-B Respiratory symptom score mean difference 7.9 (p<0.001)	Adverse events leading to discontinuation: 6.2% (tobramycin) *versus* 2.8% (placebo)
Tobramycin Terpstra *et al.* (2022) BATTLE [84]	A: 26 P: 26	Phase 3 double-blind RCT	Frequency of exacerbation	12 months	⩾2 exacerbations in previous year; culture positive for predefined microorganisms	Missed primary end-point: rate ratio 0.74, 95% CI 0.49–1.14 (p=0.15)	8.8% of tobramycin group discontinued study due to respiratory symptoms in first 4 weeks
Tobramycin inhalation powder Loebinger *et al.* (2021) iBEST [85]	A: 86 P: 21	Phase 2 double-blind RCT	*P. aeruginosa* bacterial load on day 29	Treatment for 16 weeks plus follow-up for 8 weeks	*P. aeruginosa*-colonised patients	Primary end-point was met in all three doses: *P. aeruginosa* bacterial load ($log_{10}CFU{\cdot}mL^{-1}$) −2.5 at 84 mg (p=0.0004), −2.8 at 140 mg and −3.8 at 224 mg (p=0.0001 for all)	8.8% of tobramycin group discontinued study due to respiratory symptoms in first 4 weeks
Gentamicin Murray *et al.* (2011) [86]	A: 27 P: 30	Single-blind RCT	Bacterial load	12 months	Patients colonised with any pathogens in at least three sputum samples in the previous 12 months; 2 exacerbations in the previous year; able to tolerate test dose of gentamicin; FEV_1 >30% predicted; ex-smokers of >1 year; not on long-term antibiotics	Significant difference in bacterial load at 12 months (2.69 *versus* 7.67 $log_{10}CFU{\cdot}mL^{-1}$; p<0.0001); reduction in exacerbations (median 0 in gentamicin group *versus* 1.5 in saline group; p<0.0001); improved SGRQ and LCQ scores; reduced airway inflammation	Bronchospasm in 21.9%; two withdrawals; elevated serum gentamicin levels required dose reduction in one patient; no resistant isolates detected
Colistin Haworth *et al.* (2014) [87]	A: 73 P: 71	Phase 3 double-blind RCT	Time to first exacerbation	6 months	*P. aeruginosa*-colonised patients (⩾2 positive cultures in 12 months) and within 21 days of completing antipseudomonal antibiotics for exacerbation	Missed primary end-point (colistin 165 days *versus* placebo 111 days; p=0.11); improved SGRQ (mean difference −10.5; p=0.006); improved time to first exacerbation in patients taking >80% of doses	Five (7%) patients developed bronchoconstriction leading to discontinuation; no resistant strains at follow-up

DPI: dry powder inhaler; A: active; P: placebo; SGRQ: St George's Respiratory Questionnaire; MIC: minimum inhibitory concentration; HR: hazard ratio; IRR: incident rate ratio; *P. aeruginosa*: *Pseudomonas aeruginosa*; QOL-B: Quality of Life Bronchiectasis; *H. influenzae*: *Haemophilus influenzae*; FEV_1: forced expiratory volume in 1 s; LCQ: Leicester Cough Questionnaire.

Choi H, et al. Bronchiectasis management in adults: state of the art and future directions. Eur Respir J 2024; 63: 2400518

Microbial Precision

- One in three patients with bronchiectasis does not demonstrate features of chronic infection; rather, such individuals are characterized by **amicrobiome of“commensals**” including **Streptococcus, Veillonella, Prevotella, Rothia, and Neisseria**.

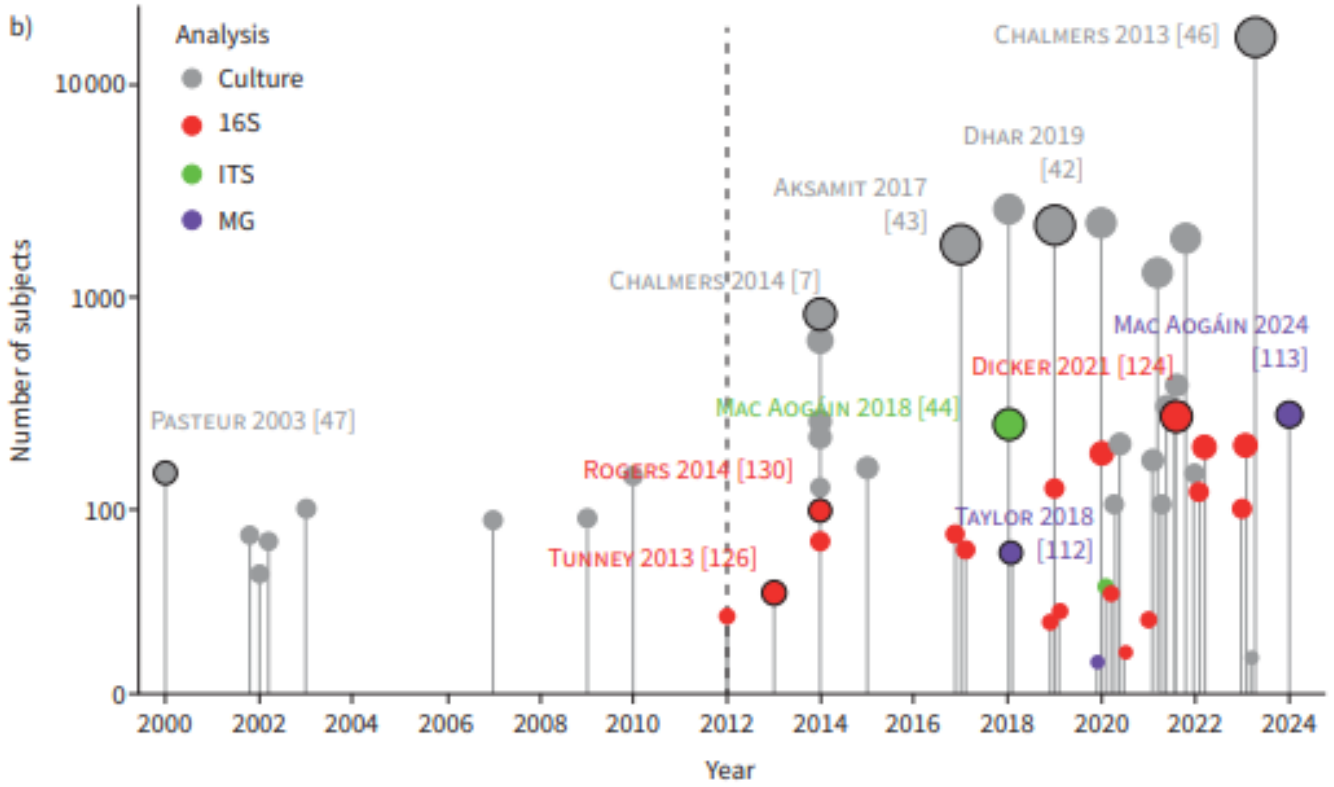


FIGURE 2 Increasing scale of culture-based and airway microbiome studies in bronchiectasis. a) Table illustrating prevalence of key bacterial taxa from several major bronchiectasis registries. b) Visual timeline of microbiological and microbiome research outputs in bronchiectasis (2000–2024) comparing culture-based and sequencing-based (microbiome) studies. Each point on the chart indicates an individual study with the size of the circle and the length of the associated vertical lines reflecting study size. Points on the chart are colour-coded by the type of analysis conducted (grey: culture based; red: bacterial 16S rRNA analysis; green: fungal internal transcribed spacer (ITS) analysis; purple: metagenomics (MG)). Selected studies specifically discussed in the review are indicated by black borders surrounding dots and have accompanying citations. A broken line demarcates the beginning of the "microbiome era" in bronchiectasis. The complete list of studies illustrated in the figure is detailed in supplementary appendix 1. *A.*: *Aspergillus*; *H.*: *Haemophilus*; *P.*: *Pseudomonas*; *Sta.*: *Staphylococcus*; *Ste.*: *Stenotrophomonas*; *Str*: *Streptococcus*.

Mac Aogáin M, et al. Infection and the microbiome in bronchiectasis. Eur Respir Rev 2024; 33: 240038

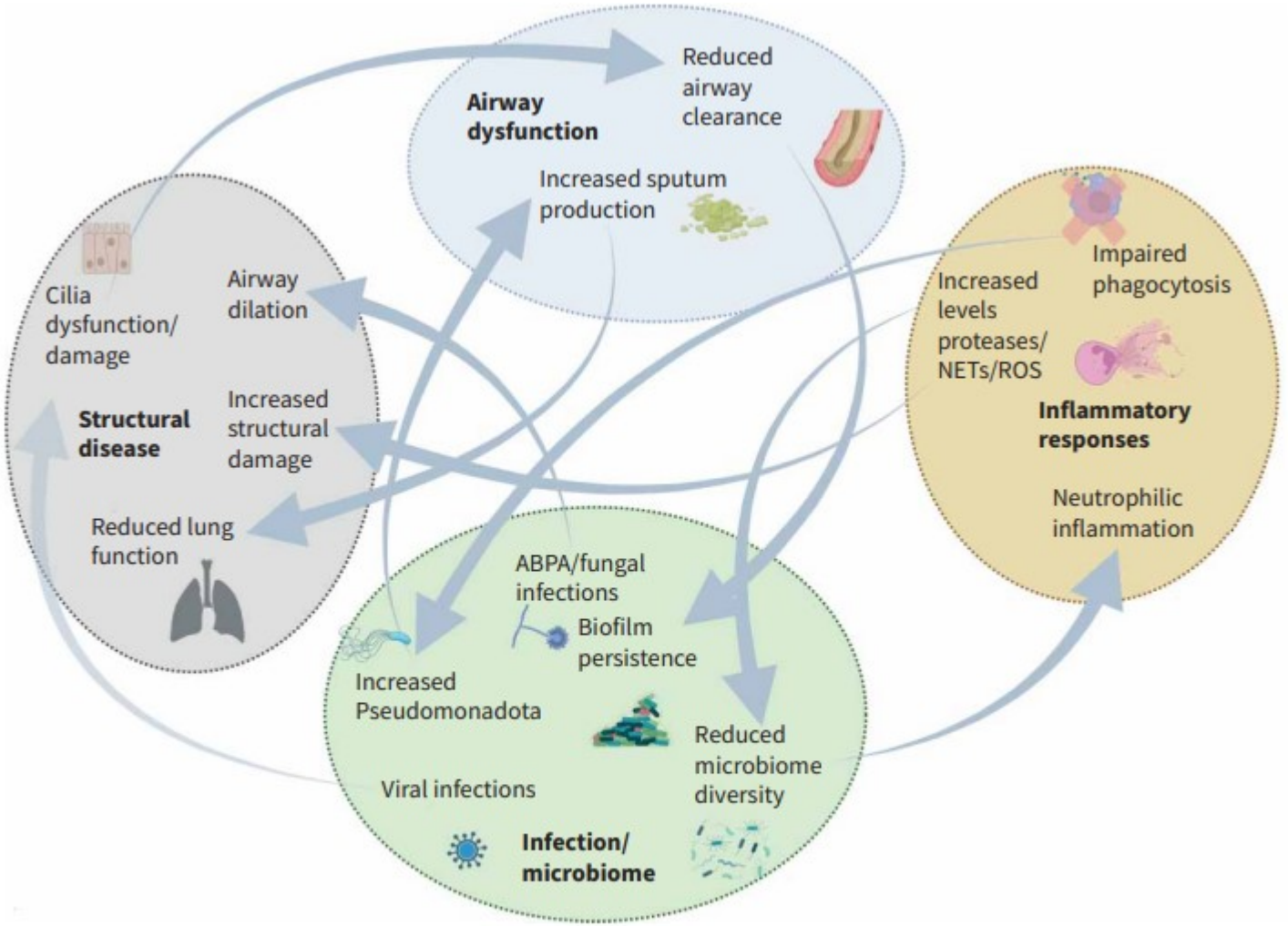


FIGURE 3 Microbiome and microbial interactions in the vicious vortex of bronchiectasis pathogenesis, adapted from the vicious vortex hypothesis of Flume *et al.* [3]. NET: neutrophil extracellular trap; ROS: reactive oxygen species. Figure created with BioRender.com.

Mac Aogáin M, et al. Infection and the microbiome in bronchiectasis. Eur Respir Rev 2024; 33: 240038

Geographic Precision

- Akin to clinical variance, microbial differences by geography exist:
  - the contrasting occurrence of **Pseudomonas across Europe**,
  - a predominance of **Neisseria spp. in Asians**,
  - multi–drug-resistant **Klebsiella in India,**
  - differences in Aspergillus spp. among continents.
- Considered holistically, it is clear that significant geographic variation exists in bronchiectasis, variation necessitating a regionally tailored approach to achieve true precision in bronchiectasis care and research.

Clinical Approach to the Patient with Suspected Bronchiectasis

History	Recurrent lower and/or upper respiratory tract infections, pneumonia Daily mucopurulent sputum production
Initial studies	CBC with differential Testing for ABPA Immunoglobulins IgG, IgM, IgA Sputum for bacterial culture
Confirms diagnosis	High-resolution chest CT scan
Other studies	Pulmonary function (spirometry pre- and postbronchodilator) Sweat chloride and/or genetic panel for CFTR alleles Connective tissue disease serologies HIV testing Sputum for AFB culture Nasal nitric oxide α_1-Antitrypsin level; phenotype Serum antibody response to bacterial antigen challenge, e.g., pneumococcal vaccine

Chotirmall SH, Chalmers JD. The Precision Medicine Era of Bronchiectasis. Am J Respir Crit Care Med. 2024 Jul 1;210(1):24-34.

Treatment options

- Several treatment options should be considered in patients with bron chiectasis. Therapies can be grouped in several categories:

(1) antimicrobials, both systemic and inhaled;

(2) airway clearance measures;

(3) antiinflammatory agents;

(4) surgery;

(5) treatment of underlying conditions.

Antimicrobial Therapy: Treatment of Acute Exacerbations

In a Delphi study of clinical experts,
15 consensus was achieved for the following issues regarding antibiotic treatment of bronc hiectasis:

(1) 10 to 14 day duration of antibiotics for acute exacerbations;

(2) sputum volume, sputum color, and exacerbation frequency as treatment endpoints;

(3)
combination antibiotics should not be given for acute exacerbations treated with oral antib iotics, regardless of Pseudomonas colonization;

(4)
combination antibiotics should be used in patients with severe exacerbations with Pseudo monas aeruginosa or MRSA; and

(5) in those individuals with
a decline in FEV1 but no changes in respiratory symptoms, antibiotics should be deferred.

Antimicrobial Therapy: Aerosolized Antibiotics

- Aerosolized antibiotics have been specifically directed at GNR infection, **par ticularly Pseudomonas aeruginosa**, which has been linked to higher mortality, high risk of hospitalization, and worse quality of life, among othe rs
- Several agents have been studied in prospective, randomized, placebo controlled clinical trials, including **tobramycin, gentamicin, and aztreonam for inhalation solution, and colistin and ciprofloxacin** in both liposomal and dry powder formulations.
- **Tobramycin has been the focus of several published clinical trials in treat ment of acute exacerbations and as chronic maintenance therapy**
- Aerosolized tobramycin has been found to have a profound microbiologic i mpact on Pseudomonas aeruginosa, without promoting emergence of resistant organisms.

Aerosolized gentamicin, aerosolized aztreonam

- **Aerosolized gentamicin** was studied in a randomized, year long, placebo controlled trial. Findings included a 31% eradication of Pseudomonas and 92.8% of other path ogens in the treatment group. No Pseudomonas isolates developed g entamicin resistance.
- Two randomized, doubleblind, placebocontrolled, phase 3 clinical trial s of **aerosolized aztreonam** did not demonstrate clinical benefit; treat ment
  emergent adverse events, including dyspnea, cough, and increased sp utum were common.

İnhaled colistin

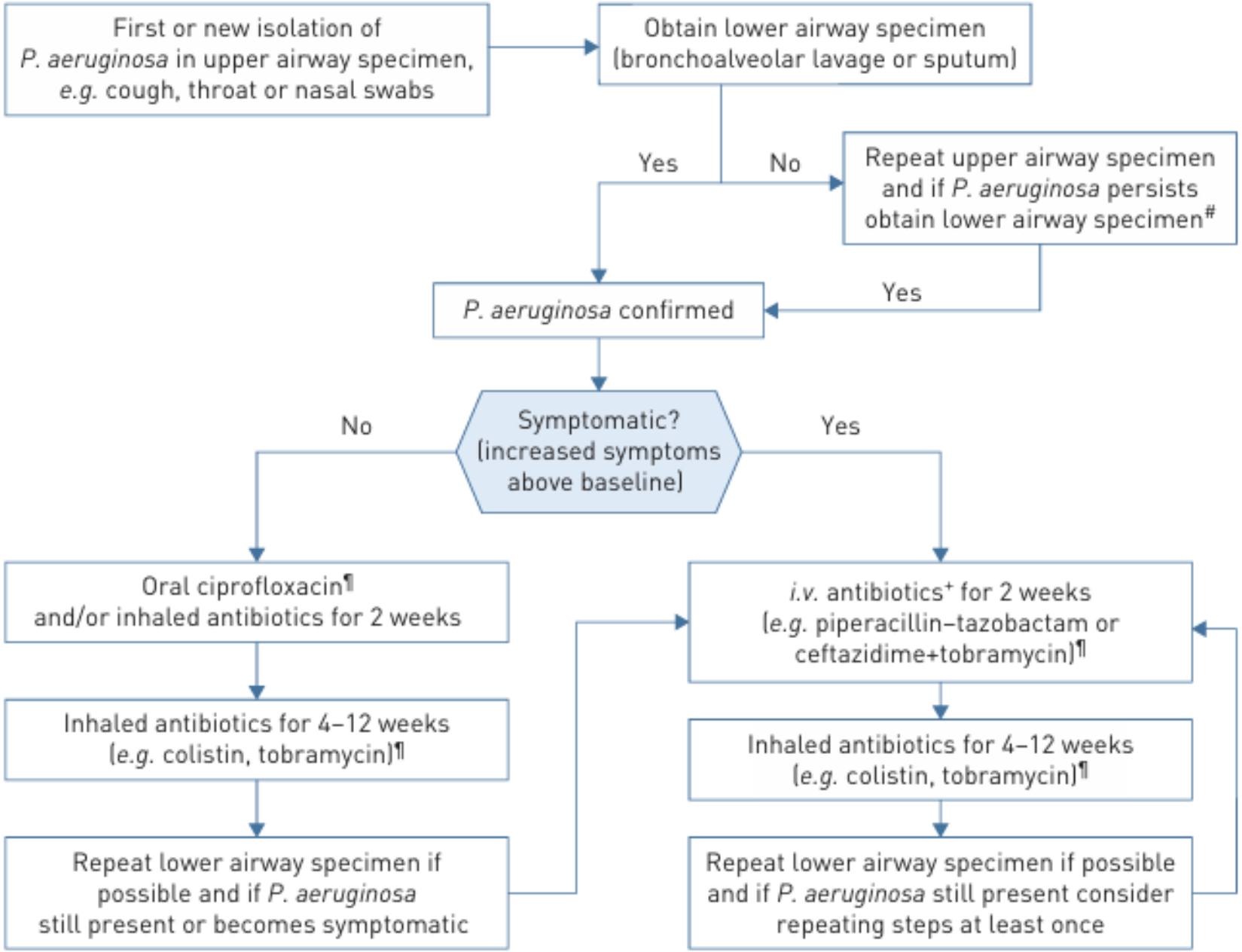
- More recently, inhaled colistin was evaluated in the UK in 144 patient s with bronchiectasis and Pseudomonas infection..
- However, for patients adherent to more than 80% of doses, **the median time to exacerbation was statistically significantly increased to** 168 days in the colistin group from 103 days in the place bo group.
- Trials of **liposomal ciprofloxacin** (ORBIT 4) and **dry powder ciprofloxacin** (RESPIRE 1) have been completed. Exacerbation reduction was significantly reduced in RESPIRE 1 and ORBIT 4 but not duplicated in t heir parallel trials

Antimicrobial Therapy: Aerosolized Antibiotics

- In summary, use of aerosolized antibiotics in treatment of acute exacerbati ons of non CF related bronchiectasis remains controversial.
- Aerosolized
  antibiotics appear to have a clear microbiologic impact, but their clinical eff icacy has not yet been conclusively proven, and none is currently approved by regulatory agencies.
- Importantly, the emergence of clinically relevant resistant pathogens has n ot been yet observed.
- **Metaanalyses have reported**
  that aerosolized antibiotics are generally safe and better than placebo in reducing bacterial load.

Antimicrobial Therapy: Aerosolized Antibiotics

- A number of professional societies, including the European Respiratory Society, the British Thoracic Society, and the Th oracic Society of Australia and New Zealand have suggested that long term nebulized antibiotics should be considered for those individuals with chronic Pseudomonas aeruginosa infection, those experiencing frequ ent exacerbations (>3/year), and when other therapies have been optimiz ed.
- Unanswered questions on the use of aerosolized antibiotics include a dministration schedule (daily versus cycling, e.g., 28 days off/on) and their role in comparison with chronic macrolide therapy.



Chang AB, et al.
EurRespirJ2021;58: 2002990

Airway Clearance Techniques

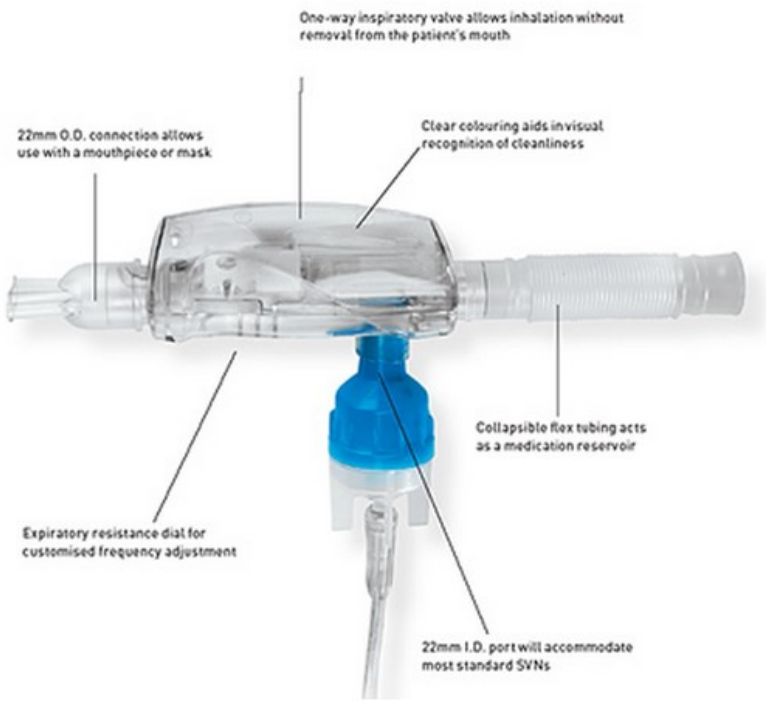
- Airway clearance techniques (ACT) are those designed to enhance mucocili ary clearance.
- The goals of ACT are to **improve symptoms, reduce exacerbation frequency, and improve quality of life.**
- There are a number of modalities, both **mechanical and pharmacologic**, us ed in clinical practice.
- ACT are safe, but there is little strong evidence to establish their efficacy.
- **However, published guidelines have recommended the use of ACT, particularly for individuals with chronic productive cough or those who h ave difficulty expectorating sputum.**

ERS 2021 guideline

- In children/adolescents with bronchiectasis, we recommend that **recombinant human DNase (rhDNase) is not used routinely**. (Strong recommendation, very low quality of evidence.)
- In children/adolescents with bronchiectasis, we suggest that **bromhexine** is **not used routinely**. (Conditional recommendation, very low quality of evidence.)
- In children/adolescents with bronchiectasis, **we suggest that neither inhaled mannitol nor hypertonic saline are used routinely.** (Conditional recommendation, very low quality of evidence.)

Mechanical Modalities

- Mechanical modalities to facilitate airway clearance include **positive e xpiratory pressure devices and highfrequency oscillation modalities**.
- Use of positive expiratory pressure (PEP) devices is based on generati on of positive expiratory pressure when an individual exhales against f ixed
  resistance, thereby preventing airway closure and promoting mobiliza tion of airway secretions.
- **Several PEP devices are available, including Acapella, Aerobika, and Flutter.**
- These devices are the most commonly utilized ACTs in the United Stat es, as reported by the U.S. Bronchiectasis Registry.



Flutter

Oscillating PEP with an Acapella – mouthpiece, mask and nebuliser attached to Acapella Duet

positive expiratory pressure (PEP) devices

Mechanical Modalities

- Asmall, randomized, 3month crossover trial of the **Acapella** device reporte d an improvement in total LCQ, increased 24h sputum volume, and improved exercise capacity.
- No change in spirometry or sputum microbiology were reported. Additiona l studies are necessary to establish the benefit of PEP devices.
- With **highfrequency chest wall oscillation**, external chest oscillations are a pplied to the chest using a fitted vest.
- Once again, convincing data on efficacy, both short and longterm, are lacking; however, enhanced sputum expectoration and quality of life, and a decrease in hospitalization for exacerbations have been suggested.

Highfrequency chest wall oscillation

High-frequency chest wall oscillation involves an inflatable vest that is attached to a machine.

The machine mechanically performs chest physical therapy by vibrating at a high frequency.

The vest vibrates the chest to loosen and thin mucus. Every five minutes, the person stops the machine and coughs or huffs.

Maddie, a young adult with CF, doing chest physical therapy with a vest.

Bu cihazlar, markalarıyla bilinebilir (The Vest® Sistemi, inCourage®, Smart Vest® ve AffloVest®).

https://www.cff.org/managing-cf/high-frequency-chest-wall-oscillation-vest

Pharmacologic Agents

- A variety of pharmacologic approaches have been employed in facilitating airway clearance.
- The most common are considered below.
- **Hyperosmolar agents, including inhaled mannitol and hypertonic saline, a re commonly used agents.**
- A phase 3, multicenter, randomized, controlled, doubleblind clinical trial of **inhaled mannitol** in 485 patients did not reveal a statistically significant reduction in the rate of acute exacerbations.
- There were statistically significant improvements in time to first exacerbation and QOL. Therapy was well tolerated.

Pharmacologic Agents

- Use of **hypertonic saline** is part of **standard care for CF** and has been demo nstrated to reduce the frequency of pulmonary exacerbations and, perhaps , improve quality of life.

- It is available in 3% and 7% formulations.

- Small clinical studies in bronchiectasis suggest a decrease in sputum viscosi ty and a
decrement in disease exacerbations, but more definitive data are lacking.

- Reported associated adverse effects include throat irritation, salty taste, an d dyspnea.

Pharmacologic Agents

- Use of bronchodilator agents, such as **albuterol**, have generally not been fo und to enhance bronchopulmonary hygiene.
- Although use of **recombinant human deoxyribonuclease (rhDNase)** has be en shown to be efficacious in individuals with cystic fibrosis, in a large clinical trial, pulmonary exacerbations were found to be more frequent and decline in FEV1 greater in patients with nonCF bronchiectasis who receive d rhDNase.
- Therefore, the agent should not be used routinely in bronchiectasis.
- This underscores the principle that extrapolation of data on treatment for patients with cystic fibrosis to those without cystic fibrosis be done caut iously.

Pharmacologic Agents

- **In summary,**
- **ACT should be considered in symptomatic patients, in those who ha ve chest congestion and difficulty expectorating sputum, and, perhaps, in those with frequent exacerbations.**

- In the absence of data, the modality chosen should be one that maxi mizes patient adherence and minimizes expense.

Anti Inflammatory Therapy

Anti inflammatory therapy for bronchiectasis includes **macrolides and other pharmacologic agents.**

Macrolide Antibiotics

- Macrolide antibiotics have been a focus of study because of their myriad anti **inflammatory and immunomodulatory properties.**
- Among other effects, macrolides
- inhibit mucus hypersecretion,
- reduce IL8 and neutrophil elastase,
- inhibit neutrophil adhesion to epithelial cells,
- reduce biofilm formation, and
- inhibit production of reactive oxygen species from neutrophils.

Anti Inflammatory Therapy

- **The EMBRACE trial** was carried out at three centers in New Zealand.
- A total of 141 patients who had at least one exacerbation in the prior year were treated with thrice weekly azithromycin versus placebo for 6 months.
- **Those receiving azithromycin were found to have a 62% reduction in the rate of acute exacerbations at both 6 and 12 months,** as well as increased time to first e xacerbation. There were no significant differences in FEV1, SGRQ, or 6 min walk test distance.
- **The BAT trial** from the Netherlands included patients who had experienced at lea st three exacerbations in the previous year.
- A total of 83 patients were treated with **azithromycin 250 mg daily or placebo for 12 months**. An absol ute **risk reduction of 33.5%** was demonstrated in those taking azithromycin.
- **A 1.03% increase in FEV1 per 3 months** versus a decrement of 0.1% in the placeb o group also was noted.

Anti Inflammatory Therapy

- **The BLESS trial,** the largest of the three trials, was conducted in Australia.
- Of 679 screened patients, 107 completed a double blind, placebo controlled, singlecenter trial.
- Enrolled individuals had at least 2 exacerbations in the preceding 12 month s and were treated with **erythromycin, 40 mg twice daily,** for 48 weeks (with a 4week washout) versus placebo.
- A significant reduction in the rate of protocol defined pulmonary exacerbations from **1.97** in the placebo group to 1.29 in the treatment group was reported.
- In addition, a reduction in 24h sputum production and a 2.2% attenuation i n the rate of FEV1 decline were noted.

Anti Inflammatory Therapy

- **At present, macrolide therapy may be targeted specifically to those patients with frequent exacerbations (>3/year), normal ECG, and no significant underlying cardiac disease.**
- **Macrolides should be avoided** in patients with known or strongly suspected **non tuberculous mycobacterial infection** in whom macrolide monotherapy is the main risk factor for development of macrolide resistance, which is associated with a poorer prognosis, including increased mortality.

- **The optimal duration of treatment has not yet been established.**
- Little published data are available to guide a decision on when to use inhaled antibiotics versus long term macrolide treatment.

Anti Inflammatory Therapy

- The 2017 ERS guidelines suggest that **inhaled antibiotics** be used in patients with **chronic Pseudomonas infecti on and ≥3 exacerbations per year.**

- **Macrolides can be used in those with frequent exacerbations with non Pseudomonas pathogens or those who exhibit intolerance or lack of efficacy with inhaled antibiotics.**

- **Combined therapy with a macrolide and inhaled antibiotics may be considered when there is a suboptimal response to either agent alone.**
- Use of macrolide antibiotics in bronchiectasis is certainly not without other concerns.
- These include commonly reported adverse **gastrointestinal symptoms, ototoxicity, and possible development of bacterial antibiotic resistance.**
- In addition, a small risk of a **sudden cardiac event**, particularly in those at highest risk for cardiovascular disease.

Other Pharmacologic Therapies

Brensocatib,

- an oral, reversible inhibitor of **dipeptidyl peptidase 1 (DPP1)**,

an enzyme responsible for activating neutrophil serine proteases (NSPs, **such as neutrophil elastase**), was recently reported to be well tolerated and associated with a significant reduction in the rate of exacerbation and
significantly prolonged time to first exacerbation over 24 weeks versus placebo.

- An international phase 3 trial is currently underway.

Other Pharmacologic Therapies

- **A rotating antibiotic strategy** was commonly employed by clinicians in the past.
- In general, there is no evidence to support the use of systemic, non macrolide, suppressive, or maintenance therapy.
- **Inhaled or chronic systemic corticosteroids should not be used routinely** in bron chiectasis unless indicated for other comorbidities, such as asthma or COPD.
- There have been reports of an increased risk of nontuberculous mycobacterial inf ection associated with inhaled corticosteroid therapy.
- Specific therapy should obviously be used in patients with significant underlying d isorders.
- **Examples include immunoglobulin replacement for CVID, systemic corticosteroids and antifungal agents for ABPA, α1antitrypsin augment ation therapy in α1antitrypsin deficiency, and guideline based antibiotics for non tuberculous mycobacterial infection.**

Surgery

- No robust prospective data are available comparing surgical resection to m edical therapy for individuals with bronchiectasis.
- Surgery for selected patients can be accomplished with acceptable morbidi ty and mortality.
- **Surgery is an option to be considered for those with**

➢**massive hemoptysis refractory to other measures, such as bronchial arter y embolization;**

➢**those with localized bronchiectasis who have frequent exacerbations des pite medical therapy;**

➢**and as an adjunct to antibiotics for patients with nontuberculous mycobacterial infection.**

Supportive Measures

- Important supportive measures for bronchiectasis include appropriat e **vaccination**, **supplemental oxygen for associated hypoxemia**, and **p ulmonary**
  rehabilitation therapy for those with functional impairment.

- Short courses of systemic corticosteroids for bronchospasm associate d with some exacerbations may be warranted.

- Finally, **lung transplantation** can be successfully utilized in patients wi th advanced disease.

The natural history and prognosis of bronchiec tasis

- The natural history and prognosis of bronchiectasis are not well described.
- A study of 91 patients in the United Kingdom followed consecutively over 13 years starting in the mid1990s demonstrated a **mortality rate of 29.7%.**
- This was higher than the expected death rate for males and females of 14.7% and 8.9%, respectively, in an age matched cohort. Of note, **respiratory causes accounted for about 70% of a ll deaths.**
- Predictors of mortality in this study included **older age, history of Pseudomonas aeruginosa infectio n, impaired lung function, and poor quality of life.**

SUMMARY AND FUTURE DIRECTIONS

- In summary, **bronchiectasis is a heterogeneous clinical entity** that is more common and clinically impactful than previously thought.

- Recurrent
  respiratory infections and impairment of quality of life are its clinical hallm arks. Prompt and accurate diagnosis requires vigilance for suggestive clinical signs and symptoms and initiation of objective studies. Treatment is multifaceted and includes both specific and supportive measures, many of which have limited evidencebased support. Despite progress, much work li es ahead to expand basic knowledge of the pathophysiology of bronchiectasis and potential novel treatment options.

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Thank you for your attention,
have a great meeting…