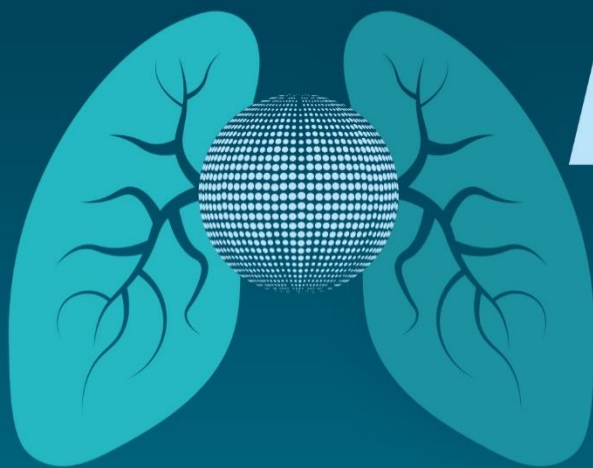




7th WORLD BRONCHIECTASIS CONFERENCE

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RISING STARS

Chemical and genetic effects on mycobacterial drug combinations

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Background/Aims:

Combination therapies have great potential to enhance antibacterial efficacy, but their clinical benefits and performance in multi-drug trials have often been disappointing. *Mycobacterium abscessus*, a highly resistant pathogen responsible for increasing respiratory infections worldwide, exemplifies this challenge, as extensive and prolonged multi-drug regimens mostly fail. In this study, we sought to systematically assess *M. abscessus* drug combinations to uncover general principles of drug interactions.

Methods:

We assessed 50 drugs with antibacterial activity in *M. abscessus* individually, in every possible pairwise combination (checkerboards), and in combination with 2582 inactive compounds encompassing antibiotics, food additives, and human-targeting drugs. Additionally, we tested 28 commonly used combinations against clinical *M. abscessus* isolates from 271 patients with *M. abscessus* lung infections (diagonal checkerboard approach for each combination and isolate) and mapped interaction phenotypes to whole-genome sequencing data of each isolate. All interactions were experimentally analysed in quadruplicate and quantified using optical densities.

Results:

When combining drugs with anti-*M. abscessus* activity, including many of the used antibiotic combinations, synergistic and especially antagonistic interactions were common and frequently shared within antibiotic classes. Moreover, compounds inactive against *M. abscessus* often influenced the activity of effective drugs. Organising 2582 such compounds in chemical space revealed clusters of functionally related groups, enhancing or decreasing antibiotic potency. To understand the role of bacterial genetic backgrounds in drug interactions, we tested 28 clinically relevant drug combinations on 271 clinical *M. abscessus* isolates. We found that interactions were highly heterogeneous and that interaction phenotypes commonly converged with phylogenetic clades, suggesting a genetic basis for these interactions. Finally, via genome-wide association studies (GWAS), we identified genes and genetic variants driving antibiotic synergy and antagonism.

Conclusions:

This comprehensive analysis of drug combinations, with over 1.2 million performed assays, provides an unprecedented glimpse into the complex landscape of drug interactions in *M. abscessus*. Our findings highlight the chemical and genetic determinants of drug

interactions, offering insights into the challenges of current antibiotic treatments and proposing targets for enhancing combination treatment efficacy against multi-resistant bacterial pathogens.

Conflict of interest(s):

no

The relationship between blood eosinophil count, airway eosinophilic inflammation and bronchiectasis disease severity: data from the EMBARC-BRIDGE study

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Background/Aims: Eosinophilic bronchiectasis has been defined by a blood eosinophil count >300cells/μL in the absence of asthma or ABPA. Blood eosinophil counts are an imperfect surrogate of airway eosinophilic inflammation. Whether airway eosinophilic inflammation relates to bronchiectasis severity is unknown.

Methods: Sputum from patients enrolled in a prospective observational study (EMBARC-BRIDGE) was assayed using a novel liquid chromatography-mass spectrometry (LC-MS)-based assay for the parallel detection of eosinophil cationic peptide (ECP), eosinophil peroxidase (EPX), major basic protein (MBP), eosinophil derived neurotoxin (EDN) and galectin-10 (Gal-10). Resulting proteomic data were analysed for relationships with clinical parameters.

Results: 180 patients were included (mean age 67 years, SD 12.4), 55% female, mean severity index score 7.0 (SD 3.9). All eosinophil biomarkers were detectable in sputum by LC-MS. Eosinophil biomarkers were highly correlated in sputum (Spearman $r = 0.5-0.9$) and airway eosinophil proteins were significantly elevated in those with elevated blood eosinophil counts (>300cells/μL vs <150cells/μL, $p=0.005$, **Fig1A**). All eosinophil proteins were significantly elevated in the 10.5% infected with *P. aeruginosa* ($p=0.0019$, **Fig1B**). Gal-10, ECP and EDN correlated with FEV1% predicted (Gal-10 $r=-0.20$, $p=0.01$; ECP $r=-0.25$, $p=0.001$; EDN $r=-0.24$, $p=0.002$) and Reiff radiological severity score (Gal-10 $r=0.24$, $p=0.001$; ECP $r=0.24$, $p=0.001$; EDN $r=0.23$, $p=0.002$).

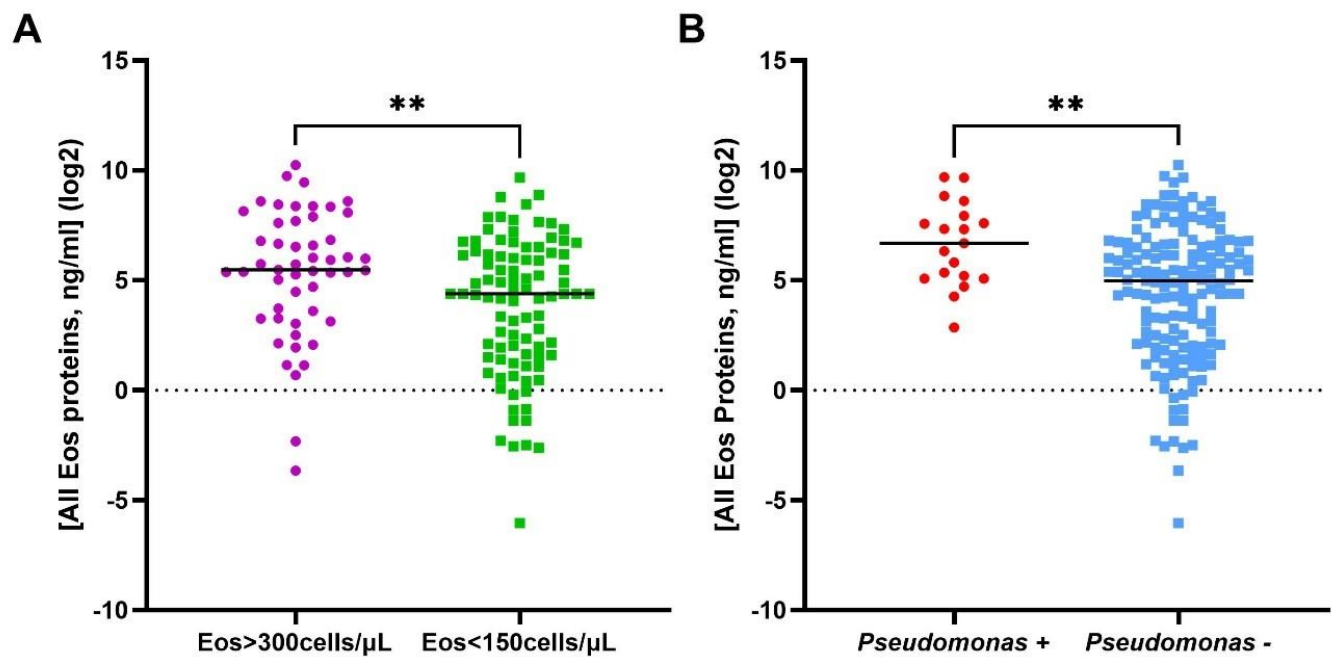


Fig1: Eosinophil proteins were significantly elevated in those with peripheral blood eosinophilia (A) and in those culturing *Pseudomonas aeruginosa* (B). Data are presented as log2 of the mean protein concentration (measured in ng/ml).

Conclusions: Airway eosinophilic inflammation can be quantified using a novel LC-MS assay and associates with *P. aeruginosa* infection and disease severity in those with bronchiectasis. Airway eosinophilic inflammation is only modestly correlated with blood eosinophil count in bronchiectasis.

Conflict of interest(s) (if any – not included in the 500 words): This work was supported by the Innovative Medicines Initiative (IMI) and EFPIA companies under the European Commission funded project, iABC (grant 115721) and by the European Respiratory Society through the EMBARC3 consortium. EMBARC3 is supported by project partners Armata, AstraZeneca, Boehringer-Ingelheim, Chiesi, CSL Behring, Grifols, Insmmed, Janssen, LifeArc and Zambon. This work was funded by an independent research grant from AstraZeneca.

ORAL COMMUNICATIONS

Mycobacterial drug tolerance assessments reveal clinical outcomes

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Background/Aims:

Antimicrobial susceptibility testing is critical for drug development and guiding treatment of mycobacterial infections. However, *in vitro* drug assessments often do not translate into clinical outcomes, causing unexplained treatment and trial failures. Conventional susceptibility measures evaluate bacterial growth across different antibiotic concentrations but not bacterial killing, which may be required to clear long-lasting infections. By overcoming the poor scalability and reproducibility of killing assessments, we establish the relevance of sterilising anti-mycobacterial activity in *Mycobacterium abscessus*, a particularly difficult-to-treat pathogen causing increasing rates of chronic pulmonary infections globally.

Methods:

We developed Antimicrobial Single-Cell Testing (ASCT), an experimental and analytical platform for quantifying bacterial killing at scale. Herein, we immobilise, successively image and automatically track millions of bacteria using AI-driven image analysis, to evaluate single-cell dynamics and population time-kill kinetics.

Results:

With ASCT, we assessed over 7000 kill curves in *M. abscessus* isolates from more than 300 patients and found various time-kill profiles across and within the drugs tested, indicating that bacterial killing is a fundamental bacterial phenotype. The distinct killing rate of each isolate (drug tolerance) was not related to drug resistance (MIC) and was genetically determined, as revealed through whole-genome sequencing. Cefoxitin and Imipenem killing, which were most rapid and presumably drive mycobacterial clearance in *M. abscessus* lung disease, were associated with clinical outcomes in patients (tolerant isolates with persisting infection, non-tolerant isolates with *M. abscessus* clearance). Importantly, antimicrobial tolerance was independent and additive to resistance measurements and predicted, in contrast to resistance, lung function decline during mycobacterial infection. Finally, by applying a genome-wide association study (GWAS) approach, we discovered several potential molecular mechanisms underlying mycobacterial multi-drug tolerance.

Conclusions:

We present Antimicrobial Single-Cell Testing for assessing sterilising antibiotic activity, demonstrate highly diverse killing kinetics in *M. abscessus* and validate its importance via predicting clinical outcomes, thereby reducing the gap between *in vitro* assessments and *in*

vivo antibiotic efficacy. Our findings highlight the relevance of antimicrobial killing mechanisms, could advance anti-mycobacterial drug development and personalise treatment decisions in patients.

Conflict of interest(s) (if any – not included in the 500 words):

Cluster analysis identifies distinct sputum inflammatory profiles in bronchiectasis: data from the EMBARC-BRIDGE study

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Background/Aims:

Bronchiectasis is a chronic inflammatory lung disease. The pathways underlying excessive inflammation in the lungs of bronchiectasis patients are not fully understood. We explored the relationship between sputum levels of antimicrobial peptides, inflammatory cytokines and the known bronchiectasis severity marker neutrophil elastase.

Methods:

We used soluble sputum from 190 patients with bronchiectasis recruited to the Bronchiectasis Research Involving Databases, Genomics and Endotyping (BRIDGE) study (NCT03791086). The antimicrobial peptides SLPI and α -defensin-3 were measured by ELISA and 45 inflammatory cytokines were measured using Olink® Target 48 proximity extension assay. Cluster analysis was performed using the K-means algorithm. Differences in markers between clusters were tested using Kruskal-Wallis tests. The relationship between NE activity in sputum and biomarkers was examined by Spearman rank correlations.

Results:

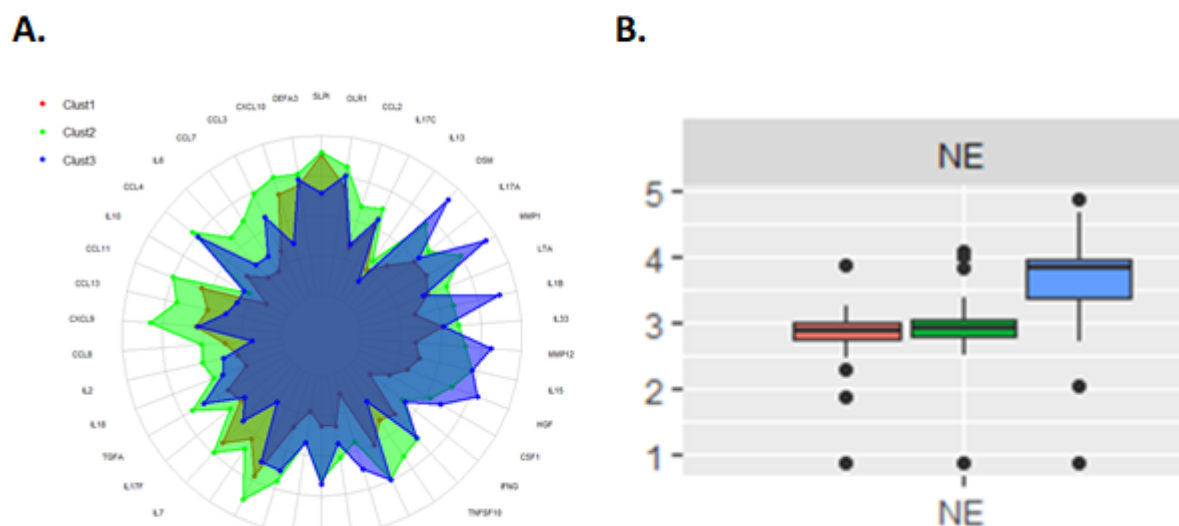
We identified three distinct clusters of patients differentiated by inflammatory protein and cytokine levels (Figure). Cluster 1 (red) had low levels of most markers. Cluster 2 (green) had high levels of antimicrobial peptides and of the interleukins IL2, IL7, and IL18; the chemokine ligands CCL3, CCL7, CCL8, CCL11, CCL13 and CCL19; the chemokine (C-X-C motif) ligands CXCL9 and CXCL10; Epidermal growth factor and Transforming growth factor A. These cytokines are predominantly chemotactic for monocytes, macrophages, dendritic cells, T-cells and/or eosinophils or mediators of epithelial repair. Cluster 3 (blue) was defined by high levels of IL-1 β and Tumour necrosis factor alpha (both of which are markers of neutrophilic inflammation and are associated with severe disease in bronchiectasis) as well as Matrix metalloproteinases 1 and 12, hepatocyte growth factor and Oncostatin M. (FDR adjusted p-values <0.001 for all differences in markers between clusters). Median sputum NE was 730ng/ml (IQR 525-981) in Cluster 1, 794ng/ml (IQR 602-1088) in cluster 2 compared to 6312ng/ml (IQR 2293-8621) in cluster 3 (p<0.001). A statistically significant inverse correlation, where high levels of NE were associated with lower levels of each

marker, was observed for SLPI, IL7, IL13, CCL2, CCL7, CCL8, CCL11, CCL13, CCL19, CXCL9, CXCL10, CXCL11, EGF and LTA after FDR correction.

Conclusions:

Cluster analysis revealed distinct inflammatory profiles in the airways of bronchiectasis patients. Our data suggest a cluster with overall low levels of inflammation (Cluster 1), a cluster defined by neutrophilic inflammation (Cluster 3) and a non-neutrophilic cluster defined by other inflammatory pathways (Cluster 2). Further research into these distinct inflammatory profiles and their clinical associations could inform endotype-guided treatment approaches.

Figure: A. Cluster analysis showing three distinct clusters of patients defined by levels of antimicrobial peptides and inflammatory cytokines. B. Box plot showing difference in mean sputum neutrophil elastase between clusters



Conflict of interest(s) (if any – not included in the 500 words):

ARINA-1 Demonstrates Improved Quality of Life in a Phase 2a, Randomized, Double-blind, Placebo-controlled Study in Individuals with Non-CF Bronchiectasis (NCFBE) with Excess Mucus and Cough (RVN-301)

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Background/Aims:

Excessive mucus production contributes to disease progression and symptom burden in non-CF bronchiectasis (NCFBE). Currently, there are no approved therapies targeting mucus and symptom burden in NCFBE. ARINA-1 (ascorbic acid/reduced glutathione) is an investigational nebulized treatment that directly upregulates mucus clearance by reducing mucus viscosity. This study aimed to determine the safety of ARINA-1 in NCFBE and explore its impact on quality of life (QOL) and mucus rheology and neutrophil elastase (NE).

Methods:

Forty participants were randomized (7:3) to receive either ARINA-1 or control (0.9% isotonic saline) nebulized twice daily for 28 days. Eligible participants included adults with confirmed NCFBE and a Chronic Airways Assessment Test (CAAT) score >10 and ≥2 on question 2. Patients were followed for an additional 28 days off study drug. The primary endpoint was the comparison of treatment-emergent adverse events (TEAEs) between the two arms. Secondary endpoints included changes in QOL measured using the St. George's Respiratory Questionnaire [SGRQ; minimally clinically important difference (MCID) -4] and CAAT (MCID -2). Exploratory endpoints included change of sputum rheology and NE. A prespecified responder analysis was assessed based on achieving the SGRQ MCID. All efficacy data are shown as the mean change (standard deviation) from baseline in the ITT population.

Results:

Forty participants were randomized to ARINA-1 (72%, n=29) or control (28%, n=11). Twenty-five (86%) participants in the ARINA-1 arm experienced a TEAE compared to five (45%) in the control arm. All the TEAEs were expected for a nebulized medication, with the most common TEAEs being cough and dyspnea.

Notable improvements in QOL were observed in the treatment arm. The mean changes in the SGRQ total score and subdomains exceeded the MCID at days 28 and 56 of the study. The mean change in the SGRQ total score at day 28 in the ARINA-1 arm was -8.5 (10.75); the control group did not demonstrate an MCID at day 28 [-2.6 (SD 13.63)]. At day 56, the treatment arm improvement persisted [-6.1 (11.64)]. The control arm remained unchanged with -1.4 (13.18). In the treatment arm, the CAAT improved by -3.7 points (5.07) at day 28 but returned to baseline at day 56 [-1.5 (1.07)]. The CAAT scores in the control arm remained unchanged (day 28, -1.3 (4.71); day 56, -0.5 (3.98)]. In the pre-specified responder analysis for the SGRQ, 62% of the participants in the ARINA-1 arm and 27% of the control

arm had an MCID response at day 28. Exploratory analyses at day 28 demonstrated a signal toward improved mucus viscosity and NE in the ARINA-1 arm while the control arm remained unchanged.

Conclusions:

ARINA-1 was safe and tolerable for participants after 28 days of use and demonstrated improved QOL. Exploratory analyses suggest a signal toward improved sputum viscosity and NE, complementing previous studies demonstrating ARINA-1's impact on mucus clearance and potential to improve QOL. Overall, ARINA-1 shows promise as a therapy for individuals with NCFBE, and further studies are warranted.

Conflict of interest(s) (if any – not included in the 500 words):

Clinical trial sponsored by Renovion, Inc.

The profile of blood methylation is associated with disease severity in bronchiectasis

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Background/Aims: DNA methylation integrates host exposures and can lead to cellular changes and influence disease status. This has not been explored before in bronchiectasis (BE). Here we studied the association of the blood DNA methylation profile with BE severity (measured by the Bronchiectasis Severity Index) (BSI), and type and intensity of lung inflammation.

Methods: The blood DNA methylation profile was determined in 167 clinically stable BE patients (Illumina 850k), split into a discovery (n=94) and a validation cohort (n=73). Differentially methylated positions (DMPs) associated with BSI were determined using sex-adjusted linear models. Gene set Enrichment Analysis was used for functional enrichment. Blood RNA-seq was studied in a subset of patients (n=57), and sputum neutrophil elastase levels were measured by ELISA in these patients.

Results: In the discovery cohort we identified 251 BSI-associated DMPs (p-aj<0.05), 89% of which were hypomethylated in more severe patients (BSI>9); 98% of them were validated in the second cohort. BSI-associated DMPs were enriched in leukocyte activation, migration and adhesion pathways. Methylation and mRNA expression levels were significantly related with 35 DMPs, which in turn were associated with neutrophils, T and B cells. Finally, the methylation and expression levels of 12 DMPs were related to sputum neutrophil elastase levels.

Conclusions: Severe BE patients have a distinct blood methylation profile, associated with functional changes and lung inflammation, suggesting a systemic effect of BE, and identifying potential novel biomarkers and therapeutic targets.

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Conflict of interest(s) (if any – not included in the 500 words): LP, JV, BS, NM, SCR, PMO, PM, RA and OS report no conflict of interest. AA reports honoraria from AstraZeneca, Chiesi, GSK, Menarini, MSD, Sanofi and Zambon; and research grants from AstraZeneca, GSK and Menarini. AS reports Consulting fees from Spirovant and Translate Bio; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Translate Bio, Ethris and Insmed; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid - Involvement in European Respiratory Society Clinical Research Collaborations (EMBARC, BEATPCD, AMR). JDC reports Grants or contracts from AstraZeneca, Boehringer Ingelheim, Genentech, Gilead Sciences, GlaxoSmithKline, Grifols, Insmed, LifeArc and Novartis; Consulting fees from Astrazeneca, Chiesi, GlaxoSmithKline, Insmed, Grifols, Novartis, Boehringer Ingelheim, Pfizer, Janssen,

Antabio and Zambon. **RF** reports Grants or contracts from AstraZeneca, Chiesi, GSK, Menarini, ISCIII, ERC, FEDER; Payment from AstraZeneca, Zambon and Chiesi.

Highly symptomatic patients have an increased risk of exacerbations and benefit from long-term macrolide treatment in Bronchiectasis

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Background and Aims: Prior exacerbations are the main risk factor for exacerbations in bronchiectasis. Guidelines recommend macrolide only in frequent exacerbators. Other studies suggest that symptoms are related to increased exacerbation risk. We aimed to investigate if symptoms could independently predict future exacerbations and identify responders to long-term macrolide therapy.

Methods: Prospective observational study including 8328 patients from EMBARC registry with symptoms (Quality-of-life questionnaire Bronchiectasis (QoL-B) at baseline) and follow-up for at least one year, and posthoc analysis of 3 randomized clinical trials (RCTs) of macrolides in 341 bronchiectasis patients.

Results: Prior exacerbations (RR for every exacerbation=1.10, 95%CI 1.09-1.11, $p<0.001$) and symptoms (RR for every 10 points lower QoL-B=1.10, 95%CI 1.08-1.11, $p<0.001$) were identified as independent risk factors for future exacerbations in the EMBARC registry. The expected number of exacerbations in 1-year was similar between the group with 3 prior exacerbations and average symptom scores (1.49, 95% CI 1.38-1.60) and the group with no prior exacerbations but high symptom scores (1.47, 95% CI 1.34-1.60). The same pattern was observed in the post-hoc analysis of RCTs, both in macrolide and placebo arms. The number needed to treat to prevent exacerbations with macrolides was similar among patients selected based on frequent exacerbations and in those with no prior/few exacerbations but high symptom scores.

Conclusions: Symptoms are an independent risk factor for exacerbations in bronchiectasis, and highly symptomatic patients may benefit from long-term macrolides.

Conflict of interest(s) (if any – not included in the 500 words): The first author, OS, reports no conflict of interest. The last author, JDC, reports Grants or contracts from AstraZeneca, Boehringer Ingelheim, Genentech, Gilead Sciences, GlaxoSmithKline, Grifols, Insmmed, LifeArc and Novartis; Consulting fees from Astrazeneca, Chiesi, GlaxoSmithKline, Insmmed, Grifols, Novartis, Boehringer Ingelheim, Pfizer, Janssen, Antabio and Zambon. The conflict of interest of the rest of the authors is now being collected and they will be stated in the final presentation of the work during the congress.

Disease Phenotype In Bronchiectasis (Ntm- And Ntm+) Is Associated With Lower Airway Dysbiosis And Neutrophil Extracellular Traps

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RATIONALE: Non-tuberculous mycobacterial pulmonary disease (NTM-PD) is commonly associated with bronchiectasis. Here, we investigated the lower airway microbiome and bronchoalveolar lavage (BAL) neutrophil extracellular trap (NET) levels as associated with disease phenotypes in NTM-/± bronchiectasis.

METHODS: BAL samples were collected from bronchiectasis subjects (108 NTM-, 92 NTM+) undergoing clinically indicated bronchoscopies. Samples underwent 16S rRNA sequencing and were analyzed using QIIME2, PhyloSeq and EdgeR. Host immune signatures (NET ELISA assay in 184 subjects and transcriptomic gene expression in 43 subjects) associated with disease phenotypes (cavitary disease, exacerbator profile) were also investigated.

RESULTS: Upon investigation of the lower airway microbiota, there were no significant differences in the 16S rRNA gene copies/mL, alpha diversity and beta diversity of NTM- and NTM+ subjects but differential taxonomical enrichment was noted between the groups (**Fig. 1A**). Dirichlet Multinomial Modeling (a clustering method) identified three microbial metacommunities that were unique in bacterial burden, diversity and composition and were marked by the predominance of background contaminants (cluster 1), oral commensals (cluster 2) and *Pseudomonas* (cluster 3), respectively (**Fig. 1B**). NET levels were significantly higher in the NTM+ group ($p < 0.001$) and significantly different between the DMM clusters (**Fig. 1C**, $p < 0.001$). Significant cluster differences were also noted between BAL neutrophil, macrophage and lymphocyte cell count differentials (**Fig. 1D**). A biplot analysis of the taxa distribution showed that a higher abundance of *Pseudomonas* was associated with higher NET levels and neutrophil counts in NTM- subjects (**Fig. 1E**) whereas the same was noted for *Mycobacteria* in NTM+ subjects (**Fig. 1F**). NET Levels were significantly higher in patients with cavitary or exacerbator phenotypes. Bray Curtis Dissimilarity and differential taxonomic enrichment was noted in subjects with cavitary disease (*Pseudomonas*) and exacerbator phenotype (*Hemophilus*). The host transcriptome was investigated in 43 subjects and variable gene expression was found between NTM-/NTM+ subjects, NTM+ subjects with/without cavitary lesions and NTM+ subjects with/without an exacerbator profile. Unsupervised hierarchical heatmap of canonical pathways analyzed using the host transcriptome of NTM+ subjects showed the up-regulation of NET, IL-8, senescence, IL-17, autophagy and PI3K/AKT signaling (**Fig. 1G**).

CONCLUSIONS: In this study, we have demonstrated that the lower airway microbiome in bronchiectasis is compositionally different between NTM- and NTM+ subjects. NET levels are significantly different between lower airway metacommunities. Higher NET levels/increased NET gene expression was noted in NTM+ and *Pseudomonas*+ patients as well as those with more aggressive disease, illustrating that the taxonomic drivers of neutrophilic/severe disease phenotypes are disparate in NTM-/NTM+ subjects.

Conflict of interest(s) (if any – not included in the 500 words): No Conflict of Interests to Declare.

Clinical characteristics, treatment, and outcomes of patients with *M. avium* complex pulmonary disease: results from the IRENE registry.

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Abstract

Introduction: *Mycobacterium avium* complex (MAC) pulmonary disease (PD) is a health concern worldwide. Understanding epidemiology, clinical characteristics, and management of MAC-PD patients in a real-life setting is key. An Italian registry of patients with non-tuberculous mycobacteria (NTM) pulmonary infection has been recently implemented.

Methods: The IRENE registry is an observational prospective cohort study of adults with NTM pulmonary infection enrolled from 2017 to date across 79 centers in Italy. Patients with MAC-PD were evaluated according to the 2020 ATS/ERS/ESCMID/IDSA Guidelines. Those with either cystic fibrosis or concomitant infection with MAC and other NTM were excluded.

Results: 705 patients [median (25-75 IQR) age: 69 (60-75) years; 74.9% female] with MAC-PD were evaluated: 9.8% had a fibro-cavitary disease, while 47.2% were smear positive. Among those with a drug susceptibility testing done, at least one macrolide-resistant (500 patients evaluated) or amikacin-resistant (402 patients evaluated) mycobacteria was identified in 3.8% and 8.2% of patients, respectively. 576 (81.7%) patients underwent treatment. Median (IQR) time from MAC-PD diagnosis to treatment initiation was 160 (46-738) days and 51.6% of the patients underwent treatment within 6 months from diagnosis. Treatment was adherent to the 2020 ATS/ERS/ESCMID/IDSA guidelines in 73.8% of the patients. The median (IQR) duration among those who completed treatment was 561 (396-717) days. At least one treatment-related adverse event was recorded in 45.1% of the patients. 61 (8.7%) patients were lost in follow up while 24 (3.4%) died. Treatment was interrupted in 20.3%. Among those who completed treatment, culture conversion (according to the NTMNET definition) was evaluated in 195 patients and it was achieved in 47 (24.1%) patients. A refractory disease was diagnosed in 81 (11.5%) patients, while a recurrence was detected in 35 (11.2%) of patients.

Conclusions: Longitudinal data are crucial to understand disease evolution and treatment efficacy in real-life settings.

Radiological assessment of bronchial and arterial dimensions and mucus plug presence in 640 bronchiectasis patients: insights from the EMBARC registry

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Background/Aims:

Bronchial widening and thickening are key features in bronchiectasis patients enrolled into the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) registry. To date, the EMBARC registry lacks objective quantitative data to define the severity and extent of these bronchial changes. Recently, an artificial intelligence-based algorithm has been developed to measure bronchus and artery (BA) dimensions of all visible BA-pairs and detect mucus plugs on chest CTs. This study aims to use automatic algorithms to establish the severity and extent of BA-dimensions and to detect mucus plugs in bronchiectasis patients.

Methods:

A total of 885 CTs were received from eight centres. CT scans with volumetric acquisition and slice thickness equal to or less than 1.5 mm were eligible for automatic analysis using LungQ (Thirona, The Netherlands). The BA-analysis automatically segments the bronchial tree and identifies segmental (G_0) and distal ($G_{1,2,3,\dots}$) generations. For each BA-pair, the following dimensions are quantified: diameters of bronchial outer edge (B_{out}), inner edge (B_{in}), and artery (A), and wall thickness (B_{wt}). From these dimensions, the following BA-ratios are computed: B_{out}/A , B_{in}/A , B_{wt}/A , and bronchial wall area/outer area (B_{wa}/B_{oa}). To define bronchial widening, a cut-off for $B_{out}/A > 1.1$ and a conservative cut-off of > 1.5 were used. For bronchial wall thickening, a cut-off for $B_{wt}/A > 0.14$ was used. The mucus plug analysis automatically segments the bronchial tree, detects the total mucus plug number, and quantifies its total volume. Data are expressed as median (interquartile range) or n (%).

Results:

A total of 640 CTs could be successfully analysed. 245 CTs were excluded because of poor image quality or missing information (n=14), slice thickness larger than 1.5 mm or number of slices less than 150 (n=120), slice spacing larger than 0 mm (n=72), and failure to run (n=39). For BA-analysis, a total of 141,978 BA-pairs from G₀ until G₂₉ were detected and on average 222 BA-pairs per CT. B_{out}/A > 1.1 or > 1.5 were observed in 73% and 39% of all BA-pairs, respectively. B_{wt}/A > 0.14 was observed in 49% of all BA-pairs. The G₁₋₆ analysis included 130,314 (92%) BA-pairs. The median B_{out}/A, B_{in}/A, B_{wt}/A, and B_{wa}/B_{oa} for G₁₋₆ were 1.34 (1.07, 1.72), 1.04 (0.81, 1.35), 0.13 (0.1, 0.2), and 0.37 (0.29, 0.47), respectively. For mucus plug analysis, 12,943 mucus plugs were detected on 533 (83%) CTs with a median count of 8 (2, 25) and a volume of 0.44 (0.06, 1.63) mL.

Conclusions:

Our study demonstrates the capability of AI-based algorithms to measure BA-dimensions and detect mucus plugs on chest CT scans of bronchiectasis patients. Our findings show widespread bronchial widening and thickening, along with the presence of mucus plugs, indicative of active infection and/or inflammation. However, we observe a heterogeneous spectrum of severities and extents. The next step is to correlate BA and mucus plug outcomes with other clinical parameters within the EMBARC registry.

Conflict of interest(s) (if any – not included in the 500 words):

Yuxin Che, Angelina LP Pieters, Tjeerd vd Veer, Elrozy Andrinopoulou and Punit Makani declare no conflict of interest. **Stefano Aliberti** has received grants or contracts fees from INSMED incorporated, CHIESI, Fisher&Paykel; and received consulting fees from GSK, McGRAW HILL, Zambon, AstraZeneca, CSL Behring GmbH, Moderna, Chiesi, MSD Italia, Pysioassist SAS, GlaxoSmithKline. **Pierre-Regis Burgel** has received research grants or contracts from GSK and Vertex; and received consultancy or speaker fees from Asta Zeneca, Chiesi, GSK Insmed, Moderna, MSD, Vertex, Viatris, Zambon. **Pieter Goeminne** has received grants or contracts from GSK; and has received payment or honoraria for lectures, presentations etc from Ismed and RMEI. **Michal Shteinberg** has received grants or contracts from GSK, Trudell medical international and Tel Aviv league for lung disease; and has received consulting fees from AstraZeneca, Boehringer Ingelheim, Dexcel, Kamada, Synchrony medical, Trumed and Zambon; and has received payment or honoraria for lectures, presentations etc from AstraZeneca, Boehringer Ingelheim, Kamada, Sanofi and Ismed. **Michael Loebinger** has received consulting fees from Armata, 30T, AstraZeneca, Parion, Ismed, Chiesi, Zambon, Electromed, Recode and Boehringer Ingelheim; and received payment or honoraria for lectures, presentations etc from Ismed. **Charles Haworth** has received consulting fees from 30 technology, CSL Behring, Chiesi, Ismed, Janssen, LifeArc, Meiji, Mylan, Pneumagen, Shionogi, Vertex and Zambon; and has received payment or honoraria for lectures, presentations etc from Chiesi, Ismed, Mylan and Zambon. **Francesco Blasi** has received grants or contracts from AstraZeneca, GlaxoSmithKline, Chiesi and Ismed; and has received consulting fees from GlaxoSmithKline, OMPharma and Menerini; and has received payment or honoraria for lectures, presentations etc from AstraZeneca and Chiesi, GlaxoSmithKline, Ismed, Novartis, Pfizer, Vertex and Zambon. **Daan Caudri** has received payment or honoraria for lectures, presentations etc from Vertex and Sanofi. **Pierluigi Ciet** has received grants or contracts fees from NOW-Dutch Research Council and Horizon Pathfinder; and has received payment or honoraria for lectures, presentations etc from Chiesi and Vertex. **James D Chalmers** has received research grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Gilead Sciences, Grifols, Novartis, Insmed and Trudell; and received consultancy or speaker fees

from Antabio, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Insmmed, Janssen, Novartis, Pfizer, Trudell and Zambon. **Harm AWM Tiddens** has received research grants from Thirona as Chief Medical Officer and Emeritus Professor ErasmusMC Sophia; and has received payment or honoraria for lectures, presentations etc from Vertex.

POSTER PRESENTATIONS

[01.01] Ciliary function and Upper airway microbiota in patients with Bronchiectasis: data from the EMBARC-BRIDGE study

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Introduction: Cilia dysfunction plays a key role in bronchiectasis pathophysiology. In vitro studies show that pathogenic bacteria can damage the epithelium and reduce ciliary beat frequency. It has been suggested mucociliary clearance dysfunction in bronchiectasis is predominantly secondary to infection and/or inflammation.

Aim: To investigate the relationship between the upper airway microbiome and cilia function in bronchiectasis.

Methods: Nasal sampling was performed as part of an international cohort study (EMBARC-BRIDGE). Epithelial samples were taken by nasal brush biopsy and cilia function measured by high-speed video microscopy (HSVM). Cilia length, beat frequency, beat amplitude per second and change in cilia function after sterile air liquid interface culture were recorded. Epithelial disruption was measured on a scale of 1-4. DNA was extracted from nasopharyngeal swabs before undergoing 16S rRNA sequencing. Microbiome data was analysed using Dada2 and MicrobiomeAnalyst.

Results: 144 bronchiectasis patients were included. The most predominant microbiota were *Staphylococcus*, *Dolosigranulum*, *Corynebacterium* and *Moraxella*. Cilia function parameter groups were created based on either the median cilia length (5.24[4.96-5.5]µm), median cilia beat frequency (14.67[13.17-15.97]Hz), median amplitude per second (59.02[52.96-

67.03]µm/s) or the median change in amplitude per second after culture (35.87[22.84-46.68]µm/s). Lefse comparison at a phylum level, revealed a significant dominance of proteobacteria associated with increased epithelial disruption. There were no significant differences in alpha diversity (Chao1, Shannon, and Simpson diversity indices), Beta-diversity (Bray-Curtis index), LEfSe, or random forest between the different cilia function groups.

Conclusion: In the bronchiectasis patient upper respiratory tract environment there is no clear relationship between the microbiome and ciliary function however a proteobacteria dominant profile is associated with increased epithelial damage.

Conflict of interest(s) (if any – not included in the 500 words):

[01.02] Impact of Rheumatoid Arthritis and Seropositivity on the Risk of Non-Cystic Fibrosis Bronchiectasis

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Background/Aims:

Despite the coexistence of bronchiectasis and rheumatoid arthritis (RA) and the poor prognosis associated with the combination of conditions, no longitudinal studies that comprehensively evaluated whether patients with RA have a higher risk of bronchiectasis compared with those without bronchiectasis have been published. Whether seropositivity is associated with an increased risk of bronchiectasis in RA is the subject of ongoing controversy. Thus, this study aimed to assess whether RA influences the development of bronchiectasis and whether seropositivity is associated with an increased risk of bronchiectasis in RA.

Methods:

The incidence of bronchiectasis was compared between patients with RA (n=50,651; 35,879 seropositive RA [SPRA] and 14,772 seronegative RA [SNRA]) and 1:5 age- and sex-matched controls (n=253,255) enrolled between 2010 and 2017 in the Korean National Health Insurance Service database. The participants were followed for 1 year after RA diagnosis or the corresponding index date to the date of bronchiectasis incidence, censored date, or December 2019.

Results:

During a median follow-up of 4.3 years (interquartile range, 2.6–6.3 years), patients with RA showed a 2.16-fold higher risk of developing bronchiectasis compared with matched controls even after adjusting for potential confounders related to bronchiectasis development (95% confidence interval [CI], 2.04–2.28). In an analysis of RA serologic status using a fully adjusted model, patients with SPRA and those with SNRA showed 2.38-fold (95% CI, 2.24–2.53) and 1.58-fold (95% CI, 1.42–1.76) increased risks, respectively, compared with matched controls.

Conclusions:

Individuals with RA had approximately twice the risk of developing bronchiectasis than matched controls even after adjusting for potential confounders. The increased risk was more evident in individuals with SPRA than in those with SNRA, implying that rheumatic inflammation plays a major role in the development of RA-bronchiectasis.

Conflict of interest(s) (if any – not included in the 500 words):

This research was supported by Basic Science Research Program through the Korean Ministry of Education (No. 2021R1I1A3052416). The funders had no role in the design of the study, the collection and analysis of the data, or the preparation of the abstract.

[01.03] Clinical experience in the management of patients with non-cystic fibrosis bronchiectasis with bronchial hypersecretion.

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Background/Aims:

There is a need to evaluate the usefulness of new airway clearance techniques (ACT), used so far in muco-obstructive lung diseases such as non-cystic fibrosis bronchiectasis (NCFB) with chronic mucus hypersecretion (CMH). The aim of this pilot study was to assess the feasibility, safety and efficacy of a new ACT in NCFB patients with CMH treated at hospital for pulmonary exacerbation (PEx) and then at home for regular airway clearance after discharge.

Methods:

A prospective, open-label, multicenter observational study was performed in NCFB patients admitted to hospital for PEx treatment between July 2022-April 2023. Patients with CMH were treated in hospital with their usual conventional chest physiotherapy (CPT) for those who using one, and Simeox technology (PhysioAssist-Inogen, France) was introduced on day 2 of hospitalization after device training. After discharge patients used Simeox alone, without assistance for 2 months at home. Clinical evaluation according to CAT score, mucus drainage, tolerability, usability, side effects and satisfaction of patients and health practitioners were assessed during the study.

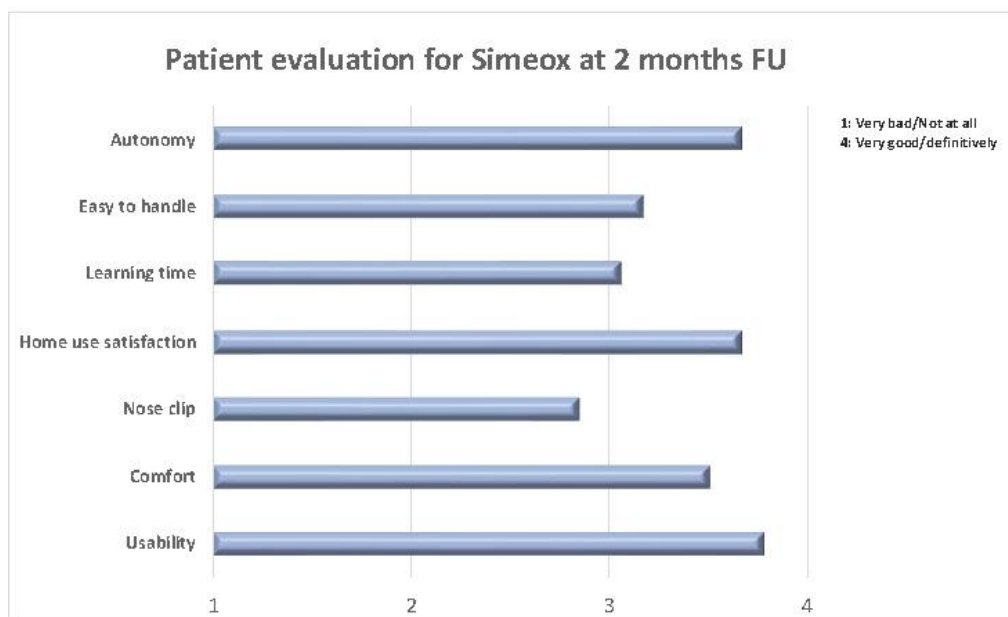
Results:

18 NCFB patients with CMH of different main etiology, COPD (n=6), asthma (n=5), post infectious bronchiectasis (n=2), ciliary dyskinesia (n=2), idiopathic (n=2) and connective tissue disease (n=1) were enrolled. 5 Males/13 Women (28%/72%), age: 62.6±15.1 years, BMI: 26.3±4.0 kg/m². Routine treatments: SABA/SAMA (n=14, 78%), LABA/LAMA (n=10, 56%), ICS (n=7, 39%), expectorants (n=5, 28%), mucolytics (n=7, 39%), antibiotics (n=3, 17%), inflammatory inhibitors (n=2, 11%), macrolides (n=1, 6%), oral corticoids (n=1, 6%). About 55% of patients (n=10) used CPT (FET/directed cough, n=7; Autogenic drainage, n=1; PEP/oPEP, n=1; others ACT/breathing exercise, n=5).

The average therapy duration was 15 to 20 minutes per Simeox session. Mucus drainage with the device was abundant, regular over time with purulent mucus.

After 2 months of treatment, total CAT score (p<0001), and respiratory (cough, dyspnea, sputum) and quality of life items (sleep, energy, home activities) significantly improved. Patients reported no pain but improvement in fatigue, breathing fluidity, cough, dyspnea, and reduction in sputum production. Patient and healthcare professional satisfaction with device therapy was high.

None of the patient experienced exacerbation nor side effect during the 2-month observation. Simeox compliance was >3 sessions/week with 1 to 2 daily sessions, and stable over time.



Conclusions:

The study showed a significant improvement in mucus drainage, respiratory symptoms and quality of life after 2 months of home treatment with Simeox. Device compliance was very good, and the therapy was safe. These promising preliminary data need to be confirmed in a RCT.

Conflict of interest(s) (if any – not included in the 500 words):

Investigators of studies sponsored by Physio-assist

[01.04] Strong Lungs: a website for First Nations with Bronchiectasis

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Background/Aims: The incidence of bronchiectasis in First Nations Australians is amongst the highest reported globally, with substantial morbidity and early mortality. Physiotherapy is key to management, but there is an absence of accessible and culturally appropriate resources specific to airway clearance techniques (ACTs) and exercise for the adult population. The primary aim was to develop an online website focused on ACTs and exercise therapy for clinical use in the care of First Nations adults with bronchiectasis and to identify enablers and barriers to clinical application.

Methods: A 3-phase, participatory action research approach was applied. Phase-1: Stakeholders representing multiple healthcare professions from the Northern Territory, including First Nations primary healthcare centres, tertiary and regional hospitals and First Nations Elders were invited to participate to inform key content of the website, including preferred format for resources and local languages used. Phase-2: Website and its content were developed with feedback from stakeholders prior to launch. Phase-3: Evaluation using semi-structured interviews with healthcare professionals was undertaken to identify enablers and barriers for implementation.

Results: Thirty stakeholders participated in meetings (2020-21) to identify preferable content, format and recommended languages. The website (www.stronglungs.com.au) launched in December 2021, with videos for ACTs, exercise, general health advice, smoking cessation and two patient stories available in seven local languages. Three enablers were: (i) ease of navigation with appropriate language; (ii) relatable resources that enhance engagement; and (iii) promoting socialisation in lung health education. Two barriers were: (i) knowledge of website's availability; and (ii) inconsistent access due to devices or technology limitations.

Conclusions: The Strong Lungs website appears to be easy to navigate, with relatable resources, which enhance the engagement of First Nations with bronchiectasis. Technology limitations should be addressed to improve access.

Conflict of interest(s) (if any – not included in the 500 words): No conflicts of interests to declare for any authors. Funded by Hot North Translation Grant, Australian Physiotherapy Association, Collier Charitable Foundation, Jean Hailes Foundation.

[01.05] Airway clearance in bronchiectasis patients in Tayside: Data from the EMBARC registry

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Background/Aims:

Guidelines recommend that bronchiectasis patients practice regular airway clearance to help with symptom management. The European Bronchiectasis register (EMBARC) records airway clearance management in all study participants. The aim of this study was to compare local practices with national and international data.

Methods:

Daily sputum volume, methods of chest physiotherapy, physiotherapy devices and mucolytic drugs were recorded at baseline for all participants between March 2015 and December 2023. Data for Tayside was compared with data from other European sites.

Results:

528 bronchiectasis patients from Tayside were included in the study. Age 69 years (IQR 61-76), 58.7% were female. 74.2% of all participants reported daily sputum production. 328 (62.1%) participants reported using at least one regular airway clearance method at baseline. The most frequently reported method was active cycle of breathing (239, 72.9%) and the most widely used drug treatment was N-acetylcysteine (87, 36.6%). Only 24 (7.3%) patients reported using a physiotherapy device. 151 (28.6%) patients felt they did not need assisted clearance despite 34% experiencing 3 or more exacerbations per year.

Tayside was slightly above the UK average for using airway clearance methods (62.1% vs 58.9%, n=8163 patients, p=0.1) and was significantly higher than Northern and Western Europe (62.1% vs 51.5%, n=3261 patients, p<0.0001). Airway clearance management was lower in Southern Europe (40.8%, n=4295) and Central and Eastern Europe (33.0%, n=1061)

Conclusions:

Most patients with bronchiectasis in Tayside practice airway clearance, and the most common technique is active cycle of breathing.

Conflict of interest(s) (if any – not included in the 500 words):

[01.06] Insights into Spirometry Trends in Bronchiectasis: A Detailed Examination of Pulmonary Function Patterns from the U.S. Bronchiectasis and NTM Research Registry

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Background/Aims: Bronchiectasis has traditionally been associated with obstructive spirometry patterns, including the use of FEV1 for disease severity assessment. However, population analyses of spirometry in those with bronchiectasis have shown patients may have normal or even restrictive patterns characterized by reduced FVC. The aim of our study was to describe the relationship between spirometry abnormalities and disease severity of adults enrolled in the U.S. Bronchiectasis and NTM Research Registry (BRR).

Methods: We analyzed adult bronchiectasis patients with spirometry results at baseline and first annual follow-up in the BRR. Descriptive statistics were computed, and patients were categorized into three groups: normal (FEV1/FVC >0.7, FEV1 >80% predicted), restrictive (FEV1/FVC >0.7, FVC <80% predicted), and obstructive (FEV1/FVC <0.7, FEV1 <80% predicted). Covariates queried included demographics, modified bronchiectasis severity index (mBSI) scores, co-morbidities, sputum cultures, and airway hygiene use. F-tests and chi-square tests were used to assess the mean differences and associations across the three groups for continuous and categorical variables, respectively. We fit two Gaussian generalized estimating equation (GEE) models with an exchangeable working correlation matrix to determine the association between obstructive versus restrictive physiology and a decline in spirometry over time.

Results: The 1453 patients who met the study inclusion criteria were predominantly White (90.7%), female (79.3%), with a median age of 67.0 years (Table 1). A restrictive pattern predominated (n=708, 48.7%), followed by normal (n=593, 40.8%), then obstructive airflow (n=152, 10.5%). We observed a significant difference in mean mBSI score across the spirometry groups, noting mBSI includes FEV1 which affects the association (p<0.0001). History of at least 1 exacerbation in the previous 2 years and *P. aeruginosa* isolation differed significantly across groups (p<0.0001). We observed a significant difference across the groups with bronchial hygiene and inhaled corticosteroid use (p=0.012 and <0.0001, respectively) (Table 1). After adjusting for predicted covariates, patients with an obstructive physiology had a pre-bronchodilator FEV1 %predicted lung function of 16.6% less on average than patients with a restrictive physiology (95% CI 13.8-19.5% less; p<0.0001). Adjusting for the same covariates, there was no significant difference in patients with an obstructive physiology and a pre-bronchodilator FVC %predicted compared to patients with a restrictive physiology.

Conclusions: Most patients with bronchiectasis appear to have restrictive or normal physiology, where obstructive physiology is noted in more severe phenotypes. Despite this difference, there is no significant difference in FVC decline over time between obstructive and restrictive groups. While FEV1 remains a powerful marker for declining lung function, whether FVC is a more sensitive marker of disease progression or exacerbations in milder disease phenotypes is an area for further investigation.

Conflict of interest(s) (if any – not included in the 500 words): A Mirza, M Marmor, A Brunton, K Jakharia, R Choate, T Aksamit, P McShane - no conflicts. S Zha- Consulting for Insmed, Genentech. D Maselli- involved in clinical trials with NIH and Gates Foundation. Consulting for Insmed, Sanofi/Regeneron, GlaxoSmithKline, AstraZeneca, Amgen. C Swenson- Consulting for Insmed, Pharming, Inc.

[01.07] A Systematic Review to determine the presence and effectiveness of Shared Decision-Making interventions for Airway Clearance Techniques in adults with Bronchiectasis.

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Background:

Bronchiectasis is a chronic lung disorder. Impaired muco-ciliary clearance and sputum retention are core elements in bronchiectasis pathophysiology. Airway clearance is regarded as the cornerstone of therapy in bronchiectasis. There is currently a lack of randomised controlled trials (RCTs) proving the efficacy of one specific airway clearance technique (ACT) over another. Shared decision-making (SDM) interventions are usually designed for situations where there is some uncertainty about the best treatment option and provide information about the advantages and disadvantages in as balanced a way as possible.

Aims:

To determine if and how SDM is used when choosing ACTs for adults with bronchiectasis.

To determine the effectiveness of SDM when choosing ACTs for adults with bronchiectasis.

Methods:

The Protocol was registered on the international Prospective Register of Systematic Reviews (PROSPERO) database on 17th June 2021 (Registration number: CRD42021261640). We conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

A systematic literature review was conducted using the electronic databases CINAHL, EMBASE, Medline, PsycINFO, Google Scholar, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL). Additionally a search of the clinical trials registries, ClinicalTrials.gov and grey literature through Open Grey and grey matters was completed. All databases were searched from their inception to 29th June 2021. Search terms were developed from the review questions, which were derived from the PICO and PEO frameworks.

We planned to use tables with supporting narrative to determine whether the included studies were sufficiently similar in design, participants, interventions and outcomes to be combined in a meta-analysis. We intended to use a random-effects model using standardised mean differences with a 95% confidence interval. If appropriate, we planned to use forest plots as a graphical representation to assess heterogeneity using I^2 .

Results:

A total of 4414 studies were initially identified from the searches. 864 duplicate studies were removed; resulting in 3550 studies in total for title and abstract screening. All 3550 titles and abstracts underwent double-blind screening. No studies were identified for inclusion in the review.

Limitations

With no studies meeting criteria for inclusion, it may appear to offer no conclusions or offer conclusions not based on evidence and may seem disappointing among some clinicians and policymakers. We argue that this empty review remains important and highlights a major research gap and has identified the state of the evidence at this point in time in SDM for ACTs in bronchiectasis.

Conclusions:

Bronchiectasis is an increasingly prevalent disease. ACTs are the cornerstone of bronchiectasis management. We have presented clear justification for further research for development of a SDM intervention for ACTs in adults with bronchiectasis. This is supported by the recent NICE guideline on SDM, which make specific recommendations for research including: research on differing SDM interventions in different groups and the acceptability of these SDM interventions. We aim to progress in this field in the near future to assess any impact SDM for ACTs may have for the bronchiectasis population.

Conflict of interest(s) (if any – not included in the 500 words):

None.

[01.08] Correlation of symptom burden, disease severity and 1-year outcomes with sputum point-of-care neutrophil elastase activity test in adults with bronchiectasis

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Background: In bronchiectasis, symptom burden, progression and severity of disease relate to airway neutrophil elastase activity. Validated biomarkers are needed to identify patients, who are at risk of future moderate and severe pulmonary exacerbations and associated hospitalisations, respectively, so that these could benefit from potentially disease modifying drugs such as Dipeptidyl peptidase-1/cathepsin C inhibitors that are currently under development.

Aims: (a) To correlate qualitative and semi-quantitative NEATstik® point-of-care test results with symptom burden; and (b) to evaluate its predictive power for the identification of patients with an unfavourable clinical course, i.e. pulmonary exacerbations and associated hospitalisations, in the coming year among adult participants of the German Bronchiectasis Registry PROGNOSIS.

Methods: Sputum samples were collected from registry participants between 2021 and 2024 and stored at -80°C within the adjunct biobank. After thawing, samples were tested for the presence of active neutrophil elastase with the commercially available point-of-care lateral flow test NEATstik® according to the manufacturer's instructions. In addition, fresh sputum samples were processed immediately for comparison with results from frozen samples for a subset of patients. We assessed assay positivity visually by two independent investigators as well as digital image analysis.

Results and Conclusions: So far, sputum samples were tested with the NEATstik® from 63 patients, including 26 retested samples for the assessment of reliability as well as 10 pairs of fresh and frozen-thawed samples. The final analysis of patient data, including symptom burden, quality of life, annual exacerbation and hospitalisation rate, and NEATstik® test results is currently pending and will be reported at the 8th World Bronchiectasis Conference in Dundee, Scotland.

[02.01] The role of comorbidities in bronchiectasis patients hospitalized for COVID-19

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Background/Aims: Patients with bronchiectasis are susceptible to viral infections, often resulting in hospitalizations. COVID-19 has been linked to an increased risk of hospitalization in patients with bronchiectasis. In the general population, hospitalization for bronchiectasis has been linked to comorbidities. However, the data for comorbidities in patients with bronchiectasis hospitalized for COVID-19 are still poor. We aimed to evaluate comorbidities in bronchiectasis patients infected with COVID-19 and hospitalized with COVID-19.

Methods: We use data from SCIFI-PEARL (Swedish Covid-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage), a Swedish COVID-19 nationwide register-based cohort study with linked data including the National Patient Register (NPR). We identified patients diagnosed with Bronchiectasis in the NPR spanning 2015 to 2019 (ICD-10 code J47.9), excluding the ones with cystic fibrosis (ICD-10 code E84). COVID-19 infection was defined as a SARS-CoV-2 test positive by polymerase chain reaction (PCR) or secondary medical care records with U07.1 or U07.2 as a primary or secondary diagnosis. Hospitalization was defined as hospitalization records with U07.1 or U07.2 as a main or secondary diagnosis, with data presented here collected until the end of March 2023.

Results: We identified 6576 bronchiectasis patients, with a mean age of 67.2 (standard deviation [SD] 16.5), primarily women (65.3%). Among them, 1255 (19.1%) had a verified COVID-19 infection, with a mean age of 62.4 (SD 18.3) and 61.3% being women. Four hundred fifteen patients (33.1% of the infected patients) were hospitalized, with a mean age of 71.4 (SD 14.4), and 56.9% were women. The most common comorbidity in all patients was cardiovascular diseases (CVD, 43.4%), followed by hypertension (HT, 28.6%), asthma (25.7%), COPD (23.3%), and diabetes type II (DM II, 8.4%). Asthma was the only comorbidity with statistically significant increased frequency in bronchiectasis patients with a COVID-19 infection (29.4%, $p = 0.001$). The prevalence of several comorbidities was significantly increased in the COVID-19 hospitalized bronchiectasis patients (CVD, 64.6%, HT 43.4%, asthma 34.0%; COPD 39.0% and DM II 17.4%, all $p < 0.001$)

Conclusions: As of March 2023, one-third of patients with bronchiectasis with a verified COVID-19 diagnosis were hospitalized. Comorbidities were prevalent among these patients, with cardiovascular diseases being dominant alongside high representation of airway diseases like asthma and COPD. Notably, all comorbidities showed an increased prevalence among the bronchiectasis patients who needed hospitalization for COVID-19. Thus, our data indicate the need for increased awareness in bronchiectasis patients with cardiovascular and airway diseases infected with COVID-19 for risk of serious COVID-19 outcomes.

Conflict of interest(s) (if any – not included in the 500 words):

[02.02] Poor cardiovascular outcomes are associated with *Pseudomonas Aeruginosa* in patients with non-cystic fibrosis bronchiectasis

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Background/Aims:

Non-cystic fibrosis bronchiectasis (NCFBE) is a chronic lung condition with no approved therapy. Chronic colonization with *Pseudomonas aeruginosa* (PsA) is associated with poor clinical outcomes including more frequent exacerbations. Although the risk of cardiovascular (CV) complications is associated with high NCFBE exacerbations frequency, studies investigating the relationship between PsA and CV outcomes are lacking.

Methods:

We conducted a retrospective analysis of US electronic medical records (EMR) for NCFBE patients, with or without PsA, diagnosed between 2009 and 2014. We used the TriNetX database which is an integrated EMR system that includes clinical data from 60 major healthcare organizations treating over 85 million patients in the US. NCFBE and PsA diagnoses were identified using ICD-10 diagnostic codes within the dataset. Patients with cystic fibrosis and pre-existing CV diseases were excluded. Number of exacerbations, major adverse cardiac events (MACE), hospitalization and overall mortality were compared in the 5-year period following an acute exacerbation, which was the index event (see Figure 1). Propensity-score matching for co-morbidities, baseline characteristics and inhaled/cardiac medication use was applied to account for potential confounders. Data analysis was performed using the built-in statistical analysis tools provided by the TriNetX platform.

Results:

We identified 6,429 and 618 patients aged ≥ 18 years without/with PsA, respectively. After matching, the number of patients was 595 for each group. The risk for exacerbations was higher in patients with PsA compared to those without (Risk Ratio: 1.32, 95% CI: 1.21,1.43). This was associated with a greater number of exacerbations in the former patients (median 4 vs 3, $p=0.003$). The risk for MACEs following the index event was higher in patients with PsA compared to those without (Risk Ratio: 1.49, 95% CI: 1.16,1.92). The median time to hospitalisation was 184 and 848 days for NCFBE patients with and without PsA, respectively. The survival probabilities for hospitalisation in patients without PsA were approximately two times higher than those for patients with PsA ($p<0.0001$, Log-Rank test). The probability of death was higher in patients with PsA compared to those without (Risk Ratio: 1.67, 95% CI: 1.40-1.98). A summary of risk differences between the two cohorts is shown in Table 1.

Conclusions:

This real-world data analysis confirmed that PsA is associated with poor clinical outcomes in NCFBE including an increased risk of adverse CV outcomes. These findings support a potential role in of PsA in contributing to CV risk in NCFBE. The development of an anti-

infective that targets PsA may provide multiple potential benefits for NCFBE patients: it could not only address critical treatment goals including improved symptom control and quality of life, and reduction in exacerbation frequency but also reduce the risk of CV events and associated death in NCFBE.

Conflict of interest(s) (if any – not included in the 500 words):

All authors are employees of AstraZeneca

[02.03] Clinical variables associated with new growth of *Pseudomonas aeruginosa* in Bronchiectasis patients: Data from the European Bronchiectasis registry (EMBARC).

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Background/Aims:

Acquisition of *Pseudomonas Aeruginosa* in bronchiectasis patients is associated with a 7-fold increase in hospitalisation and a 3-fold increase in mortality. Early identification of bronchiectasis patients at increased risk of pseudomonas will allow prompt intervention with eradication treatment. This study aims to establish which clinical factors are associated with an increased risk of new growth of *P. aeruginosa*.

Methods:

We analysed a large cohort of patients with bronchiectasis from the EMBARC registry (enrolled 2015-2022). Cox proportional hazard regression was used to analyse time from baseline until first new isolation of *P. aeruginosa* or censor. Only patients with sputum cultures performed during follow-up were included for analysis. Multivariable analysis was performed including all clinically relevant candidate variables. Patients with *P. aeruginosa* isolation in the previous 2 years were excluded.

Results:

7860 patients were included for analysis. During follow-up 795 (10.1%) of patients had a new isolation of *P. aeruginosa*. Following multivariate analysis positive associations were observed with primary ciliary dyskinesia (Hazard ratio (HR) 1.88 95%CI1.20-2.84 p=0.01), age >65 (HR 1.01 95%CI1.00-1.01 p=0.02), growth of *Aspergillus* (HR 1.95 95%CI1.32-2.87 p<0.001), *Enterobacteriaceae* (HR 1.59 95%CI1.28-1.97 p<0.001), *M. catarrhalis* (HR 1.43 95%CI1.09-1.88 p=0.01) or *S. pneumoniae* (HR 1.39 95%CI1.10-1.77 p=0.01), Radiological severity (HR 1.05 95%CI1.03-1.07 p<0.001), MRC dyspnoea score of 4 (HR 1.62 95%CI1.18-2.23 p=0.03), macrolide use (HR 1.21 95%CI1.01-1.45 p=0.36), and prior growth of *P. aeruginosa*(HR 1.38 95%CI1.60-2.44 p<0.001).

Further multivariate analysis, excluding the cohort of patients with previous *P. aeruginosa* (n=547), showed positive associations with age >65 (HR 1.01 95%CI1.00-1.02p=0.04), co-morbid COPD (HR1.49 95%CI1.23-1.80p<0.001), Inhaled steroid use (HR 1.25 95%CI1.06-1.48 p=0.009), macrolide use (HR 1.29 95%CI1.05-1.57) p=0.013), growth of *M. catarrhalis* (HR 1.57 95%CI1.17-2.12 p=0.003), *Enterobacteriaceae* (HR 1.84 95%CI1.46-2.32 p<0.001), *S. pneumoniae* (HR 1.36 95%CI1.05-1.78 p=0.02), *Aspergillus* (HR 1.93 95%CI1.25-3.00 p=0.003), radiological severity (HR 1.05 95%CI1.03-1.08 p<0.001), aetiology of primary ciliary dyskinesia (HR 1.71 95%CI1.01-2.89 p=0.05), Tuberculosis (HR 1.44 95%CI1.02-2.04 p=0.04) and inflammatory bowel disease (HR 1.91 95%CI1.04-3.51 p=0.04). Patients from Southern (HR 1.52 95%CI1.23-1.88 p<0.001) or Eastern Europe (HR 1.68 95%CI 1.29-2.20 p<0.001) were more likely to isolate new *P. aeruginosa* even after adjustment for confounders.

Conclusions:

There are multiple factors associated with an increased risk of new growth of *Pseudomonas* in bronchiectasis patients. The most significant of these include radiological severity, growth of aspergillus or Enterobacteriaceae, aetiology of primary ciliary dyskinesia and residency in Southern or Eastern Europe.

Conflict of interest(s) (if any – not included in the 500 words):

[02.04] Population-based Prevalence of Bronchiectasis in the USA: 2018–2022

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Background/Aims: Bronchiectasis appears to be becoming more prevalent in the USA. Given the lack of up-to-date epidemiological data, the aim of the study was to provide an estimate of the total, non-cystic fibrosis (CF)-associated and CF-associated prevalence of bronchiectasis between 2018 and 2022, thereby determining if the disease burden has increased in the USA.

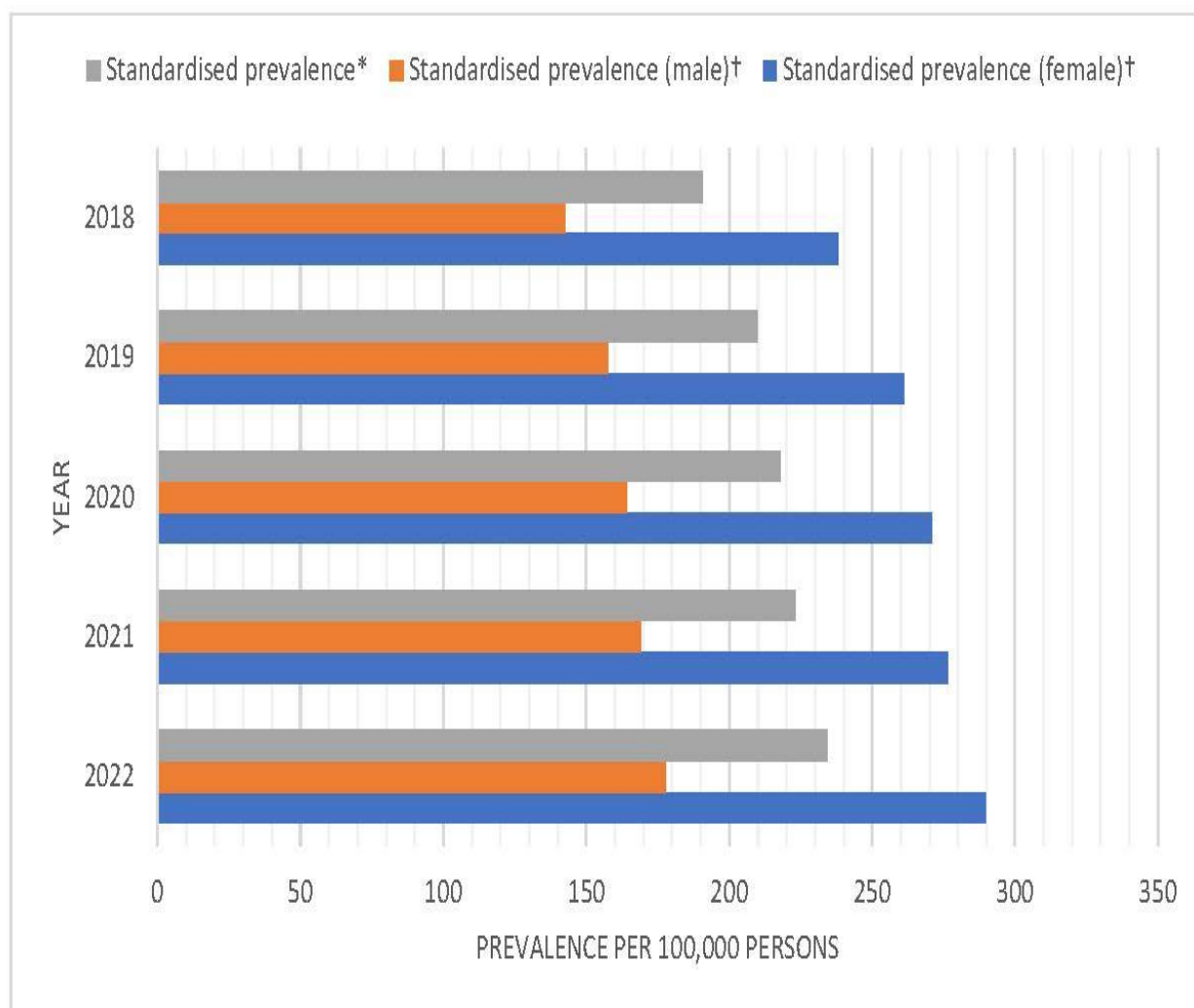
Methods: Using anonymised healthcare claims data from a large US database, Optum Clinformatics Data Mart, the prevalence of bronchiectasis from 1 January 2018 to 31 December 2022 was estimated. The study population comprised patients with ≥1 day of registration during the study period, plus continuous registration for ≥365 days prior to the last day they were registered. A non-CF bronchiectasis case was defined as ≥2 outpatient claims with a diagnosis code of bronchiectasis, or ≥1 hospitalisation record with a principal/secondary diagnosis of bronchiectasis. A CF-associated bronchiectasis case required additional ≥2 outpatient claims with a diagnosis code of CF or ≥1 hospitalisation record with a principal/secondary diagnosis of CF. Patients with missing or ambiguous age or sex information were excluded. The cumulative and annual crude prevalence of bronchiectasis were estimated then stratified by age and sex. The crude prevalences were standardised to the age and sex distribution of the 2022 US population. In addition, the cumulative crude and standardised prevalences were stratified by CF diagnosis.

Results: Over the cumulative period, a total of 94,392 patients (out of a cohort of 27,885,672; 0.34%) met the criteria for bronchiectasis case, with a mean age of 74 years (63.9% female). The standardised annual prevalence increased from 190.6 (95% confidence interval [CI]: 188.8–192.4) in 2018 to 234.1 (95% CI: 232.3–236.1) per 100,000 persons in 2022, an increase of ≥2.3% (range: 2.3–10.0%) per year, which was consistently greater among females (Figure 1). The standardised cumulative prevalence was estimated to be higher in females than males: 274.6 (95% CI: 272.3–276.8) vs 167.8 (95% CI: 165.9–169.6) per 100,000 persons. The standardised annual prevalence showed a marked and consistent increase with advancing age (Table 1). The standardised prevalence of bronchiectasis stratified by non-CF and CF aetiologies were available for the cumulative period only, and was estimated to be 216.5 and 5.0 per 100,000 persons, respectively.

Conclusions: In the USA, the prevalence of bronchiectasis is increasing, the highest of which is consistently observed in the 75+ age group. A similar rising trend is also observed in younger (18–75) age groups. The prevalence of non-CF bronchiectasis is higher than previously reported.¹ This highlights the importance of promoting awareness. Further research is warranted to validate and identify the cause of the rising prevalence of bronchiectasis.

¹Weycker D, *et al.* Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. *Chron Respir Dis.* 2017;14(4):377-384.

Figure 1. Standardised annual prevalence of bronchiectasis in the overall, male and female populations (2018–2022)



*Standardised to the 2022 US population by sex and age; †Standardised to the 2022 US population by age.

Table 1. Standardised prevalence and crude cases of bronchiectasis in the overall population (2018–2022)

Time Period	Age (years)	Standardised prevalence* (per 100,000 persons) [95% CI]	Crude prevalent cases (n)
2018	<18 [†]	12.7 (11.2–14.2)	46,748
	18 – <35	22.9 (21.2–24.7)	
	35 – <45	37.8 (35.1–40.7)	
	45 – <55	81.6 (77.6–85.7)	
	55 – <65	232.3 (225.6–239.2)	
	65 – <75	504.9 (496.4–513.6)	
	75+	1210.1(1195.3–1224.9)	
2019	<18 [†]	12.7 (11.2–14.3)	55,052
	18 – <35	23.7 (21.9–25.5)	
	35 – <45	42.2 (39.3–45.2)	
	45 – <55	86.3 (82.1–90.6)	
	55 – <65	254.7 (247.7–261.9)	
	65 – <75	553.6 (544.9–562.3)	
	75+	1349.3 (1334.3–1364.4)	
2020	<18 [†]	12.5 (11.1–14.2)	59,029
	18 – <35	23.3 (21.5–25.2)	
	35 – <45	42.1 (39.2–45.2)	
	45 – <55	90.8 (86.4–95.3)	
	55 – <65	274.1 (266.8–281.6)	
	65 – <75	569.5 (561.0–578.2)	
	75+	1402.1 (1387.1–1417.2)	
2021	<18 [†]	12.2 (10.7–13.9)	64,600
	18 – <35	24.4 (22.5–26.4)	
	35 – <45	45.0 (41.9–48.3)	
	45 – <55	96.0 (91.4–100.8)	
	55 – <65	293.4 (285.6–301.3)	
	65 – <75	578.5 (570.2–586.9)	
	75+	1410.8 (1396.5–1425.2)	

Conflict of interest(s) (if any – not included in the 500 words):

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William K. Mountford, Lu Zhang and Amy L. Olson are employees of Boehringer Ingelheim. Kristy Iglay has received consulting fees for this project through her employer CERobs Consulting. Christina M. Mingora has received grants or contracts from the Cystic Fibrosis Foundation, received consulting fees from Boehringer Ingelheim, and payment or honoraria from The France Foundation. Patrick A. Flume has received grants or contracts from Boehringer Ingelheim, Insmed and Synchrony, and consulting fees from Insmed.

[02.05] Population-based Prevalence of Paediatric Bronchiectasis in the USA: 2018–2022

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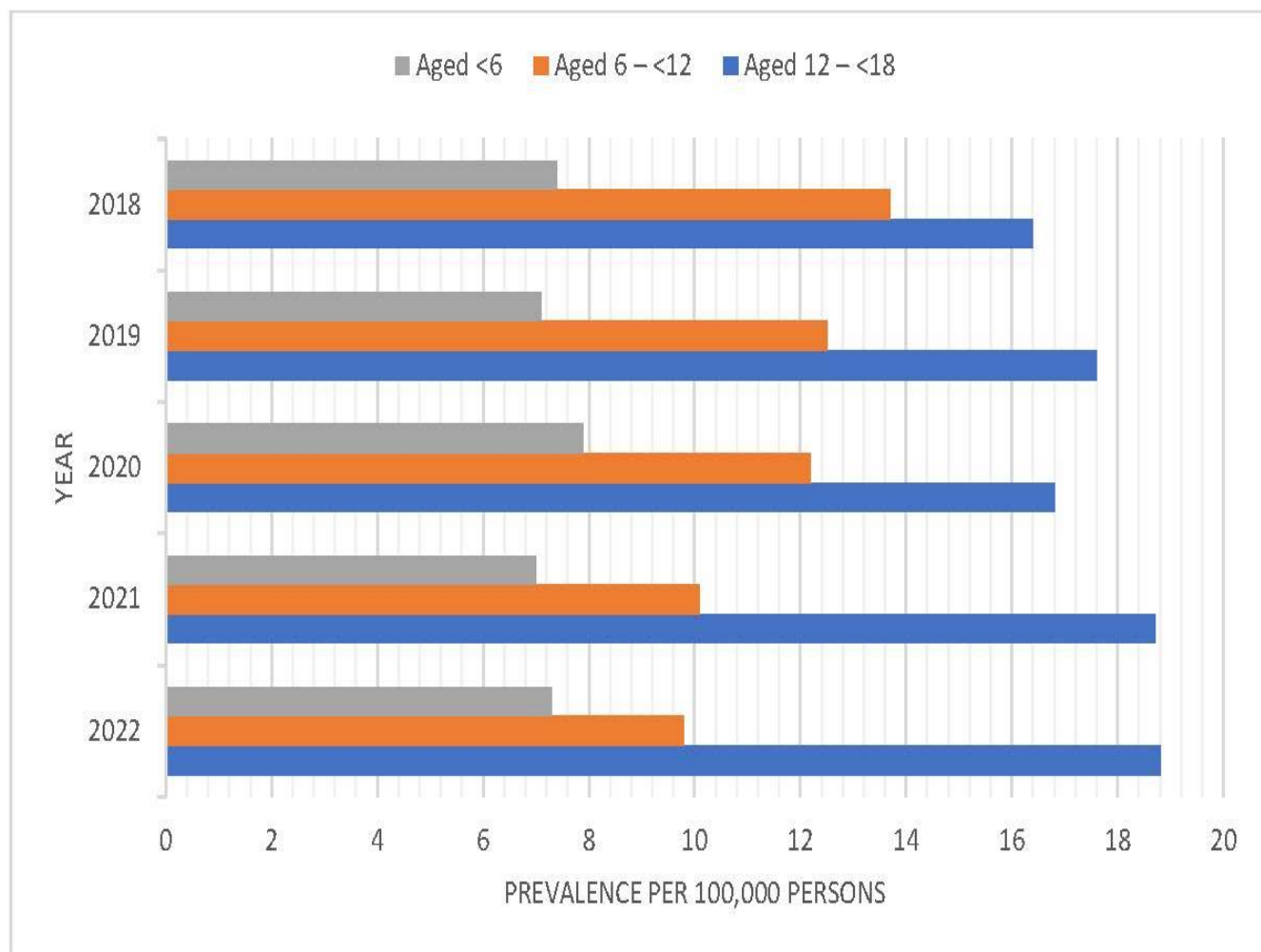
Background/Aims: Most estimates of prevalence of bronchiectasis are based on adult data, excluding children and adolescents. The aim of the study was to provide an assessment of the prevalence of bronchiectasis in children and adolescents in the USA, between 2018 and 2022.

Methods: Using anonymised healthcare claims data from a large US database, Optum Clinformatics Data Mart, the prevalence of bronchiectasis from 1 January 2018 to 31 December 2022 was estimated. The study population comprised patients (<18 years) with ≥1 day of registration during the study period, plus continuous registration for ≥365 days prior to the last day they were registered. A bronchiectasis case was defined as ≥2 outpatient claims with a diagnosis code of bronchiectasis, or ≥1 hospitalisation record with a principal/secondary diagnosis of bronchiectasis. Patients both with and without cystic fibrosis (CF) were included in this study. Patients with missing or ambiguous age or sex information were excluded. The cumulative and annual crude prevalence of bronchiectasis were estimated then stratified by age and sex. The crude prevalences were standardised to the age and sex distribution of the 2022 US population.

Results: Over the cumulative period, a total of 465 patients aged <18 years met the criteria for bronchiectasis case. The annual crude and standardised prevalence remained consistent: from 13.1 (95% confidence interval [CI]: 11.6–14.7) and 12.7 (95% CI: 11.2–14.2) in 2018 to 12.7 (95% CI: 11.2–14.5) and 12.2 (10.7–14.0) in 2022, respectively. When stratified by age, the crude and standardised prevalence rose with increasing age; standardised annual prevalence among children aged 12–17 years was consistently more than double the figure observed in those aged <6 years (Figure 1). Annual and overall analyses are shown in Table 1.

Conclusions: The prevalence of paediatric bronchiectasis demonstrates that it should be a disease of interest in the USA. Further research is needed to identify the underlying aetiologies, and potentially inform management and prevention strategies.

Figure 1. Standardised annual prevalence* of paediatric bronchiectasis (2018–2022)



* Standardised to the 2022 US population by sex.

Table 1. Age-specific prevalence and crude cases of paediatric bronchiectasis (2018–2022)

Time Period	Age (years)	Standardised prevalence* (per 100,000 persons) [95% CI]	Crude prevalent cases
2018	<6	7.4 (5.3–10.0)	
	6 – <12	13.7 (11.2–16.5)	
	12 – <18	16.4 (13.7–19.3)	
	<18 [†]	12.7 (11.2–14.2)	285
2019	<6	7.1 (5.1–9.7)	
	6 – <12	12.5 (10.1–15.3)	
	12 – <18	17.6 (14.9–20.7)	
	<18 [†]	12.7 (11.2–14.3)	280
2020	<6	7.9 (5.7–10.7)	
	6 – <12	12.2 (9.8–15.0)	
	12 – <18	16.8 (14.1–20.0)	
	<18 [†]	12.5 (11.1–14.2)	263
2021	<6	7.0 (4.8–9.8)	
	6 – <12	10.1 (7.8–12.8)	
	12 – <18	18.7 (15.8–22.1)	
	<18 [†]	12.2 (10.7–13.9)	240
2022	<6	7.3 (5.1–10.3)	
	6 – <12	9.8 (7.5–12.6)	
	12 – <18	18.8 (15.7–22.3)	
	<18 [†]	12.2 (10.7–14.0)	224

*Standardised to the 2022 US population by sex; [†]Standardised to the 2022 US population by sex and age.

Conflict of interest(s) (if any – not included in the 500 words):

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[03.01] Measles as a cause of bronchiectasis: five case reports

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Background/Aims:

The most frequent etiology of non-cystic fibrosis bronchiectasias is post-infectious; whooping cough and measles are common childhood infections strongly related to the occurrence of bronchiectasis. Measles induces transitory immunosuppression with secondary bacterial infection. With the advent of anti-vaccination movements against measles it is important to address this issue. The following cases show the outcomes of this association.

Methods:

This retrospective study includes five patients from the Bronchiectasis Outpatient Clinic in a Portuguese tertiary hospital in which the etiology of bronchiectasis was measles infection in childhood. Thorough investigation ruled out other possible causes. The E-FACED score was used to characterize the population.

Case 1 - Male, 35 years old with a history of recurrent respiratory infections since childhood. He was hospitalized at the age of 13 months for pneumonia due to measles. Currently asymptomatic. E-FACED - Final score: 2 due to the extent of the bronchiectasis seen on chest CT.

Case 2 - Male, 36 years old, with persistent bronchorrhea and frequent exacerbations (1-2/year). Recurrent pneumonia between 2011-2017. Documented history of measles in childhood. Complaints of daily sputum. E-FACED - Final score:0, with bronchiectasis only in the middle lobe.

Case 3 - Female, 69 years old with recurrent respiratory infections especially in winter. She had a history of severe measles in childhood. Currently, she has daily complaints of bronchorrhea and occasional haemoptysis. E-FACED - Final score: 0. Chest CT showed bronchiectasis in the middle lobe and lingula.

Case 4 - Female, 75 years old, with a history of chronic sinusitis and rhinitis. Complaints of a daily productive cough and a history of recurrent respiratory infections since the age of 40. Symptomatic measles in childhood. E-FACED - Final score: 3. Chest CT with bronchiectasis in more than two lobes.

Case 5 – Female, 43 years old, in follow up since childhood for recurrent respiratory infections with bronchiectasis secondary to severe measles infection at 18 months of age with prolonged paediatric hospital admission. Currently the patient has *Pseudomonas aeruginosa* colonization, but with no exacerbations in the last year. E-FACED final score: 1. Chest CT shows cylindrical and cystic bronchiectasis in the right lung.

Conclusions:

Bronchiectasis is a cause of reduced quality of life for patients and measles is not only one of the most well recognized contagious infectious diseases it is also a leading preventable

cause of death among patients. This study underlines the importance of taking into account this co-relation when considering health literacy measures concerning vaccination.

[03.02] Baseline respiratory pathogens and clinical outcomes in patients with bronchiectasis: data from the EMBARC registry

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Background: Infection is a key component of the vicious vortex of bronchiectasis. The aim of this analysis was to investigate the independent contribution of individual respiratory pathogens to clinical outcomes in patients with bronchiectasis

Methods: The EMBARC registry is a prospective observational cohort of patients enrolled 2015-2022.

Patients with sputum or BAL data at baseline were included. Follow-up for up to 5 years was used to identify the relationship between individual respiratory pathogens and future exacerbation frequency, hospitalizations and mortality. Multivariable models were constructed incorporating potential co-infections, region, FEV1, age and sex.

Results: 13041 patients with available microbiology data at baseline were included. *Pseudomonas aeruginosa* (rate ratio 1.18 95% CI 1.10-1.26, $p < 0.0001$), *Stenotrophomonas maltophilia* (RR 1.21 95%CI 1.01-1.44, $p = 0.04$), *Enterobacteriaceae* (1.30 95%CI 1.20-1.41, $p < 0.0001$) and *Aspergillus fumigatus* (RR 1.19 95%CI 1.02-1.40, $p = 0.03$) were all independently associated with future exacerbations. *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Staphylococcus aureus* were not. For future hospitalisations. *P. aeruginosa* (RR 1.49 95CI 1.45-1.65, $p < 0.0001$), *S. maltophilia*

RR 1.55 95%CI 1.23-1.97, $p<0.0001$ and Enterobacteriaceae RR 1.76 95%CI 1.57-1.97, $p<0.0001$) were associated with increased hospitalization while *S. aureus* (RR 0.79 95%CI 0.67-0.94, $p=0.007$) and *H. influenzae* (RR 0.61 95%CI 0.55-0.68, $p<0.0001$) were associated with reduced risk. For mortality, *P. aeruginosa* HR 1.35 95%CI 1.16-1.57, $p<0.0001$ and Enterobacteriaceae (HR 1.50 95%CI 1.27-1.77, $p<0.0001$) were independently associated with mortality. *H. influenzae* isolation was associated with reduced risk (HR 0.76 95%CI 0.64-0.91, $p=0.002$).

Conclusion: The infecting pathogen has a major impact on clinical outcomes in adults with bronchiectasis.

[03.03] The microbiome of sputum samples among Portuguese patients with bronchiectasis

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Background/Aims:

Non-cystic fibrosis bronchiectasis (BC), a chronic respiratory disease characterized primarily by chronic cough, thick sputum, lower airway microbial colonization and frequent infectious exacerbations, is seeing a rise in its prevalence. A vicious cycle of infection, inflammation, and progressive lung tissue damage is frequently associated with the identification of multiple sputum microorganisms and chronic infection. While the role of pathogens has been extensively studied in cystic fibrosis, how the lung microbiome evolves over time, and whether changes within the microbiome correlate with disease progression is not well known in BC. The main objective of our study was to describe the sputum microbiome of Portuguese patients diagnosed with BC.

Methods:

We included patients with BC aged over 10 years, followed at the outpatient department between February 2022 and December 2023, excluding those with cystic fibrosis or treated with long-term inhaled antibiotics or macrolides within the last three months. After obtaining informed consent, a single spontaneous sputum sample was collected during a clinically stable period. The sputum samples were stored at -80°C. DNA extraction was conducted using the DNeasy Blood & Tissue Kit (Qiagen) with an additional step using sterilized glass beads for bacterial disruption. PCR amplification was performed using universal primers targeting the V3-V4 region of the bacterial 16S rRNA gene and sequencing analysis was performed in the Illumina Novaseq 6000 platform.

Results:

We enrolled 55 patients, 80% females, median age 56 years (17 to 75 years) with the following aetiologies: idiopathic BC (38%), post-infectious BC (23%), primary ciliary dyskinesia (11%), gastroesophageal reflux disease (11%), and asthma (9%). The median baseline predicted FEV₁ was 72%. An extensive set of bacterial sequencing reads was found in the sputum samples, being mostly identified as *Neisseria*, *Haemophilus*, *Porphyromonas*, *Streptococcus*, *Prevotella*, *Veillonella*, *Fusobacteria*, and *Rothia*, among others. One to four microorganisms dominated most of the sputum samples. *Haemophilus* was the most dominant taxa among our group of sputum samples (25%), followed by *Streptococcus* (20%), and *Pseudomonas*, *Actinomyces*, *Neisseria*, *Rothia*, and *Moraxella* (10% each). In addition, each patient was colonized by a very distinct range of bacterial taxa belonging to multiple taxonomic genera (ranging from 11 to 60) and very large number of amplicon sequence variants per sample. Shannon's index of diversity ranged from 3.0 to 4.9.

Conclusions:

The sputum microbiome profiles of Portuguese BC patients were very diverse, but it was possible to group sputum samples with similar microbiome profiles into subtypes.

Haemophilus subtype was the most frequently found. Streptococcus was more prevalent in our cohort compared to other European series. Further investigation is ongoing to understand the relationship between microbiome subtypes, BC aetiology, symptoms, clinical severity and the influence of antibiotic treatments.

Conflict of interest(s) (if any – not included in the 500 words):

[03.04] Depletion of commensal taxa is a feature of severe bronchiectasis: data from the BRONCH-UK microbiome substudy

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Background/Aims:

BRONCHUK is a UK-wide multicentre, prospective, observational cohort study of non-cystic fibrosis bronchiectasis patients. The aim of this study is to investigate the lung microbiota of the BRONCHUK participants and to investigate the relationship between the microbiota and clinical characteristics.

Methods:

Patients were recruited between November 2015 and November 2019. Clinical characteristics were recorded including aetiology, BSI, hospitalisation, exacerbations per year, lung function, sputum production, and the Bronchiectasis Quality of Life Questionnaire. DNA extraction was performed on frozen sputum samples obtained at clinically stable state, followed by Illumina 16S rRNA gene sequencing. Sequence analysis was performed with DADA2 and R.

Results:

176 patients (59% female, age 67 (IQR 64-72)) provided a sputum sample, 174 were included in analysis after passing quality checks. The most common aetiologies were idiopathic (43.7%), post-infective (30.5%), post-TB (3.4%) and rheumatoid arthritis (3.4%). 21.3% had had at least one exacerbation in the year before baseline sampling and 31.6% were classed as having a severe BSI score.

Severe bronchiectasis showed a significant depletion of commensal taxa. There was a significant decrease in alpha diversity found in patients with a severe BSI classification (Shannon index $p=0.003$); LEfSe analysis showed the most discriminating genera between groups were a lower prevalence of *Haemophilus*, *Actinomyces*, *Veillonella*, and *Neisseria* in patients with severe bronchiectasis. Alpha diversity was significantly decreased in those who had been hospitalised for severe exacerbations in the previous year, with beta diversity showing differences too (PERMANOVA $p=0.016$).

Proteobacteria largely dominated in patients with three or more exacerbations per year and alpha diversity was also decreased in those with a history of exacerbations ($p=0.006$). *Proteobacteria* and significant decreases in alpha diversity also dominated in patients with poor lung function, alongside significant differences in beta diversity, with *Streptococcus* driving much of the difference in those with higher lung function.

Alpha diversity was significantly decreased in patients with lower scores in three of the eight Quality of Life Questionnaire sections – Physical, Social Functioning, and Respiratory Symptoms. *Streptococcus* was also found to dominate by LEfSe analysis in those with higher scores for the Respiratory Symptoms category.

Conclusions:

The BRONCHUK cohort provides independent validation that lower diversity and depletion of commensal taxa in the lung microbiota is associated with poorer clinical characteristics. Those with lower diversity have overall worse BSI scores, lung function, QoL Respiratory scores, and frequency of exacerbations.

Conflict of interest(s) (if any – not included in the 500 words):

[03.05] Investigation of rapid multiplex PCR against traditional culture in the study of bronchiectasis microbiology – preliminary data from the BRILLIANT study

Lucy Bidgood¹; Hollian Richardson¹; Daniela Alferes de Lima Headley¹; Chandani Hennayake¹; Thomas Pembridge¹; Emma Johnson¹; Holly Lind¹; Morven Shuttleworth¹; Kateryna Viligorska¹; Erin Cant¹; Megan Critchon¹; Helen Liddicoat²; David Connell²; Amelia Shoemark¹; Eve McIntosh¹; Kris Ostridge^{4,3}; Adam Platt³; Maria Belvisi^{3,5}; Merete Long¹; Alison Dicker¹; James D Chalmers¹

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Background/Aims:

BRILLIANT (Bronchiectasis Research Into Leukocyte biology and Lung Infections to Accelerate New Therapies) is a cross-sectional study into endotypes of bronchiectasis. Molecular diagnostics have demonstrated greater sensitivity than traditional culture; this however has not been evaluated extensively in bronchiectasis. Whilst sputum is often used as a proxy for the lung microbiota profile, comparisons with bronchoalveolar lavage (BAL) have been limited to date.

Methods:

Stable patients with CT-confirmed bronchiectasis and healthy controls underwent bronchoscopy and bronchoalveolar lavage (BAL) sampling, while patients also provide a sputum sample if able. Samples were analysed on the BioFire® FilmArray® Pneumonia (PN) Panel for bacterial, viral and AMR detection. BAL samples also underwent traditional culture and microscopy.

Results:

53 patients (age 71 (61-76), 54.7% female, BSI 5 (4-7)) and 11 healthy volunteers (age 42 (37-55), 72.7% female) have been recruited and provided samples as of March 2024. Traditional culture detected infectious agents in 18/53 patient BAL samples (34%) compared with 28/53 detected by BioFire (52.8%). While all healthy volunteer culture gave negative results, BioFire detected viral hits in 2/11 controls (18.2%). The most frequent pathogens detected (culture vs PCR) were *Haemophilus influenzae* (18.9% vs 24.5%), *Pseudomonas aeruginosa* (5.7% vs 9.4%), *Staphylococcus aureus* (3.8% vs 9.4%), *Escherichia coli* (3.8% vs 5.7%), and *Moraxella catarrhalis* (1.9% vs 5.7%).

36 patients provided both a sputum and BAL sample. 28/36 (77.8%) of patients had broadly concordant results by sharing at least one pathogen between samples. While copies/mL were mostly higher in sputum compared to BAL, there were no radical differences.

Conclusions:

The BioFire provided an overall more sensitive method of detecting infectious pathogens against traditional culture methods. Future work will also compare the additional sequencing methods - 16S rRNA gene and nanopore sequencing.

Conflict of interest(s) (if any – not included in the 500 words):

[03.06] Fertility and pregnancy in women with bronchiectasis: a multicenter study

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Background/Aims: Bronchiectasis is a common respiratory disease, with a minority of patients presenting at young age. Compared to other respiratory disorders affecting young women, such as asthma and cystic fibrosis, there is little data on the obstetric outcomes in women with bronchiectasis. We aimed to investigate fertility and outcomes of pregnancy among patients diagnosed with bronchiectasis.

Methods: We conducted a multicenter, multinational, retrospective study from bronchiectasis centers. Female patients with bronchiectasis who had documentation on pulmonary follow-ups and obstetric and labor histories were included. We analyzed demographic and clinical data as well as pulmonary and obstetric outcomes in women with bronchiectasis.

Results: We identified 62 women who completed 100 pregnancies (104 newborns). The median age of the cohort was 29 (range 19-46) years, with a mean pre-pregnancy body mass index of 21.63 (SD 6.3). Etiology of bronchiectasis were post-infectious (n=8,) primary ciliary dyskinesia (PCD) (n=28) and concomitant respiratory morbidities, such as asthma (n=9), chronic obstructive pulmonary disease (n=3) and allergic bronchopulmonary aspergillosis (ABPA) (n=3). Data on assisted fertility techniques (ART) were available in 40 pregnancies. ART was required in 47.5% of pregnancies, with a higher prevalence observed among women with PCD (64.7% vs. 33.3%, p= 0.063). Mean weight gain was 8.6 (SD 6.3) kilograms. Lung function, measured by forced expiratory volume (FEV1), (median FEV1 78, range 26-111, p=0.471) and exacerbation (median 2, range 0-5, p=0.342) rates remained stable, with no significant changes before and after pregnancy. Most pregnancies (74%) were delivered vaginally, at a median of 39 (range, 28-42) weeks. Newborn birth weight significantly correlated with maternal pre-pregnancy FEV1 (p= 0.013, r= 0.36). APGAR scores were within normal range, and no significant newborn malformations were reported.

Conclusions: Pregnancy outcomes are generally favorable for most women with bronchiectasis, providing reassurance to affected women and clinicians alike. However, birth weight is correlated to lung function, suggesting higher risk in women with advanced lung disease. Assisted fertility was common, particularly in women with PCD, suggesting a higher rate of female subfertility. These findings may be reassuring for young women with

bronchiectasis.

Conflict of interest(s) (if any – not included in the 500 words): None

[03.07] A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Brensocatib in Patients With Non-cystic Fibrosis Bronchiectasis – The ASPEN Trial

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Background/Aims:

Non-cystic fibrosis bronchiectasis (hereafter bronchiectasis) is a chronic and progressive inflammatory respiratory disease with diverse causes and variable clinical features. There are currently no approved therapies indicated for bronchiectasis, and international guidelines are based predominantly on limited evidence and expert opinion.

Neutrophil-mediated inflammation is central to the pathophysiology of bronchiectasis, and neutrophil serine proteases (NSPs), including neutrophil elastase (NE), are believed to be key mediators of neutrophil-related respiratory disease. NSPs are activated during neutrophil maturation in the bone marrow by dipeptidyl peptidase 1 (DPP1). Brensocatib is a selective, investigational, oral inhibitor of DPP1. In the phase 2 WILLOW trial, compared with placebo, daily treatment with brensocatib 10 or 25 mg for 24 weeks prolonged the time to first exacerbation and reduced NE activity in sputum in adults with bronchiectasis (Chalmers et al. *NEJM*. 2020). ASPEN (NCT04594369) is a global, phase 3, randomized, double-blind, placebo-controlled trial in patients with bronchiectasis evaluating the impact of brensocatib 10 and 25 mg on the annualized rate of exacerbations over a 52-week treatment period vs placebo.

Methods:

ASPEN enrolled patients with clinically and CT-confirmed bronchiectasis and a history of bronchiectasis exacerbations in the 12 months prior to screening (≥ 2 for adults aged 18 to 85 years; ≥ 1 for adolescents aged ≥ 12 to <18 years). Patients were randomized to receive brensocatib (10 or 25 mg) or matching placebo once daily for 52 weeks (1:1:1 randomization for adults; 2:2:1 for adolescents). Adults were stratified according to geographic region, *Pseudomonas aeruginosa* culture status at screening, and exacerbation frequency (**Figure**).

The primary end point of the study was the annualized rate of exacerbations over the 52-week treatment period, with separate comparisons between each brensocatib dose and placebo. Secondary end points included time to first pulmonary exacerbation; proportion of patients remaining exacerbation free at week 52; change from baseline to week 52 in post-bronchodilator forced expiratory volume in 1 second (FEV₁); annualized rate of severe exacerbations over 52 weeks; change from baseline to week 52 in the Quality-of-Life

Questionnaire-Bronchiectasis Respiratory Symptoms domain score; safety; and brensocatib pharmacokinetics.

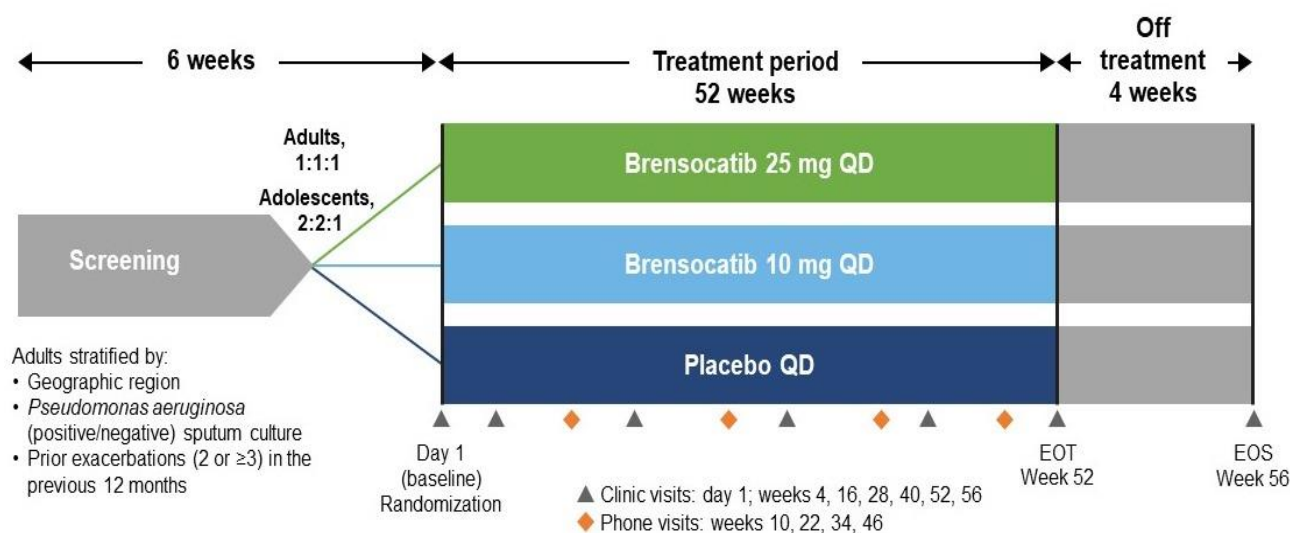
Results:

Baseline demographics for the adult population were available in September 2023 and submitted for publication in January 2024; top-line data will be available in the latter part of Q2 2024.

Conclusions:

The pivotal phase 3 ASPEN trial evaluating the efficacy and safety of brensocatib is the largest bronchiectasis global clinical trial program to date, enrolling over 1700 patients spanning 35 countries and 5 continents. Brensocatib is a first-in-class, selective, and reversible DPP1 inhibitor developed to directly target neutrophil-mediated inflammation, which may have the potential to improve clinical outcomes in patients with bronchiectasis. There are currently no indicated treatments for bronchiectasis approved by the FDA or EMA.

FIGURE. Study design



EOS, end of study; EOT, end of treatment; QD, daily.

Conflict of interest(s) (if any – not included in the 500 words):

This study was funded by Insmed Incorporated. Editorial support was provided by Envision Pharma Group.

James D. Chalmers, Pierre-Régis Burgel, Charles L. Daley, Anthony De Soyza, Charles S. Haworth, David Mager, and Mark L. Metersky served as members of the ASPEN trial steering committee. James D. Chalmers, Pierre-Régis Burgel, Charles L. Daley, Anthony De Soyza, Charles S. Haworth, and Mark L. Metersky were investigators in the ASPEN trial.

James D. Chalmers: grants and personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Zambon, and Insmed Incorporated; a grant from Gilead; and personal fees from Novartis and Chiesi.

Pierre-Régis Burgel: grants from Vertex and GSK, outside the submitted work. Dr Burgel also reports the following: clinical trials: acting as main investigator, advisory activity for AstraZeneca, Chiesi, GSK, Insmmed Incorporated, MSD, Viatris, Vertex, and Zambon; substantial financial contributions to the budget of an institution you are responsible for: GSK, Vertex, and Association Vaincre la Mucoviscidose, Société Française de la Mucoviscidose, Filière MUCO-CFTR.

Charles L. Daley: grant support, advisory board fees, and consulting fees from Insmmed Incorporated. Dr Daley also reports grant support from AN2 Therapeutics, Bugworks, Paratek Pharmaceuticals, and Juvabis; advisory board work with AN2 Therapeutics, AstraZeneca, Cepheid, Hyfe, MannKind, Matinas Biopharma, NobHill, Spero Therapeutics, and Zambon; consulting with Genentech and Pfizer; data monitoring committee work with Otsuka Pharmaceutical, Eli Lilly and Company, and the Bill and Melinda Gates Foundation.

Anthony De Soyza: grants and fees from AstraZeneca, Boehringer Ingelheim, Bayer, Chiesi, Gilead Sciences, GSK, Insmmed Incorporated, and Zambon.

Charles S. Haworth: consultancy/speaker fees from 30 Technology, AstraZeneca, CSL Behring, Chiesi, Infex, Insmmed Incorporated, Janssen, LifeArc, Meiji, Mylan, Novartis, Pneumagen, Shinogi, Teva, Vertex, and Zambon.

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[03.08] Fractional excretion of nitric oxide measurements and respiratory symptom profile among patients with non-CF bronchiectasis – data from the U.S. Bronchiectasis and NTM Research Registry

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Background/Aims:

Bronchiectasis is defined as permanent bronchial dilation. It is characterized by the continuous interaction of both endogenous and exogenous factors affecting the respiratory endothelium, setting up an ongoing interplay between inflammation, infection, and epithelial dysfunction, ultimately resulting in bronchial structural abnormalities. Fractional excretion of nitric oxide (FeNO) is a noninvasive measure of Type 2 airway inflammation, in particular IL-13 activity, often used in the evaluation and management of asthma and related diseases. Prior studies evaluating the utility of FeNO in bronchiectasis have been conflicting. We identified patient- and disease-level factors associated with an elevated FeNO in individuals with bronchiectasis.

Methods:

We conducted a cross-sectional analysis of bronchiectasis patients enrolled in the U.S. Bronchiectasis and non-tuberculous mycobacteria (NTM) Research Registry with a FeNO measurement available at baseline or any follow-up visit. Patients were excluded if they had a diagnosis of primary ciliary dyskinesia (PCD) or CF. Descriptive statistics for clinical characteristics and respiratory symptom profile collected at the visit corresponding to the FeNO measurement were retrospectively analyzed and stratified by normal v. elevated FeNO results. Kruskal-Wallis, t-test, chi-square and Fisher's exact were used to measure the association in continuous and categorical variables respectively.

Results:

Among 117 patients who met the inclusion criteria, FeNO was elevated in 25 (21%). Overall, patients were predominantly female (75.2%) with a median age of 65.0 years at enrollment (interquartile range: 55.0-72.0) and no racial or ethnic differences between groups. Patients with normal FeNO measurements were older (median age 67 vs. 57, $p=0.019$), more likely to be current or former smokers compared to patients with elevated FeNO measurements (40.5% v. 5%, $p=0.003$), while patients with elevated FeNO measurements were more likely to have asthma (72.0% v. 45.7%, $p=0.019$). Between groups, there were no significant differences in lung function, exacerbation history or hospitalizations during the visit window, NTM isolation, Gram negative culture growth, respiratory symptoms (Table 1) or the use of inhaled corticosteroids.

Conclusions:

In patients with bronchiectasis, FeNO elevation is often encountered, but it displayed no clear correlation with respiratory symptom or infection status. Notably, elevated FeNO was significantly associated with a preexisting diagnosis of asthma in these individuals.

Conflict of interest(s) (if any – not included in the 500 words):

CS has served on advisory boards for Insmed and Pharming and is a consultant and expert speaker and for Insmed; DJM is involved in clinical trials with NIH and Gates Foundation and has served as a consultant for Insmed, Sanofi/Regeneron, GlaxoSmithKline, AstraZeneca and Amgen; MLM COI: Insmed, Boehringer Ingelheim, Tactile—Consultant; Investigator-Insmed; Renovion, AN2—Data Safety Monitoring Board; NL COI: INSMED Inc. - Advisory Board Panel; Consultant, Educational speaker; AEB, KJ, MM, CR report no conflicts.

Table 1. Respiratory symptom profile of bronchiectasis patients enrolled in the U.S. Bronchiectasis and NTM Research Registry, stratified by normal v. increased fractional excretion of nitric oxide

	Overall n=117	eNO Result		p-value
		Normal n=92	Increased n=25	
Respiratory Symptoms				
Dyspnea grade, n (%)	77 (66.4)	60 (65.9)	17 (68.0)	0.846
data available	116	91	25	
Fatigue, n (%)	72 (62.6)	60 (66.7)	12 (48.0)	0.088
data available	115	90	25	
Cough, n (%)	103 (88.8)	83 (91.2)	20 (80.0)	0.150
data available	116	91	25	
Hemoptysis, n (%)	14 (12.2)	13 (14.3)	1 (4.2)	0.294
data available	115	91	24	
Experienced chest pain, n (%)	14 (15.2)	12 (15.8)	2 (12.5)	1.000
data available	92	76	16	
Wheezing, n (%)	22 (19.0)	16 (17.6)	6 (24.0)	0.565
data available	116	91	25	

eNO = exhaled nitric oxide, NTM = non-tuberculous mycobacteria

[04.01] Impact of Long-term Home High-Flow Nasal Therapy on Mucus Plugs in Patients with Bronchiectasis

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Background: Mucus plugs (MPs) are a hallmark of severity in muco-obstructive lung diseases and are associated with increased all-cause mortality in patients with COPD. Long-term domiciliary high-flow nasal therapy (HFNT) may represent a promising approach to reduce exacerbations, hospitalizations and symptoms while improving lung function in patients with muco-obstructive diseases such as COPD and bronchiectasis (BE) [Crimi C. *et al.* Journal of Clinical Medicine Dec. 2022; Weinreich, Ulla M. *et al.* European Clinical Respiratory Journal Feb. 2023]. However, its effect on MPs is unknown.

Aims: To assess the effect of HFNT on the change in MPs in patients with BE after 12 months of treatment.

Methods: We conducted an observational case-control study. BE patients already receiving optimized medical treatment and prescribed with home HFNTs were matched 1:1 for age, gender, bronchiectasis severity index (BSI), exacerbations (n/year) and *P. aeruginosa* colonization to a group of BE patients on optimized medical treatment alone (control group). Ten patients in the HFNT group and 10 patients in the control group who underwent chest High-Resolution Computed Tomography (HRCT) at baseline and after 12 months of treatment (optimized medical treatment alone or optimized medical treatment + HFNT) were included and the MP score [range 0-20] was calculated at baseline and after 12 months.

Results: All patients had severe bronchiectasis according to BSI (median 13 (IQR 11.5-15.5) and 11 (IQR 10-13.5) for the HFNT and control groups, respectively). At baseline, median MP score was 5.5 (IQR 3.8-7.5) in the HFNT group and 5.5 (IQR 4-6.8) in the control group. In both cohorts, 60% of patients had high MP scores (≥ 5). No correlation was found between baseline BSI and MP score ($R=0.007$, $P=0.7824$). A reduction in MP score was found in the HFNT group after 12 months [-2 (95% CI: -5 to -0), $P=0.0156$], with a significant difference of -2 (95% CI: -4 to -0), $P=0.0221$ compared to the control group.

Furthermore, the number of lung lobes with MPs was reduced by -1 (95%CI -2 to -0) in the HFNT group vs controls ($P=0.0061$). The percentage of patients with high MP scores was reduced by 20% in the HFNT group.

Conclusions: These preliminary data showed that long-term home HFNT may reduce MPs in patients with BE.

Conflict of interest(s) (if any – not included in the 500 words): NO conflict of interest

[04.02] Physical Activity Levels and Influencing Factors in Individuals with Bronchiectasis: a cross-sectional study.

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Background/Aims: Bronchiectasis is a chronic respiratory condition marked by an irreversible dilatation of the bronchi. People with bronchiectasis have recurrent infections and high inflammation, that leads to a poor quality of life and a low functional capacity, resulting in progressive lung damage and frequent exacerbations. They have a less active lifestyle than healthy people, so it's recommended increasing physical activity (PA), reducing sedentary time to avoid a decline of the performance status (PS). This last one is crucial since PA can improve mucus clearance, reduce inflammation, enhance respiratory function and improve quality of life. We investigate the impact of bronchiectasis on physical activity and the aim was to evaluate some several respiratory and inflammatory markers in patients with non-CF-bronchiectasis, based on the degree of PA and lifestyle.

Methods: This cross-sectional study conducted at the Bronchiectasis Program of Policlinico Bari, Italy, involved 30 participants (≥ 18 years), all diagnosed with non-CF-bronchiectasis. The participants, who wore an AX3 actigraph (Axivity, UK) on their dominant wrist for 7 consecutive days, were divided into two groups based on their levels of PA: 15 in the light activity group and 15 in the moderate/vigorous activity group. We collected demographics data, health characteristics, lifestyle factors, respiratory and inflammatory markers, and other clinical measurements. Initially, we performed a univariate binomial regression analysis to identify individual predictors of the outcome variable. Subsequently, significant predictors identified from the univariate analyses were included in a multivariate binomial regression model to adjust for potential confounders and to determine the independent effects of each predictor on the outcome.

Results: The analysis revealed several significant parameters related to PA levels among participants with bronchiectasis. The participants had a median age of 67 years. In the light activity group, there were older people (median age of 70 years) compared to the moderate/vigorous activity group (median age of 59 years) ($p=0.004$). The study measured several respiratory and inflammatory markers. Participants in the light activity group had higher airway resistance, as indicated by median Raw Values of 170, compared to 130 in the moderate/vigorous activity group ($p = 0.018$); eosinophil counts were also significantly higher in the light activity group (median 145 $n/\mu L$), compared to the moderate/vigorous activity group (median 130 $n/\mu L$, $p = 0.004$); levels of fractional exhaled nitric oxide (FeNO) were lower in the moderate/vigorous activity group (median 14), compared to the light activity group (median 34, $p=0.024$).

Conclusions: Lower airway resistance and lower inflammation markers are associated with higher physical activity levels in our cohort. These real-life data remark the importance of promoting PA and provide other interventions to reduce high inflammation in bronchiectasis patients.

Conflict of interest(s) (if any – not included in the 500 words): All authors have no conflict of interest to declare.

[04.03] Bronchiectasis: Optimising Azithromycin prevention Treatment to reduce exacerbations (BOAT): A double blind pragmatic randomised controlled trial

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Background/Aims:

One of the best evidenced therapies in international guidelines for Bronchiectasis are long term macrolides e.g., Azithromycin. These reduce exacerbations over 6- or 12-month studies. However, data after this duration of treatment is lacking and there are concerns over antimicrobial resistance and cardiac toxicity. We hypothesized that patients could be withdrawn from long-term macrolides without significant worsening of health status.

Study Design:

A pragmatic multicentre double blind randomised trial based on the current NIHR HTA funded OPACE Azithromycin cessation study in COPD. We have a simplified two arm design (cessation vs continuation).

Participants: Adults with Bronchiectasis who have taken Azithromycin for at least 3 months. We will record demographic data (gender, ethnicity), smoking status, Pseudomonas status and duration of prior macrolide therapy. Additionally, we will record Bronchiectasis severity index score at baseline.

Intervention: Stopping Azithromycin- matched placebo will be used and dosing frequency matched to baseline Azithromycin regimens.

Comparator: Continued therapy with trial specific placebo-matched Azithromycin. Patients will be treated with trial stock at the same dosing regimen as they were on at baseline. Most clinicians use 250mg once daily thrice weekly, but other regimens are used; our broad entry criteria accommodate this.

Primary outcome: Time to first acute exacerbation of Bronchiectasis, with acute exacerbation of Bronchiectasis defined as per the European Respiratory Society (ERS). At each clinic visit and telephone contact, study personnel will determine if an acute exacerbation of Bronchiectasis has occurred in the previous period. The date of each acute exacerbation will be taken as the date treatment was started. Secondary objectives will be assessed over the whole duration of participant follow up in the trial even though the participant may have reached the primary outcome measure and may therefore include evaluation on trial medication and subsequently off trial medication. 1) Further evaluation of clinical effectiveness; number/rate and severity of exacerbations 2) Health status will use Eq5DI, St Georges Respiratory questionnaire (SGRQ) and Quality of Life Bronchiectasis tools (QOL-B

)) 3) Hospitalisation and healthcare use (using the same methodology in OPACE trial) 4) Mortality (all-cause, respiratory, cardiac). 5) Adverse events.

Setting:

We will conduct this in 40-50 centres across the UK with particular emphasis on areas with high unmet need (as defined in the NIHR ODP platform e.g., North East, North West, West Midlands, Scotland, deprived urban areas e.g. Camden, Bradford). We will recruit from both primary and secondary care. We will use patient directed recruitment Be Part Of Research and highlight the study via Asthma & LungUK patient newsletters.

Conclusions:

The BOAT trial is a highly ambitious study that will answer a key question in Bronchiectasis management. We welcome sites within the UK to join the study and are open to potential international collaboration.

Conflict of interest(s) (if any – not included in the 500 words):

This study was funded by Insmed Inc.

James D. Chalmers: grants and personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Zambon, and Insmed Incorporated, a grant from Gilead, and personal fees from Novartis and Chiesi.

Anthony De Soyza: grants and fees from AstraZeneca, Boehringer Ingelheim, Bayer, Chiesi, Gilead Sciences, GSK, Insmed Incorporated, and Zambon.

[04.04] The burden of cough and sputum production in bronchiectasis: data from the EMBARC registry

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The burden of cough and sputum production in bronchiectasis: data from the EMBARC registry

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Background: Cough and sputum production are the defining symptoms of the clinical syndrome of bronchiectasis. There are few studies characterising the severity, clinical impact and outcomes of cough and associated symptoms in people with bronchiectasis. The aim of this analysis was to describe the frequency, severity and associated clinical outcomes of cough in bronchiectasis.

Methods: The EMBARC registry is a prospective observational cohort of patients enrolled 2015-2022. Individual item level questionnaire data from the Quality of life bronchiectasis questionnaire was used to quantify the severity of cough “have you been coughing during the day” with responses as “a lot” “a moderate amount”, “a little” and “not at all”. Sputum volume was quantified at baseline. Follow-up for up to 5 years was used to identify the relationship between symptoms and future exacerbation frequency.

Results: 8810 patients were included in the analysis from 28 countries. 2127 (24.1%) responded they coughed “a lot”, 2497 (28.3%) a moderate amount, 3077 (34.9%) “a little” and 1109 (12.6%) not at all. Nocturnal cough was reported 5543 (62.9%) of patients. Sputum volume was highly variable. 2503 (28.4%) of patients reported minimal sputum production (<1ml per day). 3508 (39.8%) reported up to 20ml per day, 1619 (18.4%) reported 20-50ml per day and 1081 (12.3%) reported >50ml per day. Data were missing in 99 patients. Cough severity was associated with markers of severe disease including bronchiectasis severity index, FEV1 and *Pseudomonas aeruginosa* infection. Future exacerbations were directly related to baseline cough severity (rate ratio 1.14 95%CI 1.03-1.27, RR 1.48 95%CI 1.33-1.64 and RR 1.87 95%CI 1.67-2.08 for progressively increasing cough severity compared to patients without daily cough). Relationships remained significant after adjustment for BSI. Compared to patients with <1ml daily sputum there was also increased exacerbations with increasing daily sputum volume after adjustment for BSI (RR 1.17 95%CI 1.08-1.27, RR 1.38 95%CI 1.26-1.52 and RR 1.48 95%CI 1.33-1.65, all $p<0.0001$).

Conclusion: Cough is a common but not universal symptom during stable state in bronchiectasis with a highly variable clinical impact. The severity of cough and sputum production are strongly associated with the risk of future exacerbations.

[04.05] Bronchiectasis among adult Indigenous Australians in the Top End Northern Territory of Australia – an insight into prevalence, clinical characteristics and comparison against global bronchiectasis registry cohorts

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Background/Aims: To describe the bronchiectasis disease burden in the adult Indigenous population in the Top End Northern Territory of Australia.

Methods: A cross-sectional study of Indigenous Australians aged >18 years with chest computed tomography (CT) confirmed bronchiectasis between 2011 and 2020 were assessed on several clinical fronts.

Results: A total of 459 patients were identified with bronchiectasis during the study period, resulting in an estimated prevalence of 19.4/1,000. The median age of patients on enrolment was 47 years, with 55% females. Comorbidities and multimorbidity were common, at 97.4 & 82.8% respectively. The most frequent comorbidities were COPD (83%), hypertension (63%), diabetes (50%) and other cardiovascular diseases (43%). Smoking was prominent, with 85% of patients reporting a smoking history. Lung function parameters are significantly affected, with median Forced expiratory volume in 1 second (FEV₁) at 38% predicted. On CT multilobe involvement is common (73%), the LLL is the most commonly afflicted (73%), and cylindrical type is the most commonly reported (50%). *Haemophilus* spp. (57%) and *Pseudomonas* spp. (31%) were the most commonly isolated microorganisms. Hospitalisation rates are substantial, with 87% recording ≥1 through the study period, and a median rate of 1 per year. Associated all-cause mortality was 42%, with a median age of death 60 years. Compared against five published international bronchiectasis registry reports [Australian (ABR), European (EMBARC-Europe), Indian (EMBARC-India), Korean (KMBARC) and the United States of America (USBRR)], the majority of disease outcomes are substantially worse among adult Indigenous Australians.

Conclusions: The bronchiectasis disease burden, including all-cause mortality, is alarmingly high among Indigenous Australian adults in the Top End of the NT, especially in comparison to international cohorts. Future interventions are desperately required to address this disparity.

Conflict of interest(s) (if any – not included in the 500 words): Nil

This research received the *Thoracic Society of Australia and New Zealand (TSANZ)* - Robert Pierce Grant-In-Aid for Indigenous Lung Health. The TSANZ did not have any role in the study design, data collection, analysis, or interpretation.

[04.06] Psychometric validation and determination of the minimal clinically important difference for the Bronchiectasis Health Questionnaire in adults with bronchiectasis

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ABSTRACT

Background The Bronchiectasis Health Questionnaire (BHQ) is a concise, self-administered and disease-specific instrument for measuring health-related quality-of-life (HRQoL) in bronchiectasis. We sought to assess the psychometric properties of BHQ and determine the minimum clinically important difference (MCID) as a reliable clinical endpoint for assessing the efficacy of bronchiectasis treatments.

Methods We enrolled a cross-sectional observational cohort of 436 bronchiectasis patients and another cohort of 357 patients treated with tobramycin inhalation solution or saline inhalation for *Pseudomonas aeruginosa* infection in a randomized trial. Psychometric analyses encompassed internal consistency, test-retest reliability, construct validity, known-groups validity, and responsiveness. Both anchor-based and distribution-based approaches were utilized to calculate the MCID for therapeutic response.

Results There were significant positive correlations between BHQ scores and the Quality of Life - Bronchiectasis Respiratory Symptom Scale (QoL-B-RSS), with the correlation coefficients of 0.567 in the observational cohort and 0.698 in the trial cohort (both $P < 0.0001$). Known-groups validity indicated significant differences in BHQ scores stratified by the baseline Bronchiectasis Severity Index. BHQ scores correlated modestly with both FEV₁% predicted and exacerbation frequency within the previous year. In the trial cohort, the BHQ demonstrated excellent internal consistency (Cronbach's alpha: 0.893) and test-retest reliability (intraclass correlation coefficient: 0.853). An 8-point improvement in QoL-B-RSS corresponded to a mean increase of 5.49 points in BHQ scores after 4-week treatment. The MCID for BHQ was consistently identified as 3 points.

Conclusions The BHQ represents a clinically meaningful tool for evaluating therapeutic intervention outcomes and patient-centered outcomes.

Conflict of interest(s) (if any – not included in the 500 words):NO

[04.07] Study designs of three Phase II trials of the novel cathepsin C inhibitor BI 1291583 in patients with bronchiectasis

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Background/Aims:

Bronchiectasis is a heterogeneous respiratory disease characterised by abnormal and permanent widening of the bronchi and impaired mucociliary clearance, underpinned by high, uncontrolled neutrophil serine protease (NSP) activity. The latter is associated with severity and future risk of pulmonary exacerbations, ultimately resulting in irreversible and progressive structural lung damage, morbidity and mortality. As NSPs are activated by cathepsin C (CatC, also known as dipeptidyl peptidase 1) in the bone marrow during neutrophil maturation, inhibition of CatC is expected to ameliorate protease burden associated with neutrophilic inflammation in the lungs of people with bronchiectasis. BI 1291583 is a potent, selective, reversible inhibitor of CatC. Here, we outline the study designs of three Phase II trials (Airleaf™, Clairafly™ and Clairleaf™) assessing the safety and efficacy of BI 1291583 in patients with bronchiectasis.

Methods:

Airleaf™ (NCT05238675) and Clairafly™ (NCT05865886) are Phase II, randomised, double-blind, placebo-controlled, parallel-group trials being conducted in patients with non-cystic fibrosis bronchiectasis (N=322) and cystic fibrosis-related bronchiectasis (N=24; profiling study), respectively. Clairleaf™ (NCT05846230) is a Phase II rollover trial that will enrol patients who have completed parent Phase II trials. Adults (18–85 years) with bronchiectasis confirmed by computed tomography, and currently producing sputum, with a history of two exacerbations requiring antibiotic treatment in the last year or one exacerbation if St. George's Respiratory Questionnaire (SGRQ) symptoms score is >40, are included in Airleaf™ and Clairafly™. In Clairleaf™, patients who received BI 1291583 in the parent Phase II trial will remain on the same dose, while patients who received placebo will be randomised to one of the three BI 1291583 doses from Airleaf™ in a 1:1:1 ratio. If development of BI 1291583 is continued, all patients may continue to receive open-label treatment with the selected Phase III dose, subject to Clairleaf™ protocol amendment. Study designs of all three trials are shown in Figure 1. The primary endpoint of the Airleaf™ trial is time to first pulmonary exacerbation up to Week 48, while the primary endpoint of both the Clairafly™ and Clairleaf™ trials is occurrence of treatment-emergent adverse events over the course of each trial. Secondary endpoints for the Airleaf™ trial are rate of pulmonary exacerbations (key secondary), change in Quality of Life-Bronchiectasis respiratory symptoms domain score, change from baseline in sputum neutrophil elastase (NE) activity, change in SGRQ symptoms score, change in post-bronchodilator per cent predicted forced expiratory volume in 1 second and the occurrence of an exacerbation by Week 24 after first

drug administration. Secondary endpoints for the Clairafly™ trial are change from baseline in sputum NE activity, and AUC_T and C_{max} after the first dose and at steady state. Secondary endpoints for the Clairleaf™ trial are time to first pulmonary exacerbation and the rate of pulmonary exacerbations.

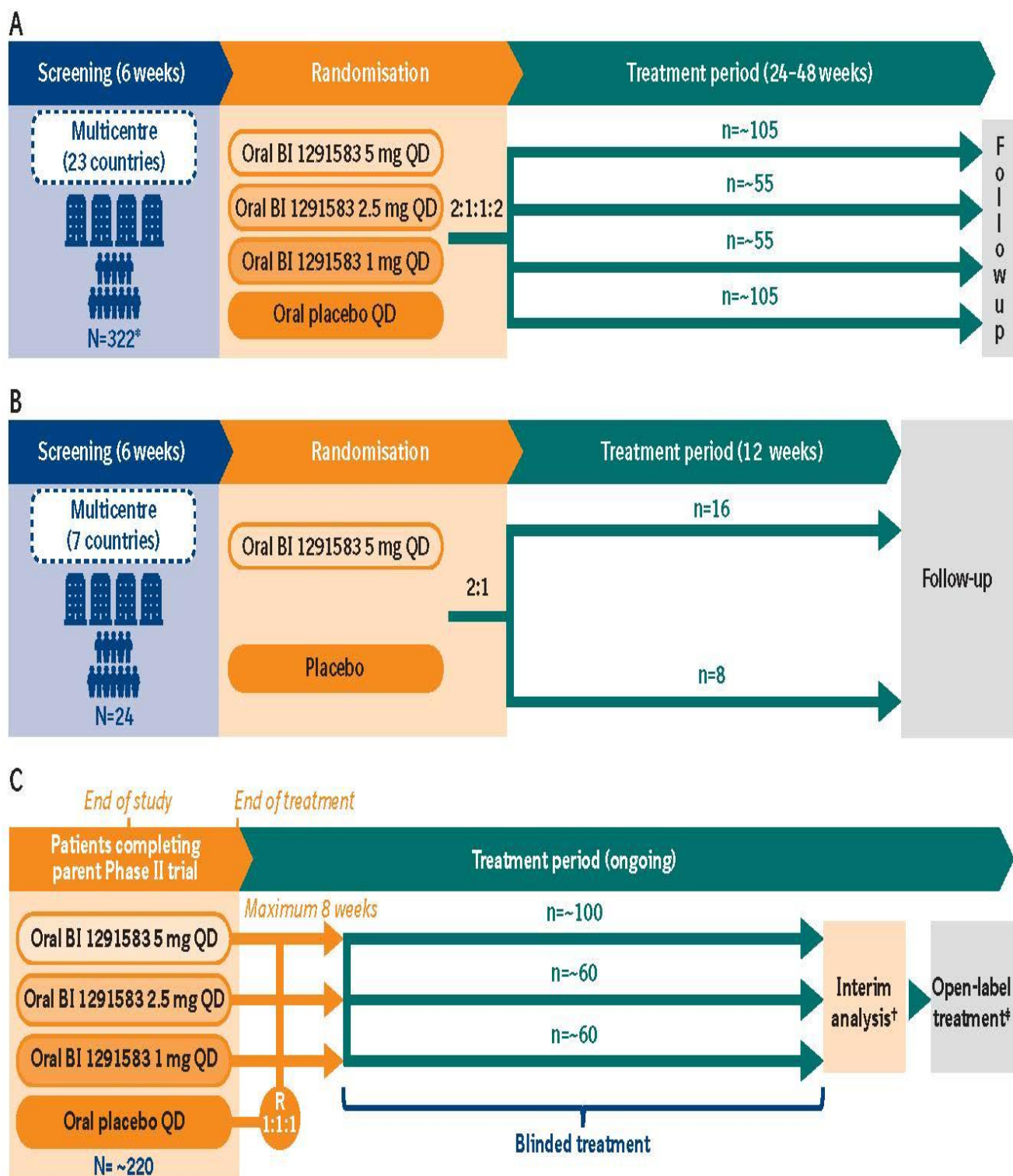
Results:

Recruitment into Airleaf™ is complete and the readout is expected mid-2024. Clairafly™ is expected to reach completion in early 2025.

Conclusions:

These trials will provide information on the safety and efficacy of BI 1291583 in patients with bronchiectasis and inform the design of Phase III trials.

Figure 1. Study designs of the (A) Airleaf™, (B) Clairafly™ and (C) Clairleaf™ trials of BI 1291583.



*322 patients recruited into the Airleaf™ trial.

†Time to interim analysis is approximately one year after First Patient In.

‡Open-label investigation of long-term safety may be added (subject to amendment of Clairleaf™ protocol).

QD, once daily.

Chalmers, J.D., et al. A Phase 2 randomised study to establish efficacy, safety and dosing of a novel oral cathepsin C inhibitor, BI 1291583, in adults with bronchiectasis: Airleaf™. ERJ Open Res. 2023; 9(3):00633-2022, <https://doi.org/10.1183/23120541.00633-2022>. © 2023, The Author(s). Reused under a CC BY 4.0 licence.

Conflict of interest(s) (if any – not included in the 500 words):

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[05.01] Prevalence of treatable traits in bronchiectasis

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Background/Aims: Bronchiectasis is a very heterogeneous chronic respiratory disease. A “treatable traits” (TTs) approach has been suggested in literature since different years and implemented in clinical practice. The aim was to describe prevalence and characteristics of treatable traits in adults with bronchiectasis.

Methods: This was a secondary analysis of a prospective, observational study conducted at the Bronchiectasis Program of the IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico Milano, Italy, from 2016 to 2020. All consecutive patients (≥18 years) with clinically and radiologically significant bronchiectasis were enrolled. Those with cystic fibrosis or traction bronchiectasis were excluded. Bronchiectasis patients were managed according to standard operating procedures based on the 2017 European Respiratory Society (ERS) guidelines. A list of 31 treatable traits was evaluated according to four different domains: pulmonary, extrapulmonary/comorbidities, etiological and behavioural/lifestyle/environmental risk-factors.

Results: A total of 700 bronchiectasis patients [median (IQR) age: 62 (48-71) years; female: 77%] were enrolled during the study period. The median (IQR) Bronchiectasis Severity Index (BSI) value was 5.5 (3-9); 26.2% had severe bronchiectasis. Prevalence of different TTs according to the 4 domains is depicted in *Table 1*. The five most common TTs were: daily sputum production (65.7%), hypovitaminosis D (54.1%), gastroesophageal reflux (44.4%), airway neutrophilic inflammation (39.5%) and airflow obstruction (34.7%).

Table1

PULMONARY	N = 700*
Daily sputum production	460 (65.7%)
Airway neutrophilic inflammation ^{a,b}	79 (39.5%)
Airflow obstruction	243 (34.7%)
Th2-high endotype ^c	168 (24.0%)
Frequent exacerbator (≥3/years)	160 (22.9%)
Chronic <i>Pseudomonas aeruginosa</i> infection	126 (18.0%)
Asthma	118 (16.9%)

Chronic infection with other bacteria	105 (15.0%)
<i>P. aeruginosa</i> isolation (without chronic infection)	101 (14.4%)
NTM ^e pulmonary disease	69 (9.9%)
COPD ^f	57 (8.1%)
Dyspnoea ^d	48 (6.9%)
Chronic respiratory failure (oxygen therapy or NIV ^g at home)	33 (4.7%)
EXTRAPULMONARY/COMORBIDITIES	N = 700*
Hypovitaminosis D (<30 ng/mL)	379 (54.1%)
Gastroesophageal reflux	311 (44.4%)
Chronic rhinosinusitis	236 (33.7%)
Underweight	110 (15.7%)
Osteoporosis	107 (15.3%)
Anaemia	90 (12.9%)
Depression	59 (8.4%)
Nasal/sinus polyps	57 (8.1%)
Anxiety	52 (7.4%)
Obesity	35 (5.0%)
ETIOLOGICAL	N = 700*
Primary or secondary immunodeficiency	147 (21.0%)
Primary Ciliary Dyskinesia	36 (5.1%)
Connective tissue diseases	24 (3.4%)
Rheumatoid Arthritis	13 (1.9%)
Inflammatory Bowel Disease	12 (1.7%)
ABPA ^h	5 (0.7%)
AAT ⁱ Deficiency	5 (0.7%)
LIFESTYLE	N = 700*
Active smoking	17 (2.4%)

Conclusions: A variety of treatable traits can be identified in bronchiectasis patients leading to relevant interventions.

*. Data are presented as N(%)

a. Defined as neutrophil elastase activity on sputum ³ 20 mg/mL

b. This trait was calculated on 200 patients

c. Eosinophils ³ 300/cells or FeNO ³ 25 ppb

d. mMRC score: 3-4

- e. NTM: NonTuberculous Mycobacteria
- f. COPD: Chronic Obstructive Pulmonary Disease
- g. NIV: Non-Invasive Ventilation
- h. ABPA: Allergic Bronchopulmonary Aspergillosis
- i. AAT: Alpha-1 Antitrypsin

Conflict of interest(s) (if any – not included in the 500 words): All authors have no conflict of interest to declare.

[05.02] Activity of Cathepsin G in sputum is associated with disease severity and activity and predicts exacerbations in bronchiectasis

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Background/Aims: Cathepsin-G (Cat-G) is a neutrophilic serine protease implicated in airway neutrophilic inflammation in bronchiectasis. We aimed at evaluating its activity in sputum and its association with disease severity and outcomes in bronchiectasis.

Methods: A European, prospective, multicentre, cohort study enrolling consecutive adults with clinically and radiologically significant bronchiectasis has been conducted in Milan (Italy), Dundee (UK) and Barcelona (Spain). Cat-G activity was evaluated in the sputum of bronchiectasis adults during their stable state. Patients were divided in three study groups according to Cat-G tertiles. Comparison between groups were performed using the Kruskal-Wallis test or the Chi-squared test, when appropriate. A negative binomial model has been used for the estimation of exacerbation rates during follow-up.

Results: Among 389 patients (63.8% females, median age: 68.0) enrolled, the median [IQR] levels of Cat-G were 45.12 [1.34 – 128.75] ng/mL. Patients with Cat-G activity lower than 10 ng/mL were assigned to the “Low” group (n = 128), those with Cat-G between 10 and 97 ng/mL were assigned to the “Medium” group (n = 132), while those with activity greater than 97 were assigned to the “High” group (n = 128). Disease severity was associated with Cat-G activity, in terms of BSI (Low: 5[4-8] vs Medium: 6[4-9] vs High: 8[5-12]; P<0.001), E-FACED score (Low: 2[1-3] vs Medium: 2[1-3] vs High: 3[1-5]; P<0.001) and Reiff score (Low: 3[2-4] vs Medium: 4[2-6] vs High 4[3-8]; P<0.001). The proportion of people with chronic bacterial infection (27.3% vs 45.9% vs 70.3%; P<0.001) and with chronic *Pseudomonas* infection (Low: 6.3% vs Medium: 19.5% vs High: 42.2%; P<0.001), were significantly different across groups. In terms of disease activity, Cat-G was associated with an increased sputum production (Low: 10[5-20] vs Medium: 12[5-45] vs High: 18[5-43]; P=0.005) and a higher burden on quality of life in terms of QoL-B scores (Low: 70.4[59.3-77.8] vs Medium: 70.4[51.9-77.8] vs High: 66.7[40.7-74.1]; P=0.036). Median follow up was 717 [413 - 1,064] days. Both the Medium (IRR 1.312 [1.004 – 1.714]) and the High (IRR 1.666 [1.281-2.167]) groups were associated with higher exacerbation rate during follow-up when compared to patients in the Low Group.

Conclusions: Cat-G might be a reliable neutrophilic inflammation biomarker associated with both disease severity and prognosis in bronchiectasis patients.

[05.03] Macrolides versus inhaled antibiotics to prevent exacerbations in adults with bronchiectasis: results from a network meta-analysis.

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Background/Aims: ERS guidelines suggest long-term (LT) treatments with either macrolides or inhaled antibiotics in bronchiectasis patients who remain frequent exacerbators despite optimised management.

Methods: In view of the absence of a head-to-head comparison among these two interventions in the literature, we designed a systematic review of randomised controlled trials (RCTs) with a parallel group design testing the efficacy and safety of LT (≥ 6 months) inhaled antibiotics vs LT (≥ 6 months) macrolides or each intervention against placebo (PROSPERO CRD42023446134). A two-step meta-analysis (first pairwise, then network meta-analysis) was performed to compare the three interventions with exacerbation frequency as primary endpoint.

Results: 4 RCTs compared macrolides vs placebo, 9 inhaled antibiotics vs placebo. Both macrolides and inhaled antibiotics were superior to placebo in the pairwise comparison (IRR 0.50, 95% CI [0.36-0.68] and IRR 0.73 [0.64-0.84], respectively). The network meta-analysis model revealed that macrolides were superior to inhaled antibiotics in terms of reduction of exacerbation frequency (IRR 0.69, 95% CI [0.51-0.92]). The effect was mainly driven by azithromycin. Macrolides were also associated with a prolonged time to first exacerbation (HR 0.44, 95% CI [0.29-0.66]) and a lower prevalence of patients experiencing an exacerbation during the study period (OR 0.54, 95% CI [0.32-0.91]) compared to inhaled antibiotics.

Conclusions: Our data support the use of macrolides as first-line treatment in preference to inhaled antibiotics for frequent exacerbating patients with bronchiectasis.

[05.04] Signs and symptoms of bronchiectasis during steady state in an international multicentre cohort: the 4S study

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Introduction: A definition of clinically significant bronchiectasis has been recently proposed through a Delphi Consensus (Lancet Resp Med 2021). This definition was ideated for clinical trials, while in the real world a wide heterogeneity in signs and symptoms can be expected.

Aims: 1) To evaluate signs and symptoms during the stable state of adults with radiologically significant bronchiectasis. 2) To validate the 2021 definition of bronchiectasis as a clinically significant disease in the real world.

Methods: The 4S (Steady State Signs and Symptoms) study is an international, multicentre, observational, cross-sectional study conducted across 15 Bronchiectasis Programmes in Europe and Asia. Consecutive adults (≥ 18 years) with radiologically and clinically significant bronchiectasis according to the judgement of the attending physician have been enrolled. A comprehensive evaluation of signs and symptoms during stable state was performed. Patients were divided into two study groups, according to the adherence (group A) or lack of adherence (Group B) to the 2021 definition.

Results: Among 729 enrolled patients (70.9% female; median [IQR] age: 63 [54-71] years), 43.1% had cough daily or most days per week, 50.2% had sputum production daily or most days per week, and 29.8% had purulent sputum during their stable state. Additionally, 31.2% reported fatigue, 13.8% weight loss, 12.3% suffered from night sweats, 11.0% had nocturnal respiratory symptoms, 9.9% showed significant exertional dyspnoea, 8.2% had breathlessness at rest, 7.9% had fever or low-grade fever and 7.9% suffered from chest pain. 35.5% had a history of exacerbations, defined by at least 3 respiratory infections in the previous 2 years. 41.0% belonged to Group A. Among Group B, 13.7% had cough at least most days per week, 21.4% had sputum production at least most days per week, while 18.4% had a history of exacerbations. Group A patients were more frequently males (33.8% vs 25.8%, $P = 0.021$), and reported a higher disease severity expressed through the Bronchiectasis Severity Index (6 [3-10] vs 5 [3-8], $P < 0.001$), the evidence of chronic *Pseudomonas* infection (29.3% vs 13.6%, $P < 0.001$), and a lower FEV₁% (78 [55-96] vs 86 [56-107], $P = 0.009$) when compared to Group B. However, Group A patients had a higher Body Mass Index (22.0 [20.0-24.7] vs 21.4 [19.0-24.1], $P = 0.016$) than those in Group B. Furthermore, Group A patients were more frequently treated with inhaled corticosteroids (36.2% vs 22.3%, $P < 0.001$) and long-acting beta agonists (50.2% vs 35.6%, $P < 0.001$) and underwent daily physiotherapy more frequently than those in Group B (35.8% vs 18.8%, $P < 0.001$).

Conclusions: Patients with clinically significant bronchiectasis have heterogeneous signs and symptoms during stable state and they often do not fulfil the 2021 criteria developed for clinical trials.

[05.05] Effectiveness of Surgical Intervention in Symptom Resolution for Bronchiectasis Patients: A Retrospective Analysis

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Background/Aims:

This study aimed to evaluate the impact of surgical intervention on symptom improvement and clinical outcomes in patients diagnosed with bronchiectasis

Methods:

A retrospective analysis was conducted on 27 patients who underwent surgical treatment for bronchiectasis at Kangdong Kyung Hee University Hospital in Korea from 2006 to August 2023. The primary endpoint was improving symptoms post-surgery, defined as the disappearance of symptoms or reduced severity.

Results:

The cohort included 51.9% males (n=14), with an average age of 58.96 (SD=8.60). There was no significant sex difference in outcomes. Although age and symptoms such as cough, sputum, and hemoptysis showed no significant association with post-surgical outcomes, dyspnea severity pre-surgery was significantly related to symptom improvement (p=0.048). A smaller decrease in FEV1 after surgery was observed in patients whose symptoms disappeared (p<0.001 for symptom resolution, p=0.067 for delta_FEV1).

Conclusions:

Surgical treatment in bronchiectasis patients significantly impacts symptom resolution. While the type of surgery and pre-existing dyspnea did not considerably influence symptom resolution, the overall high rate of symptom improvement highlights the effectiveness of surgical intervention. These findings suggest a beneficial role of surgery in selected patients with bronchiectasis, warranting further research to optimize treatment strategies.

Conflict of interest(s) (if any – not included in the 500 words): none

[05.06] Prevalence and clinical relevance of eosinophilic bronchiectasis

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Background/Aims:

Bronchiectasis is classically considered a neutrophilic disorder. However, recently, eosinophilic subtypes have been described. Our primary objective was to ascertain the prevalence of eosinophilic bronchiectasis. The secondary objectives were to evaluate lung function and the severity of bronchiectasis between eosinophilic and non-eosinophilic bronchiectasis.

Methods:

The current study is a retrospective analysis of patients with non-cystic fibrosis bronchiectasis being managed at our center. We investigated all patients with spirometry, chest CT, complete blood count, serum *Aspergillus fumigatus* specific IgE, sweat chloride, serum immunoglobulin levels, and sputum cultures. We also performed tracheal mucosal biopsy or whole exome sequencing in selected patients. We then diagnosed the cause of underlying bronchiectasis. We excluded patients with underlying asthma or allergic bronchopulmonary aspergillosis. Eosinophilic bronchiectasis was defined in those with blood eosinophil count ≥ 300 cells/ μ L. Data are presented as number (percentage), mean $\pm$ standard deviation (SD), or median [interquartile range (IQR)]. The differences between continuous and categorical variables were analyzed using the Mann-Whitney U or chi-square tests. We performed a multivariable logistic regression analysis to evaluate the factors associated with bronchiectasis severity (≥ 9 segments on chest CT). A p-value < 0.05 was considered statistically significant.

Results:

We included 239 patients with bronchiectasis. The mean $\pm$ standard deviation age of the study population (124 [51.9%] women) was 42 ± 15.1 years. The median (IQR) duration of symptoms was 3 (0.7-8) years. We could identify a cause of bronchiectasis in 191 patients (post-tuberculous [n=155], primary ciliary dyskinesia [n=12], common-variable immunodeficiency [n=4], Macleod's syndrome [n=8] and others. The median (IQR) segments involved by bronchiectasis was 5 (3-8). The median blood eosinophil count was 163 (50-290) cells/ μ L.

Fifty-eight (24.3%) patients had eosinophilic bronchiectasis. Patients with eosinophilic bronchiectasis had significantly lower mean % predicted FVC (50.1 vs. 59.2, $p=0.042$), fewer median segments with bronchiectasis (4 vs. 5, $p=0.097$) and TB (77.6% vs. 60.8%, $p=0.026$) as the underlying cause of bronchiectasis. We found no difference in the FACED score or *Pseudomonas* colonization between the two groups.

On a multivariable logistic regression analysis, post-tuberculous bronchiectasis (OR, 95% confidence interval [95% CI], 0.035 [0.10-0.12, $p<0.001$]) was associated with less extensive bronchiectasis (< 8 segments of bronchiectasis). Patients with eosinophilic bronchiectasis

also had less extensive bronchiectasis (OR [95% CI], 0.21 [0.04-1.1], $p=0.058$) but it was not statistically significant.

Conclusions:

We found eosinophilic bronchiectasis in one-fifth of our cohort. However, it was not associated with the extent of bronchiectasis on chest CT.

Conflict of interest(s) (if any – not included in the 500 words):

NIL

[05.07] Peripheral immune cells are associated with disease severity and chronic *P. aeruginosa* infection in Bronchiectasis

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Background/Aims: Bronchiectasis is characterized by alterations in the pulmonary immune response which are associated with disease severity and poor clinical outcomes. We aimed to explore their association with the systemic immune cells profile, which remains unclear.

Methods: Clinically stable patients with bronchiectasis were recruited from the Clinic Barcelona Hospital (Spain). The presence of bronchiectasis was determined by CT scan and its severity by the Bronchiectasis Severity Index (BSI) score. The immune profile in whole blood was assessed using flow cytometry analysis.

Results: Fifty-nine patients with clinically stable bronchiectasis were studied: the mean age was 63±9 years, 62.7% were female and 28% had chronic infection with *P. aeruginosa* (PA). According to their BSI score, 51.7% of the cases were mild, 32.8% moderate and 15.5% severe. The latter group presented a lower percentage of CD56^{bright}CD16⁻NK cells (p=0.027), and a higher percentage of monocytes (p=0.002), T CD8⁺CD28⁻ (p=0.044) and Tregs (p=0.02), compared to mild or moderate. Regarding the presence of chronic infection, patients with chronic PA showed a similar profile, with activated (HLA-DR⁺) Th17 and effector T CD4⁺ (p=0.033 and p=0.028).

Conclusions: A decrease in NK cells and an increase of monocytes, T lymphocytes with an "exhausted/activated" phenotype and an inverted Th17/Tregs ratio in peripheral blood was observed in patients with severe bronchiectasis and/or chronic PA infection, suggesting that systemic alterations in the immune response.

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[05.08] Safety and efficacy of biological drugs in bronchiectasis patients: the BIO-BRO study

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Background/Aims:

Although most bronchiectasis patients have a neutrophilic airway inflammation, a Type 2 (T2)-high inflammatory endotype was found in up to one third of the patients. Several biologicals targeting T2-high inflammation are currently available on the market although not approved for bronchiectasis. The aim of the study is to evaluate the effectiveness and safety of biological drugs targeting T2 inflammation administered to patients with clinically significant bronchiectasis because of other pulmonary or extra-pulmonary indications.

Methods:

The BIO-BRO study was an international, multi-centre, observational, retrospective study enrolling adults with clinically significant bronchiectasis from 20 Bronchiectasis Programs across 9 countries worldwide who underwent at least one dose of any biologicals (Benralizumab, Dupilumab, Mepolizumab, Omalizumab or Reslizumab) from January 1st 2005 to December 31st 2021 for different indications. Outcomes were evaluated during treatment with biologicals (up to 5 years of follow-up) and compared to the year before treatment initiation. The primary endpoint was the rate of exacerbations, whereas secondary endpoints were the reduction of exacerbations up to 5 years, lung function (FEV₁), quality of life and disease severity (mMRC, CAT, ACQ, ACT, SGRQ), and safety. Quantitative variables were expressed via mean and standard deviation (SD) or median and interquartile range (25-75 IQR), qualitative variables via absolute frequency and relative percentage. The Chi-square test or the Fisher's exact test were used to evaluate differences in qualitative variables, while the Mann-Whitney or the Kruskal Wallis tests were used for quantitative ones. The statistical significance threshold was set at $p < 0.05$; the analyses were conducted using the STATA17 statistical software.

Results:

244 patients [51.6% females; mean (SD) age: 58 years (12.2)] were enrolled: median (IQR) Bronchiectasis Severity Index value was 6 (3-10), 31.1% had severe bronchiectasis and 9.4% had chronic *P. aeruginosa* infection. The median (IQR) number of exacerbations in the year before biologicals administration was 3 (2-6). 32.0% were exposed to Mepolizumab, 30.3% to Benralizumab, 25.0% to Omalizumab, 11.9% to Dupilumab and 0.8% to Reslizumab. Main indications for biologicals included severe asthma (89.3%), allergic bronchopulmonary aspergillosis (2.9%), eosinophilic granulomatosis with polyangiitis (2.9%) and intrinsic asthma (2.5%). After one year of treatment, the median (IQR) number of exacerbations significantly dropped to 1 (0-2), $p < 0.001$. The prevalence of frequent exacerbators (≥ 3 exacerbations per year) decreased from 58.2% to 14.4% after one year ($P < 0.001$). After a year of treatment, the median FEV₁% significantly improved from 69.3% to 75.8% ($P < 0.001$), as well as CAT (30.55 vs. 17.05, $p = 0.003$), mMRC (2 vs. 1, $P < 0.01$), ACT (16.5 vs. 21.0, $P < 0.001$), ACQ (1.49 vs. 1.02, $P = 0.001$) and SGRQ (18.94 vs. 15.56, $P = 0.038$). 12 patients had side effects after the first year of treatment and fever was the most prevalent symptom (3 cases), with 2 treatment interruptions due to anaphylactic reaction and skin rash.

Conclusions:

Biological drugs targeting T2-high related inflammation seem to be safe and effective in bronchiectasis patients across different outcomes including exacerbation rates.

Conflict of interest(s) (if any – not included in the 500 words):

[06.01] Characteristics and Outcomes for Bronchiectasis Patients Receiving Intravenous Antibiotics Under the Respiratory Virtual Ward at Torbay Hospital from May 2023 to December 2023

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Background/Aims:

Virtual wards are an evolving area of healthcare, initially used during early Covid-19 pandemic surges to remotely monitor patients using pulse oximeters. Nationally, this led to the expansion of virtual wards to manage other acute respiratory infections and deliver care at home that would previously have required hospital admission.

An important focus of the Torbay Hospital Respiratory Virtual Ward is expanding the home intravenous (IV) antibiotic treatment service for patients with complex infections, with specialist nursing input, physiotherapy appointments, and twice-weekly remote consultant reviews. It also provides early supported discharge which shortens hospital admissions and helps to avoid complications like hospital-acquired infections and deconditioning.

Records of patients with bronchiectasis who received IV antibiotics during the first seven months of the Torbay Hospital Respiratory Virtual Ward were reviewed to assess patient characteristics and outcomes.

Methods:

We carried out a retrospective case-notes review of patients who received IV antibiotics under the Respiratory Virtual Ward from May to December 2023. This evaluated patient demographics, diagnosis, baseline antibiotic therapy, sputum microbiology, antibiotic duration/administration, and outcomes.

Results:

17 patients with bronchiectasis received IV antibiotic therapy under the Respiratory Virtual Ward during the 7-month timeframe. Mean age was 73 years. 65% (11/17 patients) were taking prophylactic antibiotics (either nebulised or oral) at the time of starting IVs.

16 patients (94%) had a positive sputum culture prior to starting IV therapy, of whom 11 (69%) had *Pseudomonas aeruginosa*. 25% of the total positive sputum cultures had antibiotic-resistance, namely to ciprofloxacin, tobramycin & gentamicin. Other significant cultured organisms included *Haemophilus influenzae*, *Serratia marcescens*, and *Proteus* species.

IV antibiotics administered included piperacillin with tazobactam (Tazocin) and meropenem. 18% (3/17 patients) received elastomeric once-daily Tazocin 13.5g only; 47% (8/17) received Tazocin 18g only; and 12% (2/17) received meropenem only. 4 patients (24%) required escalation of IV antibiotic treatment to either an increased dose or a different antibiotic.

41% of patients (7/17) self-administered IV antibiotics. 53% (9/17) had their IV antibiotics administered by virtual ward nurses either at home or at an outpatient clinic. One patient deteriorated on the first planned day of home IV treatment and so was admitted to complete their course.

10/17 patients (59%) completed their IV antibiotics as an outpatient, saving 245 inpatient bed-days. 7 patients (41%) required admission during their outpatient treatment due to clinical deterioration. Of these, 3 patients required a longer antibiotic course than initially planned, and 3 patients required a further course of IV antibiotics within the study timeframe.

Conclusions:

The Torbay Hospital Respiratory Virtual Ward has begun to expand its scope to manage patients requiring IV antibiotics for severe exacerbations of bronchiectasis by supporting them to receive treatment at home. The majority of patients avoided hospital admission, saving 245 inpatient bed-days during the Virtual Ward's first 7 months. However, several required escalation of antibiotics or a period of hospital admission, emphasising the need for personalised treatment plans and close clinical monitoring to provide successful at-home treatment.

Conflict of interest(s) (if any – not included in the 500 words):

[06.02] Audit of Paediatric Bronchiectasis Service at Alder Hey Children's Hospital: Investigation, Management and Outcomes

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Background/Aims:

Non-cystic fibrosis, non-primary ciliary dyskinesia (PCD) bronchiectasis in children and young people presents a complex aetiology, with limited specific evidence regarding the management and outcomes. The impact of improving respiratory health in children with bronchiectasis, both limiting further damage and potentially improving existing damage, has implications extending into adulthood. Understanding the factors influencing bronchiectasis outcomes is crucial. This audit describes the data collected from the paediatric bronchiectasis service at Alder Hey Children's Hospital, which maintains comprehensive patient records from both a respiratory bronchiectasis clinic and joint respiratory - immunology clinic.

Methods:

The project was registered and approved with the trust's audit and research department. Included patients were those under the care of the respiratory MDT bronchiectasis service or joint respiratory immunology clinic. Patients had a CT confirmed diagnosis of bronchiectasis, a negative sweat test and normal nasal brushings or no clinical suspicion of PCD.

Data was manually extracted and anonymized, focusing on suspected underlying causes (which were grouped into themes), management strategies, and disease status at audit time.

Results:

50 patients were included, 28 male and 22 Female. 21 were recorded by the audit as not having a definite or obviously stated suspected cause, The remaining identified suspected causes were themed into the following categories: 'Post-infective process' (n=16), 'specific predisposing diagnoses or risk factors' (n=6), 'immunodeficiency' (n=5), 'iatrogenic' (n=2).

With respect to management at their most recent clinic, data was available for 47 patients. 22 were on prophylactic antibiotics. 28 patients had data available stating a plan for regular physio, of which 2 have a dysfunctional breathing plan, and 1 documented as having a plan but not participating. 6 patients have a documented plan to start physio when needed. 3 patients documented as preferring/using exercise in place of their physio. 4 patients are documented as having stopped and/or no longer requiring physiotherapy. The remainder did not have a recorded plan for regular or intermittent physio. 29 patients had 'other treatments' including inhaled bronchodilators, inhaled steroids, nebulised sodium chloride and oral antihistamines. 4 have subcutaneous immunoglobulins.

20 patients had one CT, 26 had two CTs, 2 had three CTs, 2 had four CTs. Mean average time between scans was 1311.8 days (IQR 850.8 - 1645.3 days, data available for 26 intervals between scans, as dates of some scans were not available). According to CT results 3 patients progressed, 31 were stable, 9 improved, and 6 resolved. Data on this was

unavailable for 1 patient. Ongoing work includes retrospective analysis of disease causation and chest management compared to outcomes.

Conclusions:

The findings underscore the complexity of bronchiectasis aetiology and the different approaches to management. Whilst challenges such as variability in physiotherapy adherence and the identification of underlying causes persist, the audit illuminates areas for potential improvement in patient care. The audit also serves as a foundation for future research and quality improvement initiatives aimed at advancing the standard of care for this patient population.

Conflict of interest(s) (if any – not included in the 500 words): no conflict of interest to declare

[06.03] Prevalence of allergic bronchopulmonary aspergillosis in adults based on asthma severity

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Background/aims: The revised International Society of Human and Animal Mycology-allergic bronchopulmonary aspergillosis working group (ISHAM-AWG) guidelines have recommended screening all adult asthmatics for ABPA. However, there is a lack of evidence to support this recommendation. Our primary objective was to determine the prevalence of ABPA in patients with different asthma severity. The secondary objective was to compare the clinical, immunological, and radiological characteristics of ABPA in different asthma categories.

Methods: We retrospectively analyzed the data of 543 adult asthmatics collected prospectively between July 2017 and September 2018. We classified asthma as mild intermittent, mild persistent, moderate persistent, and severe persistent asthma per the 2004 Global Initiative for Asthma (GINA) recommendations that adjust for the effect of treatment on disease severity. We diagnosed ABPA using the revised ISHAM-AWG criteria. We categorized ABPA as serological ABPA (ABPA-S), ABPA with bronchiectasis (ABPA-B), ABPA with mucus plugging (ABPA-MP), and ABPA with high-attenuation mucus (ABPA-HAM) using chest computed tomography (CT).

Results: We classified 23, 58, 257, and 205 subjects as mild intermittent, mild persistent, moderate persistent, and severe persistent asthma, respectively. Subjects with severe persistent asthma were older and had a longer asthma duration than milder forms of asthma (Table 1). Patients with severe asthma had poorer lung function and required higher doses of inhaled corticosteroids for asthma control. We diagnosed 106 (19.5%) ABPA subjects. The prevalence of ABPA was similar in the various asthma categories (Table 2). ABPA subjects had similar clinical and immunological profiles across different asthma categories (Table 3). ABPA subjects with severe persistent asthma had worse lung function (spirometry) and more lung segments with bronchiectasis (on CT thorax) than mild and moderate asthma. We categorized 8, 32, 27, and 39 ABPA subjects as ABPA-S, ABPA-B, ABPA-MP, and ABPA-HAM. The distribution of different ABPA imaging categories was similar in mild, moderate, and severe asthma (Table 3).

Conclusion: We found the ABPA prevalence unaffected by the severity of underlying asthma, which supports the revised ISHAM-ABPA working recommendations for screening all asthmatics for ABPA. Studies from other geographic locales should confirm our study findings.

Table 1. Baseline characteristics

Variables	Mild intermittent asthma (n=23)	Mild persistent asthma (n=58)	Moderate persistent asthma (n=257)	Severe persistent asthma (n=205)	P value
Age, years (mean±standard deviation)	32.2±13.6	31.3±12.2	35.9±13.7	39.9±13.8	<0.001

Female sex, n (%)	12 (52.2)	34 (58.6)	410 (54.5)	133 (64.9)	0.137
History of atopy, n (%)	9 (39.1)	20 (34.5)	73 (28.4)	71 (34.6)	0.410
Family h/o atopy, n (%)	6 (26.1)	20 (34.5)	105 (40.9)	93 (45.4)	0.193
Duration of asthma, years	4 (1-12)	5 (2-10)	6 (3-15)	10 (4-15.5)	<0.001
Rhinitis, n (%)	20 (87)	43 (74.1)	157 (61.1)	143 (69.8)	0.017
Spirometry					
FEV1, % predicted	97.9 (85.1-114.3)	86.8 (71.6-95.3)	73.8 (60-92.8)	63.5 (44.6-87.6)	<0.001
FVC, % predicted	94.3 (85-106.3)	87.8 (78.4-99.2)	84.7 (72.5-100)	80.4 (61.6-93.2)	<0.001
FEV1:FVC ratio	96.7 (89.8-103.8)	90.3 (83.9-97.9)	83 (71.3-90.6)	79.6 (67-89.1)	<0.001
Asthma treatment					
Dose of Budesonide, µg/day	-	400 (200-400)	800 (400-800)	800 (800-800)	<0.001
Dose of Fluticasone propionate, µg/day	-	250 (250-500)	500 (250-500)	500 (500-1000)	<0.001
Dose of LABA, µg/day	-	12 (6-12)	24 (12-24)	24 (24-24)	<0.001
Tiotropium, n (%)	0	0	1 (0.4)	26 (12.7)	<0.001
Montelukast, n (%)	1 (4.3)	0	8 (3.1)	200 (97.6)	<0.001
Theophylline, n (%)	0	0	0	10 (4.9)	<0.001

All values are expressed as mean±standard deviation or number (percentage) unless otherwise specified

Table 2. Prevalence of ABPA across different asthma severity

	Mild intermittent asthma	Mild persistent asthma	Moderate persistent asthma	Severe persistent asthma	P value
Number (%) of ABPA	3 (13)	6 (10.3)	54 (21)	43 (21)	0.23

Table 3. Characteristics of allergic bronchopulmonary aspergillosis (ABPA) subjects across different asthma categories

	Mild asthma (n=9)	Moderate persistent asthma (n=54)	Severe persistent asthma (n=43)	P value
Hemoptysis, n (%)	2 (22.2)	15 (27.8)	11 (25.6)	0.929
Brown black mucus plugs, n (%)	2 (22.2)	19 (35.2)	13 (30.2)	0.702
<i>Aspergillus</i> sp. in sputum culture, n (%)	0	9 (16.7)	5 (11.6)	0.363
Serum total IgE, kU/mL	6633 (1457-10273)	4805 (2417-10144)	4436 (2434-9330)	1.000
<i>A.fumigatus</i> -specific IgE, kUA/L	20.2 (6.6-49.9)	25 (10.1-42.3)	31.1 (16.2-41.2)	0.760
<i>A.fumigatus</i> -specific IgG, mgA/L	200 (114.5-200)	118 (62.9-200)	112 (65-200)	0.238
Peripheral blood eosinophil count, cells/ μ L	700 (500-2605)	735 (468-1280)	720 (460-1200)	0.710
Spirometry				
FEV1, % predicted	81.4 (59.8-94.7)	66 (50.9-84.2)	46.5 (35.1-62.9)	<0.001
FVC, % predicted	77.8 (65.1-90.5)	77.5 (64.1-90.9)	62.1 (49.1-76.6)	0.008
FEV1:FVC ratio	88.5 (82.2-100.4)	82.5 (68.3-91.7)	75.5 (64.2-82.6)	0.005
Imaging findings				
Finger-in-glove opacities, n (%)	4 (44.4)	13 (24.1)	8 (18.6)	0.250
Fleeting opacities, n (%)	3 (33.3)	11 (20.4)	5 (11.6)	0.243
Number of bronchiectasis segments on CT thorax	7 (5-11.5)	7 (3-11.3)	10 (7-14)	0.024

ABPA imaging categories				0.076
ABPA-S, n (%)	1 (11.9)	6 (11.1)	1 (2.3)	
ABPA-B, n (%)	0	16 (29.6)	16 (37.2)	
ABPA-MP, n (%)	1 (11.1)	15 (27.8)	11 (25.6)	
ABPA-HAM, n (%)	7 (77.8)	17 (31.5)	15 (34.9)	

All values are expressed as median (interquartile range) or number (percentage) unless specified otherwise

[06.04] The impact of Preserved ratio impaired spirometry (PRISm) in patients with bronchiectasis: analysis of lung function data from the EMBARC registry

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Introduction: Bronchiectasis is classically regarded as an obstructive lung disease on spirometry. Data from the European, US, Indian and Australian registries show heterogeneous lung function patterns with some patients having obstructive spirometry, but also normal spirometry and Preserved ratio impaired spirometry (PRISm). While the association of obstructive spirometry with poor outcomes is well described the prognostic implications of PRISm are not well described.

Methods: The EMBARC registry is a prospective observational cohort of patients enrolled 2015-2022. Patients with valid baseline spirometry were included in this analysis. Patients

were classified as obstructive, PRISM or normal spirometry. Follow-up for up to 5 years was used to identify the relationship between symptoms and future exacerbation frequency.

Results: 17164 patients were included in the analysis. Normal spirometry was reported in 6371 (37.1%), PRISM in 4874 (28.4%) and obstruction in 5919 (34.5%). Compared to patients with normal spirometry, markers of disease severity including *Pseudomonas aeruginosa* infection and respiratory symptoms were increased in patients with PRISM. Compared to patients with normal spirometry, patients with PRISM had increased risk of exacerbations (rate ratio 1.21 95%CI 1.13-1.29, $p < 0.0001$) Hospitalization for severe exacerbations was also markedly increased in patients with PRISM (RR 1.51 95%CI 1.35-1.68, $p < 0.0001$) as was mortality over up to 5 years (HR 1.79 95%CI 1.46-2.20, $p < 0.0001$). The risk of exacerbations, hospitalizations and mortality with airflow obstruction was also confirmed.

Conclusion: PRISM is common in bronchiectasis and is associated with disease severity and increased risk of adverse outcomes.

[06.05] Can a smartphone application improve self-management of bronchiectasis?

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Background/Aims:

Bronchiectasis management should include daily physiotherapy exercises for airway clearance and prompt treatment of exacerbations with appropriate antibiotics to improve quality of life and increase exercise capacity. However, the waiting list to see a respiratory physiotherapist at our district general hospital is six months, so an alternative resource was explored to support self-management of this chronic condition.

A phone-based application (app) resource for patients was introduced aiming to improve understanding of bronchiectasis and its management, improve completion of daily chest physiotherapy, increase confidence in self-management and promote prompt treatment of exacerbations to improve quality of life and reduce morbidity.

Methods:

The CONNECTPlus Bronchiectasis app was developed in partnership with HCI digital to include information about the disease, long-term management as well as recognising and treating exacerbations. Information is in written and video format with demonstrations of chest physiotherapy techniques and equipment. There are tools to monitor symptoms, record medications and test results. There is an exacerbation management pathway prompted by an increase in symptoms.

The app was reviewed by our multidisciplinary team prior to roll out, then introduced to patients at outpatient clinic with an information leaflet. Selected patients were asked to complete a survey before and after several months using the app to assess change in their knowledge, understanding and confidence in managing bronchiectasis.

Results:

We received 15 survey responses pre-roll out and 8 responses post-roll out.

We compared patients' knowledge before and after using the app with ratings on a scale of 1-10 where 1 = very poor understanding and 10 = very good understanding. Understanding of what bronchiectasis is improved from a mean score of 8 to 9, understanding of how to manage bronchiectasis improved from a mean score of 7 to 9 and confidence in undertaking physiotherapy independently improved from a mean score of 7 to 8. Mean scores of 8 for ability to recognise a flare and how to manage a flare of bronchiectasis were unchanged.

The proportion of patients who knew how to contact the bronchiectasis team improved from 47% to 75%.

Before using the app patients thought the following information should be included: condition understanding, symptom management, flare recognition and management, physiotherapy and breathing exercises.

Further suggestions from patients after using the app included: more information about how to exercise, a way to message the team for non-urgent questions and information on how weather affects symptoms.

Conclusions:

The CONNECTPlus bronchiectasis app led to a small improvement in patient understanding of what bronchiectasis is, how to manage the condition and confidence in undertaking physiotherapy. However, there are limitations to this study including small sample size and significant variability in how much patients used the app. A significant number of our patients did not own a smart phone or did not feel confident using apps. This highlights a limit to the benefit technology-based patient resources can achieve in our patient population. In conclusion, we think that in some patients an app can modestly improve patient understanding and self-management of bronchiectasis.

Conflict of interest(s) (if any – not included in the 500 words):

HCI digital have been employed by Torbay and South Devon Foundation Trust to create digital patient resources for several clinical conditions in a variety of specialities.

[06.06] Renal dysfunction in bronchiectasis patients receiving intravenous antibiotics for pulmonary exacerbations

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Background/Aims:

Non-cystic fibrosis bronchiectasis is associated with frequent pulmonary exacerbations caused by *Pseudomonas aeruginosa*. The ERS and BTS guidelines recommend the use of antibiotics for 14 days during these exacerbations. The BTS recommends IV antibiotics only when the patient is systemically unwell, has resistant organisms, or has failed to respond to oral therapy. Renal dysfunction is a known adverse effect of systemic antibiotics and can result in acute kidney injury. This study aimed to analyze the impact of intravenous antibiotics on renal dysfunction in patients with infective exacerbations of bronchiectasis.

Methods:

A retrospective, cohort multicentre study was performed, capturing data on patients admitted with a diagnosis of infective exacerbation of bronchiectasis from Jan 2022 to Jan 2024 in three different NHS hospitals. Data on patient demographics, comorbidities, number of admissions over 2 years, sputum culture results, *Pseudomonas aeruginosa* colonization status, renal function tests, and antibiotic regimen used were collected.

Results:

A total of 91 patients fulfilling inclusion criteria were included for analysis, with a mean (SD) age of 70.5 (13.1). *Pseudomonas aeruginosa* (n=44, 48.4 %) was the most frequently isolated pathogen in this cohort, followed by *Haemophilus influenzae* (n=11, 12.1%). 54 patients (59.3%) had a pre-antibiotic baseline eGFR of >90 mL/min/1.73 m² which decreased by >10% in 5 patients (9.3 %) during antibiotic therapy. 37 patients (40.7%) had an abnormal pre-antibiotic eGFR (<90 mL/min/1.73 m²) which was reduced by >10% in 17 patients (45.9%) during antibiotic therapy. Baseline creatinine was abnormal (>106 µmol/L) in 5 patients (5.5%) and creatinine levels rose by >10% of this baseline in 18 patients (19.8%) and >25% of baseline in 15 patients (16.5%) during antibiotic therapy. 29 patients (31.9%) in the cohort had multiple admissions for IV antibiotics over two years. Out of these, 11 (12.8 %) had a progressive decline in their eGFR over two years. The mean baseline eGFR for these patients was 76.2±3.2 which reduced to 70.6±3.9 by the end of two years.

Piperacillin/Tazobactam (Tazocin) was the most frequently used antibiotic (n=49, 53.8%) followed by Meropenem (n=18, 19.8%) and Ceftazidime (n=12, 13.2%). Other antibiotics used included Aztreonam and Levofloxacin (4.4% each), Co-amoxiclav (3.3%) and Cefidericoll (1.1%). No aminoglycosides were prescribed in this group. Dose adjustment of IV antibiotics due to renal dysfunction was required in 33 (36.3 %) patients.

Conclusions:

Renal dysfunction is common in bronchiectasis at baseline, with nearly 40% of our cohort showing an abnormal eGFR. This can be attributed to multimorbidity in bronchiectasis which

is associated with higher rates of exacerbations and hospitalisations. A significant minority of patients develop renal dysfunction either de novo or as a worsening of preexisting renal disease. Patients with pre-existing renal dysfunction/abnormal eGFR were at a higher risk of worsening renal dysfunction during antibiotic therapy. Dose reduction is commonly required, and this may impact microbicidal levels and patient outcomes. Strategies to both minimise exacerbations and the potential harms of IV antibiotics when required are needed.

Conflict of interest(s) (if any – not included in the 500 words):

Henil Upadhyay: none

Kirsty Mackenzie: none

Kristian Brooks: none

Lewis Marshall: none

Jaishree Ganjiwale: none

Katy Hester: none

Joanna Lumb: none

Prof James D Chalmers: none

Prof Anthony De Soyza: none

[06.07] Eosinophilia in bronchiectasis patients receiving intravenous antibiotics for pulmonary exacerbations

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Background/Aims:

Bronchiectasis is associated with frequent acute worsening of symptoms termed exacerbations. The ERS and BTS bronchiectasis guidelines recommend the use of antibiotics for 14 days during these exacerbations to reduce the bacterial load and inflammation in the lungs. Selected patients need these intravenously. Antibiotic sensitisation and allergy are well recognised in bronchiectasis.

Eosinophils have known bactericidal and antiviral properties and are activated during pulmonary exacerbations. A European multicohort study by Shoemark A., et al. showed that blood eosinophil counts >300 cells/uL are common in bronchiectasis, and a low eosinophil count was associated with high disease mortality. We have observed acute rises in blood eosinophils after starting IV antibiotics. This study aimed to analyse associations between intravenous antibiotics and blood eosinophil levels in patients with infective exacerbations of bronchiectasis.

Methods:

A retrospective, multicentre cohort study was performed capturing data of patients admitted with a diagnosis of infective exacerbation of bronchiectasis from Jan 2022 to Jan 2024 in three different NHS hospitals in the UK. Data on patient demographics, comorbidities, sputum culture results, eosinophil levels, and antibiotic regimen used was collected. The following peripheral blood eosinophil cutoff was used for this study: <0.1*10⁹/L (low), 0.1-0.29*10⁹/L (normal) and >0.3 *10⁹/L (high).

Results:

A total of 91 patients fulfilling inclusion criteria were analysed, with a mean (SD) age 70.5 (13.1). BSI scores were available for 58 patients. Out of these, 50 has severe bronchiectasis (BSI score 9+) and 8 had moderate bronchiectasis (BSI score 5-8). None of the patients in this group had mild bronchiectasis. Other causes of eosinophilia at baseline identified in this cohort includes asthma (10, 11%), vasculitis (3, 3.3%), reactive arthritis and IBD (2, 2.2% each), and ABPA (1, 1.1%).

Eosinophil Levels	Baseline Eosinophil level n (%)	Highest Eosinophil level during antibiotic therapy n (%)
Low	34 (37.4%)	15 (16.5%)

Intermediate	43 (47.2%)	40 (44%)
High	14 (15.4)	36 (39.5%)
Total	91 (100%)	91 (100%)

44 patients (48.4%) showed growth of *Pseudomonas aeruginosa* in their sputum. Out of these, 8 patients (15.1%) had a high baseline eosinophil level which increased to 23 patients (43.4%) during antibiotic therapy.

38 patients (41.7%) did not grow *Pseudomonas aeruginosa* in their sputum. Out of these, 6 patients (15.79%) had a high baseline eosinophil level which increased to 13 patients (34.21%) during antibiotic therapy.

Conclusions:

Similar to prior study by Shoemark A. et al., psnearly 15% of our population had high eosinophilia at baseline. Increased peripheral blood eosinophil count during IV therapy was particularly notable in those with baseline high eosinophils. Peripheral blood eosinophilia is dynamic in bronchiectasis and IV antibiotics may be one potential factor in this. In addition, high eosinophil count is associated with a *Pseudomonas*-dominated microbiome profile. Long term studies on the role of this as a potential marker of differential risks in future exacerbations or development of allergy are needed.

Conflict of interest(s) (if any – not included in the 500 words):

Henil Upadhyay: none

Kirsty Mackenzie: none

Kristian Brooks: none

Lewis Marshall: none

Jaishree Ganjiwale: none

Katy Hester: none

Joanna Lumb: none

Prof James D Chalmers: none

Prof Anthony De Soyza: none

[07.01] Clinical characteristics and outcomes of the phenotypes of asthma-bronchiectasis overlap

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Background/Aims:

Asthma-bronchiectasis overlap (ABO) encompasses heterogeneous manifestations, which could have accounted for distinct clinical outcomes. To explore the clinical phenotypes of ABO and compare the outcomes via unbiased phenotyping approaches.

Methods:

In this retrospective cohort study, we extracted data from electronic medical records of 292 inpatients with ABO, 901 inpatients with asthma alone and 1,192 inpatients with bronchiectasis alone who were hospitalized between 2015 and 2020. We phenotyped ABO with two-step unsupervised clustering analysis, and validated with an independent cohort.

Results:

Compared with asthma or bronchiectasis alone, ABO exhibited greater disease severity and poorer hospitalization outcomes. We identified three ABO phenotypes: asthma-dominant ABO (ABO-A, N=100) with asthma symptoms being more prominent; bronchiectasis-dominant ABO (ABO-B, N=89) with more pronounced features of bronchiectasis; co-existence of asthma and severe bronchiectasis (ABO-S, N=103) which had poorer clinical outcomes. Compared with ABO-B, both ABO-A and ABO-S were associated with significantly greater symptom burden, higher blood neutrophil ratio (55.8% vs. 59.1% vs. 64.4%, $P<0.001$), poorer lung function (FEV_1 % predicted: 79.1% vs. 67.5% vs. 50.1%, $P<0.001$), longer hospital stay (6.0 vs. 7.0 vs. 7.0 days, $P=0.004$) and higher risks of hospitalization within the next two years (ABO-A: hazards ratio: 3.76, 95% confidence interval: 1.12-12.62, $P=0.032$; ABO-S: hazards ratio: 4.05, 95% confidence interval: 1.14-14.36, $P=0.031$).

Conclusions:

Radiologic severity of bronchiectasis, receipt of systemic corticosteroids and exacerbation frequency are core determinants of the clinical phenotypes of ABO. Appraisal of the heterogeneity of clinical manifestations may inform personalized management strategies and prognostication of ABO.

Conflict of interest(s) (if any – not included in the 500 words):

There are no conflict of interest.

[07.02] Characteristics Associated with Multimorbidity in Patients with Bronchiectasis: Results from the US Bronchiectasis and NTM Research Registry

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Background/Aims:

Multimorbidity, defined as the coexistence of 2 or more conditions, is often associated with adverse health outcomes and a significant disease burden requiring tailored treatment plans. However, multimorbidity in patients with bronchiectasis (BE) remains insufficiently understood. Thus, the primary objectives of this study were to evaluate the prevalence of multimorbidity and assess associated factors in a US cohort of patients with BE.

Methods:

The cross-sectional data from patients with bronchiectasis (BE) enrolled in the US Bronchiectasis and NTM Research Registry (US BRR) between 2008 and 2023 were analyzed. Data on BE and the 10 most prevalent ($\geq 2\%$ prevalence) conditions (asthma, COPD, Alpha1, primary immunodeficiency, PCD, rheumatologic disease, IBD, GERD, otitis/rhinosinusitis, and tuberculosis) were evaluated. Patients with CF were excluded. Multimorbidity was defined as a co-occurrence of one or more conditions in addition to BE. Sociodemographic and clinical characteristics were compared across patients with and without multimorbidity. Overlap between the three most prevalent coexisting conditions was assessed.

Results:

In this study of 5,287 BE patients (mean age 66 ± 13 years, 79% female, 91% white), 69% had multimorbidity, while 31% had BE alone (Table 1). Among those with multimorbidity, 32% had ≥ 3 conditions, with an average of 2.7 ± 0.8 conditions per patient. Common comorbidities included GERD (42%), asthma (26%), and COPD (16%) (Figure 1). Multimorbidity patients were younger at enrollment and at BE diagnosis, with a higher proportion of males and whites. Patients with multimorbidity had a significantly higher prevalence of pulmonary symptoms, such as dyspnea, cough, and wheezing, compared to those with BE alone ($p < 0.0001$) (Table 1). In addition, a greater proportion of patients with multimorbidity had 2 or more positive cultures for *Pseudomonas aeruginosa* ($p < 0.0001$), and a lower proportion of them had NTM (Table 1). In BE patients with GERD, asthma, or COPD, the largest proportion of them (41%) had GERD alone, and around 6% of individuals had all three conditions in addition to BE (Figure 2).

Conclusions:

A high prevalence of multimorbidity was observed in this cohort of patients with BE. Patients with multimorbidity experience a significantly higher burden of pulmonary symptoms and chronic *Pseudomonas aeruginosa* infection compared to those with BE alone. Additional

studies are necessary to evaluate comorbidity clusters and disease trajectory in this population over time.

Conflict of interest(s) (if any – not included in the 500 words):

Radmila Choate, Meghan Marmor, Kunal Jakharia, Marcos I. Restrepo, Alan Barker, and Timothy Aksamit report no conflicts. Mark Metersky- Insmed, Boehringer Ingelheim, Tactile—Consultant; Investigator-Insmed; Renovion, AN2—Data Safety Monitoring Board

[07.03] Prevalence of chronic rhinosinusitis in patients with bronchiectasis and it's correlation with clinical presentation

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Background/Aims: Bronchiectasis is a chronic respiratory disorder characterized by irreversibly airway dilatation. Patients with bronchiectasis have respiratory symptoms and can be associated with chronic rhinosinusitis (CRS). The aim of this study to describe differences in clinical presentation patients with CRS and without them.

Methods: In this study, 94 patients with bronchiectasis were enrolled. CRS diagnosis was determined by a otorhinolaryngologist, based on upper airway symptoms and radiological and endoscopic abnormalities. Baseline characteristics, asthma and immunodeficiency comorbidity, corticosteroid inhalation therapy (ICS), number of exacerbations. Blood analysis and chest CT scan was performed in stabile phase of disease. They are divided in two groups (with and without CRS).

Results:The prevalence of CRS was 44.7%. Association with asthma was statistically higher (28.5% vs. 1.9%, $p = 0.001$) and also association with immunodeficiency (26.2% vs. 9.6%, $p = 0.007$). Patients with CRS were younger than those without CRS (54.0 years vs. 61.6 years, $p = 0.002$). All three radiological types equally were presented in patients with CRS, but cylindrical were dominant in patients without CRS. Sputum color in patients with CRS was different (green and/or purulent vs normal and/or yellow), ICS use (64.3% vs. 30.7%, $p = 0.009$), eosinophil endotype (76.2% vs. 7.7%, $p = 0.001$) compared to those without CRS. But BACI score was higher in group without CRS (19.2% vs 9.5%). There was not statistically significant differences in number of exacerbations, hospitalizations, hemoptysis presentation, use of LTOT between the two groups.

Conclusions:The prevalence of CRS was very high. Early diagnosis, asthma, immunodeficiency, abnormal sputum color, eosinophil endotype were associated with CRS, but BACI score was higher in group without CRS. We need to be aware about CRS in the clinical practice, association, and influence on bronchiectasis.

Conflict of interest(s) (if any – not included in the 500 words):No

[07.04] The association of the eosinophilic bronchiectasis phenotype and non-tuberculous mycobacterial pulmonary disease: an analysis of the US Bronchiectasis and NTM Research Registry

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Background:

There is an increase in worldwide incidence of both non-tuberculous mycobacteria (NTM) pulmonary disease and eosinophilic diseases. At this time, there is only limited information on the relationship between NTM, an infection often encountered in patients with bronchiectasis, and the presence of eosinophilic inflammation and its implications. The objective of this study is to characterize the relationship between the eosinophilic bronchiectasis phenotype and the presence of NTM pulmonary disease (or presence of positive cultures).

Methods:

Adult patients with bronchiectasis and a blood eosinophil count in the US Bronchiectasis and Non-Tuberculous Mycobacteria (NTM) Research Registry database were included in the analysis. Patients with NTM pulmonary disease were defined by physician diagnosis meeting NTM pulmonary disease criteria or met NTM culture criteria. The eosinophilic phenotype was defined as a blood eosinophil count ≥ 300 cells/mL. The highest blood eosinophil count among those with multiple results was used in the analysis. We conducted a cross-sectional descriptive analysis, stratified by NTM diagnosis, of patient characteristics, including demographics, comorbidities, lung function, symptoms, history of exacerbations, and positive cultures based on data availability in the 24 month look-back period from the time of the highest blood eosinophil result.

Results:

2115 patients were included in the analysis, with 1099 (52.0%) and 1016 (48.0%) without the diagnosis of NTM. Cystic fibrosis patients were excluded. The proportion of patients with blood eosinophils ≥ 300 cells/mL was similar in both groups (19.8 vs 17.9%). There was a similar proportion of patients with an eosinophilic vs non-eosinophilic phenotype in both NTM

and non-NTM groups with regards to age, sex and the coexisting diagnoses of COPD, GERD, rhinosinusitis and pneumonia. Asthma was more prevalent in the patients that had eosinophilia and a negative NTM diagnosis (39.8%) vs those with eosinophilia and a NTM diagnosis (25.4%). Similarly, patients with eosinophilia and without NTM were more frequently receiving inhaled corticosteroids (51.2%) compared to those with eosinophilia and NTM (35.7%). There was no difference in the lung function or rate of exacerbations in patients with eosinophilic phenotype classified by NTM diagnosis status. With regards to symptoms, patients with an eosinophilic phenotype and a NTM diagnosis reported dyspnea (71.1 vs 64.2%) and cough (85.8 vs 81.6%) more frequently than those without eosinophilia and a negative diagnosis, respectively.

Conclusions:

In patients with bronchiectasis and a diagnosis of NTM pulmonary disease, the eosinophilic phenotype is encountered in similar proportion to those without a NTM diagnosis. Asthma and the use of inhaled corticosteroids is found more frequently in patients with an eosinophilic phenotype and patients without NTM. Although patients with an eosinophilic bronchiectasis phenotype in combination positive NTM cultures had higher burden of respiratory symptoms, no differences in lung function or exacerbation rates were observed.

Funding: GSK (221135)

Conflict of interest(s) (if any – not included in the 500 words):

DJM, AEB, RC, KJ, MKS, and MIR report no conflicts of interest.

AC, BM, JM, JP and JY are GSK employees and hold stocks/shares.

MM reports fees from Insmed, Boehringer, Tactile, AN2, Renovion.

BEM is a former GSK employee and holds stocks/shares.

GMS involved in clinical trials with Vertex, Insmed, Astra-Zeneca, Spero, BiomX, Boeringer, HillRom, Electromed, and Renovion. He is a consultant for clinical trial development for GSK, Genentech, and Renovion. He is also funded by the PCD Foundation, CF Foundation, and NIH. No personal or research monies received. All support has gone to the University of Alabama at Birmingham.

TRA has been involved in clinical trial design and participation with Armata, Zambon, AstraZeneca, Insmed, Redhill Biopharma, Spero Therapeutics, and Johnson & Johnson. He has worked with Hillrom and RespirTech and serves as Medical Director of Bronchiectasis and NTM 360 for the COPD Foundation. No personal or research monies received. All support has gone to the Mayo Foundation for Medical Research and Education.

[07.05] The eosinophilic bronchiectasis phenotype: findings from the US Bronchiectasis and NTM Research Registry

Diego J. Maselli¹; Amanda E. Brunton²; Aparna Chauhan³; Radmila Choate⁴; Kunal Jakharia⁵; Michelle Korah-Sedgwick⁶; Bhabita Mayer³; John McGinniss³; Mark L. Metersky⁷; Bruce E. Miller²; Jihye Park³; George M. Solomon⁸; Julie Yates³; Timothy R. Aksamit^{2,9}; Marcos I. Restrepo¹⁰

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Background:

Bronchiectasis is a heterogenous disease, but distinct phenotypes have recently emerged. It has been largely considered to be a neutrophil driven disease with many bronchiectasis patients presenting with high levels of neutrophils and neutrophil activation markers. Yet, recent studies suggest that 20-30% of bronchiectasis patients may have features of eosinophilic inflammation. Importantly, patients with eosinophilic bronchiectasis may have a shorter time to exacerbation, worse lung function and severity of the disease, and longer hospital stays compared to those without evidence of eosinophilic inflammation, but future studies are still needed to confirm these findings. The objective of this study is to characterize the eosinophilic bronchiectasis phenotype in the US based Bronchiectasis and Non-Tuberculous Mycobacteria (NTM) Research Registry (BRR) and its clinical features with an emphasis on the burden of symptoms, exacerbations, lung function.

Methods:

Adult patients with bronchiectasis and a blood eosinophil count in the BRR were included in the analysis. The highest blood eosinophil count among patients with multiple results was used. The eosinophilic phenotype was defined as a blood eosinophil count ≥ 300 cells/mL. We conducted a cross-sectional descriptive analysis of patient characteristics, including demographics, comorbidities, lung function, symptoms, history of exacerbations, and positive cultures based on data availability in the 24 month look-back period from the time of the highest blood eosinophil result.

Results:

A total of 2122 patients were included in the analysis and 400 (18.9%) were classified in the eosinophilic phenotype group. Cystic fibrosis diagnosis patients were excluded. Age, sex, and the coexisting diagnoses of COPD, GERD, rhinosinusitis and pneumonia were comparable between groups. Asthma was more commonly seen in the eosinophilic vs non

eosinophilic phenotype (32.8% vs 24.7%). Those with the eosinophilic phenotype had worse lung function (FEV₁ 70.9 vs 75.7% predicted) and a higher proportion of patients with 1 or more exacerbations (44.5% vs 37.3%). Cough and fatigue were reported similarly between groups. Dyspnea and wheezing were more frequently reported in the eosinophilic phenotype group (67.5 vs 60.4%) and (32.5 vs 21.9%), compared to those without this phenotype. The rate of positive bacterial cultures and NTM were similar in both groups.

Conclusions:

The eosinophilic bronchiectasis phenotype is encountered in approximately 1 of every 5 adult patients with bronchiectasis. Patients with evidence of eosinophilic inflammation had more frequently coexisting asthma, reported more symptoms, had worse lung function and increased exacerbation burden. Because of the distinct clinical course, studies exploring the benefit of targeting eosinophilic inflammation are warranted in this bronchiectasis phenotype.

Funding: GSK (221135)

Conflict of interest(s) (if any – not included in the 500 words):

DJM, AEB, RC, KJ, MKS, and MIR report no conflicts of interest.

AC, BM, JM, JP and JY are GSK employees and hold stocks/shares.

MM reports fees from Insmed, Boehringer, Tactile, AN2, Renovion.

BEM is a former GSK employee and holds stocks/shares.

GMS involved in clinical trials with Vertex, Insmed, Astra-Zeneca, Spero, BiomX, Boeringer, HillRom, Electromed, and Renovion. He is a consultant for clinical trial development for GSK, Genentech, and Renovion. He is also funded by the PCD Foundation, CF Foundation, and NIH. No personal or research monies received. All support has gone to the University of Alabama at Birmingham.

TRA has been involved in clinical trial design and participation with Armata, Zambon, AstraZeneca, Insmed, Redhill Biopharma, Spero Therapeutics, and Johnson & Johnson. He has worked with Hillrom and RespirTech and serves as Medical Director of Bronchiectasis and NTM 360 for the COPD Foundation. No personal or research monies received. All support has gone to the Mayo Foundation for Medical Research and Education.

[07.06] Development of a Comprehensive Canadian Bronchiectasis and Nontuberculous Mycobacterial Infections Clinical Database: Protocol of a Prospective Multicenter Observational Cohort Study

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Background/Aims: Bronchiectasis is a complex, chronic airway disease that displays significant geographic and ethnic diversity. While the most substantial cohort studies have been conducted in Europe and the USA, Canada also faces a considerable challenge with bronchiectasis. The establishment of a Comprehensive Canadian Bronchiectasis and Nontuberculous Mycobacterial Infection Registry aims to: (1) outline the clinical characteristics and natural history of bronchiectasis in Canada, highlighting differences between Canada and other registries; (2) identify risk factors contributing to disease progression within the Canadian population; (3) integrate comprehensive clinical information to better understand the phenotypes and endotypes of bronchiectasis; (4) support the development of large-scale, randomized controlled trials in Canada.

Methods: The Canadian Bronchiectasis and Nontuberculous Mycobacterial Infection Registry is an ongoing prospective, longitudinal, multi-center, observational cohort study launched in May 2023 across Canada. It aims to enroll at least 2000 participants to extensively collect initial data such as medical history, etiological assessments, lung function tests, microbiological profiles, radiographic evaluations, comorbidities and quality of life (QoL) metrics. Participants will undergo annual follow-ups for a duration of up to 10 years to gather longitudinal information regarding outcomes, treatment regimes, and changes in QoL. The inclusion criteria are a primary diagnosis of bronchiectasis by clinical history consistent and computed tomography and/or pulmonary nontuberculous mycobacterial (NTM) infection as defined by IDSA guidelines. Exclusion criteria are: 1) Cystic fibrosis bronchiectasis; 2) age <18 years; 3) Extrapulmonary NTM disease and 4) Patients who are unable or unwilling to provide informed consent. The study's protocol received ethical approval from the lead site, the University of Calgary, with future additional approval from local ethics committees at all participating centers.

Conclusions: The outcomes of the registry will be instrumental in uncovering the clinical traits and progression of bronchiectasis. This longitudinal study will be used for analysis to form evidence-based clinical practices and serve as a critical resource in Canada to better inform future interventional studies in NTM and bronchiectasis.

Conflict of interest(s) (if any – not included in the 500 words): CST has funding from Insmed Medical and Trudell Healthcare Solutions.

[08.01] Clofazimine Inhalation Suspension for the treatment of NTM Pulmonary Disease

Wassim Fares¹; Burkhard Blank¹; Michael Castagna¹; Thomas Hoffman¹

¹*MannKind, Danbury, USA*

Background/Aims: There is a significant unmet need for the treatment of NTM Pulmonary Disease (NTM-PD). Currently available therapies have limitations, on both the efficacy and safety/tolerability sides. Clofazimine has shown in-vitro anti-mycobacterial effects and is used off-label orally for treating mycobacterial diseases including NTM. Clofazimine Inhalation Suspension has the potential to maximize anti-mycobacterial exposure in the lungs while minimizing systemic exposure that has limited the dosing and thus the efficacy of other therapies. This presentation aims at summarizing the preclinical and phase-1 studies of Clofazimine Inhalation Suspension and the study design of the phase-3 trial, ICoN-1 which will be conducted at > 100 sites globally.

Methods: Clofazimine Inhalation Suspension given once daily in cycles each comprising 3 months: 28 days on daily treatment followed by 2 months off treatment. It has been studied in preclinical models, as well as in phase-1 healthy volunteers. These studies laid the foundation for developing it in patients living with NTM-PD.

Results: The simulations from the animal models (Figure 1) show that a proposed nominal daily dose in humans of 80 mg given by a jet nebulizer would maintain lung exposure to clofazimine that is significantly higher than the *Mycobacterium Avium* Complex (MAC) MIC for the whole duration of each cycle even 2 months after the last dose taken. A significantly lower systemic exposure than (about 1/8th) was seen compared with the approved oral dose of clofazimine which has the potential to minimize if not eliminate the skin discoloration. The chronic toxicity animal studies and the phase-1 human studies did not show any safety or tolerability issues at any dose including the highest tested doses (with > 10-fold safety factor).

The ICoN-1 trial is designed as a phase-3 registrational global placebo-controlled double-blind study, evaluating the safety and efficacy of Clofazimine Inhalation Suspension for patients living with NTM-PD, after being on at least 6 months of background Guideline-Based-Therapy for MAC. The study design is summarized in Figure 2; it has a 6-month double-blind period, followed by an open label extension on active therapy for up to an additional 18 months. The co-primary endpoints are sputum culture conversion and QoL-B Respiratory Domain, and the first key secondary endpoint is pulmonary exacerbation. With a randomization schema of 2:1 (active to placebo), the target sample size is 234 participants, to have at least 180 participants with a positive sputum culture at randomization. The inclusion/exclusion criteria and the study endpoints are listed in Tables 1 & 2.

Conclusions: The ICoN-1 trial is evaluating a potential treatment for patients living with refractory NTM-PD. Benefits of this formulation include storing it at room temperature (i.e., does not need refrigeration) and giving patients the convenience of not being on inhaled therapy for 2 months after receiving one month of daily inhalation in each cycle. The high pulmonary exposure and low systemic exposure seen in animals and confirmed in humans (systemic PK) with no safety concerns support further developing Clofazimine Inhalation Suspension. The ICoN-1 study plans to start enrolling patients this summer (2024).

Conflict of interest(s) (if any – not included in the 500 words):
employees of MannKind Corporation

[08.02] Prevalence of Nontuberculous Mycobacteria and Its Impact on Disease Progression in Bronchiectasis Patients: A Longitudinal Study

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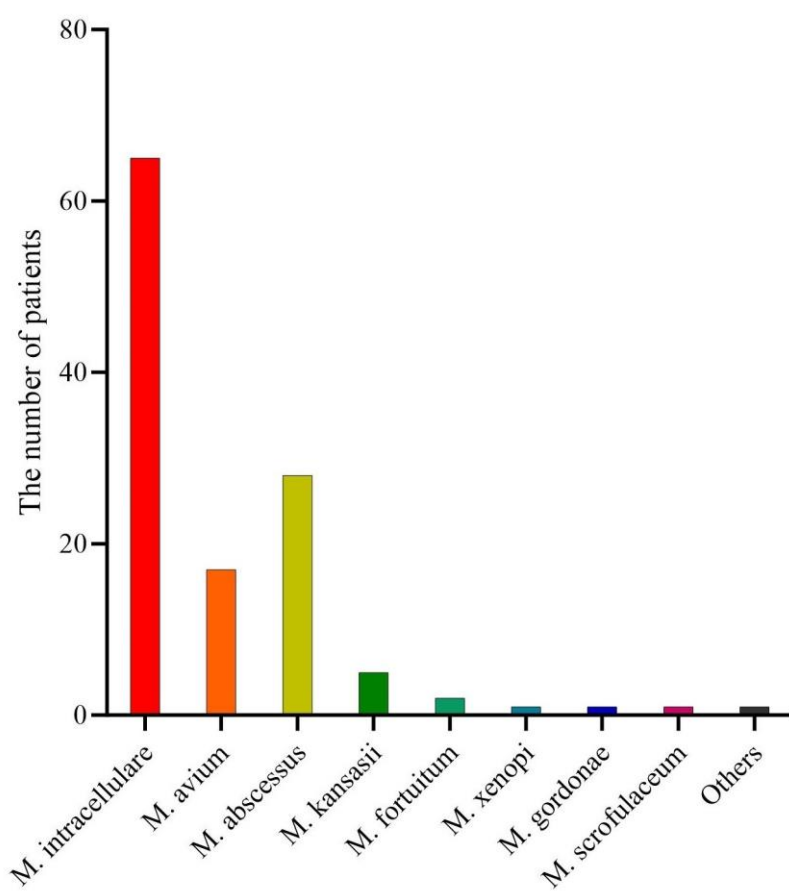
Background: The role of nontuberculous mycobacteria (NTM) in exacerbating bronchiectasis is increasingly recognized, yet the prevalence of NTM and its impact on disease progression demand further exploration.

Methods: We conducted a longitudinal study of bronchiectasis patients from the Chinese Bronchiectasis Registry at Shanghai Pulmonary Hospital between 2020 and 2022 to evaluate NTM prevalence and species distribution. Follow-up for patients diagnosed with NTM continued until August 1, 2023, to assess disease progression, employing Cox proportional hazards models to identify predictors of progression.

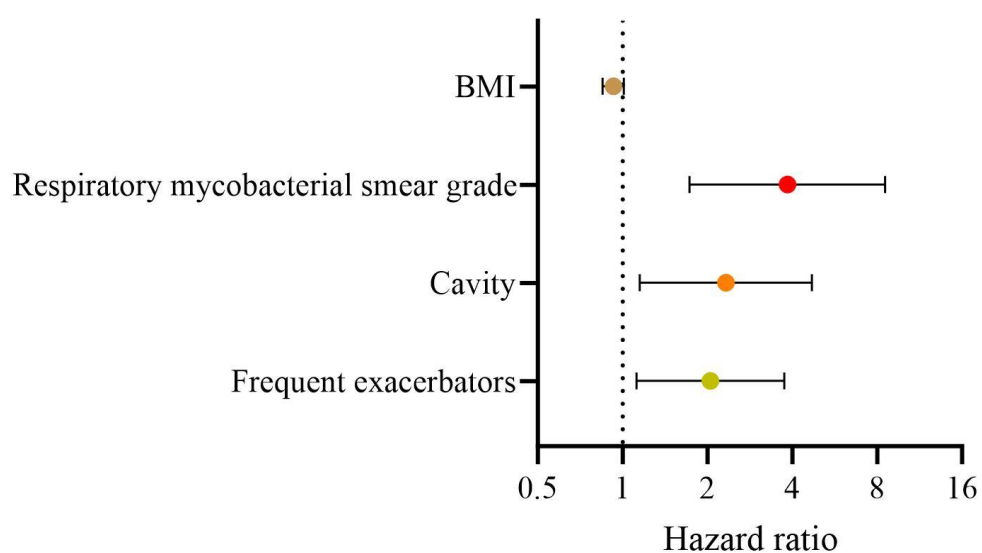
Results: Of the 754 patients analyzed, NTM was identified in 112 (14.9%), with 96 (12.7%) meeting the criteria for NTM pulmonary disease. The most frequently isolated species were *Mycobacterium intracellulare* (58.0%), *Mycobacterium abscessus* complex (25.0%), *Mycobacterium avium* (15.2%), and *Mycobacterium kansasii* (4.5%), with nine patients (8.0%) having multiple NTM species isolated. Significant predictors of disease progression included the presence of cavitory lesions (HR 2.33, 95% CI 1.1-4.70, p=0.018), high-intensity AFB smears (≥3+) (HR 3.85, 95% CI 1.73-8.54, p=0.001), and frequent pulmonary exacerbations (≥3 per year) (HR 2.05, 95% CI 1.12-3.75, p=0.021).

Conclusions: NTM isolation occurs frequently in bronchiectasis patients and significantly correlates with disease progression. Identifiable risk factors such as cavitory lesions, high-intensity AFB smears, and recurrent exacerbations are predictive of accelerated disease progression in patients with NTM, underscoring the critical need for specialized management approaches and vigilant surveillance of this vulnerable population.

The distribution of NTM species



Risk factors for overall progression



Conflict of interest(s) (if any – not included in the 500 words): no

[08.03] Longitudinal lung function in bronchiectasis patients with *Mycobacterium abscessus* colonisation

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Background/Aims:

Little is known on the influence of *Mycobacterium abscessus* (*M. abscessus*) colonisation on long term lung function in patients with bronchiectasis. This study investigated the impact of *M. abscessus* colonisation on longitudinal lung function over a 7-year period in Singapore.

Objective:

To investigate the impact of *M. abscessus* colonisation on lung function in bronchiectasis patients in a tertiary referral centre from 2016 to 2022.

Methods:

Demographic and clinical profiles of the study cohort were analysed prospectively. *M. abscessus* colonisation was defined by the presence of 2 positive cultures at least 3-months apart over a 12-month period and without association of worsening clinic-radiological features. Patients with *M. abscessus* pulmonary disease (MAPD) were excluded. Patients with idiopathic bronchiectasis were categorised as the control group.

Results:

24 *M. abscessus* colonisation patients and 68 idiopathic patients (control) were studied. *M. abscessus* colonisation patients had lower BMI than control (19 vs 22, $p=0.003$). The median age of *M. abscessus* colonisation and control was similar at 70 and 73 years respectively ($p=0.308$). Both groups of patients were equally likely to smoke ($p=0.295$). There were more patients with chronic obstructive pulmonary disease amongst control group than *M. abscessus* colonisation patients ($p=0.047$). There were more patients with pulmonary tuberculosis or a history of pulmonary tuberculosis amongst *M. abscessus* colonisation patients than control group ($p=0.001$).

The median annual rate of change of FEV₁ (ml/year) and FVC (ml/year) were similar in both groups of patients. There was no change of sputum volume annually in both groups ($p=0.326$). There was also no difference in the average annual change of modified MRC dyspnoea score in both groups ($p=0.056$).

M. abscessus colonisation patients had more *Pseudomonas aeruginosa* and *Staphylococcus aureus* in sputum than control ($p=0.003$ and $p=0.001$ respectively).

Conclusions:

Patients with *M. abscessus* colonisation had a significantly lower BMI than idiopathic bronchiectasis. A history of pulmonary tuberculosis, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were more common in patients with *M. abscessus* colonisation with

unknown reason. Our study did not show any impact of *M. abscessus* colonisation on longitudinal lung function.

Conflict of interest(s) (if any – not included in the 500 words): There is no conflict of interest.

[08.04] Medication adherence in patients with nontuberculous mycobacterial disease: a single-center study

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Background/Aims:

Nontuberculous mycobacterial (NTM) disease often requires prolonged, multi-drug treatment, complicated by a high pill burden, frequent adverse drug reactions (ADR) and uncertainty about response. Medication adherence in patients with chronic (lung) diseases is generally poor, but adherence in patients with NTM disease is currently unknown. We aimed to quantify and understand medication adherence in patients with NTM disease.

Methods:

Patients with pulmonary and extrapulmonary NTM disease, receiving antimycobacterial treatment and enrolled in the Mycobacterial Cohort Study at Radboudumc, were included in the analysis. Demographics, baseline characteristics and treatment outcomes were recorded. Patients were followed prospectively and medication adherence was assessed at 1, 3, 6 and/or 12 months on treatment. The 5-item Medication Adherence Report Scale (MARS-5) was used to determine self-reported adherence. Pharmacy refill records were obtained to calculate the Proportion of Days Covered (PDC) at 6 and 12 months for all oral antibiotics given ≥ 4 months, as a more objective adherence measure. The Beliefs about Medicines Questionnaire (BMQ) with a general medication subscale (harm-overuse) and disease-specific subscale (necessity-concern) was used to understand reasons for medication (non)adherence. Continuous outcomes are reported as percentage or median (IQR, 25th - 75th percentile).

Results:

Sixty-one patients (38 females, 23 males) were enrolled, aged 65 (57-73) years. Forty-one (67%) had pulmonary and 21 (33%) extrapulmonary NTM disease. *M. avium* complex infection was most prevalent (n= 38; 62%), followed by infections with *M. abscessus* (n = 6; 10%), *M. chelonae* (n=4; 7%), *M. kansasii* and *M. marinum* (both n = 3; 5%). The majority of patients were treated with a combination of a macrolide, ethambutol, clofazimine and/or rifampicin. ADR occurred in 56/61 (92%) patients. A favorable outcome was reached in 36/51 (71%) at 6 months and 26/30 (87%) at 12 months of treatment. The MARS-5 scored 5 out of 5 consistently throughout treatment. The average PDC was calculated for 3 (2-3) drugs per patient and was 100% (99-100%) at both 6 and 12 months. Beliefs about general medication ranged from 2.0-2.7 and 2.0-2.2 out of 5 for the BMQ overuse and harm scale, respectively. Beliefs about NTM medication varied from 3.6-3.8 and 2.7-3.0 out of 5 for the necessity and concern scales, respectively. All BMQ subscales did not change throughout treatment ($p > 0.05$) (figure 1).

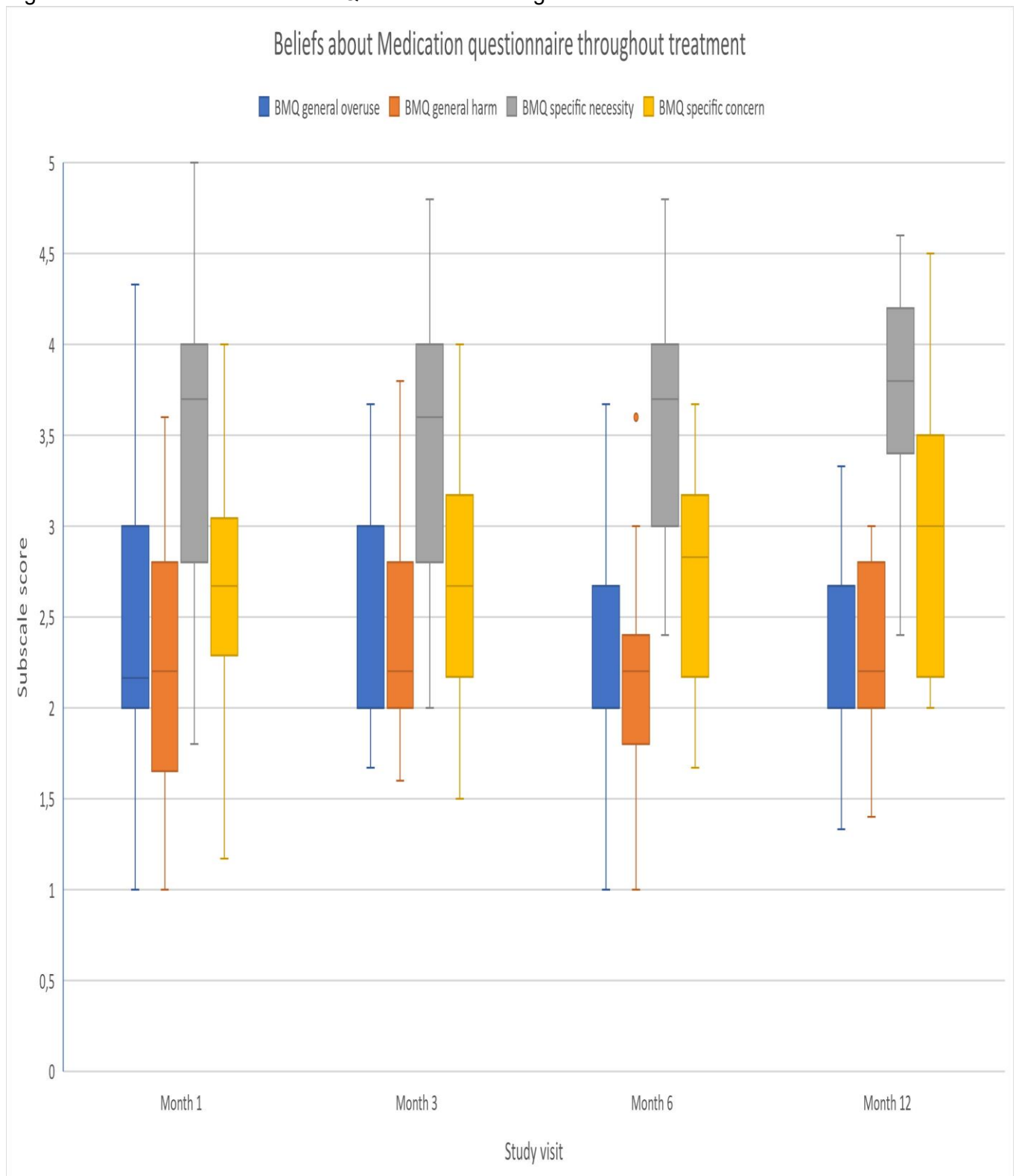
Conclusions:

This cohort is characterized by a high self-reported and objectively measured medication adherence. Although patients frequently reported concerns about their antibiotics, beliefs about their necessity were consistently stronger throughout their first year of treatment, supporting the high adherence rate. Extrapolation of these adherence outcomes to other cohorts should be done with caution, considering the intensive and multidisciplinary guidance provided at our center.

Conflict of interest(s) (if any – not included in the 500 words):

Not applicable

Figure 1. Beliefs about Medication Questionnaire throughout treatment



[08.05] Bacterial Co-Isolation Linked With Treatment Initiation and Long-term Prognosis of Patients with Nontuberculous Mycobacterial Pulmonary Disease

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Background/Aims: Nontuberculous mycobacterial pulmonary disease (NTM-PD), a chronic respiratory condition, presents a growing challenge globally. Bacterial co-isolation is prevalent in NTM-PD, often involving *Staphylococcus aureus*, *P. aeruginosa*, and *Haemophilus influenzae*. However, uncertainties exist regarding the impact of concurrent bacterial isolation on treatment initiation and long-term prognosis.

Methods: We analysed data from participants enrolled in an ongoing prospective observational cohort study on NTM-PD (NCT01616745) between 1 July 2011, and 31 December 2022, who provided sputum samples for bacterial culture at enrolment. Identifying potential pathogenic microorganisms (PPMs) from sputum was defined as a positive respiratory bacterial culture. Clinical characteristics were compared between NTM-PD patients with *Pseudomonas*, non-pseudomonal PPMs, and those without PPM isolation. Cox proportional hazard regression models were employed to assess the association of bacterial co-isolation with rates of NTM-PD treatment initiation and all-cause mortality.

Results: In total, 453 patients (median age, 62 years; 30% male) were included in the analysis. PPMs were co-isolated in 77 patients (17 %), including 13 with *Pseudomonas* species. Co-isolation of *Pseudomonas* was associated with a significantly higher erythrocyte sedimentation rate ($P = 0.02$) and St. George's Respiratory Questionnaire score ($P = 0.01$). Non-pseudomonal PPM isolation was significantly associated with a higher likelihood of NTM-PD treatment initiation (adjusted hazards ratio [aHR], 1.56, 95% confidence interval [CI], 1.03–2.36, $P = 0.043$), whereas co-isolation of *Pseudomonas* was independently correlated with increased all-cause mortality (aHR, 3.98, 95% CI, 1.34–11.81, $P = 0.01$).

Conclusions: Our findings emphasize the importance of microbial surveillance, as bacterial co-isolation affects treatment initiation and prognosis in patients with NTM-PD.

Conflict of interest(s) (if any – not included in the 500 words): None.

[08.06] Increased lung cancer risk in individuals with nontuberculous mycobacterial pulmonary disease: A Korean population-based study

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Background/Aims: Lung cancer is the leading cause of mortality in patients with non-tuberculous mycobacterial pulmonary disease (NTM-PD). However, it is unknown whether patients with NTM-PD have a higher risk of lung cancer compared to those without NTM-PD. We aimed to evaluate this topic using the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) database.

Methods: This population-based cohort study enrolled individuals with NTM-PD (n = 496) between 2002 and 2019 and 1:10 age-, sex-, and smoking status-matched controls (n = 4,960). Participants were followed up for 1 year from the date of NTM-PD diagnosis to the date of the incident lung cancer, death, or Dec 2021, whichever came first. Multivariable Cox proportional hazard regression analyses were performed to compare the risk of lung cancer between the groups.

Results: During a median follow-up duration of 5.1 years (interquartile range, 3.4-7.8 years), the incidence rate of lung cancer in the NTM-PD group was significantly higher than in the controls (43.3/1,000 person-years vs. 6.2/1,000 person-years, $p < 0.01$). Even after adjusting for potential confounders, the risk of lung cancer was significantly higher in the NTM-PD group compared to controls (adjusted hazard ratio = 4.70, 95% Confidence interval = 2.07–10.65).

Conclusions: The risk of lung cancer in patients with NTM-PD was about 4.7-fold higher than in those without NTM-PD. Future studies are needed to evaluate whether lung cancer surveillance might be beneficial in this population.

Conflict of interest(s) (if any – not included in the 500 words): none

[08.07] The longitudinal characterization of mouse respiratory function in *Mycobacterium abscessus* pulmonary infection

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³Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom; ⁴Marsico Lung Institute, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; ⁵RTI International, Research Triangle Park, North Carolina, USA;

⁶University of Tennessee Health Science Center, Memphis, Tennessee, USA

Background/Aims:

Chronic pulmonary infection with *Mycobacterium abscessus* (*Mab*) is a significant cause of morbidity and mortality in people with cystic fibrosis (CF). Developing an animal model of *Mab* pulmonary infection under CF conditions is essential to understanding the *Mab* infection in patients with CF. β ENaC transgenic mice are known to develop spontaneous CF-like disease characterized by airway mucus obstruction and inflammation. The aim of this study was to characterize respiratory function during *Mab* lung infection in β ENaC transgenic mice and their wild-type (WT) counterpart.

Methods:

Mice received an intrapulmonary aerosol of *Mab* using a high-pressure syringe device (Penn-Century) for subsequent characterization of disease progression and respiratory function. Whole body unrestrained plethysmography (WBP) data was collected to monitor lung function and endpoints determined organ bacterial burden and associated pathology.

Results:

Endpoint CFU data in the lung and spleen showed that there was no significant difference in bacterial clearance between β ENaC and WT mice. Respiratory data showed an impairment in overall respiratory function during and after *Mab* infection in both strains of mice. Interestingly, in WT mice, lung dysfunction persisted after bacterial clearance.

Conclusions:

The decline in respiratory function suggests that WBP coupled to bacterial burdens are important *in vivo* parameters to monitor while studying the long-term implications of *Mab* lung exposure. Even with CF-like features, the β ENaC transgenic mice cleared *Mab* at a similar rate than WT mice and may provide key insights towards the pulmonary effects of NTM exposure.

Conflict of interest(s) (if any – not included in the 500 words):

[09.01] The Need for Hospitalization and Antibiotic Intervention in Correlation to Colonization in the Adult non-CF Bronchiectasis Population of the UMC Utrecht.

Inez Bronsveld¹; Bart Luijk¹; Annemarie Bernard¹; Anita Veldhuisen¹; Harry Heijerman¹

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Background/Aims: Non-CF bronchiectasis is a heterogeneous disease, with few standardized treatment options. Bacterial colonization is suggested to have influence on disease burden and type of treatment. Aim for this study is to identify and characterize non-CF patients with bronchiectasis, and analyze the relation between bacterial colonization and lung function, need for antibiotics, hospitalization and ER visits.

Methods: Medical records of patients with non-CF bronchiectasis were used for data regarding demographics, etiology, microbiology and usage of antibiotics and hospital. The impact of colonization was analyzed by comparing FEV1, need for antibiotics, hospitalization and ER visits between patients with and without colonization.

Results: 106 patients were included. Most common etiology of bronchiectasis was post-infectious (17.0%), followed by primary (12.3%) and secondary (9.4%) immune deficiencies and primary ciliary dyskinesia (7.5%). 55.8% of the subjects was colonized, most commonly by *H. influenzae* (28.9%) and *P. aeruginosa* (17.3%). Negative trends were observed for the need for intravenous antibiotics and hospitalization, both for *P. aeruginosa* and for species other than *H. influenzae* compared to the non-colonized subjects, although these differences were not significant. No differences were observed for *H. influenzae*.

Conclusions:

In our cohort there is a higher incidence of people with immune deficiencies and primary ciliary dyskinesia compared to other international cohorts of people with non-CF bronchiectasis. Our results suggest a negative effect of colonization with *P. aeruginosa* and for other species, but not for *H. influenzae*, resulting in more IV antibiotics and hospitalizations.

Conflict of interest(s) (if any – not included in the 500 words):

[09.02] The Anti-inflammatory repurposing network for bronchiectasis- the EMBARC AIR-NET study

James Chalmers¹; Merete Long¹; Benjamin JM New¹; Emma Johnson¹; Margaret Band¹; Charles Haworth²; Anand Shah³; Sanjay Chotirmall⁴; Aran Singanayagam³; Michael Loebinger³; Jamie Stobo¹; Anthony De Soyza⁵

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Background: There are no licensed treatments for bronchiectasis. Neutrophilic airway inflammation is a dominant mechanism and high levels of neutrophils and neutrophil serine proteases are associated with exacerbation frequency and disease progression. There are a lack of safe effective therapeutics targeting neutrophilic inflammation in bronchiectasis.

Repurposing refers to the identification of new therapeutic uses for established drugs. A number of drugs which are known to be safe and effective for other indications have been shown to have effects on neutrophilic inflammation in-vitro and in-vivo.

Study design: The EMBARC Anti-inflammatory repurposing network (AIR-NET) trial is an adaptive platform trial designed to simultaneously evaluate multiple repurposed therapeutics with potential effects on neutrophilic inflammation. Patients with CT confirmed bronchiectasis, daily sputum production and evidence of neutrophil elastase activity in sputum during stable state will be randomized to one of several repurposed therapeutics or standard care for 28 days. The primary outcome will be neutrophil elastase activity in sputum after 28-days, a validated inflammatory biomarker that is associated with future clinical outcomes. The initial phase of the trial will test doxycycline, dipyridamole and disulfiram. The adaptive nature of the trial allows therapeutics which are ineffective to be rapidly identified and replaced with new therapeutics.

The trial will be conducted in a network of centres with expertise in performing translational research studies in bronchiectasis allowing detailed characterisation of the effects of the treatments on airway and systemic inflammation including proteomics, transcriptomics, microbiome characterisation and neutrophil functional studies.

Conclusion: AIR-NET provides a novel platform for therapeutic development in bronchiectasis. The study is open to collaboration with clinical centres and partners wishing to use the platform to test therapeutics.

Funded by Lifearc through the Chronic Respiratory Infection Translational Challenge

[09.03] Efficacy and safety of inhaled tobramycin (Vantobra) in adult patients with bronchiectasis and *P. aeruginosa* in sputum: a prospective observational study

Chrysavgi Kosti¹; Antonia Digalaki¹; Andreas Matthaiou¹; Emmanouela Zervou¹; Konstantinos Papatheodosiou¹; Ioannis Roussis¹; Ioannis Tomos¹; Adamantia Liapikou¹; Katerina Dimakou¹

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Background/Aims: Inhaled antibiotics are widely used in patients with bronchiectasis and chronic *P. aeruginosa* (PA) infection as recommended in ERS guidelines. However, none of them have been approved so far. The aim of this study was to evaluate the efficacy and safety of tobramycin inhalation solution (TIS), Vantobra (Specialty Theurapeutics), in adult patients with bronchiectasis and PA in sputum.

Methods: We prospectively enrolled clinically stable patients with bronchiectasis and PA in sputum (chronic infection or first isolation) followed up in our reference center. They received off-label 170 mg TIS twice daily in three cycles (28 days on-off) via *PARI eFlow rapid* nebulizer. Clinical data, sputum culture, spirometry and Quality of life-Bronchiectasis (QOL-B) questionnaire were assessed at week 0, 4 and 24. Adverse events were recorded. We conducted one-year follow-up on patients after completing treatment to evaluate the eradication status and exacerbation rate.

Results: Our study is ongoing and includes 17 patients so far. Thirteen completed treatment, three discontinued due to wheezing, and one missed follow-up. Upon the end of treatment, 11 patients did not grow PA in sputum culture (85%) ($p < 0.001$). Moreover, patients showed a significant improvement in respiratory symptoms according to QOL-B even after the first cycle of TIS treatment ($p < 0.001$). Similar results were observed in four additional aspects of QOL-B. TIS positive impact on respiratory symptoms was maintained at week 24. Interestingly, PA eradication was maintained in 50% of patients at one-year follow-up after the end of treatment, while a significant reduction in exacerbations was noticed during the same period ($p = 0.013$). Bronchiectasis exacerbation in four patients and transient voice hoarseness in three patients were noticed as adverse events.

Conclusions: Our findings indicate that Vantobra may be effective in eradicating PA and improving quality of life of bronchiectasis patients with a good safety profile.

Conflict of interest(s) (if any – not included in the 500 words):

[09.04] Spirometry-defined ventilatory defects and risk of acute exacerbation in patients with bronchiectasis

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Background/Aims: Obstructive ventilatory defect (OVD) is typical ventilatory defect in bronchiectasis. Accordingly, low forced expiratory volume in one second (FEV₁) is well-known risk factor for acute exacerbation (AE) in bronchiectasis patients; however, the impact of forced vital capacity (FVC) on AE in restrictive ventilatory defects (RVD) or mixed ventilatory defects (MVD) is not reported. We aimed to evaluate the association between ventilatory defects and the risk of AE and the effect modification by FEV₁ and FVC.

Methods: This prospective cohort study was conducted at 51 referral hospitals in South Korea. Patients were classified into normal (*n*=62), OVD (*n*=59), RVD (*n*=148), and MVD (*n*=223) groups by the lower limit of normal for the FEV₁/FVC ratio and FVC. The incidence rate ratios (IRR) of AE caused by ventilatory defects were compared.

Results: The IRRs of annual severe AE rates compared with normal group were the highest in the MVD group (6.489; 1.682–25.035), followed by the RVD (3.532; 0.864–14.444) and OVD groups (2.987; 0.591–15.104) (*P* for trend=0.002). Both FVC and FEV₁ were significantly associated with the risk of any or severe AE in the RVD and MVD groups. The restrictive component significantly affected relationship between FVC and any or severe AE but not the relationship between FEV₁ and any or severe AE (*P* for interaction<0.05).

Conclusions: The annual rate of any or severe AE was higher in groups with than in those without restrictive components. The restrictive component modified the effect of FVC on any or severe AE in Korean bronchiectasis cohort.

Conflict of interest(s): none

[09.05] Population pharmacokinetics of Gremubamab to inform evaluation in patients with NCFBE

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Background/Aims:

Pseudomonas aeruginosa (PsA) is a key driver of airway damage, loss of lung function and exacerbations in non-cystic fibrosis bronchiectasis (NCFBE). Gremubamab is a bispecific monoclonal antibody targeting PsrV and Psl, two virulence factors of PsA, that is being investigated in NCFBE patients chronically infected with PsA. GREAT-2 study is an ongoing study designed to assess whether gremubamab treatment reduces PsA sputum bacterial density in PsA-colonized bronchiectasis patients. We developed a population PK model for gremubamab using historical data from randomized controlled trials (RCTs) in order to determine the doses for use in the GREAT-2 study.

Methods:

PK data from two previous RCTs (in healthy participants and PsA-colonized critically ill and mechanically ventilated ICU participants) was used to fit the model. These participants were administered a single intravenous infusion of gremubamab at a rate between 71.3 mg/hr and 1138.9 mg/hr. A non-linear mixed effect model was fitted to all data simultaneously independent of the population using R 3.5.1., PsN 4.9.0, and NONMEM 7.4.4. The population PK model (PopPK) based on gremubamab data from healthy and ICU participants was then used to select the dose to be assessed in GREAT-2 study to achieve a trough concentration of 1.7 ug/mL, a concentration associated with 90% survival in an acute pneumonia mice model.

Results:

A one-compartment model with linear elimination fits adequately the PK of gremubamab in both healthy and mechanically ventilated participants. To describe the lower exposure in ICU participants, a disease-effect covariate on both clearance and volume of distribution of gremubamab have been included in the model. The mean PK parameter estimates (interindividual standard deviation) were linear clearance CL= 0.38 L/day and 1.07 L/day (13.5%), volume of distribution V=0.24 L and 0.34 L (5%), in healthy participants and ICU participants respectively. No additional covariate has been considered.

Conclusions:

The popPK model successfully captured the clinical data of gremubamab. Using the model, we predicted that depending on the changes in gremubamab PK in patients with NCFBE,

either 500 or 1500 mg monthly would achieve a trough concentration 28 days after administration above the target concentration of 1.7 $\mu\text{g/mL}$ at steady state.

The GREAT-2 study is intended to show Proof of Concept and determine the exposure required to reduce sputum bacterial density in PsA-colonized bronchiectasis patients. Next steps include updating the PK model with clinical data from GREAT-2 study and describe the exposure/response relationship on sputum bacterial density and symptoms.

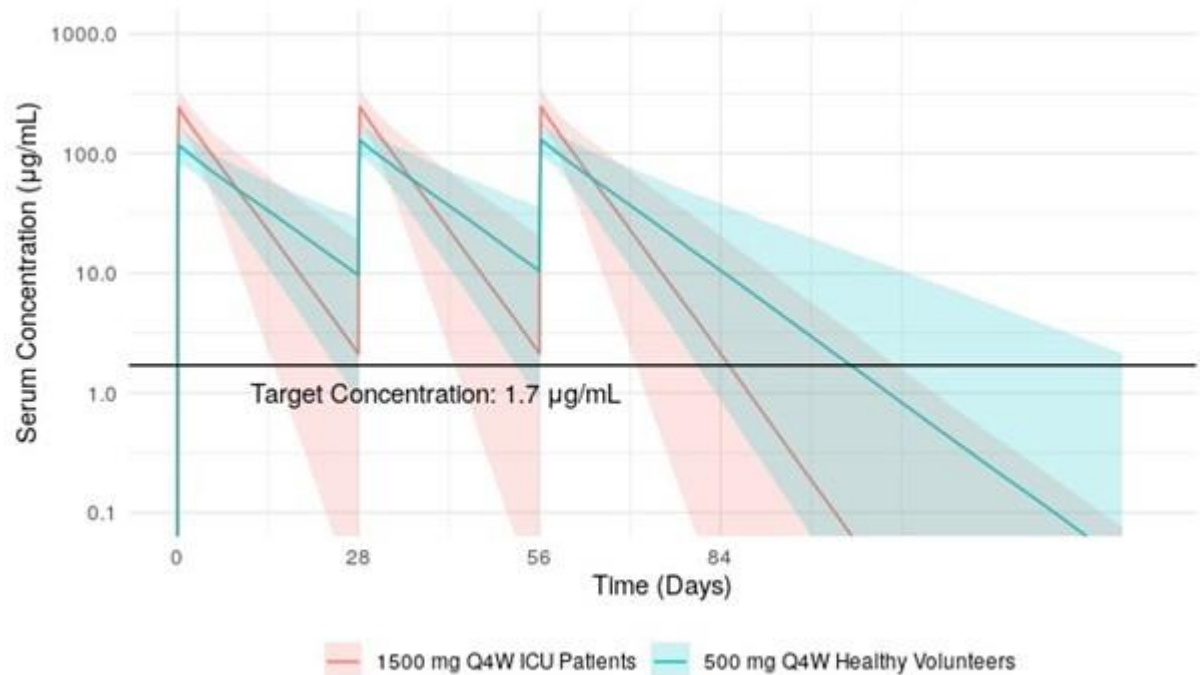


Figure: Predicted exposure after multiple doses of gremubamab following different scenarios. Lines represent simulated mean value. Shaded areas represent 90% predicted interval.

Conflict of interest(s) (if any – not included in the 500 words):

[09.06] Symptoms of bronchiectasis exacerbations: a real-life study.

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Background/Aims:

Exacerbations are crucial events in the natural history of bronchiectasis. Exacerbation symptoms may vary from patient to patient and might carry a different burden in terms of patients' perception. The aim of this study was to evaluate symptoms of bronchiectasis exacerbations in a real-life setting in terms of type, prevalence, variation in comparison to stable state and impact on patients' perception.

Methods:

This was a single-centre, observational, cross-sectional study conducted at the Bronchiectasis Programme of IRCCS Humanitas Research Hospital of Rozzano, Milan, Italy, from January 1st to May 31st, 2024. Patients with radiologically significant bronchiectasis were enrolled and interviewed about presence/absence of symptoms including cough, sputum, fever, dyspnoea, chest pain, haemoptysis and wheezing, during both stable state and their typical exacerbation. Patients were asked to prioritize their exacerbation symptoms identifying the top three ones in terms of perceived impact on their daily life. Data are reported as median (25-75 interquartile range -IQR) and absolute numbers (percentages).

Results:

126 patients [80% females; median (IQR) age: 67 (60-71) years] were enrolled: median (IQR) Bronchiectasis Severity Index value was 5 (3-9), 31 patients (25%) had chronic *Pseudomonas* infection and 33 patients (26%) were frequent exacerbators (more than 3 exacerbations/year). The most common symptoms patients had for most days of the week during stable state included sputum production (57%), cough (53%), exertional dyspnoea (mMRC ≥ 1 ; 39%), fatigue (27%), wheezing (16%), chest pain (10%), frequent haemoptysis (9%), intermittent fever (6%), dyspnoea during the night (4%) and dyspnoea at rest (1%). Sputum was purulent in 47% and with increased consistency in 44% of cases. The most common symptoms during exacerbations included new or increased cough (84%), new or increased sputum production (75%), increased consistency (66%), and purulence (67%), new or increased fatigue (67%), fever (59%) and new or increased exertional dyspnoea (58%). Changes in chest pain (26%),

wheezing (25%), haemoptysis (7%), dyspnoea at rest (14%) and at night (10%) were also reported. 85% of the patients reported a typical exacerbations consistent with the 2017 EMBARC/BRR definition. Prevalence of each sign and symptom during both stable state (blue line) and exacerbation (orange line) is reported in Fig. 1. The most impactful symptoms according to the cumulative percentage in the podium were cough (92%), changes in sputum characteristics (71%), fatigue (61%) and fever (41%) (Fig.2).

Conclusions:

A great variability in exacerbation symptoms exists in bronchiectasis patients, with different priority of impact according to patients' individual perception. These data should be confirmed in a large, international contest.

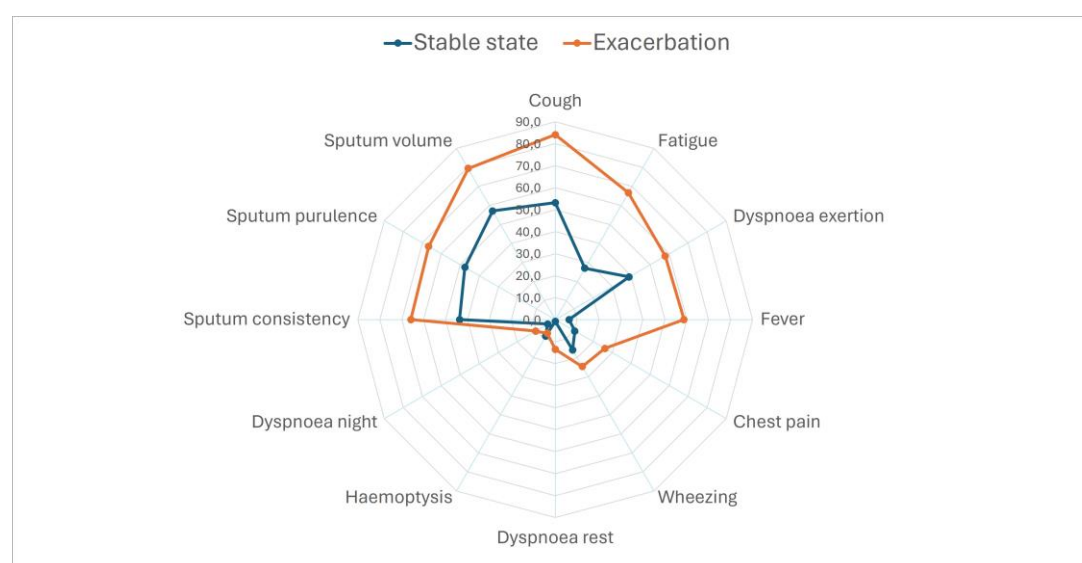


Fig. 1 – Prevalence of each symptom during stable state and exacerbation.

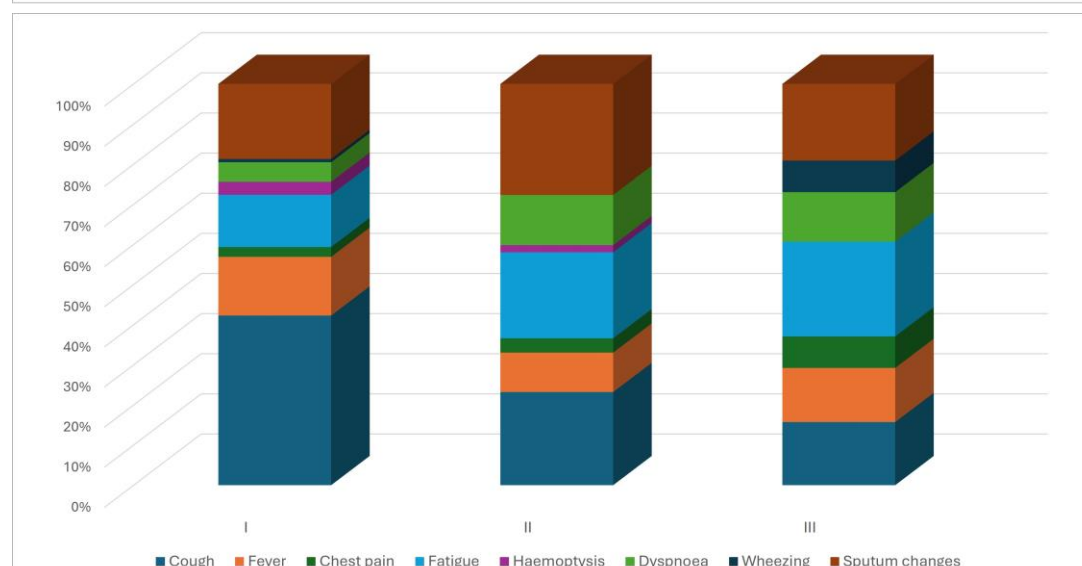


Fig. 2 – Patients' perceived priority of impact of exacerbations' symptoms.

Conflict of interest(s) (if any – not included in the 500 words): All authors have no conflict of interest to declare.

[09.07] Evaluation of New Molecular Assays for Quantitative Detection of Viable Pathogens in Pulmonary Exacerbations

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Background/Aims: LifeArc aims to advance the translation of early science in health care treatments and diagnostics to generate patient focussed solutions. LifeArc's Chronic Respiratory Infection Translation Challenge seeks to enable bronchiectasis patients to live longer with an improved quality of life. This work aims to develop a robust and accessible, quantitative, RNA based diagnostic for the detection/and or monitoring of pathogens from patient sputum.

Methods: Consultation with experts identified *Haemophilus influenzae* (HI), *Moraxella catarrhalis* (MC), *Staphylococcus aureus* (SA) and *Streptococcus pneumoniae* (SP) as important pathogens associated with exacerbations in some bronchiectasis patients. At LifeArc, development of molecular assays for each target is ongoing, with the aim to quantify bacterial load from sputum samples using ribosomal RNA (rRNA) as a proxy measurement for viability. As part of a feasibility study, the following analytical characteristics were tested: intra-assay precision, repeatability, limit of detection (LOD), limit of quantification (LOQ) and linearity. Additionally, optimisation of RNA extraction from *S. aureus* using the antimicrobial peptide lysostaphin was carried out to improve pathogen detection. Clinical samples collected from bronchiectasis patients, via the EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) network, were tested with each assay and results compared to those derived using an alternative CE-IVD marked platform, the DNA based BIOFIRE® FILMARRAY® Pneumonia Plus Panel. Similar work involving *Pseudomonas aeruginosa* is progressing as a separate project.

Results:

Prototype assays have been developed for all targets and performance rigorously evaluated. All assays met, at least, the minimum requirements for the specified analytical assessments; intra-assay precision, LOD, LOQ, and linearity (Table 1).

Table 1. Analytical performance requirements

Characteristic	Minimum	Requirement	Target
Intra-assay precision		%CV ≤ 50%	
Repeatability	%CV ≤ 50%		%CV ≤ 25%
Limit of Detection	≤ 10,000 copies/rx		≤ 1000 copies/rx
Limit of Quantification	≤ 10,000 copies/rx		≤ 1000 copies/rx
	Measurement range:		Measurement range:
Linearity	Lower limit ≤ 10,000 copies/rx	Lower limit ≤ 1,000 copies/rx	
	Upper limit ≥ 1x10 ⁷ copies/rx	Upper limit ≥ 1x10 ⁷ copies/rx	
	Deviation from linearity ≤ 30%		

CV = Correlation coefficient

Extraction of *S. aureus* RNA utilising the enzyme lysostaphin showed a significant increase in RNA yield compared to samples not treated with lysostaphin. For *S. aureus*, RNA yield was shown to be comparable when lysostaphin concentration was reduced from 0.14 mg/ml to 0.025 mg/ml; similarly, reduction in lysostaphin incubation, at 37°C, from 30-10 minutes did not impact RNA yield at any concentration tested.

Preliminary analysis of clinical samples tested with the HI, MC, SA, and SP assays has shown high levels of congruence between results generated using the BIOFIRE® FILMARRAY® Pneumonia Plus Panel. Comparison of results utilising Next Generation Sequencing and culture data will be carried out.

Conclusions: Robust assays, capable of quantifying rRNA from sputum samples, have successfully been developed and tested for HI, MC, SA, and SP. This work enables knowledge generation by demonstrating the potential for rRNA to be used as a biomarker for bacterial infection in bronchiectasis patients.

Conflict of interest(s) (if any – not included in the 500 words): None

[10.01] Chest physio a day keeps the patient away. Providing intensive outpatient physio for PCD patient.

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Background/Aims:

To provide a patient centred treatment plan for a patient with primary ciliary dyskinesia (PCD) that would reduce admissions to hospital, improve quality of life and maintain or improve lung function. The patient had sporadically attended the respiratory ward for intravenous antibiotics to treat exacerbations of her lung condition over a five year period. Treatment was offered twice daily for her two week inpatient admission and would mostly consist of support with airway clearance. She was assessed for lung transplant in Sep 2021 and was deemed an appropriate candidate but was clinically too well. Since then patient has had an increase in sputum volume, reduction in lung function and reduced quality of life. At this time the decision was made by the physiotherapy team to provide a more flexible and consistent treatment approach.

Methods:

The patient attended twice weekly to an outpatient room within the respiratory ward during a six month period (August 2022 to Jan 2023).

Treatments were completed to suit patient need on the day. Treatments varied between support with airway clearance and guided exercise in a gym setting. Airway clearance support was provided by use of manual techniques with variable use of OPEP (Aerobika), or an exercise program to include cardiovascular exercise and strength training.

Results:

During the six month period, only one admission electively was required. This is reduced from 2 inpatient admissions in 2022, 4 in 2021, 4 in 2019.

Exercise tolerance improved and was demonstrated by an improvement of 50m in a six minute walk test (6mwt) with no significant desaturations during this exercise test. A minimal clinical importance of 54m to 80m is stated to be significant for this particular exercise test.

Chest x-ray showed some improvement when compared to previous years.

The patient also had an increase in weight from 44.75kg to 45.3kg, possibly attributed to an overall improvement in her respiratory function.

Furthermore the patient reports a significant improvement in her quality of life, targeted support for her chest allowed her to finish writing her thesis for her PhD and she was able to attend a friend's wedding in India without supplementary oxygen required for the flight.

During this time period patient contracted COVID, however experienced minimal symptoms and had no change in function. Subjectively patient felt this may not have been the case if she had not received this support from physiotherapy

Conclusions:

Using a flexible model to treat a complex patient we were able to improve quality of life, reduced sputum volume and consequently minimise frequency of exacerbations. Patient reports to be feeling more positive about the management of her health since receiving more intensive physiotherapy input.

Provision of accelerated and enhanced physiotherapy input served to reduced hospital admissions, maximise quality of life and patient reported outcomes. Considering alternative opportunities for patient care thus minimising use of inpatient resources but maintaining quality of care. This is a service that can be implemented for other chronic respiratory conditions.

Conflict of interest(s) (if any – not included in the 500 words):

Nil

[10.02] BEAT-PCD CiliaVar international variant database and ClinGen Motile Ciliopathies GCEP to improve gene-variant-disease relationships in PCD

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Background/Aims: Primary Ciliary Dyskinesia (PCD) can be diagnosed by pathogenic variants in >50 genes, a number continually expanding. Due to the genetic heterogeneity, PCD genetic testing still fails to identify a genetic cause in ~30% of cases. Furthermore, 60% of genetic variants are unique to individual families, complicating interpretation. Increasing numbers of variants of uncertain significance (VUS) underlines the need for an internationally curated database of PCD variants for easier interpretation. This will aid clinicians and researchers worldwide to improve the sensitivity of genetic testing. Our aim is to establish an accessible open access online database registering PCD variants and specific combinations of variants implicated in the disorder.

Methods: A panel of PCD expert clinicians and geneticists identified database fields to link each variant with the associated diagnostic, clinical and genetic evidence supporting pathogenicity. An extensive literature search was conducted in PubMed, using search terms (“name of the gene” AND “cili” NOT “review”) to identify published variants in PCD genes. Additional entry of unpublished data from different clinical centres was also carried out. Database curators checked variant nomenclatures and classification following American College of Medical Genetics (ACMG) guidelines. Furthermore, to determine gene-disease validity for proposed PCD genes, members of BEAT-PCD collaborated in the development of a Motile Ciliopathy Gene Curation Expert Panel (GCEP) with the Clinical Genome Resource (ClinGen).

Results: Data from 1,747 unique PCD patients were collected from 4 international diagnostic centres and 262 literature papers, removing any duplications. This resulted in 1,091 unique variants in 44 genes. The most variations observed were in the genes *DNAH5* (n=358 patients), *DNAH11* (n=209), *CCDC39* (n=142) and *CCDC40* (n=133). Of all the variants included in the database, it was possible to classify 748 for pathogenicity according to ACMG guidelines, with 54% classified as pathogenic, 24% likely pathogenic and 22% VUS. 88% of the VUS are missense variants, and only 9% of missense variants are classified as pathogenic or likely pathogenic. Due to a significant South Asian founder effect, the overall most prevalent variant is *CCDC103* p.His154Pro (n=101 alleles), a known hypomorphic allele with varying clinical presentation. The ClinGen Motile Ciliopathy GCEP currently comprises 30 members and has validated 27 genes with a “Definitive” gene-disease relationship for PCD. Additional curated genes having varying classifications from “Strong”, “Moderate”, and “Limited” indicating that additional data and/or time may result in further validity in the future. Five genes (*AK7*, *CFAP43*, *BRDW1*, *MNS1*, *DNAH8*). were

assigned a “Disputed” gene-disease validity classification, indicating that these genes and variations within them may not be validated causes of PCD.

Conclusions: Establishing an open access PCD genetic database will provide essential support towards improving sensitivity of genetic testing for PCD. Both the CiliaVar database and the ClinGen Motile Ciliopathy GCEP initiatives will support better genetic testing and interpretation of results for PCD. These are vital to developments in personalised patient management and improved clinical outcomes, including through future genetic therapy trials.

[10.03] PCD Avatars: PCD airway organoids for disease modelling and personalised medicine

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Introduction/Aims: Primary Ciliary Dyskinesia (PCD) is a rare, incurable, genetic disorder characterised by abnormalities in ciliary structure and function. Although PCD is genetically heterogenous with mutations identified in over 40 genes, there is a notable correlation between a patient's genotype and the ultrastructural defect observed through electron microscopy assessment of cilia. Despite this correlation, the presentation of lung disease remains varied across most genotype and ultrastructural categories. The variability in genetics, clinical presentation and drug responses has made research into optimal PCD management challenging in the past. Personalised medicine aims to customise treatments based on individual patient profiles, optimising clinical outcomes. We have developed stem cell-derived airway organoids that facilitate *in vitro* examination of the ciliary function in PCD patients. Our aim is to establish the reliability of the *in vitro* organoid models to accurately replicate the pathological features of PCD. In the future we aim to utilise the PCD organoids to assess response to various drugs, aiming to discover individualised treatment strategies for PCD patients.

Methods: Participants of all ages with confirmed or suspected PCD are being recruited from Sydney Children's Hospital and Concord Repatriation General Hospital. Nasal epithelial cells are collected from each participant by brushing of the inferior turbinate (Fig 1a). The freshly collected airway epithelial sheets are assessed using an Olympus IX70 inverted microscope and Sisson-Ammons Video Analysis (SAVA) of ciliary beat frequency (CBF) and pattern (CBP) (Fig 1b). The epithelial cells then undergo conditionally co-culture methodology (Fig 1c) to create a biobank of patient specific stem cells (Fig 1d). An air-liquid interface (ALI) model is used to differentiate to a pseudostratified epithelium (Fig 1e). CBF and CBP are further assessed on the cells from the ALI model, which are scraped and suspended in media (Fig 1f). The CBF and CBP of the ALI model are compared with the measurements obtained from the freshly collected epithelial sheets to assess whether the models accurately replicate the pathological features of PCD (Fig 1g). Imaging is additionally performed of the ALI model with the filter cut from the transwell insert and inverted onto a slide (cilia imaged on their side) (Fig 1h) and the ALI model with cells remaining on the transwell insert (cilia imaged through the epithelial cells) (Fig 1i), for use as part of the personalised medicine pipeline.

Results: 21 participants have been enrolled so far, with a planned sample size of 30. Cells have been biobanked from 19 participants and data analysis has so far been completed for 7. The CBF analysis of the freshly collected airway epithelial sheets vs ALI models with cells scraped and suspended in media for 7 of the recruited participants is shown in Figure 1j.

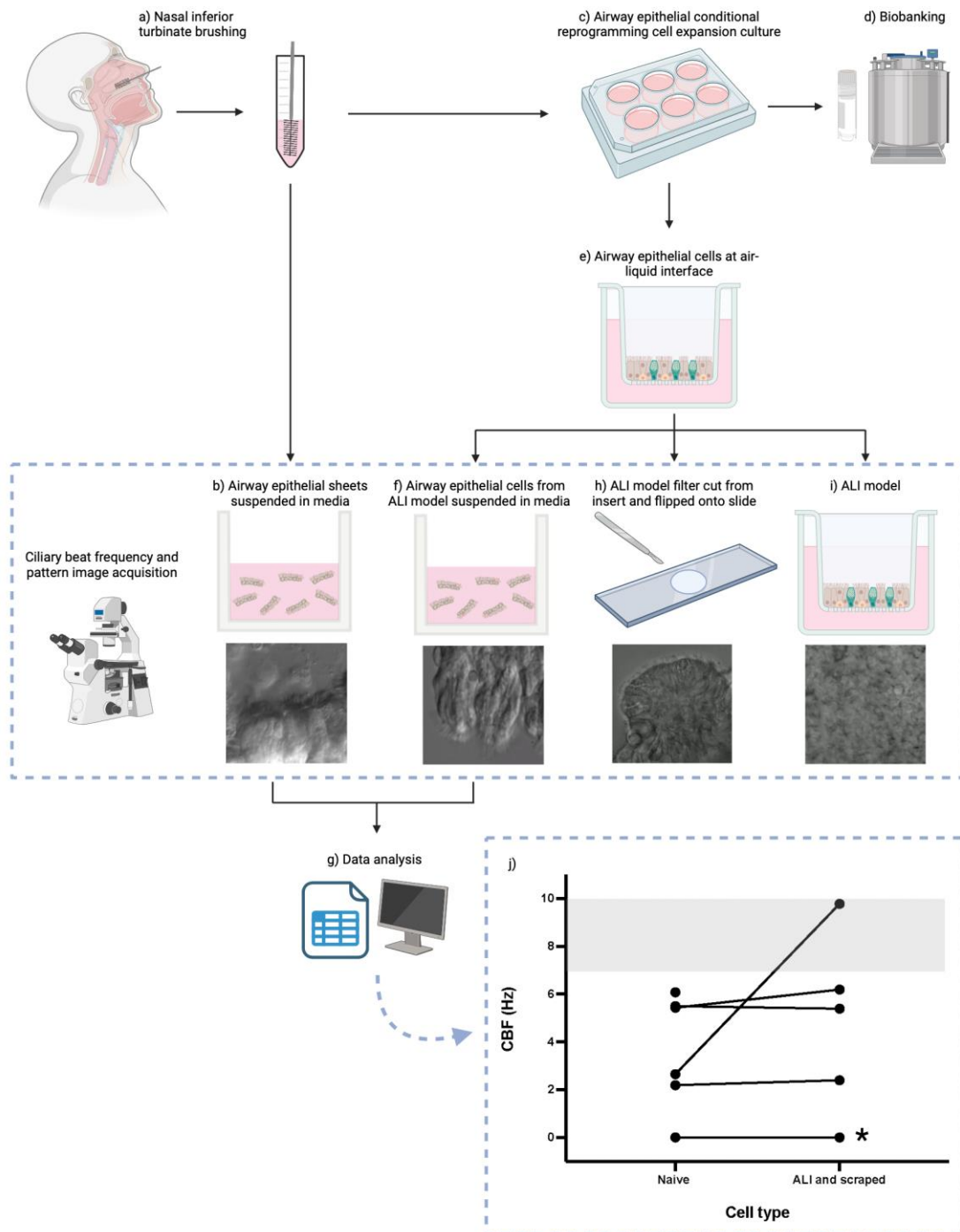


Figure 1. a-i) Schematic representation of the methods for cell collection, expansion, differentiation and imaging. j) CBF analysis performed on freshly collected (naïve) airway epithelial sheets and the ALI model with cells scraped and suspended in media for 7 of the recruited participants. The shaded area reflects the normal CBF range (7-10Hz).
 * 2 participants have a CBF of 0Hz measured on both their naive and ALI and scraped cells

Conclusion: This study will establish the use of PCD patient derived airway organoids to model their ciliary dysfunction *in vitro*. This will provide the foundations for personalised medicine research in the future.

Grant Support: This project is supported by grants received by MF from the Rotary Club of Sydney Cove and the National Health and Medical Research Council.

[10.04] Biomarkers in Primary Ciliary Dyskinesia: A systematic review

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Background/Aims:

Primary ciliary dyskinesia (PCD) is a rare heterogeneous disease which is characterised by repeated infective pulmonary exacerbation. The identification of biomarkers to predict exacerbations and disease progression could provide an opportunity for early intervention. The aim of this systematic review was to identify biomarkers which predict exacerbation or are sensitive to intervention.

Methods:

A literature search of 80 keywords related to PCD and biomarkers was undertaken using Pubmed, OVID online, clinicaltrials.gov and PROSPERO (search last run April 2024). Results were amalgamated, and duplicates removed.

Two authors sequentially reviewed the titles and then abstracts of these studies. Studies progressed past each stage if they met the agreed inclusion and exclusion criteria. At the final stage, inclusion criteria were full text, in English, includes patients with PCD, measurement of a biomarker. Exclusion criteria were abstracts only, review articles, no biomarkers (nasal NO, lung clearance or lung function, bacterial load only). Three authors read the full published articles and determined their suitability for inclusion into the systematic review. The QUADAS-2 tool was used as an adjunct to critical appraisal. Figure 1 shows the PRISMA flowchart.

Results:

Sixty articles describing potential biomarkers in PCD were included in the final analysis. These included biomarker measurement in 1288 pwPCD. The largest single study included 77 children and adolescences. Biomarkers were measured in blood, bronchial alveolar lavage, exhaled breath and biopsies and included inflammatory cytokines, nitric oxide metabolites, measures of oxidative stress and volatile organic compounds. The most frequently measured biomarker was sputum IL-8. Two studies were multicentre. Five studies measured biomarkers after an intervention (2 x mucolytics, 3 x antibiotics). Antibiotic treatment reduced sputum elastase activity in 2 studies and nitric oxide metabolites in 1 study.

Conclusions:

Multiple potential biomarkers have been identified in PCD but none have been validated in

large patient populations or multicentre studies. These results support the need for further collaboration between PCD centres and a systematic approach towards biomarker identification in this rare disease.

This work was carried out by the BEAT-PCD ERS clinical research consortium.

Conflict of interest(s) (if any – not included in the 500 words):

None

[10.05] Primary ciliary dyskinesia - a complex diagnostic process at a terciary hospital

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Background/Aims:

Primary ciliary dyskinesia is a rare genetic disease characterized by structural and/or functional changes of the *cilia* that leads to chronic respiratory disease. The variability of expression and difficulty in the diagnosis, which lacks a gold standard diagnosis test, lead to its subdiagnosis or diagnosis at more advanced phases.

Our aim was to characterize patients with suspected primary ciliary dyskinesia followed up at our center and their respective diagnostic progress.

Methods:

A descriptive analysis of the cases submitted to the diagnostic process for primary ciliary dyskinesia was carried out, with retrospective and prospective data collection.

Results:

Among the 230 patients followed at the bronchiectasis consultation at our central university hospital, 37 patients were selected for nasal nitric oxide (nNO) measurement, with a mean age of $40,5 \pm 11,31$ years and 21 patients were male (56.7%). 4 patients (10.8%) were former smokers and 32 patients (86.5%) were never smokers. 5 patients (13.5%) were transferred from Paediatrics, the mean age at bronchiectasis diagnosis was 24.24 ± 14.52 years. The most frequent clinical pattern was bronchiectasis (n=33 (89%)), followed by chronic rhinosinusitis (n=15 (40.5%)), *situs inversus* (n=10 (27%)), and recurrent otitis (n=5 (13.5%)). Mean FEV1 was 76.46 ± 22.09 (%pred) and 16 patients (43.2%) had chronic infection, 7 for *Pseudomonas aeruginosa* (18.9%) and 6 for *Haemophilus Influenza* (16.2%). 14 patients (37.8%) have a low nNO (<77nL/min), with a meanvalue of 31.15 ± 18.33 nL/min and a mean PICADAR score within this group of ± 2.74 . The mean PICADAR score among the group of patients with high nNO was only slightly lower, 4.27 ± 2.32 . 9 patients (24.3%) were already confirmed cases through complementary study with TEM (*transmission electronmicroscopy*) and/or HSVA (*high-speed video microscopy analysis*) and/or genetic testing.

Conclusions:

The authors describe a series of cases of patients with suspected primary ciliary dyskinesia, who underwent aclinically based diagnostic procedure, using nNO and genetic study. The main study limitations reflect the complexity and difficulties in diagnosing this pathology, so we need to implement a systematic and straightforward evaluation of these patients.

Conflict of interest(s) (if any – not included in the 500 words): No conflicts of interest

[10.06] Primary Ciliary Dyskinesia: a descriptive study of a Portuguese Bronchiectasis Outpatient clinic

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Background/Aims: Bronchiectasis can result from various causes; 60–80% cases are idiopathic, but a well-recognised genetic cause is the motile ciliopathy, primary ciliary dyskinesia (PCD). This rare genetic disorder causes defective ciliary movement which results in recurrent respiratory infections, bronchiectasis, chronic sinusitis and otitis media. Additionally, PCD can present with infertility due to impaired ciliary function in the reproductive tract and laterality defects such as situs inversus. PCD is underdiagnosed as clinical presentation is diverse and diagnostic testing is not straight forward.

Methods: Retrospective and descriptive study of patients with PCD from the Bronchiectasis Outpatient Clinic in a Portuguese tertiary hospital. The data assessed included demographic and clinical features as well as relevant testing results.

Results: Eleven patients with the diagnosis of PCD were included, seven female and mean age was of 35±13.6 years old. One patient had a history of preterm birth and five had relevant family respiratory history: two of asthma, bronchitis and sinusitis; two had siblings with PCD and situs inversus; one with a sibling with idiopathic bronchiectasis in follow up at the Lung Transplant Clinic. All of the patients had bronchiectasis, mostly cylindrical and mainly in the lower and medium lobes. E-FACED score was 1 or more in five patients. History of haemoptysis (n=4), rhinitis (n=9), chronic sinusitis (n=7), nasal polyposis (n=5), recurrent otitis (n=3), deafness (n=3) and infertility (n=5) were documented. Four patients had Kartagener syndrome and one had situs ambiguous. Average FEV1 was 71.7±15.0%. Regarding sputum microbiology, 2 had chronic infection with *Pseudomonas aeruginosa*, 2 with *Staphylococcus aureus* and 3 with *Haemophilus influenzae*. Medical treatment included inhaled corticoid/bronchodilator (n=5), long-term azithromycin (n=2), mucolytic (n=4), phage therapy (n=1) and montelukast (n=1). Two patients had no pharmacological therapy. All underwent kinesitherapy. Regarding PCD diagnosis, 8 patients underwent genetic testing, two performed electron microscopy, one nasal nitric oxide testing, and three nasal biopsies. PCD was genetically confirmed in seven patients. The remaining patients were diagnosed according to typical clinical features and other abnormal tests results.

Conclusions: This retrospective study highlights the diverse clinical features of PCD in a cohort of patients. Pathological diagnosis of the disorder is complex as nasal biopsies and electron microscopy are not always easily accessible. Next-generation sequencing still has limitations but it is rapidly moving from research into clinical diagnostics and the increased uptake of genetic testing has been a positive step for PCD. Management of PCD involves implications including addressing co-morbidities, implementing genetic, fertility counselling and future access to PCD-specific treatments.

Conflict of interest(s) (if any – not included in the 500 words): None

[11.01] Bronchiectasis and Airway Microbiota: a monocentric descriptive study

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Background/Aims:

Bronchiectasis is characterised by progressive bronchial dilatation, resulting in chronic infection, inflammation, impaired mucociliary clearance, and is marked by recurrent exacerbations caused by microbial or environmental triggers. We aimed to examine airway microbiota changes in steady state and during exacerbations and explore associations between the lung microbiota and clinical presentation.

Methods:

Adults with non-cystic fibrosis (CF) bronchiectasis were enrolled consecutively between June 2021 and July 2022. Nasopharyngeal swabs (URT) and spontaneous sputum samples (LRT) were collected at baseline, 3 and 6 months of follow-up, and when possible, during an exacerbation. Samples were analysed using conventional cultures for bacteria, mycobacteria and fungi. 16S rRNA gene amplicon sequencing and quantitative PCR were performed to assess bacterial communities and microorganisms.

Results:

Eighteen subjects were included in the study, with a total of 49 LRT and 41 URT samples (Table 1). Eleven exacerbation episodes were observed during the study period. Commonly identified pathogens were *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The pathogen most commonly detected was *H. influenzae* in the exacerbators, and *P. aeruginosa* in the non exacerbators. As expected, LRT and URT samples presented significantly different variance and composition of the microbial communities (Figure 1). We observed a larger variation of beta-diversity in LRT samples over time in subjects with post-infectious bronchiectasis, compared to those with other origins of bronchiectasis. During the 6-month course of follow-up, the evenness and richness of the microbiota did not show any overall significant variation. However, in the three months after exacerbation (and treatment), the evenness increased in LRT samples and the richness increased in URT samples, albeit with limited statistical significance owing to the few exacerbation events.

Conclusions:

Microbiota in patients with non-CF bronchiectasis displayed a wide variety of bacteria by conventional cultures, and we observed different trajectories of the microbial communities, in particular linked to the disease origin and exacerbation events. Improved understanding of the microbiota in bronchiectasis may enhance our understanding of mechanisms leading to exacerbations and provide potential strategies for their mitigation.

Table 1. Participants' characteristics

Age (yr)	53.5 (42-70)
Female sex, n(%)	12 (66 %)
BMI (kg/m2)	21.8 (19-26.5)
Comorbidities	
Asthma, n(%)	4 (22)
COPD, n(%)	1 (5.5)
Cardiovascular disease, n(%)	4 (22)
Connective tissue disease, n(%)	2 (11)
GERD, n(%)	3 (17)
Liver disease, n(%)	1 (5.5)
Oncological disease, n(%)	1 (5.5)
Smoking status	
Never smokers, n(%)	10 (55.6)
Previous smokers, n(%)	4 (22)
Current smokers, n(%)	4 (22)

FEV₁ (% predicted value) 78 (66-92)

Spirometric pattern

Normal, n(%) 3 (16)

Obstructive, n(%) 12 (66.5)

Restrictive, n(%) 0 (0)

Mixte, n(%) 1 (5.5)

Non-specific, n(%) 1 (5.5)

Unknown, n(%) 1 (5.5)

Severity of obstruction
(n=13)

Mild, n(%) 7 (54)

Moderate, n(%) 3 (23)

Severe, n(%) 3 (23)

BSI score

0-4, n(%) 5 (27.8)

5-8, n(%) 6 (33.3)

9, n(%) 7 (38.9)

Underlying cause of
bronchiectasis

Post-infectious, n(%) 9 (50)

Primary ciliary dyskinesia,
n(%) 6 (33.3)

HIV, n(%) 1 (5.5)

Inflammatory bowel disease,
n(%) 1 (5.5)

ABPA, n(%) 1 (5.5)

Treatment

NaCl 0.9%, n(%) 5 (27.8)

NaCl 3%, n(%) 4 (22)

Acetylcystein, n(%) 2 (11)

Inhaled
antibiotics, n(%) 1 (5.5)

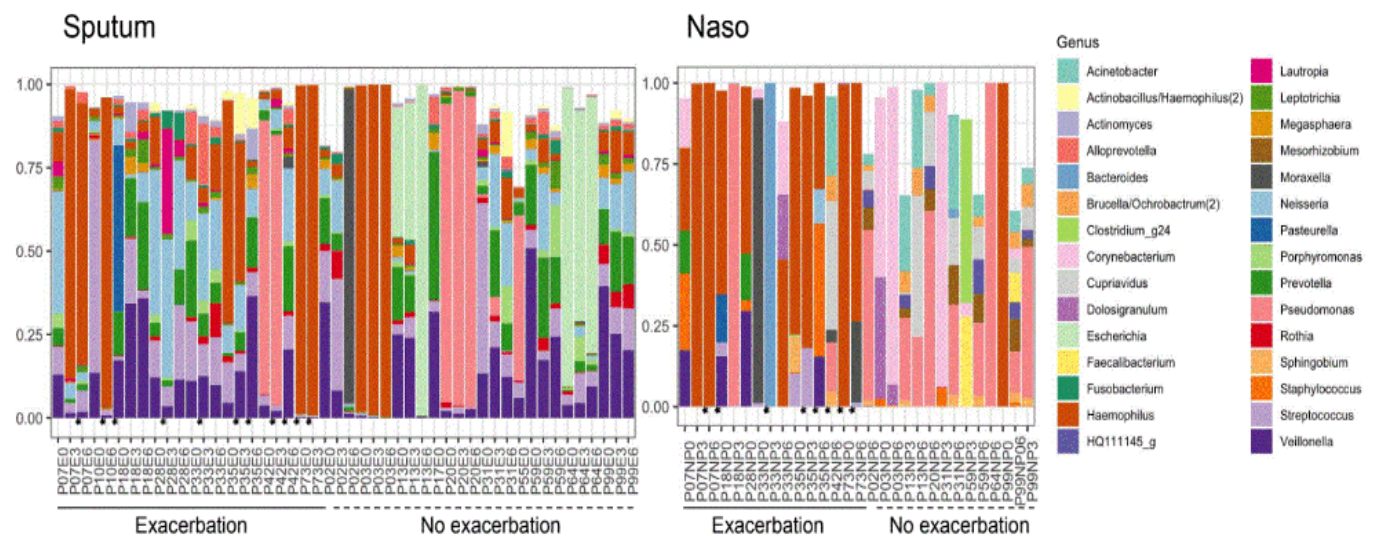
ICS, n(%) 8 (44)

Systemic
immunosuppression, n(%) 2 (11)

PPIs, n(%) 1 (5.5)

ABPA, allergic bronchopulmonary aspergillosis; BMI, body mass index; BSI, bronchiectasis severity index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 sec; GERD, gastroesophageal reflux disease, HIV, human immunodeficiency virus; ICS, inhaled corticosteroids; PPIs, proton pump inhibitors

Figure 1. Overview of results of 16S rRNA gene amplicon sequencing



* Refers to exacerbation time point

Conflict of interest(s) (if any – not included in the 500 words):

The authors declare no conflict of interest

[11.02] Use of antibiotics in patients with bronchiectasis and primary infection by *P. aeruginosa*

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Background/Aims:

There are no robust evidence-based recommendations on antibiotic treatment for patients with non-cystic fibrosis bronchiectasis (NCFB) and primary infection due to *P. aeruginosa* (PA). Therefore, knowing which antibiotic treatment regimes are being administered in these cases and their effectiveness in routine clinical practice is interesting. We aim to describe the antibiotic regimens used in patients with NCFB and primary PA infection, assessing their effectiveness. The primary objective is to assess the microbiological eradication rate one year after the treatment. The secondary objectives were to assess the number of outpatient exacerbations and hospitalizations.

Methods:

Retrospective, single-centre study in adult patients with NCFB and primary infection with PA during the study period 2019 - 2021. Primary infection has been considered the first positive culture for PA in sputum samples or a recurrence of a positive culture after one year, after two negative controls (separated a minimum of one month). Patients have been classified into five different groups, depending on the type of antibiotic administered: beta-lactams alone, beta-lactams associated with aminoglycosides, quinolones, mixed treatment (quinolones and beta-lactams in sequence for the same episode) and without antipseudomonal antibiotics.

Results:

53 patients were included, 27 women (51%), with a mean age of 69.8 years (SD 10.9). The main etiologies of NCFB were COPD (47.2%), idiopathic (22.6%), and tuberculosis (18.9%). NCFB was mild in severity (E-FACED 3 points) but had much comorbidity (Charlson Index 4.4).

At the time of primary infection, 28 patients (52.8%) presented increased symptoms (dyspnea 41.5%, cough 41.5%, purulent sputum 35.8%, hemoptysis 13.2%), and 21 patients (39.6%) required hospitalization. 32 patients received treatment with quinolones, 3 with beta-lactams alone, 2 with beta-lactams + amikacin, 5 with mixed treatment and 11 patients did not receive antipseudomonal treatment. The mean duration was 14.5 days (SD 6.1); 15 patients (28.3%) were treated for more than 14 days. Table 1 shows the baseline results and the clinical effectiveness of the treatment depending on the group.

All patients in the beta-lactam treatment groups (either alone or in combination with quinolones) had an exacerbation of symptoms at the time of primary infection, compared with only 53.8% of patients treated with quinolones alone. Furthermore, 100% of these

patients required hospitalization, compared to 36.4% in the group without antipseudomonal treatment and 25% of patients treated with quinolones.

The group treated with quinolones had a moderate eradication rate at one month and 12 months, while the groups treated with beta-lactams, especially in combination with amikacin, showed higher long-term eradication rates (50% and 60%, respectively). Additionally, the quinolone-only group had a higher incidence of outpatient exacerbations and hospitalizations at 12 months compared with other groups.

Conclusions:

These findings suggest that patients treated with beta-lactams, especially in combination with amikacin, may have greater symptom severity during primary infection but may also benefit from a higher long-term eradication rate than other treatment regimens. However, more research is needed to confirm these observations and establish the best therapeutic strategies for this patient population.

	Only Quinolones (n=32)	Only Beta-lactams (n=3)	Beta-lactams + amikacin (n=2)	Combined treatment (n=5)	No antipseudomonal treatment (n=11)
Baseline patient characteristics					
Age (years ± SD)	71.2 ± 8.0	69.3 ± 21.1	74.5 ± 9.2	61.8 ± 20.46	68.6 ± 10.6
Charlson Index points (median)	4	6	4	6	4
Immunosuppression (% of patients)	18.8%	0%	50%	20%	0%
FVC (%)	76.6	73.0	42.2	89.0	75.5
FEV ₁ (%)	58.5	58.0	39.9	42.4	50.6
FEV ₁ /FVC (%)	61.3	66.0	72.9	42.4	52.5
Cystic bronchiectasis (% of patients)	18.8%	33.3%	0%	20%	20%
Number of outpatient exacerbations previous year (mean ± SD)	0.8 ± 1.1	-	-	1.2 ± 1.1	0.5 ± 1.1
Number of hospitalizations previous year (mean ± SD)	0.3 ± 0.5	1.3 ± 1.6	0.5 ± 0.7	1.0 ± 1.4	0.8 ± 1.2
E-FACED points (median)	2	3	2	3	3
Symptoms at the moment of the primary infection (% of patients)					
Exacerbation of symptoms	53.8%	100%	50%	100%	27.3%
Hospitalization	25%	100%	0%*	100%	36.4%
Increase in usual cough	37.5%	66.7%	0%	80%	36.4%
Purulent sputum	37.5%	33.3%	50%	60%	18.2%
Dyspnoea	40.6%	33.3%	0%	80%	36.4%
Respiratory failure	6.3%	33.3%	0%	20%	0%
Haemoptysis	6.3%	66.7%	0%	20%	0%
Baseline respiratory treatments					
LABA (% of patients)	62.5%	66.7%	0%	100%	70%
LAMA (% of patients)	53.1%	33.3%	0%	80%	50%
ICS (% of patients)	37.5%	66.7%	50%	100%	33.3%
Azithromycin (% of patients)	12.5%	0%	0%	0%	20%
Treatment-related results					
Treatment duration (days)	13.9	14.3	22.5	15.2	-
Eradication at 1 mo (% of patients)	37.5%	33.3%	0%	20%	36.4%
Eradication at 12 mo (% of patients)	31.3%	33.3%	50%	60%	18.2%
Patients with outpatient exacerbations at 12 mo (% of patients)	64.3%	33.3%	0%	25%	50%
Patients with hospitalizations at 12 mo (% of patients)	19.5%	66.6%	0%	100%	25%

[11.03] Eosinophilic Bronchiectasis and Microbiological Profiles in a Slovenian Cohort

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Background: Traditionally, bronchiectasis has been seen as a neutrophilic disorder. However, emerging evidence suggests that eosinophils play a significant role. About 20% of patients have high blood eosinophil counts (>300 cells/ μ L), defining eosinophilic bronchiectasis. Some studies associate elevated eosinophil counts with specific microbiome patterns. Our study explores the association between high eosinophils and the risk of *Pseudomonas aeruginosa* (PA) colonization and the prevalence of nontuberculous mycobacteria (NTM) infection.

Methods: We conducted a retrospective study at the University Clinic of Respiratory and Allergic Diseases Golnik, including consecutive adult patients diagnosed with non-cystic fibrosis bronchiectasis (NCFBE) based on ICD coding and treated between June and December 2023. Our cohort comprised 206 patients, with 10 excluded due to incomplete data. Medical records were systematically reviewed to collect demographic, clinical, and microbiological data. Patients were stratified into two groups based on their BEC: < 300 Cells/ μ L and ≥ 300 Cells/ μ L. Multivariate analysis was employed to identify variables potentially associated with the risk of PA and NTM infection.

Results: In the analysis of 196 patients, 40.8% had BEC of ≥ 300 cells/ μ L. Table 1 presents the characteristics of the patients. In both groups, a predominance of females was noted (72.4% vs. 66.3%). No statistically significant differences in comorbidities existed between the groups, except for asthma and ICS treatment. In our multivariate logistic regression model, adjusting for FEV₁ (% predicted), number of lobes affected, ICS use, age, gender, BMI, and eosinophil count as a continuous variable, lower FEV₁ (OR = 0.956, 95% CI: 0.932-0.981, $p = 0.001$) and higher blood eosinophil counts (OR = 1.002, 95% CI: 1.000-1.004, $p = 0.032$) were associated with the risk of PA colonization. In the same model, only higher age (OR = 1.061, 95% CI: 1.003-1.121, $p = 0.037$) was associated with the risk of NTM infection.

Table 1. Characteristics of Patients, Stratified by Blood Eosinophil Count

	Blood Eosinophil Counts		
Characteristics	< 300 Cells/μl	$\geq$ 300 Cells/μl	P value
No. of subjects	116 (59.2%)	80 (40.8%)	
Age, yr	59.4 (11.5)	60.3 (12.4)	0.827
Sex, F, n (%)	84 (72.4%)	53 (66.3%)	0.355
BMI, kg/m ²	24.3 (6.0)	27.4 (6.2)	0.422
Ever smokers, n (%)	46 (39.7%)	41 (51.3%)	0.108
FEV ₁ , mL	2213 (782)	2124 (794)	0.742
FEV ₁ % predicted	80.7 (24.3)	74.9 (25.0)	0.945
Lobes involved, n	2.55 (1.27)	2.38 (1.28)	0.759
ICS therapy, n (%)	41 (36.6%)	40 (52.6%)	0.029
Comorbidities n (%)			
Asthma	31 (26.7%)	35 (43.8%)	0.013
COPD	16 (13.8%)	17 (21.3%)	0.170
GORD	23 (19.8%)	17 (21.3%)	0.808
postTB	7 (6.0%)	8 (10.0%)	0.305
Sputum microbiology			
Pseudomonas aeruginosa, n (%)	12 (13.6%)	13 (18.8%)	0.376
Haemophilus influenzae, n (%)	14 (15.9%)	12 (17.4%)	0.804
Multiple bacteria isolation, n (%)	20 (22.3%)	11 (15.9%)	0.289
NTM infection, n (%)	14 (15.6%)	8 (11.4%)	0.452
T2 markers			
eNO	16.1 (17.2)	32.9 (34.3)	0.029
Elevated total IgE (>100), n (%)	4 (10.0%)	16 (38.1%)	0.003
Eosinophil count, cells/ μ l	142.1 (72.3)	567.6 (306.3)	< 0.001

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; GORD= Gastro-oesophageal reflux disease; NTM = nontuberculous mycobacteria; TB = tuberculosis. All values are mean (SD) unless otherwise stated.

Conclusions: In our cohort, the eosinophilic group was more prominent than previously reported (41%), potentially due to the high prevalence of comorbid asthma among patients. We found no significant differences in the frequencies of PA and NTM between the two BEC groups. Notably, while lower lung function, as measured by FEV₁, was independently associated with an increased risk of PA, the number of involved lung lobes showed no association. Elevated eosinophil levels were associated with an increased risk of PA. The use of ICS use was not associated with either PA or NTM risk in our cohort.

[11.04] Fungal Co-Cultures in a Bronchiectasis/NTM Program Registry in New Orleans, Louisiana, USA

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Background/Aims: Fungal spores are ubiquitous in the environment, and the lungs are exposed to these microbes daily. While fungal spores are quickly cleared by the mucociliary escalator in the normal lung, this function may be impaired in bronchiectatic airways. Fungi are frequently cultured in sputum of patients with non-CF bronchiectasis (NCFBE) and non-tuberculous mycobacterial (NTM) infection. Although previously reported data in the U.S. population correlates fungal culture positivity with decreased lung function, there is a paucity of information surrounding fungal growth in patients with NCFBE and NTM. The clinical significance of fungal co-cultures in this cohort is not clear. Our objective was to determine the co-prevalence and characteristics of bacterial and/or NTM residence in NCFBE patients with and without fungal growth from airway samples.

Methods: Participants enrolled in the Louisiana State University (LSU) Nontuberculous Mycobacterium Clinical Database and Biospecimen Bank who had at least one fungal culture concomitantly ordered with acid-fast bacilli (AFB) and/or bacterial cultures were included. All instances of simultaneous cultures were included in this analysis. We performed chi-square analysis to determine correlation between fungal culture positivity and AFB or bacterial positivity.

Results: 57 of 74 participants in the registry had fungal cultures collected simultaneously with AFB and/or bacterial culture. A total of 119 unique co-collections were identified. The cohort had a mean age of 61.8 years (range 26-83 years) and 75.4% were female. The cohort was 63.2% white, 28.1% Black or African American, 5.3% Asian, and 3.5% other. Table 1 shows fungal culture positivity with mycobacterial and bacterial co-culture results. We found no statistically significant relationship between fungal culture positivity and AFB positivity (p0.84) or between fungal culture positivity and bacterial culture positivity (p0.12). No statistically significant difference was found in bacterial culture positivity with negative fungal cultures compared to cultures that grew candida species (p0.08).

Conclusions: Fungal culture collections were often performed simultaneous with AFB and/or bacterial cultures. While multiple organisms were frequently identified in the same participant, the presence of fungal organisms did not affect the isolation of bacterial or NTM pathogens on culture.

Conflict of interest(s) (if any – not included in the 500 words):

None

Table 1:

n = 119

Fungal Culture Growth
Positive Culture 73 (61%)

	Negative Culture 46 (39%)	Any Fungi 73 (61%)	Candida spp 52 (71%)	Aspergillus spp 7 (10%)
Bacterial Cx +	8 (17%)	22 (30%)	17 (33%)	1 (14%)
P. aeruginosa	4 (9%)	5 (7%)	5 (10%)	-
S. aureus	-	9 (12%)	7 (14%)	1 (14%)
Other Bacteria**	4 (9%)	8 (11%)	5 (10%)	-
AFB Cx +	21 (46%)	32 (44%)	24 (46%)	2 (29%)
MAC	15 (33%)	22 (30%)	16 (31%)	2 (29%)
MAbC	6 (13%)	7 (10%)	6 (12%)	-
Other NTM***	2 (4%)	3 (4%)	2 (4%)	-

MAC = *Mycobacterium avium complex*

MAbC = *Mycobacterium abscessus complex*

NTM = Nontuberculous mycobacterium

AFB = Acid Fast Bacilli

Cx = Culture

**C. albicans, C. tropicalis, C. dubliniensis, C. candida, C. sake, C. parapsilosis, C. glabrata*

***A. fumigatus, A. niger, Aspergillus spp non-fumigatus*

****Cladosporium spp, Alternaria spp, S. prolificans, Penicillium spp, Trichosporon spp, Pseudallescheria, Saccharomyces spp, Rhizopus*

*****M. catarrhalis, A. odontolyticus, S. Marcescens, Streptococcus spp, Staphylococcus spp, B. bronchiseptica, S. maltophilia*

******M. gordonae; M. terrae; M. porcinum; Gr III nonphotochromogen*

[11.05] Allergic bronchopulmonary aspergillosis in patients with bronchiectasis: a single centre experience

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Background/Aims:

Allergic bronchopulmonary aspergillosis (ABPA) is a common aetiology and complicating factor of bronchiectasis. Although current guidance applies to patients with asthma and cystic fibrosis (CF), data are lacking for the optimal diagnostic and management strategies in bronchiectasis patients.

In this study we describe the characteristics of ABPA among bronchiectasis patients in our cohort, including baseline serology, treatment, relapse rate, radiological findings, and other comorbid respiratory conditions.

Methods:

Utilising data from 466 patients enrolled in the European Bronchiectasis Registry (EMBARC) at a single centre (Ninewells Hospital, Dundee, UK), we identified those with ABPA based on previous clinical diagnosis and/or diagnostic criteria as described by the revised International Society for Human and Animal Mycology (ISHAM)-ABPA Working Group (AWG).

Serum *Aspergillus* IgE, *Aspergillus* IgG and total IgE at diagnosis were analysed, in addition to blood eosinophil count most recent to date of diagnosis. Chest computed tomography most recent to date of diagnosis was assessed for radiological features suggestive of ABPA, specifically mucus plugging, high attenuation mucus (HAM) and central bronchiectasis. Clinical records were reviewed to determine treatments used, including corticosteroids, itraconazole and biologic therapies, as well as for evidence of relapse or refractory ABPA. Records were also checked for previous diagnoses of asthma and/or chronic obstructive pulmonary disease (COPD).

Results:

Of 466 bronchiectasis patients, 443 had aspergillus serology available and 33 (7.08%) were identified as having ABPA.

17 (51.52%) patients had a previous diagnosis of asthma, 6 (18.18%) had COPD and 6 (18.18%) had asthma/COPD overlap. 1 patient initially diagnosed with non-CF bronchiectasis was subsequently diagnosed with CF.

Aspergillus IgE was 0.35-0.69kUA/L in 2 (6.06%), 0.70-3.49kUA/L in 4 (12.12%), 3.5-17.4kUA/L in 14 (42.42%), 17.5-49.9kUA/L in 11 (33.33%), and >50kUA/L in 2 (6.06%). Total IgE was ≥500kUA/L in 29 (87.88%) and *Aspergillus* IgG was >40mgA/L in 20 (60.61%). Mean eosinophil count at diagnosis was 0.49 x10⁹/L (SD 0.31).

In terms of radiological features, central bronchiectasis was present in 11 (33.33%), mucus plugging in 26 (78.79%) and HAM in 7 (21.21%).

Initial treatment consisted of oral corticosteroids (OCS) alone in 12 (36.36%), OCS plus itraconazole in 13 (39.39%) and itraconazole monotherapy in 1. 7 (21.21%) patients were managed only with inhaled corticosteroids or received no specific treatment for ABPA. 6 (18.18%) patients were treated with biologics due to refractory disease, with Omalizumab the most frequently prescribed. One patient initially treated with Omalizumab required switch to an alternative biologic.

3 (9.09%) patients suffered a relapse following treatment cessation and 6 (18.18%) had refractory disease on initial treatment. 6 (18.18%) relapsed then developed treatment refractory ABPA.

Conclusions:

ABPA was not uncommon among our cohort and many patients had other co-existing respiratory pathologies in addition to bronchiectasis. Most patients met serological criteria, however, although mucus plugging was commonly seen, the hallmark signs of HAM and central bronchiectasis were less prevalent.

Treatment approaches showed great variability, although nearly all patients received corticosteroids. Biologic therapies were prescribed in a minority of patients. Rates of relapse and treatment refractory disease were high among this cohort.

Conflict of interest(s) (if any – not included in the 500 words):

No conflicts of interest to declare

[11.06] Prevalence and outcomes of patients with allergic bronchopulmonary aspergillosis and extensive bronchiectasis

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Background/Aims: Whether extensive bronchiectasis influences outcomes of allergic bronchopulmonary aspergillosis (ABPA) remains unknown.

Methods: We retrospectively included subjects with ABPA-complicating asthma (2007-2019) and compared lung function and immunological parameter in those with and without extensive (≥ 9 segments) bronchiectasis. The differences between continuous and categorical variables were analyzed using the Mann-Whitney U or chi-square tests. We also performed a multivariable logistic regression analysis to determine whether patients with extensive bronchiectasis experience more ABPA exacerbations.

Results: We included 705 ABPA patients with a mean age of 35 years (49.1% women). The mean FEV1 (1.64 vs. 2.11 liters; $p < 0.001$) and FVC (2.49 vs. 2.90; $p < 0.001$) were significantly lower in those with extensive bronchiectasis. There was a significant difference in the mean serum total IgE (11025 vs. 6994 IU/mL; $p < 0.001$), *Aspergillus fumigatus* - specific IgE (31.8 vs. 27.6 kUA/L; $p = 0.03$), and *A. fumigatus* -specific IgG (117 vs. 92 mgA/L; $p = 0.002$) in those with and without extensive bronchiectasis. Eosinophil counts were similar in the two groups. On multivariable analysis, extensive bronchiectasis (adjusted odds ratio [aOR] 1.60; 95% CI [1.1-2.4], $p = 0.02$) and age (aOR, 0.98; 95% CI [0.97-0.99], $p = 0.04$) influenced ABPA exacerbations after adjusting for sex, FEV1, serum total IgE, high-attenuation mucus, and peripheral blood eosinophil count ≥ 1000 cells/ μ L.

Conclusions: We found that extensive bronchiectasis was associated with poor lung function and immunological severity in ABPA patients and significantly increased the occurrence of ABPA exacerbation.

Conflict of interest(s) (if any – not included in the 500 words): None

[11.07] Changes in microbiology in bronchiectasis (BE) patients from adolescence to young adulthood.

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Background/Aims:

BE is a chronic disease that can be progressive. The clinical history of the disease is not fully known since a considerable gap exists regarding progression of paediatric BE through adolescence to adulthood

The aim of our study is to describe sputum microbiology in a cohort of patients with paediatric onset BE followed up in an adult BE outpatients clinic.

Methods:

We retrospectively analysed demographic and microbiological data from Vall d'Hebron University Hospital. We retrospectively reviewed data of adult BE patients (max 26 years old) whose follow up had started during childhood (< 18 years of age) in Paediatric Pneumology outpatient clinic. We recorded and analysed results of bacterial and fungal cultures from airways samples (spontaneous sputum and pharyngeal exudate).

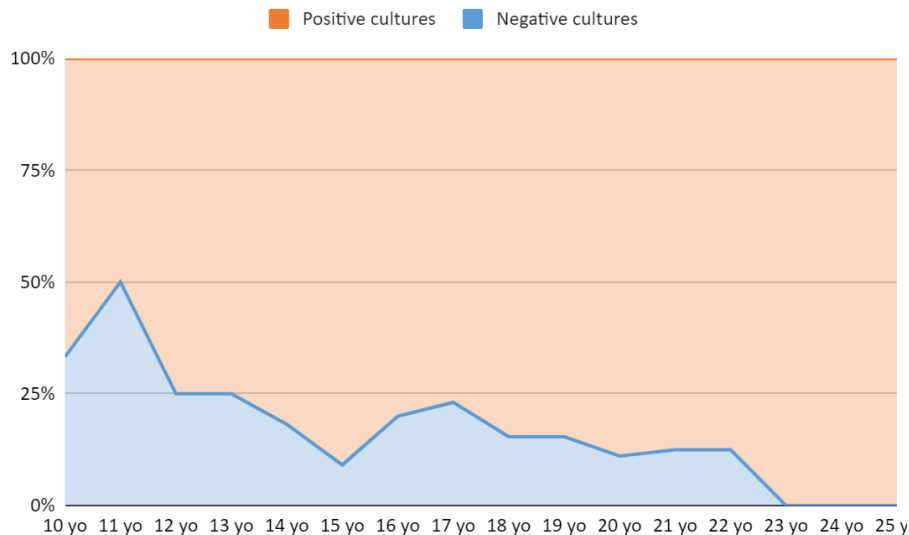
Data were categorised according to patients' age at the time of testing, from the age of 10 to 25 yrs old. We included one entry per patient per year of age, combining all positive results. Patients were considered negative only when no pathogenic microorganism was isolated in all the samples available within the same year.

Results:

We included 36 patients in our study, mean age 23 years old, mean follow-up 12 years.

For each group of age, on average the 34% of patients had at least one cultured sample (min 24%, max 50%, median 32%) per year of age.

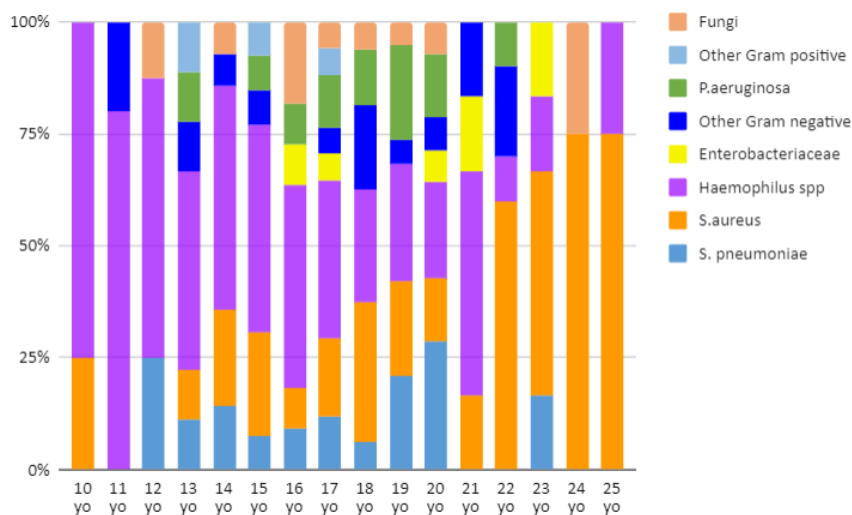
Positive culture rate increased with age, rising from less than 75% before the age of 14 to 100% by age 23 ($p < 0.001$) (Fig 1).



The distribution of isolated pathogens changed with age: *H. influenzae* is the most prevalent pathogen in prepubertal age (75-83% before age 12), but tended to decrease from age 15 (0- 62% from age 16, average 35%) ($p<0.001$).

On the other hand, *S. aureus* prevalence was relatively infrequent at younger ages (0-41% before age 21, average 21%), but it raised until an average of 80% from age 22, with a concomitant trend to develop resistant strains (19% on average before age 21 vs 60% after) ($p<0.001$).

Also, the diversity of isolated microorganisms seemed to be higher during adolescence and young adulthood: from age 13 to 20, on average 6 different pathogens were isolated per year of age (5-8), while in younger and older patients only 2-3 different species were identified (Fig.2).



Conclusions:

Our results suggest a change in microbiological history of patients with paediatric onset BE across puberty and young adulthood, in terms of risk of infection and isolated microbes. The triggers of this change are unknown, and could be related to physiopathological age-related

factors, differences in clinical management and adherence to treatment or the socio-economic environment.

Unfortunately, the small size of our sample is a considerable limitation to draw firm conclusions. However, to our knowledge this is the first series describing the microbiology of a cohort of BE patients from childhood to adulthood, and these initial results suggest the need for further studies.

Conflict of interest(s) (if any – not included in the 500 words):

None of the authors has conflicts of interest to declare related with this original work.

[11.08] Deciphering the Lung Microbiome during Pulmonary Exacerbations and Clinical Stability in Non-Cystic Fibrosis Bronchiectasis (NCFB)

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Background/Aims: Bronchiectasis is characterized by cycles of inflammation and chronic infection. Pulmonary exacerbations are defined by periods of worsening symptoms and dropping lung function. Traditional dogma suggests these adverse events are due to overgrowth of canonical bacterial pathogens; however recent studies have shown this to not fully represent all events. The cause(s) of exacerbations are currently unknown, representing a knowledge gap. Rapid and accurate microbiological diagnostics have the ability to enable tailored treatments and reduce overuse of broad-spectrum antibiotics. The 'gold standard' of culture and susceptibility testing is often too slow, with typical turnaround times of 48 to 72 hours and with low clinical sensitivity, thus limiting applicability in research. Metagenomic sequencing-based approaches have the potential to overcome the shortcomings of both culture and PCR, by combining speed with comprehensive coverage of all microorganisms present. Next-generation sequencing platforms, such as Illumina, are widely used for metagenomics sequencing, but requires completion of the sequencing run prior to analysis. In contrast, long-read DNA technologies, such as Oxford Nanopore Technology, is advantageous in translational clinical studies as it allows for rapid preparation and real-time data acquisition. The central hypothesis of this research project is different pulmotypes in bronchiectasis, unique to the individual, can be used for future applications to delineate appropriate clinical therapy.

Methods: A retrospective cohort of sputum samples and metadata (from 1980), including those with bronchiectasis (>20,000 samples) were analysed for different periods of clinical stability and acute exacerbation. Long-read DNA sequencing (MinION) was performed, Relative abundance, alpha and beta-diversity using an in-house developed R pipeline was done. Simultaneously, Fastq WIMP (What's In My Pot) and Fastq Antimicrobial Resistance analysis was done using EPI2ME Desktop Agent.

Results: We evaluated 48 samples from 16 patients during periods of stability, acute exacerbation and recovery. Sequencing data demonstrated the majority of microbes were *Pseudomonas*, *Staphylococcus* and *Escherichia*. Anaerobic genera present included *Prevotella*, *Gemella* and *Veillonella*. We observed varying degree of inter and intra patient variability and heterogeneity with some patients that demonstrate relative stability and others showing considerable temporal variation. Our preliminary data using Nanopore sequencing technology demonstrates our ability to sequence the microbiome of patient samples within ~6h of sample collection for measures of community composition and dominance, such as Shannon Diversity. We have further validated our sequencing strategy with Nanopore whereby we have sequenced the same samples on traditional Illumina MiSeq with similar results

Conclusions: Our preliminary data suggests that certain cohorts of patients with NCFB experience temporal change during periods of exacerbation, whereas others do not. This suggests pulmotypes exist and may be used to personalize therapeutic approaches.

Expansion of our cohort across more subjects will be required to validate our initial findings and delineate clinical associations. Conventional shotgun metagenomic data analysis requires a seasoned bioinformatician to generate usable data (which often takes days to weeks). We seek to revolutionize the back-end analysis by combining proprietary software from Oxford Nanopore (Epi2Me) with custom sequencing reference databases optimized for human microbiome metagenomics, to deliver a “point-and-click” analysis pipeline used without any programming/bioinformatics experience.

Conflict of interest(s) (if any – not included in the 500 words): CST declares funding from Canadian Institutes for Health Research, CHEST Foundation, Insmmed Medical and Trudell Healthcare Solutions.

[12.01] Evaluation of treatment response with serial CT in patients with non-tuberculous mycobacterial pulmonary disease

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Background/Aims:

In patients with nontuberculous mycobacterial pulmonary disease (NTM-PD) the response to treatment is evaluated based on microbiological, clinical and radiological data. However, little is known about the dynamics of CT findings. The aim of this study was to evaluate CT changes in NTM-PD in order to define radiological criteria for treatment success.

Methods:

Retrospective single centre study. 30 patients with NTM-PD and at least two consecutive CT were included. Scoring for NTM-PD was performed evaluating bronchiectasis, mucus plugging, bronchiolitis, cavities, nodules, and consolidations on an ordinal scale from 0-3. Differences between baseline and follow-up were calculated and patients with/without cultural conversion were compared using the Mann-Whitney U test. For paired comparison of the two consecutive CT scans the Wilcoxon test was used.

Results:

Comparing patients with and without culture conversion there were significant differences for bronchiectasis, cavities and the total score. In case of culture conversion, there was a decrease of the total score (0.50 in persistent cultures versus -1.93 with conversion; $p=0.011$) and cavities (0.00 in persistent cultures versus -0.86 with conversion; $p=0.024$), whereas bronchiectasis were increasing (0.69 in persistent cultures versus 0.00 with conversion; $p=0.016$). The Wilcoxon test showed significant differences for bronchiectasis between baseline and follow-up with an increase from 4.25 to 4.94 ($p=0.014$).

Conclusions:

In case of culture conversion, cavities and bronchiolitis decreased in patients with NTM-PD whereas chronic lung changes such as bronchiectasis and nodules remained constant and even increased with persistence of positive cultures.

Conflict of interest(s) (if any – not included in the 500 words):

none

[12.02] Novel application of phase-resolved functional lung (PREFUL) MRI to assess outcomes in a child with Primary Ciliary Dyskinesia

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Background/Aims: Primary Ciliary Dyskinesia (PCD) is a rare lung disease characterised by defects in ciliary function leading to peripheral airway dysfunction. Spirometry and lung clearance index (LCI) are available techniques to measure lung ventilation but these techniques estimate whole lung ventilation and do not provide regional information. CT chest is used to monitor the progress of regional structural disease however does not provide ventilation information and involves radiation exposure. Phase-resolved functional lung (PREFUL) MRI is a radiation free imaging technique that offers assessment of both lung morphology and regional lung ventilation during free breathing. In this case report we describe the novel application of PREFUL MRI in assessment of treatment outcomes pre and post lung bilobectomy in a person with PCD.

Methods: A 13 year old boy with PCD (homozygous DNAAF11 mutation, outer and inner dynein arm defects on transmission electron microscopy) had progressive severe cystic bronchiectasis of the left middle and lower lobes (in the context of situs inversus totalis and a trilobed left lung) on CT scans and was infected with *Pseudomonas aeruginosa* and *Mycobacterium avium complex*. The decision was made to proceed to left middle and lower bilobectomy to prevent further destruction of less diseased lung. Spirometry, LCI and PREFUL MRI were performed 1 week prior and 16 weeks after bilobectomy.

MRI examinations were performed on a 3T Siemens scanner during free breathing with no contrast agent administered. PREFUL processing¹ was used to derive regional pulmonary ventilation and perfusion distribution from proton MRI data.

Results: Following surgery, LCI improved from 10.09 to 9.32. There was no change in spirometry parameters (FEV1 z-score -2.65 vs -2.34, FVC z-score -2.24 vs -2.36, FEV1/FVC z-score -1.18 vs -0.25) (Table 1a). Pre-operative morphology MRI confirmed bronchiectasis of the left middle and lower lobes, correlating with findings seen on pre-operative CT chest (Figure 1a and b). PREFUL MRI demonstrated an improvement in mean ventilation from

3.5% pre-op to 22.7% and a reduction in ventilation/perfusion (V/Q) defect from 38.7% to 23.9% (Table 1b and Figure 1c).

	<i>Pre-op</i>	<i>Post-op</i>
a. Lung function		
FEV1 (% predicted)	68	72
FEV1 (z-score)	-2.65	-2.34
FVC (% predicted)	75	73
FVC (z-score)	-2.24	-2.37
FEV1/FVC (%)	80	86
FEV1/FVC (z-score)	-1.18	-0.25
LCI	10.09	9.32
b. PREFUL MRI		
Mean ventilation	3.5%	22.7%
V/Q mismatch defect	38.7%	23.9%

Table 1. Lung function and PREFUL MRI parameters pre and post op.

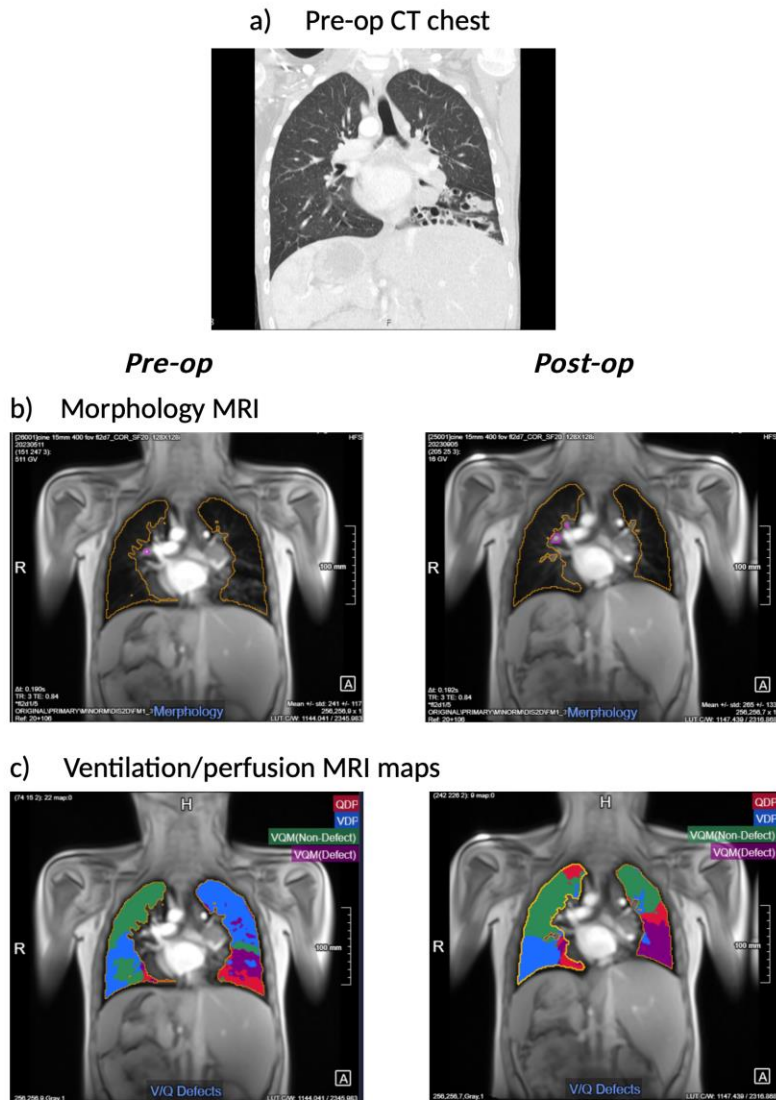


Figure 1. a) Pre-op CT chest showing cystic bronchiectasis of the left lower lobe. b) Morphology MRI pre-op confirming bronchiectasis of the left lower lobe. On post-op morphology MRI, the bronchiectatic area is no longer seen. c) Ventilation/perfusion (V/Q) maps showing improvement in V/Q defect post-op. QDP = exclusive perfusion defect (red); VDP = exclusive ventilation defect (blue); VQM/Non-Defect = ventilation and perfusion match (green); VQM/Defect = ventilation/perfusion defect (purple).

Conclusions: PREFUL MRI is a novel radiation free imaging technique which allows lung morphology and regional ventilation assessment, with utility in monitoring treatment outcomes.

Grant Support: This pilot project was supported by Research Imaging NSW

References:

1. Voskresbenzev A, Gutberlet M, Klimes F, et al. Feasibility of quantitative regional ventilation and perfusion mapping with phase-resolved functional lung (PREFUL) MRI in healthy volunteers and COPD, CTEPH, and CF patients. *Magn Reson Med*. 2018;79(4):2306-2314.

Conflict of interest(s) (if any – not included in the 500 words): Nil

[12.03] Assessment of Coronary Artery Calcification in Patients with Bronchiectasis

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Background: Cardiovascular disease (CVD) is an important co-existing condition with bronchiectasis. Coronary artery calcification (CAC) can be identified on routine chest computed tomography (CT) performed without ECG gating. The presence of CAC can serve as a predictor of prospective coronary events.

Aims: To investigate whether the assessment of CAC is related to bronchiectasis disease severity.

Methods: A retrospective evaluation of 165 (82 male 83 female) CT scans for patients with bronchiectasis from the BRIDGE study. The analysis was conducted to determine the presence of CAC using a semi-quantitative Weston method. Consequently, the correlation between bronchiectasis severity index and CAC was assessed.

Results: The analysis revealed a strong linear relationship between CAC and Bronchiectasis Severity Index (BSI) scores, with the latter being a significant predictor of CAC scores. Multiple linear regression indicated that BSI predicts CAC and that BSI can explain 69.4% of the variance in CAC, while one-way ANOVA confirmed significant differences in BSI scores across CAC categories.

Conclusions: These results highlight the importance of the CAC score in clinical assessment and decision-making, suggesting the need for further research to explore the complexities and potential non-linear interactions affecting BSI scoring and CV outcomes in patients with bronchiectasis.

[12.04] Identifying molecular determinants of bronchiectasis associated with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) dysfunctions

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Background/Aims: Bronchiectasis, is characterized by cycles of inflammation associated with infection or an insult to the airways. Acute deteriorations, known as pulmonary exacerbations, are major adverse events in the natural history of bronchiectasis defined by periods of worsening symptoms and dropping lung function. Emerging evidence suggests they are complex and multifactorial. A history of exacerbations is the best predictor of future exacerbations and frequent exacerbations are associated with worse prognosis. In previous work performed on CF bronchiectasis, we have shown that Cystic Fibrosis Transmembrane conductance Regulator (CFTR) dysregulation leads to MAPK hyper-activation and increased secretion of cytokines associated with neutrophilic inflammation, contributing to the vicious vortex; clinical *P. aeruginosa* strains deficient for bacterial proteases can lead to neutrophilic inflammation via increased levels of IL-6, IL-8 and ICAM-1, and C-reactive protein, an acute phase reactant is associated with the risk of future exacerbations in CF adults. Since it is well established that there is an association between CFTR gene dosage and its function, at least as exemplified in sweat chloride measurements, we explored the relationship between single nucleotide variants (SNVs) in CFTR and the circulating proteome using data from the Biobanque québécoise de la COVID-19 (BQC19).

Methods: BQC19 is a biobank that provides global access to molecular and clinical data from patients with COVID-19 and control subjects in Quebec, Canada (<https://www.bqc19.ca/>). Blood samples collected from 1254 participants underwent proteomic profiling on the SomaScan 5K array (4,907 aptamers). To identify SNV in CFTR we used a GWAS meta-analysis from the COVID-19 Host Genetics Initiatives data release 7 (<https://www.covid19hg.org/>).

Results: Here we report that while no genetic determinants in the CFTR gene are associated with COVID-19 outcomes, we identified five protein Quantitative Trait Locus (pQTL) between CFTR variants and circulating proteins, including REG3γ, an antimicrobial C-type lectin associated with IL-6-signaling and pulmonary Th17 antifungal immunity that could be involved in bronchiectasis.

Conclusions: This approach illustrates the power of combining genomic and proteomic information to identify potential molecular regulators of pathogenesis. The contribution of heterozygous CFTR single nucleotide variants to non-CF bronchiectasis remains an active area of investigation, with conflicting data. This suggest that other factors in addition to certain CFTR SNVs may be required for pathogenesis. In the last 15 years, evidence has emerged showing that cigarette smoke impairs CFTR activity, leading to “acquired” CFTR dysfunction in a subset of COPD patients. Overall, this highlights a complex relationship between smoking, CFTR and lung inflammation that can create conditions favourable to infection in the bronchi of some COPD smokers, thus providing clues to some molecular determinants of bronchiectasis and their potential interactions.

Conflict of interest(s) (if any – not included in the 500 words): The authors have no conflict of interests to declare regarding the content of this abstract.

[12.05] The association of bronchiectasis and rhinosinusitis is associated with increased symptom burden and biomarkers of type 2 inflammation: analysis of the EMBARC registry

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Background/Aims: Chronic rhinosinusitis (CRS) with or without nasal polyps (NP) is common in bronchiectasis. Previous analysis of idiopathic bronchiectasis identified increased airway eosinophilia in people with bronchiectasis and CRS, compared to bronchiectasis without CRS, with similar microbiota. It is unknown whether type 2 inflammation is common in bronchiectasis of other aetiologies when associated with CRS.

Methods:

We analyzed EMBARC- the European bronchiectasis registry- for people with and without investigator- reported CRS and NP and compared clinical, radiologic, and laboratory features. Multivariable models were formed for various outcomes including exacerbations, hospitalizations, and mortality with CRS included in the variables, with adjustment to various confounders.

Results:

Among 16640 people with bronchiectasis, 3477 (20.9%) had CRS and 1223 (7.4%) had nasal polyps. Aetiologies with an elevated prevalence of CRS were Primary Ciliary Dyskinesia (PCD, 59% CRS and 30.9% NP), immunodeficiency (28.2% CRS and 5.3% NP), allergic bronchopulmonary aspergillosis (ABPA, 24.4% CRS, 12.9% NP) and asthma (27.9% CRS, 15.9% NP). Compared to bronchiectasis without CRS, people with bronchiectasis and CRS were younger (mean (SD) 60.4 (15.5) vs. 65.1 (14.0)). Females were overrepresented in CRS (63.8%) but not in NP (54.4%) compared to no CRS (60.1). Compared to no CRS, people with CRS reported increased sputum volume (mean(SD) 10 (3-25) vs. 5 (0-20) ml/day) and more exacerbations (median (IQR) 2 (1-4) vs. 2 (0-4)). Asthma prevalence was increased in people with bronchiectasis and CRS (41.2% vs. 28.5% in bronchiectasis without CRS), but COPD was decreased- 17.2% vs. 27.8% in bronchiectasis without CRS. CRS was associated with eosinophilia and elevated IgE levels in people with bronchiectasis of idiopathic/post infectious aetiology, PCD, and immune deficiency, and this was even more common in people with NP. Chronic airway infection was more common in people with CRS than without CRS (53.4% CRS vs. 43.7% no CRS). In multivariable analyses adjusted for BSI and sex, as well as for various confounders, the presence of CRS was associated with worse symptom score as measured by the QOL-B questionnaire (-2.16 points, 95%CI, -1.64 to -3.58), increased exacerbations at baseline and during follow up (HR 1.14, 95% CI 1.09-1.20 at baseline), but decreased hospitalizations and mortality: HR (95% CI): hospitalizations 0.75 (0.67-0.83), mortality 0.84 (0.70-1.01)

Conclusions:

CRS involvement is common in bronchiectasis, and associated with increased symptoms, exacerbations, and airway infection compared to no CRS. CRS and especially NP is associated with markers of type 2 inflammation

Conflict of interest(s) (if any – not included in the 500 words):

[12.06] A ciliopathies approach to understanding the genetic basis of bronchiectasis

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Background/Aims:

Bronchiectasis is a complex and heterogenous chronic respiratory condition, with disease drivers including immunological, inflammatory based mechanisms and also some rare genetic disorders, such as primary ciliary dyskinesia (PCD). Currently, 40% of bronchiectasis cases do not have a known cause. With recent studies suggesting PCD may be underdiagnosed, there could be a large group of idiopathic bronchiectasis patients with novel PCD associated genetic variants. Discovery of novel genes/variants associated with PCD will improve diagnostic rates and advance clinical care for patients with bronchiectasis. We have sequenced the protein-coding genome of a large cohort of bronchiectasis patients, to identify disease-causing mutations in a motile cilia structure and function gene panel.

Methods:

1,536 patients were recruited from 6 European centres (Dundee, London, Newcastle), Belgium (Leuven) and Germany (Hanover) as part of EMBARC “Genes encoding complex ciliopathies of bronchiectasis” GECCO study. Exome sequencing (Agilent SSXT HS2) on a NovaSeq S4 yielded an average mean 75x read depth. An inhouse custom bioinformatics pipeline provided an initial assessment of variants, focused on 770 genes upregulated during motile ciliogenesis (includes PanelApp PCD gene panel) with 5 previously linked to bronchiectasis (PanelApp Non-CF bronchiectasis gene panel, including *CFTR*). Cilia functional studies were conducted on cultured ciliated epithelial samples (nasal brushings) from individuals with variants of interest. An Exomiser-based gene burden analytical framework which was previously developed and successfully applied to the 100,000 Genomes Project (100KGP) data will be used to identify genes with an excess of rare, protein coding, pathogenic variants in cases versus non-ciliopathy individuals from the 100KGP. Exomiser is a Java-based variant prioritisation tool that can annotate, filter and score variants by allele frequency and predicted pathogenicity as well as score genes based on their phenotypic relevance using Human Phenotype Ontology (HPO) features. We will use bronchiectasis (HP:0002110), chronic cough (HP:0034315), recurrent lower respiratory tract infections (HP:0002783), productive cough (HP:0031245) and dyspnoea (HP:0002094) to describe our case cohort.

Results:

A preliminary screen of 768 individuals identified putative causal biallelic gene variants in 11 known PCD genes: *DNAAF1*, *DNAH11*, *DNAH5*, *DNAH9*, *DNAI2*, *DRC1*, *GAS2L2*, *GAS8*, *HYDIN*, *OFD1* and *RPGR*. Four individuals had biallelic mutations in *CFTR*. Predicted causal variants were also identified in potential candidate genes, including two dynein heavy chains (*DNAH2*, *DNAH7*) and two intraflagellar transport proteins (*IFT122*, *IFT172*) not linked before to motile ciliopathies. We will extend exome sequencing analysis to the full 1,536 cohort, including the Exomiser-based gene burden analysis using non-ciliopathy individuals from the 100KGP.

Conclusions:

Our preliminary work suggests that exome sequencing will offer a valuable tool for novel disease gene association discovery in a bronchiectasis cohort. PCD is confirmed as underdiagnosed as a cause of bronchiectasis, and we also find that previously unrecognised ciliary genes may play a significant role in bronchiectasis aetiology. Further investigation in this large bronchiectasis cohort will allow us to understand the wider genic landscape of bronchiectasis, and whether the nature of the causal gene variants differs from those found in classic PCD.

Conflict of interest(s) (if any – not included in the 500 words):

[13.01] Study Design of a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of Itepekimab in Patients with Non-Cystic Fibrosis Bronchiectasis

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Background/Aims:

Bronchiectasis is a long-term inflammatory lung disease. Patients with bronchiectasis frequently experience exacerbations that lead to worsened quality of life, decline in lung function, hospitalizations, and increased mortality. Despite available standard of care therapies such as bronchodilators, mucolytics, and antibiotics there is still significant unmet need.

Interleukin 33 (IL-33) is a pro-inflammatory cytokine that initiates and amplifies inflammatory responses in both innate and adaptive immune systems when epithelial cells are stressed or damaged. Itepekimab is a monoclonal antibody that binds to IL-33 inhibiting IL-33 signaling, thus potentially reducing inflammation. Itepekimab has demonstrated clinical efficacy in patients with asthma and former smokers with chronic obstructive pulmonary disease, with both conditions having overlap with bronchiectasis pathophysiology.

In experimental murine models including type-2 and non-type 2 inflammation, blocking IL-33 with itepekimab reduced the established inflammation and improved remodeling of both the lung epithelium and lung parenchyma. Specifically, IL-33 blockade normalized persisting and exacerbating inflammatory end points, including eosinophilic, neutrophilic, and ST2+CD4+ T-cell infiltration in addition to a restoration of ciliated cells and reduction in airways mucus producing goblet cells.

Here we propose to investigate whether inhibition of IL-33 signaling may reduce the vicious cycle of lung inflammation in non-cystic fibrosis bronchiectasis (NCFB) promoting return of normal epithelial function and simultaneously reducing inflammation.

Methods:

This phase 2 (international) multi-center study is a randomized, double-blind, placebo-controlled trial with 3 arms evaluating the efficacy, safety, and tolerability of two different dosing regimens of itepekimab in patients with NCFB. The study treatments consist of subcutaneous administration of itepekimab every 2 weeks (Q2W), itepekimab every 4 weeks (Q4W), or a matching placebo.

Eligible participants include those with confirmed NCFB who are receiving standard of care therapy and who have had two moderate or one severe exacerbation in the last 12 months. A total of 300 participants will be randomized with treatment duration consisting of a minimum of 24 weeks and a maximum of 52 weeks. Following the treatment period, there will be a 20-week safety follow-up period. The primary endpoint is the annualized rate of moderate or severe Pulmonary Exacerbations (PE) which optimizes understanding of

efficacy over the treatment period. The definition of PE is closely aligned with the European Bronchiectasis Registry (EMBARC) recommended definition of a PE. Additionally, time to first exacerbation and percent of patients who are PE free over the treatment period will be analyzed.

Results:

This Phase 2 trial began in February of 2024 and plans to enroll 300 participants.

Conclusions:

Results from this Phase 2 trial will provide information about efficacy, safety, and dosing for itepekimab in the treatment of NCFB.

Acknowledgements: Research sponsored by Sanofi and Regeneron Pharmaceuticals Inc. ClinicalTrials.gov Identifiers: NCT06280391.

Conflict of interest(s) (if any – not included in the 500 words):

ADS has received grants/ fees from AZ, GSK, Bayer, Chiesi, Insmed, Forest, Gilead and Zambon unrelated to this work.

MB, PAK, YL, MM are employees of Sanofi.

AB is an employee of Regeneron.

[13.02] Profiling peripheral blood neutrophils in patients with bronchiectasis

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Background/Aims:

Bronchiectasis is commonly associated with neutrophilic airway inflammation, however bronchiectasis patients have increased incidence of extrapulmonary conditions, suggesting a systemic inflammatory component.

Aim: Investigate the peripheral blood neutrophil profile in bronchiectasis patients.

Methods:

Single-centre observational study of patients with stable bronchiectasis enrolled in Dundee, UK. Peripheral blood was collected from bronchiectasis patients and a control group. Following neutrophil isolation, activation and functional surface markers were measured by flow cytometry. The neutrophil extracellular trap marker, citrullinated histone 3 (CitH3) was measured in serum by ELISA.

Results:

22 patients with bronchiectasis were included (age 68.05±12.13(mean±SD); 59.09% female) and 15 controls with no known respiratory disease. The neutrophil activation marker CD11b was higher in patients with higher lung function. CD11b positively correlated with FEV1 % predicted ($r=0.53$; $p=0.04$) and FVC % predicted ($r=0.57$; $p=0.007$) scores. Consistent with neutrophil activation being greater in milder disease, CD11b was significantly increased in bronchiectasis patients with an MRC dyspnoea score 0-1 ($n=14$; mild-to-no breathlessness) compared to those with higher scores of 2-4 ($n=8$) ($p=0.024$). However, no significant difference was observed in neutrophil surface markers between bronchiectasis patients and controls. Serum CitH3 levels were significantly elevated in bronchiectasis patients in the lower quartile for FEV1 % predicted compared to those in quartiles 2-4 ($p=0.009$). A non-significant trend towards increased CitH3 in those with more severe disease was observed.

Conclusions:

Changes in systemic neutrophil markers associated with clinical characteristics in people with bronchiectasis. Surprisingly, patients with less severe lung disease had more neutrophil activation.

Conflict of interest(s) (if any – not included in the 500 words):

[13.03] Lung clearance index in children with bronchiectasis

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Background/Aims:

Bronchiectasis not due to cystic fibrosis (CF) or primary ciliary dyskinesia (PCD) is rare in children and results from multiple aetiologies (Lancet 2018,392(10150), 866-879. There is a lack of evidence for physiological clinical monitoring of these children after diagnosis, and a recent scoping document identified the utility of novel lung function tests rather than spirometry to be a priority (ERJ Open 2021,7, (3)). We hypothesised lung clearance index (LCI) calculated from the multiple breath washout (MBW) would be more abnormal in children with bronchiectasis than spirometry, even during periods of stability, and so would have potentially as a monitoring tool and treatment endpoint in these children.

Methods:

18 children with bronchiectasis not due to CF or PCD were seen at a routine follow up outpatient appointment when well. MBW was conducted on the Exhalyzer D (Spiroware v. 3.3). Spirometry was conducted according to ATS/ERS guidelines.

Results:

Results are shown in Table and Figure, below.

n	18
Gender (M:F)	4:14
Age (years) (median, range)	12 (4-18)
Aetiology	
Post infection	6
Immunological condition	3
Unsafe swallow	2
Other/Idiopathic	7
FEV1 % predicted (median, range) (n=17)	68% (53%-101%) abnormal value n=12
LCI (median, range)	8.0 (5.7-12.9) abnormal value n=13

Table – demographic data and lung function testing results. One child (aged 4) was unable to perform spirometry, all children completed MBW.

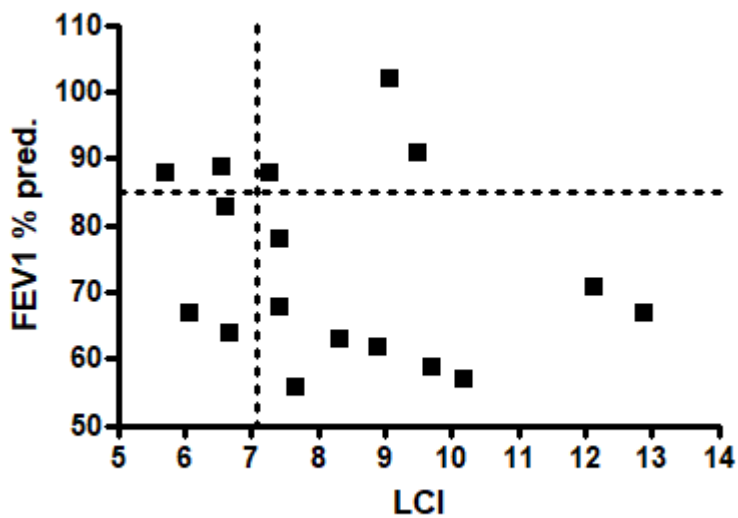


Figure – FEV1% predicted vs. LCI. Most children had abnormal measures for both tests, but 6/18 children had either abnormal LCI or spirometry but a normal result for the other test.

Conclusions:

LCI is abnormal in the majority of children with bronchiectasis, when measured during a period of clinical stability. 3 children were found to have abnormal LCI in the presence of normal spirometry, and one additional child who was not yet able to perform spirometry was able to perform MBW, and had an abnormal LCI. There was no direct linear correlation between LCI and FEV1, suggesting the two provide different information, potentially due to LCIs sensitivity to small airway pathology but insensitivity to collapsed or consolidated regions, a known disadvantage with this methodology. Our results suggest that MBW provides additional information to spirometry, and should be considered as an additional test when monitoring these children.

Conflict of interest(s) (if any – not included in the 500 words):

(none)

[13.04] MULTIFOCALITY IN BRONCHIECTASIS – PHENOTYPE AND CLINICORADIOLOGICAL DIFFERENCES AND PROGNOSTIC IMPLICATIONS

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Background/Aims: Bronchiectasis is a chronic progressive respiratory disease characterized by permanent irreversibly dilatation of the bronchi. It is a complex condition with numerous different etiologies, co-morbidities and a heterogeneous presentation. As we know there is a lack of studies that describe the differences and compare the characteristics between focal and multifocal bronchiectasis. The aim of this study is to differentiate differences in clinical characteristics and presentation, severity or distribution in focal and multifocal bronchiectasis and prognostic implications

Methods: 126 patients with CT verified bronchiectasis were enrolled. Baseline characteristics that included age, sex, smoking history, respiratory symptoms with special attention to hemoptysis appearance, BMI, comorbidities were recorded. Type of bronchiectasis determined by CT scan and the modified Reiff scores indicating radiological severity. Patients divided in two groups (I is focal, II is multifocal).

Results: There was not statistically significant differences in age, smoking status, comorbidity and BMI between two groups. Multifocality was associated with a significantly higher rate of female (p 0.014), hemoptysis (p 0.023), number of hospitalization but not for exacerbations, prevalence of immunodeficiency (p 0.049). Significantly, higher number with moderate severity were observed in subjects with multifocality and post-infective and with asthma associated phenotypes were dominant. Unexpectedly, the cystic and varicose radiological phenotype (which need more time to develop) was more dominant in focal group, and equal for cylindrical phenotype.

Conclusions: Our study suggests that multifocality holds no substantial prognostic relevance for age and number of exacerbations, radiological phenotype. The findings indicate that multifocality is associated with clinical post-infective phenotype and immunodeficiency

Conflict of interest(s) (if any – not included in the 500 words): no conflict of interest

[13.05] Bronchiectasis In Early Childhood - a Case Report

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Background/Aims:

Case report of a 4-year old boy with recurrent pulmonary infections and diagnosis of Non-CF bronchiectasis.

Methods:

Our patient was born a preterm twin 30+1 weeks. He received initially three times Surfactant, because of IRDS and suffered from a pneumothorax. He needed a chest drainage for four days, was intubated for two days and needed oxygen for 43 days. He was discharged from hospital without oxygen after 57 days. In 2021 he had twelve episodes of obstructive bronchitis and in the following year 6 episodes, five of these had to be managed in hospital, three of these had an additional need for antibiotics. Because of his recurrent pulmonary infections we did a thorough clinical work up including sweat testing, PCD Screening, genetic testing for pulmonary diseases, screening for immunodeficiency, bronchoscopy regarding foreign body aspiration and a CT Scan. The results were negative, except for the CT scan. Here we could notice bronchiectasis.

Results:

The synopsis of the findings provided the diagnosis of Non-CF bronchiectasis and we started him on daily inhalations with salbutamol, hypertonic Solution (3%) and daily chestphysiotherapy. Because of this therapy the episodes of obstructive bronchitis and pneumonia were drastically reduced and he had only one hospital admission in the last winter because of a RSV Infection.

Conclusions:

Children with a lot of recurrent respiratory infections and hospital admissions should be thoroughly checked for an underlying disease. We need further recommendations for patients with Non-CF bronchiectasis regarding the treatment and follow-ups.

Conflict of interest(s) (if any – not included in the 500 words):

No conflict of interest

[13.06] Single-cell RNA sequencing reveals activated neutrophil heterogeneity in induced sputum from bronchiectasis patients

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Bronchiectasis (BE) is a heterogeneous respiratory disease that is characterized by irreversible dilation of the bronchi and recurrent bronchial infections. A complex interaction of structural airway damage, disturbed mucociliary clearance, chronic infection and chronic inflammation contribute to the development and maintenance of BE, with immune-mediated inflammation being the critical link between the pathophysiological mechanisms. It is therefore essential to identify key immune cell types and better understand the molecular pathways that drive disease progression. Here, we employed multi-color flow cytometry and single-cell transcriptomics to investigate the immune compartment in induced sputum samples from BE patients at different severity stages. Moreover, ELISA was utilized to measure the expression levels of secreted cytokines and chemokines in sputum. Neutrophils were the most abundant immune cells, followed by monocytes and T cells, and comprised 4 distinct molecular states. Phenotypical comparison between neutrophils from severe and mild severity stages revealed the upregulation of inflammatory pathways, including DAP12 interactions, interferon alpha/beta signaling, sphingolipid metabolism, apoptosis and phagocytosis. In contrast, we observed the downregulation of CSF1 and AKT signaling and signaling by receptor tyrosine kinases in neutrophils from severe BE donors. The changes in neutrophil activation status were consistent with the elevated presence of pro-inflammatory mediators, such as CCL3, CCL4, CXCL16 and CXCL8. Taken together, our data show that neutrophils are a diverse immune population in BE sputum and their stimulation correlates with disease severity. Further investigation into severity stage-dependent neutrophil functions will shed light on the interplay between the immune system and airway damage in BE patients.

[13.07] A pragmatic, multicentre, placebo-controlled, 3-arm, double-blinded, randomised controlled trial, incorporating an internal pilot, to determine the role of bronchodilators in preventing exacerbations of bronchiectasis

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Background/Aims:

Bronchiectasis is a long-term lung condition associated with bronchial dilatation, chronic inflammation and infection. Treatment is empirical and extrapolated from other lung conditions with inhaled therapies such as inhaled corticosteroids (ICS) or long-acting bronchodilators such as long-acting beta agonists (LABA) or long-acting muscarinic antagonists (LAMA) licenced for use in asthma or chronic obstructive pulmonary disease, commonly used in bronchiectasis with scanty evidence on exacerbation reduction.

Objective

Assess if:

- Dual bronchodilators (LABA/LAMA) either as standalone therapy or in combination with ICS are superior to placebo at reducing mean exacerbation rates over 12 months
- Dual bronchodilators (LABA/LAMA) are non-inferior to triple therapy (ICS/LABA/LAMA) at reducing mean exacerbation rates over 12 months

Methods:

Design

Pragmatic, multi-centre, placebo controlled, three-arm, double blinded, prospective, randomised controlled trial incorporating a 12 month internal pilot.

Target population

600 adults with bronchiectasis and a history of 2 or more exacerbations in any 12-month period within the preceding 2 years.

Setting

Respiratory departments at UK NHS secondary care sites.

Interventions

12 months one puff daily of either dual therapy (55 micrograms umeclidinium [LAMA] and 22 micrograms vilanterol [LABA]), triple therapy (as per dual therapy plus 92 micrograms fluticasone furoate [ICS]) or matched placebo dry powder inhalers, randomised in a 2:2:1 ratio respectively.

Outcome Measures

Primary: number of participant reported bronchiectasis exacerbations requiring treatment with antibiotics during the 12-month treatment period.

Primary economic: incremental cost-per QALY at 12 months.

Results:

Recruitment rates did not follow projections due to the COVID 19 pandemic. Eighty-five potentially eligible patients were screened, of which 33 (39%) were randomised. Of the 33 participants randomised 30 (91%) completed follow-up at 12 months. There were 3 withdrawals (1/14 (7%) LABA/LAMA, 1/12 (8%) ICS/LABA/LAMA and 1/7 (14%)). Five participants discontinued therapy during the trial (1/14 (7%) LABA/LAMA, 2/12 (17%) ICS/LABA/LAMA and 2/7 (29%) Placebo).

Given the small sample size, the statistical and economic analysis is descriptive and exploratory. Exacerbation data was available on 32/33 (97%) of randomised participants (13 LABA/LAMA, 12 ICS/LABA/LAMA and 7 placebo). The median number of exacerbations during the follow-up period (the primary outcome) was 1 (IQR 0, 3) for LABA/LAMA, 2 (1, 2.5) for ICS/LABA/LAMA and 3 (2, 3) for Placebo. Additionally, the median time to first exacerbation was 167 days for dual bronchodilators compared to 81 days for triple therapy and 41 days for placebo. No safety concerns were identified.

Conclusions:

COVID-19 impacted delivery of the trial affecting staff capacity, set-up timelines and ultimately recruitment to the pilot. The trial is unable to provide evidence on the superiority or cost-effectiveness of LABA/LAMA or ICS/LABA/LAMA to placebo at reducing mean exacerbation rates over 12 months or the non-inferiority of LABA/LAMA to ICS/LABA/LAMA. However, the results do suggest there is a signal of efficacy and that a larger trial may be able to provide evidence. These results underscore the importance of completing a large-

scale trial of these therapies to help improve the understanding of the best treatment for patients with bronchiectasis.

Conflict of interest(s) (if any – not included in the 500 words):

[13.08] Geographic variation of the airway microbiome and resistome in bronchiectasis: Data from the European Bronchiectasis Registry (EMBARC)-BRIDGE study

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Background: Recent publication of the EMBARC registry data demonstrates geographic variation in sputum microbiology across Europe, however, underlying microbiomes and resistome profiles have not been explored. **Methods:** Prospective assessment of sputum by shotgun metagenomics of patients with bronchiectasis (N=349) recruited into the EMBARC-BRIDGE study from 3 European regions: Northern and Western Europe (NWE); Southern Europe (SE) and the United Kingdom (UK) were included and microbiome and resistome profiles assessed in relation to clinical outcomes. **Results:** Metagenomics recapitulates the reported variation across Europe, determined by culture, as reported in Chalmers et al, Lancet Respiratory Medicine 2023. Significant variation in microbial composition across Europe (PERMANOVA p<0.001) is evident with the top differential microbes (by region) including *Gemella sanguinis* and *Actinomyces oris* in NWE; *Pseudomonas aeruginosa* in SE; *Haemophilus influenzae* and *Streptococcus spp.* in the UK. Unsupervised clustering of metagenomic microbiomes identifies 3 clusters dominated by *Pseudomonas aeruginosa*, *Streptococcus spp.*, and *Haemophilus influenzae* respectively with the *Pseudomonas*-dominant cluster exhibiting increased exacerbations, greater disease severity and poorest lung function. The highest prevalence of the *Pseudomonas*-dominant cluster occurs in

SE, while the *Haemophilus*-dominant cluster predominates in the UK. The *Streptococcus*-dominant cluster, while lower proportionally in SE (56%) demonstrates comparable frequency between NWE (72%) and the UK (73%). Resistome profiles significantly varied across Europe (PERMANOVA $p < 0.001$) with increased tetracycline resistance gene determinants observed in the UK and multidrug and aminoglycoside resistance gene determinants in NWE and SE. Two established resistotypes (RT1 and RT2), described by Mác Aogáin, Ivan et al, AJRCCM, 2024 were validated in the EMBARC-BRIDGE cohort with high degrees of concordance to the published CAMEB2 cohort: 100% in RT1 (N=235), characterized by resistance gene determinants expressed by *Streptococcus* and *Haemophilus* and 93% (N=83) for RT2, characterized by resistance genes associated to *Pseudomonas*. Bronchiectasis resistotypes further demonstrate geographic variation between European regions with the more severe RT2 resistotype occurring at highest frequency in SE ($p < 0.001$). **Conclusions:** Metagenomics recapitulates the microbial variation across Europe described in the first EMBARC registry report (Lancet Resp Med 2023). Microbiomes and resistomes across Europe exhibit geographic variation and associate with clinical outcomes, however, key bronchiectasis pathogens including *Haemophilus* and *Pseudomonas* harbour comparable resistome profiles across regions despite differences in frequency of occurrence. **Funding:** This work is supported by the Singapore Ministry of Health's NMRC under the Clinician-Scientist Individual Research Grant MOH-001356 (S.H.C.) and a Clinician-Scientist Award MOH-000710 (S.H.C) and EMBARC3. EMBARC3 is funded by the European Respiratory Society through the EMBARC3 clinical research collaboration.

[14.01] Anxiety, Depression, Physical Disease Parameters and Health-Related Quality of Life in the BronchUK national Bronchiectasis cohort.

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Background: Long term medical conditions are associated with increased psychological comorbidity. Bronchiectasis is known to be associated with psychological comorbidity and poor health related quality of life (HrQoL), yet guidelines lack focus on psychological morbidity.

Research Question: How common is psychological comorbidity in patients with bronchiectasis and does it associated with increased healthcare usage?

Study Design: Cross sectional and longitudinal multicentre study; Using data obtained from the BronchUK database (1341 patients; www.bronch.ac.uk), we examined the link between anxiety/depression and physical disease severity, QoL, and long-term outcomes in bronchiectasis.

Methods: Adult patients across 15 centres in the United Kingdom with CT-confirmed bronchiectasis were enrolled in the BronchUK study, Hospital Anxiety and Depression Scale (HADS-A/D) data were studied. HADS-A/D scores ≥ 8 were used to indicate anxiety/depression. QoL measured by St. George's Respiratory Questionnaire and QoL-Bronchiectasis Questionnaire. Exacerbations during annual follow-up were analysed by negative binomial regression with time in study as an offset adjusted for age, BMI, sex, Pseudomonas infection, diabetes and FEV1. Cox regression determined probability of hospitalisation using Time-to-First exacerbation.

Results: We enrolled 1521 patients into BronchUK but limited the analysis to those where baseline HADS data were available. Of the 1341 patients included; 418 had anxiety (31%), 269 (20%) had depression and 201 (15%) had both conditions. HADS-A/D ≥ 8 associated with worse QoL ($p < 0.0001$) and clinical severity e.g., Bronchiectasis Severity Index, FEV1 and MRC dyspnoea score (all $p < 0.01$). HADS-A/D ≥ 8 each associated with exacerbation

(RR 1.42 95%CI1.32-1.52 for HADS-A; RR 1.45 95%CI1.34-1.56 HADS-D, both $p<0.0001$) and hospitalisation risk (RR 1.58 95%CI1.29-1.92 HADS-A; RR 1.76 95%CI1.43-2.17 HADS-D, both $p<0.001$). HADS-A/D $\geq$ 8 each predicted future hospitalisation (HR 1.30 95%CI0.98-1.72, $p=0.067$ HADS-A; HR 1.40 95%CI1.04-1.88, $p=0.027$ HADS-D).

Conclusions: Anxiety and depression are common in bronchiectasis, correlate with disease severity, and predict poorer outcomes including exacerbations and hospitalisations. Psychological symptoms are common and consideration of psychological support is important in bronchiectasis care.

Conflict of interest(s) (if any – not included in the 500 words): None.

[14.02] Baseline Demographics from the BronchUK database; unmet need in Bronchiectasis?

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Background:

BronchUK is a multicentre study of Bronchiectasis recruiting adult patients with CT confirmed bronchiectasis with long term follow up and biobanking. The protocol for inclusion and data collection has already been published.

Results:

Between November 2015 to April 2022, 1637 individuals with Bronchiectasis were enrolled from across 15 centres spread across the UK. Median age was 67 years (IQR 59–73), 1011 (61.8%) participants were female and 626 (38.2%) were male. The most common cause of bronchiectasis from the 1,621 cases submitted to the database was found to be idiopathic, in 682 patients (42%), with 471 participants (29%) post-infective disease. There were 53 current smokers, 623 ex-smokers (945 never smoked).

Asthma was deemed a comorbidity of bronchiectasis in 623 (38%) patients and COPD in 253 patients (15.6%). Individuals with bronchiectasis experienced a median of two exacerbations (IQR 0–3) per year and 292 (18%) patients had a hospitalisation for exacerbation in the previous year.

The median FEV1 was 1.8 and 77.1 % predicted. Positive cultures for *Pseudomonas* were found in 579 (35.7%) patients; 208 male (36%) and 371 female (64%). *Haemophilus influenzae* was reported in 247 (15%) patients; 104 male (42%) and 143 female (58%). When split into bronchiectasis severity index (BSI) categories, 360 were mild (22%), 795 Moderate (49%) and 466 severe (29%). These categories split by gender were male: 143 mild; 298 moderate; 177 severe, and females: 217 mild; 497 moderate; 289 severe.

The proportion of patients who had exacerbations in the preceding 12 months to enrolment were 1196 (78%), with 581 patients have 1-2 exacerbations (36%), and 615 recorded as having 3 or more (38%). Of the patients with 3 or more exacerbations, 57 (9%) were not on baseline macrolide nor nebulised antibiotic. There were a reported 39 patients on long term oxygen therapy.

The proportion of patients on a long-term oral antibiotic treatment was 518 (32%) and for long term nebulised antibiotics 203 (12.5%). Long term oral antibiotics prescribed either alone or in combination as follows: Azithromycin 346 (67%), Doxycycline 69 (13%), Amoxicillin 41 (8%), Ciprofloxacin 23 (4%), Clarithromycin 16 (3%), Trimethoprim 8 (1%), Erythromycin 8 (1%), Moxifloxacin 2 (<1%), Tetracycline 2 (<1%). Long term nebulised antibiotics prescribed: Colistimethate Sodium 94 (46%), Colistin 33 (16%), Gentamicin 29 (14%), Tobramycin 19 (9%), Ciprofloxacin 10 (5%), Amikacin 5 (2%), "Other" 39 (19%).

Conclusions:

Prior published Bronchiectasis cohorts show there are a range of aetiologies with the BronchUK demographics being broadly similar to prior reported. The available data suggests that within the NHS system in the UK there remain significant numbers of patients with exacerbations. Although treatment with macrolides and/or long-term nebulised antibiotics are guideline recommended, there remain patients with high exacerbation rates who are not receiving these therapies.

Conflict of interest(s) (if any – not included in the 500 words): none.

[14.03] Insights into the Relationship Between Bronchiectasis Exacerbation and Rate of Decline in Spirometry: An Examination of a National Prospective Cohort

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Background/Aims:

Bronchiectasis exacerbations are thought to lead to an accelerated loss of lung function as measured historically by spirometry. While both FVC and FEV1 may decline in the setting of an exacerbation, we hypothesize that the FVC may be more susceptible to change as compared to FEV1 as it will reflect air trapping from mucus plugging. The primary aim of our study was to evaluate the decline in FEV1 and FVC from baseline to 1 year between patients with frequent versus infrequent exacerbations in the U.S. Bronchiectasis and Nontuberculous Mycobacteria Research Registry (BRR).

Methods:

Adult bronchiectasis patients with known exacerbation history at baseline and pulmonary function testing results at both baseline and first annual follow-up in the BRR were included in the analysis. Patients with a history of cystic fibrosis or supplemental oxygen use were excluded. Descriptive statistics were computed overall and by 0-1 vs. [≥]2 exacerbations during the baseline period. Covariates included demographics, co-existing conditions, FVC and FEV1 values, both absolute and %predicted, positive bacterial cultures, and use of airway hygiene. Kruskal-Wallis, t-tests, and chi-square tests were used to assess the mean differences and associations across the exacerbation groups for continuous and categorical variables, respectively. We fit Gaussian generalized estimating equation (GEE) models with an exchangeable working correlation matrix to determine the association between [≥]2 vs. 0-1 exacerbations and both the absolute and percent predicted FEV1 and FVC over time.

Results:

1318 patients met inclusion criteria (*Figure 1*); 815 (62%) experienced infrequent (0-1) exacerbations and 503 (38%) experienced frequent ([≥]2) exacerbations. Frequent exacerbations were associated with certain comorbidities (see *Table 1*), more frequent hospitalizations at baseline (36.8% vs 11.2%, $p < 0.0001$), *Pseudomonas aeruginosa* isolation (34.8% vs 20.4%, $p < 0.0001$), and greater use of inhaled bronchodilators (77% vs 63.3%, $p = 0.001$) compared to those with infrequent exacerbations. At baseline, patients with frequent exacerbation had a lower % predicted FEV1 and FVC compared to those with infrequent exacerbations (69.4 vs 76.2%, $p < 0.0001$; 80.4 vs 84.8%, $p = 0.0001$). In unadjusted models, patients with a history of ≥ 2 exacerbations at baseline had a pre-bronchodilator % predicted FEV1 and FVC of 6.8% and 4.2% lower on average for a given visit than patients with a history of ≤ 1 exacerbation at baseline (95% CI: 3.9-9.8% less; $p < 0.0001$ and 1.5-7.0% less; $p = 0.003$, respectively) (*Table 2*). However, there was no significant difference in the decline in % predicted FEV1 compared to the decline in % predicted FVC (95% CI: -1.7-6.8).

Conclusions:

Despite a greater burden of hospitalizations, *Pseudomonas aeruginosa* isolation, and inhaled bronchodilator use, patients with frequent bronchiectasis exacerbations experienced a similar annual decline in lung function as those with infrequent exacerbations after one year of follow up. Additional research is needed to identify factors associated with potential differences in decline in FEV1 and FVC and over a longer period of time.

Conflict of interest(s) (if any – not included in the 500 words): Zha- Consulting for Insmmed and Genentech.

[14.04] Does eosinophilic bronchiectasis exist in the paediatric population?

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Background/Aims:

Eosinophilic bronchiectasis has been reported in up to 20% of adults with bronchiectasis, where inhaled corticosteroids (ICS) have been shown to reduce exacerbation frequency.¹ To date, there is limited data in children with bronchiectasis. Our study aimed to determine the prevalence of airway eosinophilia and to compare this to systemic eosinophil levels in children with bronchiectasis.

Methods:

We combined data from children being investigated for bronchiectasis due to chronic cough who were prospectively recruited at our hospital between 2008 to 2021. All children had flexible bronchoscopy and bronchoalveolar lavage (BAL), and blood eosinophil levels were measured. We considered airway eosinophilia present if the BAL eosinophil count was $\geq 1.5\%$. We correlated airway eosinophils to blood eosinophil levels using Spearman's correlation.

Results:

355 children were included, of which 59% were male with a median age of 3.46 years (range 0.36-16.24) at time of investigation. For the full cohort, airway eosinophils had a median of 0% (range 0-49%) and blood eosinophil levels had a median of $0.34 \times 10^9/L$ (range $0.01-5.67 \times 10^9/L$). There was a weak but significant correlation between airway and blood eosinophil levels ($r=0.24$, $p<0.001$). There was no correlation between either airway or blood eosinophils and age. Airway eosinophilia was present in 67 (19%) of the children with a median of 3% eosinophils on lavage (range 1.5-49%). Children with airway eosinophilia had significantly higher levels of blood eosinophils than those with no airway eosinophilia (median 0.58 (range 0-5.67) vs median 0.29 (range 0-4.08) $\times 10^9/L$, $p<0.001$).

Conclusions:

In children with bronchiectasis, blood eosinophil levels were weakly correlated to airway eosinophils. Our findings that 19% of the children studied with bronchiectasis had airway eosinophilia is similar to the reported adult level of 20%. As ICS would likely be beneficial in those with airway eosinophilia, eosinophilic bronchiectasis should be considered in the paediatric population and further explored.

Reference:

1. Shoemark A, Shteinberg M, De Soyza, et al. Characterisation of Eosinophilic Bronchiectasis: A European Multicohort Study. *AJRCCM*. 2022;205(8).
<https://doi.org/10.1164/rccm.202108-1889OC>

Conflict of interest(s) (if any – not included in the 500 words):

None that I am aware of.

[14.05] Automatic Bronchus Artery Analysis of Bronchiectasis in Adults Treated with Dornase Alfa

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Background/Aims:

Chest CT scans [CTs] are performed in patients with bronchiectasis [BE] to assess the severity and extent of BE, airway wall thickening, and mucus plugs [MP]. However, the objective assessment of airway dimensions and MP on CTs is not feasible in clinical practice. Recently, artificial intelligence-based software was validated to measure fully automatically MP number and bronchus and artery [BA] dimensions of a large number of BA-pairs on a CT. This MP and BA-analysis could be used to assess, at an individual level, the response to treatments in BE patients. In this retrospective study we analysed CTs of BE patients to assess changes in MP number and BA-dimensions in response to inhaled dornase alfa that was started for clinical reasons. We hypothesized that dornase alfa treatment in BE patients reduced the number of MP and airway wall thickening.

Methods:

In this retrospective observational study, we selected adults with BE who were treated for clinical reasons with dornase alfa and who had a baseline and follow up CT meeting LungQ requirements were selected while on dornase alfa treatment. Coded and randomized CTs were analysed using the fully automatic MP and BA-analysis (LungQ®, Thirona, Nijmegen) to quantify the number and volume of MP and BA dimensions and ratios. LungQ segments the bronchial tree and identifies for each bronchus the matching artery. For each BA-pair it computes the following diameters: bronchus outer and inner diameter (B_{out} and B_{in}), arterial diameter (A), and bronchial wall thickness (B_{wt}). Next, it computes the following ratios: B_{out}/A , B_{in}/A , B_{wt}/A and B_{wa}/B_{oa} (bronchus wall area/bronchus outer area) for each segmental generation. We compared volume and number of MP and the median of B_{out}/A , B_{in}/A , B_{wt}/A and B_{wa}/B_{oa} for segmental generations G_{1-6} .

Results:

A total of 10 adults (all females, age 78[24-82] years) with baseline and follow-up CTs. Time between CTs 236 days [25-1399]. LungQ-MP detected a total of 228 MP with a total volume of 16.1ml at baseline (per subject mean 22.8; 1.6ml) MP and 168 MP with a volume of 8.9 ml at follow up (per subject mean 16.8; 0.9). For baseline CTs 1.416 BA-pairs from G_{1-6} (mean 142, SD 91) and for follow up CTs 1.187 BA-pairs (mean 119, SD 72) were analysed. For all patients there was no statistically significant differences (p values all >0.29) between the on treatment and baseline CT for MP number and volume and for BA-dimensions and ratios. Raincloud plots suggest a substantial reduction in the number and volume of MP in 4 patients, and in B_{wt} and B_{wa}/B_{oa} in 2 patients. Progressive thickening of B_{wt} and B_{wa}/B_{oa} and widening of arterial diameters was observed in 9/10 patients.

Conclusions:

We used the fully automatic MP and BA-analysis to assess the individual response to dornase alfa treatment in 10 BE patients. LungQ-MP and BA analysis allowed sensitive and accurate monitoring of MP number and volume and BA-dimensions and ratios over time which could play a role to assess the efficacy of treatments at an individual level.

Conflict of interest(s) (if any – not included in the 500 words):

H.A.W.M. Tiddens CMO of Thirona

[14.06] Artificial Intelligence identifies emerging trends in bronchiectasis clinical care and research.

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Background: Natural Language Processing (NLP) models including ChatGPT represent an evolving frontier of everyday application of artificial intelligence (AI), capable of mining text data and generating novel insight. Despite its growing potential, little work has used such approaches to extract insights from the dynamically evolving and increasing medical literature. Here, we use AI to map and visualize the dynamics of the bronchiectasis clinical and research landscape to identify emerging trends. **Methods:** Eligible PUBMED publications were identified using the search term “BRONCHIECTASIS [MeSH Major Topic]” between 1949 to 2023. Only original research articles in English were included. Each identified publication was reviewed to exclude studies focusing on Cystic Fibrosis (CF) related bronchiectasis. ATLAS: an AI based long-text embedding model was implemented on all identified abstracts to perform unsupervised topic modelling and visualization. The dynamics and evolution of the respective identified topics were evaluated over time to determine emerging trends in bronchiectasis. **Results:** Pre-2000, the annual number of new bronchiectasis publications rose by ~0.8/year which significantly increased eight-fold to approximately ~6.6 more articles/year post 2000 ($p < 0.001$). Topic modeling (using ATLAS) on 2,087 original research articles identified 51 separate topics. The diversity of topics in bronchiectasis increased over time from 1967-2023. Assessment of topic patterns reveal increasing numbers of studies on ‘CT scans’ from the mid-1990s when chest CT became the gold-standard for the diagnosis of bronchiectasis. Studies on infection in bronchiectasis increased steadily until the first description of Cole’s vicious cycle hypothesis, following which this flattened, before resuming growth along with Microbiome studies from the mid-2000 when the first commercial availability of next-generation sequencing equipment occurred. Studies focused on the management of bronchiectasis gained traction and accelerated following the first publication of management guidelines in 2010 [See Figure 1]. The analysis of bronchiectasis trends over the past decade indicates a consistent rise in research focused on bronchiectasis management, infection, inflammation, microbiome, mortality, overlap disease and associated physical activity indicating all of these as ‘hot topics’. Assessing topics that have surfaced only in recent times (termed “pop-ups”) includes studies of bronchiectasis associated with alpha-1 anti-trypsin deficiency and haemoptysis. **Conclusion:** AI-based NLP models identify inflammation, microbiome and bronchiectasis overlap diseases as emerging trends in the literature in relation bronchiectasis clinical care and research. These emerging tools facilitate a deeper understanding of emerging trends, research gaps and the evolving landscape in this disease state, offering promising avenues for future investigation, intervention and innovation. **Funding:** This research is supported by the Singapore Ministry of Health’s National Medical Research Council under its Clinician-Scientist Individual Research Grant (MOH-001356) (S.H.C) and Clinician Scientist Award (MOH-000710) (S.H.C) and the Singapore Ministry of Education under its AcRF Tier 1 Grant (RT1/22) (S.H.C). **Conflicts of interest:** S.H.C has served on advisory boards for CSL Behring, Pneumagen Ltd. and Boehringer-Ingelheim, on DSMBs for Inovio Pharmaceuticals and Imam Abdulrahman Bin Faisal University and has received personal fees from Astra-Zeneca and Chiesi Farmaceutici, all unrelated to this work. All other authors have no conflicts of interest to disclose.

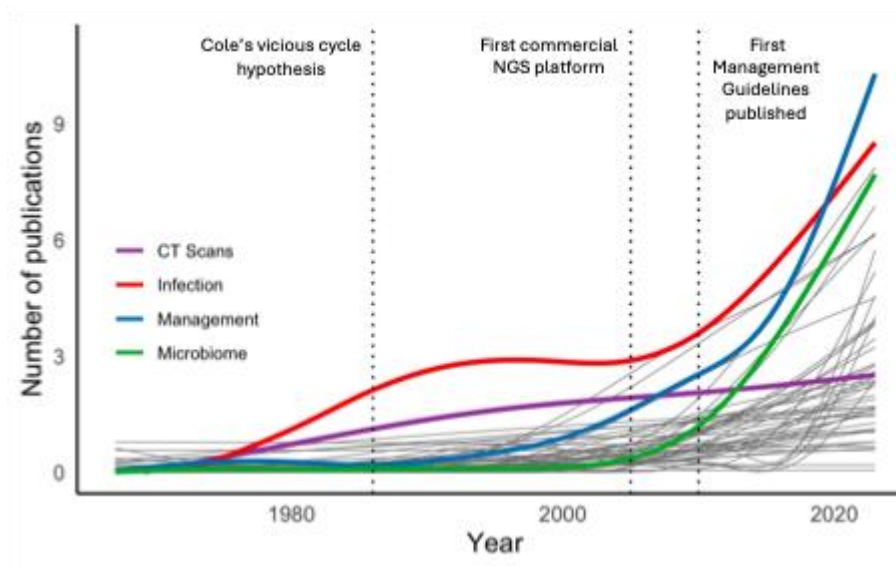


Figure 1: A line plot, depicting trends of topics (grouped by ATLAS) in bronchiectasis clinical care and research over time (x-axis) from 1967 to 2023. The x-axis denotes years, and y-axis quantity of bronchiectasis original research articles published annually by topic.

[14.07] Artificial Intelligence software seems to properly answer bronchiectasis patients' questions about disease management: results from the AIR-CAD-Bx study.

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Introduction: Artificial Intelligence (AI) might help patients in better understanding their respiratory conditions, including bronchiectasis.

Methods: The AIR-CAD-Bx (Artificial Intelligence Responses on Chronic Airway Disease - Bronchiectasis) is a cross-sectional study evaluating AI-generated answers in response to questions formulated by European Lung Foundation (ELF) patients' representatives on the clinical management of bronchiectasis. Three software were tested, namely Chat-GPT, Google Bard, and Microsoft Bing. Both experts selected from European Respiratory Society (ERS) Assemblies and the ERS CONNECT CRC and ELF patients' representatives were asked to evaluate answers in terms of precision (experts), comprehensiveness (experts), and understandability (patients) on a 0-10 scale. 15 questions of different complexity have been selected and administered to the three software.

Results: Answers were extracted and evaluated by 28 bronchiectasis experts and 33 patients' representatives. Median precision scores for each answer ranged between 7.0 and 9.0 for Chat-GPT, between 6 and 8 for Google Bard, and between 6 and 8 for Microsoft Bing. Precision scores of Chat-GPT (median 8, IQR [7-9]) were overall higher than the ones of Google Bard (median 7, IQR [6-8]) and Microsoft Bing (median 7, IQR [6-8]) ($P < 0.0001$). Median comprehensiveness scores for each answer ranged between 7.5 and 9.0 for Chat-GPT, between 6.5 and 9.0 for Google Bard, and between 6.0 and 8.0 for Microsoft Bing. Comprehensiveness scores of Chat-GPT (median 8, IQR [7-9]) were overall higher than the ones of Google Bard (median 8, IQR [6-9]) and Microsoft Bing (median 7, IQR [6-8]) ($P < 0.0001$). Median understandability scores for each answer ranged between 8.0 and 9.0 for Chat-GPT, between 8.0 and 10.0 for Google Bard, and between 7.0 and 9.0 for Microsoft Bing. Understandability scores of Chat-GPT and Google Bard (median 9, IQR [8-10 for both]) were higher than the ones of Microsoft Bing (median 9, IQR [7-10]) ($P = 0.0002$).

Conclusions: Despite not being a replacement for medical counselling, AI software, and particularly Chat-GPT, seem to provide precise, comprehensive, and understandable answers to the 15 submitted questions on bronchiectasis management.

[14.08] Evaluating Elexacaftor/Tezacaftor/Ivacaftor (ETI) for the treatment of patients with non-cystic fibrosis bronchiectasis (NCFB)

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Background

Non-cystic fibrosis bronchiectasis (NCFB) is a clinical syndrome characterized by abnormal dilatation of the airways, which can lead to cough, excessive sputum production and recurrent lung infections. Airway dilatation and impaired mucociliary clearance resulting in recurrent bacterial infections and endobronchial inflammation are thought to be pathophysiologic drivers of NCFB, in a complex interplay that has been termed the “Vicious Vortex” (Flume, Chalmers et al. 2018). The number of adults with NCFB in the United States is estimated at 350,000 - 500,000 (Weycker, Hansen et al. 2017), much higher than adults with cystic fibrosis (CF) (approximately 30,000-40,000). Unfortunately, there are no curative therapies or medications specifically approved to address fundamental mechanisms that underlie NCFB.

NCFB shares a number of clinical and pathologic features similar to CF, and prior studies have found that a significant number of individuals with NCFB encode CFTR mutations and abnormal CFTR function (Bienvenu et al. 2010).

Aim

Our study is an open-label, single center trial of orally administered elexacaftor, tezacaftor and ivacaftor (ETI) in 30 individuals with NCFB who have one known CFTR mutation and/or mildly elevated sweat chloride measurements (i.e., 30-59 mEq/L). The study will also assess the proportion of patients with NCFB with CFTR heterozygosity and/or mildly elevated sweat chloride. iPSC derived airway epithelial monolayers will be examined as a means to predict patients with NCFB likely to respond to CFTR modulators.

Methods

The study consists of two components:

- 1) Lead-in study: Participants with a diagnosis of NCFB will undergo CFTR genotype and sweat chloride testing. We anticipate approximately 200 subjects will participate in the ‘lead-in’ study.
 - 2) Main study: Subjects who exhibit a single CF-causing mutation in CFTR (e.g., F508del) and/or sweat chloride 30-59 mEq/L will be invited to participate in the ‘main’ study (Figure 1).
- Primary Endpoints: iPSC-derived evidence of an ETI response and pulmonary function testing of FEV₁ (forced expiratory volume in one second) following ETI administration *in vivo*
 - Secondary Endpoints: sweat chloride, QOL-B assessment, weight gain, safety laboratory evaluation/EKG

Conclusions

This study will assess iPSC-derived evidence of an ETI response and pulmonary function testing of FEV₁ (forced expiratory volume in one second) following CFTR modulator administration in patients with NCFB. We will also determine the incidence of diminished CFTR activity among individuals with NCFB

Funding Source: Marcus Foundation, Inc.

Figure 1. Summary of trial design.

[15.01] Clinical characteristics and outcomes of the phenotypes of COPD-Bronchiectasis Association

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Background/Aims: Although COPD may frequently co-exist with bronchiectasis [COPD-bronchiectasis associated (CBA)], little is known regarding the clinical heterogeneity. We aimed to identify the phenotypes and compare the clinical characteristics and prognosis of CBA.

Methods: We conducted a retrospective cohort study involving 2,928 bronchiectasis patients, 5158 COPD patients, and 1,219 patients with CBA hospitalized between July 2017 and December 2020. We phenotyped CBA with a two-step clustering approach and validated in an independent retrospective cohort with decision-tree algorithms.

Results: Compared with patients with COPD or bronchiectasis alone, patients with CBA had significantly longer disease duration, greater lung function impairment, and increased use of intravenous antibiotics during hospitalization. We identified five clusters of CBA. Cluster 1 (N=120, CBA-MS) had predominantly moderate-severe bronchiectasis, Cluster 2 (N=108, CBA-FH) was characterized by frequent hospitalization within the previous year, Cluster 3 (N=163, CBA-BI) had bacterial infection, Cluster 4 (N=143, CBA-NB) had infrequent hospitalization but no bacterial infection, and Cluster 5 (N=113, CBA-NHB) had no hospitalization or bacterial infection in the past year. The decision-tree model predicted the cluster assignment in the validation cohort with 91.8% accuracy. CBA-MS, CBA-BI, and CBA-FH exhibited higher risks of hospital re-admission and intensive care unit admission compared with CBA-NHB during follow-up (all $P < 0.05$). Of the five clusters, CBA-FH conferred the worst clinical prognosis.

Conclusions: Bronchiectasis severity, recent hospitalizations and sputum culture findings are three defining variables accounting for most heterogeneity of CBA, the characterization of which will help refine personalized clinical management.

Conflict of interest(s) (if any – not included in the 500 words): none declared.

[15.02] The development of the Bronchiectasis Awareness Questionnaire.

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Background: Disease awareness (DA), which relates to knowledge and acceptance of the disease and its treatments is key for management and treatment outcomes in bronchiectasis. No data are currently available on patients' DA in bronchiectasis and no validated tools have been proposed so far.

Aim: To develop a questionnaire on DA for adults with bronchiectasis.

Methods: An initial list of questions about disease awareness was developed by 2 pulmonologists, 1 physiotherapist and 1 health psychologist who are experts in bronchiectasis management. Across 3 Delphi rounds a group of 10 experts (8 pulmonologists, 1 physiotherapist, 1 health psychologist) and 10 patients were asked by email to evaluate the relevance and the quality of the items, to propose additional items and to reformulate the existing ones as necessary. The procedure adopted to generate items is in line with the approach recommended by the US Food and Drug Administration.

Results: A list of 32 items covering 4 dimensions of awareness (knowledge, acceptance, awareness of treatment need and perception) was initially identified.

As a result of the first Delphi round, redundant items were combined, 4 items were reformulated, and 16 items were added at the suggestion of the participants, for a 42-item list. The second Delphi round resulted in a tool of 29 items selected from those with median relevance ≥ 7 . This list was sent to experts and patients for the third final Delphi round. A consensus was reached at this stage and the Bronchiectasis awareness questionnaire (BAQ) was developed.

Conclusion: The psychometric properties of the provisional BAQ are currently under validation in a real-life, multicenter, study.

[15.03] Experience with inhaled levofloxacin in patients with bronchiectasis not due to cystic fibrosis

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Background/Aims: Currently, there are four inhaled antibiotics (colistimethate sodium, tobramycin, aztreonam, and levofloxacin) approved for the treatment of chronic bronchial infection (CBI) caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis. However, there is no experience in the literature on inhaled levofloxacin in patients with non-cystic fibrosis bronchiectasis.

The main objective of this study is to present the experience of our center with inhaled levofloxacin on a series of four patients with bronchiectasis, non-cystic fibrosis and CBI due to potentially pathogenic microorganisms.

Methods: Retrospective case series, including four patients with non-cystic fibrosis bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa* or *Stenotrophomonas maltophilia*, who received at least 6 months of inhaled levofloxacin. Clinical and microbiological data, previous inhaled antibiotics, adverse effects, pre- and post-treatment exacerbations were collected at 6 months, through the computerized medical record.

Results: A total of 4 patients treated with inhaled levofloxacin were included. The mean age was 77±4 years, 75% of whom were women. Two of the patients had severe COPD. All of them were being treated with triple therapy, except for case 3. Chronic bronchial infection was due to *S. maltophilia* or *Pseudomonas aeruginosa*. All patients had previously received other inhaled antibiotics, which were discontinued, mainly due to intolerance. At 6 months, since inhaled levofloxacin was initiated, there has been no exacerbation, good tolerance and improvement in the clinical symptoms, volume and purulence of the sputum. The rest of the results are shown in Figure 1.

Conclusions: Inhaled levofloxacin is the first quinolone used for the treatment of chronic bronchial infection with *Pseudomonas aeruginosa* in patients with cystic fibrosis. Currently, there are no published data on the experience of inhaled levofloxacin in patients with non-cystic fibrosis bronchiectasis, which is why this case series is presented. At 6 months, since inhaled levofloxacin was initiated, they have presented clinical improvement, reduction in sputum volume and no new exacerbations.

Patient	Sex	Age	Respiratory Disease	Etiology Bronchiectasis	Inhaled Treatment	Chronic Bronchial Infection?	Pre-treatment exacerbations	Previous antibiotic treatment	Reason for suspension	Current inhaled antibiotic treatment	Exacerbations at 6 months
Case 1	♀	81	Bronchial asthma	Postinfectious	Triple therapy	Yes S.maltophilia	3 income	Sodium colistimethate	Intolerance	Inhaled levofloxacin	0 Good tolerance
Case 2	♂	81	Severe COPD	COPD	Triple therapy	Yes S.maltophilia	2 income	Sodium colistimethate	Intolerance	Inhaled levofloxacin	0 Good tolerance
Case 3	♀	73	Severe Bronchiectasis	Postinfectious	Long-acting anticholinergic (LAMA)	Yes P. aeruginosa	2 income	colistimethate sodium, tobramycin, aztreonam.	No clinical improvement and exacerbations	Inhaled levofloxacin	0 Good tolerance
Case 4	♀	74	Severe COPD + Alpha-1 antitrypsin deficiency (AAT)	COPD +AAT	Triple therapy	Yes P. aeruginosa	3 income	colistimethate sodium, tobramycin, aztreonam.	Intolerance	Inhaled levofloxacin	0 Good tolerance

[15.04] PROGNOSTIC IMPLICATIONS OF CLUSTER ANALYSIS IN PATIENTS WITH CHRONIC BRONCHIAL INFECTION UNDER NEBULIZED ANTIBIOTIC THERAPY: A MULTICENTRE RETROSPECTIVE COHORT STUDY (INBREATHING STUDY)

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Background/Aims: The clinical heterogeneity of patients with chronic bronchial infection (CBI) under nebulized antibiotics (NA) suggests the existence of different phenotypes with prognostic implications. Our objective was to analyse sociodemographic and clinical characteristics prior to the start of NA in these patients and evaluate their influence on prognosis and treatment response.

Methods: Multicentre, retrospective, observational study of patients with CBI under NA were included between January 2018 and December 2022 in 8 centres in Spain. Patients were classified by Partitioning Around Medoids algorithm on clinical characteristics prior the start of treatment. The response outcomes were exacerbations and eradication. Specific predictors of response for each cluster were assessed using stepwise logistic regression.

Results: A total of 244 patients were recruited, predominantly male (50.4%) with a median age of 73 [61.0;80.2] years. Two clusters were identified: (1) females with bronchiectasis and fewer comorbidities, and (2) older males with COPD and a higher burden of comorbidities (Figure 1). Cluster 1 demonstrated a superior response to NA, showing a greater reduction in exacerbations [100% vs 66.7%; $p<0.001$] along with clinical enhancements, including reduced sputum production [87.6% vs 74.2%; $p=0.05$], diminished purulence [89.9% vs 75.8%; $p=0.03$] and decreased dyspnoea [72.4% vs 54.8%; $p=0.04$]. Cluster 1 experienced fewer adverse events [12.7% vs 29.8%; $p<0.001$]. Specific predictors of eradication were observed only in cluster 2: cystic bronchiectasis (OR: 3.14; $p=0.04$) and concomitant treatment with hypertonic saline solution (OR: 0.55; $p=0.07$).

Conclusions: In this pilot study, specific phenotypes were identified and showed differences in responses to treatment with NA.

[15.05] Association between participation in the German bronchiectasis registry PROGNOSIS and improved patient care

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Background/Aims: Bronchiectasis research has advanced significantly through international and national registries, such as the European bronchiectasis registry (EMBARC) revealing crucial insights into the disease's heterogeneous nature and guiding more effective, tailored treatment strategies. These efforts underscore the importance of precise patient phenotyping and the identification of underlying causes to improve management and outcomes in bronchiectasis.

Methods: The German bronchiectasis registry PROGNOSIS, initiated in 2015 at Hannover Medical School has gathered data from over 1,500 CT-confirmed bronchiectasis patients across 38 German sites, aligning with the EMBARC registry for comprehensive clinical data collection. It employs strict protocols for data protection and analysis, focusing on adults over 18, excluding those with cystic fibrosis or lung transplants. Statistical analysis of baseline and follow-up data, using tests corrected for multiple comparisons, aims to assess disease progression and patient outcomes.

Results: We consecutively recruited 1696 adults with CT-confirmed bronchiectasis into the PROGNOSIS registry from July 2015 to April 2022 from 38 different healthcare sites across Germany. Of those, 1222 patients had at least one follow-up visit. Key outcomes include a noticeable reduction in the median exacerbations and hospitalizations, demonstrating an improvement in managing the disease. Lung function, as measured by FEV1, remained stable over time, contradicting the expected decline in such chronic lung conditions. Additionally, there was a significant decrease in active smokers, and improvements were seen in sputum quantity and quality. There was an increase in the detection of pathogens, particularly *Pseudomonas aeruginosa*, most likely due to better and more focused microbiological diagnostics as a result of inclusion in the registry. Notable shifts in the underlying causes of bronchiectasis, including a decrease in idiopathic cases to a proven etiology underscoring the effectiveness of targeted management strategies over the registry period.

Conclusions: The PROGNOSIS registry highlights the critical role of comprehensive management in bronchiectasis, emphasizing smoking cessation, infection control, and treatment adherence. It underscores the need for personalized treatment by understanding the evolving etiology and highlights the ongoing importance of research for improving patient care and quality of life.

[15.06] Upper airway microbiota and clinical outcomes in patients with Bronchiectasis: data from the EMBARC-BRIDGE study

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Background:

Previous research into the bronchiectasis lower airway microbiota has shown profiles dominated by either *Pseudomonas* or *Haemophilus*. Research into the upper airway microbiota of bronchiectasis patients is limited. Whether the upper airway microbiota can provide clinically useful information as an alternative to sputum sampling is yet to be discovered.

Aim:

To investigate the relationship between the upper airway microbiota and clinical outcomes in bronchiectasis patients.

Methods:

Nasopharyngeal swabs were collected from 327 bronchiectasis patients at baseline from five European centres (Amsterdam, Dundee, Hannover, London and Leuven) as part of a European observational cohort study NCT03791086. Nasopharyngeal swabs underwent DNA extraction and 16S rRNA Illumina metagenomic sequencing. Sequencing data was analysed using MicrobiomeAnalyst, which included alpha-diversity analysis (Chao1, Shannon, and Simpson diversity indices), beta-diversity analysis (Bray-Curtis index), LEfSe, and random forest. Patients were grouped according to clinical characteristics and differences in the upper airway microbiota were assessed. Clinical characteristics included disease severity, FEV₁, exacerbation history, hospitalisation history, symptoms, and rhinosinusitis status.

Results:

A total of 327 patients were included. The mean age was 65.0 years (SD±14.7). The mean FEV₁ was 84.1% predicted. 87/327 (26.6%) had documented rhinosinusitis. 23/327 (7.0%) had a history of severe exacerbations and 73/327 (22.3%) had two or more exacerbations in the previous year. The core nasal microbiota included high relative abundance of *Corynebacterium*, *Staphylococcus* and *Cutibacterium*.

There were significant differences in beta-diversity between patients who had severe exacerbations or not (p-value=0.002). Random forest analysis identified *Pseudomonas* and *Anaerococcus* as the most discriminating taxa for severe exacerbation status. LEfSe analysis identified reduced levels of *Corynebacterium* in patients who had experienced severe exacerbations (LDA score 3.94, FDR adjusted p-value=0.04). There was no significant difference in alpha-diversity for severe exacerbation status.

There was a significant difference in Chao1 alpha-diversity for disease severity group (p-value=0.0016). Shannon and Simpson alpha-diversity metrics were not significantly different. Random forest analysis identified *Staphylococcus* and *Pseudomonas* as the most discriminating taxa between severity groups. LEfSe analysis identified increased levels of *Peptoniphilus* in patients with more severe bronchiectasis (LDA score 2.31, FDR adjusted p-value=0.027).

There were significant differences in beta-diversity between the five centres (p-value=0.003). Random forest analysis identified *Pseudomonas* and *Fusobacterium* as the most discriminating taxa between centres. LEfSe analysis identified lower levels of *Pseudomonas* in the Dundee, London and Amsterdam centres (LDA score 3.84, FDR adjusted p-value<0.001). There was no significant difference in alpha-diversity between the five centres.

Conclusions:

We demonstrate heterogeneity in the upper airway microbiota of bronchiectasis patients. Differences in the microbiota were observed for clinical characteristics such as disease severity. Differences in the upper airway microbiota were observed for patients from different geographical centres.

Conflict of interest(s) (if any – not included in the 500 words):

[15.07] Bronchiectasis in a patient with Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy

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Background

The rare monogenic syndrome Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) leads to a defect in central immune tolerance with multisystemic autoimmunity manifestations. In several cohorts lung involvement as autoimmune pneumonitis has been described in up to 40 % of patients with bronchiectasis being the most frequent radiologic manifestation and rare fatal outcome due to respiratory and infectious complications being documented. The Sardinian population has a high incidence of APECED (1:14.000), although no cases of lung manifestation have been reported yet. *Ferre et al.* treated some of APECED patients with pulmonary involvement with lymphodepleting agents, demonstrating an ameliorating effect on clinical and functional parameters.

We present a case of a Sardinian APECED patient treated at the bronchiectasis clinic of IRCCS Humanitas Research Hospital with the aim to raise awareness on this underestimated cause of bronchiectasis and the necessity to screen these patients earlier for pulmonary involvement for better outcome.

Case Presentation

A 49-year-old female originating from Sardinia from consanguineous parents was diagnosed with APECED syndrome in childhood (R139X/R139X genotype) and was referred to our bronchiectasis clinic in March 2023. Her brother and nephew were also APECED patients. Apart from typical APECED features, she presented also favism, gastroesophageal reflux, familial hip dysplasia and osteopenia. She

reported recurrent respiratory infections since childhood, purulent sputum since 2018, and she was hospitalized in 2019 for pneumonia with a single episode of hemoptysis. From October 2022 she lamented worsening respiratory and systemic symptoms (night sweats, fever), as well as recurrent respiratory exacerbations treated with empiric antibiotics. On the first respiratory culture in January 2023 *P. aeruginosa* was isolated and on the chest CT in February 2023 diffuse cylindrical and varicoid bronchiectasis with tree-in-bud and mucous impaction were shown. She underwent etiologic screening for bronchiectasis with no evidence of another cause of disease and started a respiratory physiotherapy program. At lung function tests, a moderate obstructive syndrome was recognized. After confirmation of chronic *P. aeruginosa* infection, two-week eradication therapy with endovenous meropenem was initiated in May 2023. Due to persistence of *P. aeruginosa* infection and two isolates of *M. intracellulare* on sputum cultures and worsening clinical conditions, she was hospitalized in August 2023 for initiation of antimycobacterial treatment with azithromycin, rifampicin and ethambutol.

Conclusions

This is the first documented case of a patient with lung involvement by APECED in the Sardinian population and the first patient ever to enter a bronchiectasis program. After etiologic screening, APECED itself was indicated as the underlying cause of bronchiectasis. Infectious complications as chronic *P. aeruginosa* infection and *M. intracellulare* pulmonary disease were diagnosed and treated. Pulmonary involvement in APECED is an underdiagnosed entity and a watchful waiting approach with early radiologic screening at insurgence of respiratory symptoms should be implemented for these patients. Although lymphodepleting treatments have proven effective in patients with autoimmune pneumonitis, special attention should be put on management of possibly fatal infectious complications. Therefore, APECED patients with bronchiectasis could benefit from a multidisciplinary management and entrance in a bronchiectasis program.

[15.08] The role of microbiota in explaining the varying response to inhaled antibiotics in bronchiectasis patients with chronic *Pseudomonas aeruginosa* infection: a post-hoc analysis of the ORBIT-3 and ORBIT-4 trials

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Background/Aims:

Replicate randomized controlled trials of inhaled antibiotics in bronchiectasis have given conflicting results. We hypothesised that differences in microbiota could explain differences in trial results.

Methods:

ORBIT3 and ORBIT4 were two replicate, global, double-blind, randomized placebo-controlled trials of inhaled liposomal ciprofloxacin in bronchiectasis patients with chronic *Pseudomonas aeruginosa* infection. Random forest models were used to search for differences in relative abundance of species in baseline sputum, measured by full length 16S rRNA sequencing (LoopSeq), between trials and arms. The impact of selected taxa on treatment estimates was examined using negative-binomial regression for exacerbation frequency.

Results:

A subset of 377 patients of the 598 randomized across both trials had baseline microbiota data available for analysis. Individual differences in taxa and diversity between trials were relatively small at baseline. *Pseudomonas* abundance appeared lower in ORBIT4 vs ORBIT3 ($p=0.159$), and lower within the ORBIT4 treatment arm vs placebo ($p=0.134$). *Rothia* abundance appeared higher in the treatment arms vs placebo in ORBIT3 ($p=0.157$) and ORBIT4 ($p=0.184$), and higher in ORBIT4 vs ORBIT3 overall ($p=7 \times 10^{-7}$). Joint modelling provided evidence of greater treatment efficacy at lower *Pseudomonas* abundance ($p=0.180$) and at higher *Rothia* abundance ($p=0.00471$), consistent with the larger estimated treatment effect from ORBIT4 (Figure 1). Treatment benefit appeared greater in patients with more diverse microbiota (measured by Shannon index, $p=0.0710$), with a suggestion of greater diversity in ORBIT4 patients vs ORBIT3 ($p=0.161$). Particularly within ORBIT4, there is considerable variation in Shannon index by region (ORBIT3: $p=0.305$; ORBIT4: $p=2 \times 10^{-5}$), and differences in the regional pattern between ORBIT4 arms (ORBIT-3: $p=0.776$; ORBIT-4: $p=0.111$; Figure 2). After adjusting for both region and differences in the entire microbiota profile, using linear discriminant analysis to reduce the dimension, the treatment estimate for exacerbation frequency obtained from the ORBIT4 subset was in line with that from ORBIT3 (ORBIT3: RR=0.81, 95% CI 0.54-1.22; ORBIT4: RR=0.82, 95% CI 0.56-1.22). As for the microbiota subset, only adjusting for region in the analysis of all randomized patients also gives a smaller, but not identical, treatment estimate from ORBIT4 (ORBIT3: RR=0.87, 95% CI 0.66-1.15; ORBIT4: RR=0.75, 95% CI 0.59-0.96).

Conclusions:

Differences in baseline microbiota may partly explain inconsistent efficacy results in replicate randomized clinical trials of inhaled antibiotics. Region may have some value as a surrogate for microbiota profile.

Conflict of interest(s) (if any – not included in the 500 words):
NA

[16.01] In vitro and in vivo activity of a novel antibiotic in the polymyxin class against *Pseudomonas aeruginosa*

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Background/Aims:

Pseudomonas aeruginosa (Pa) is an important contributor in the pathogenesis of bronchiectasis. It secretes a range of virulence factors that promote cellular adhesion and tissue invasion, inhibits muco-ciliary function, which collectively result in airway inflammation and tissue damage. Treatment for Pa includes cycles of inhaled antibiotic treatments or their continuous use. However, over time antibiotic resistant Pa strains prevail and impede the effectiveness of treatment, leading to substantial patient morbidity and death. Therefore, new agents which overcome resistance are needed to treat Pa. MRX-8 is a novel antibiotic in the polymyxin class, its *in vitro* and *in vivo* anti-Pa activity is investigated in this study.

Methods:

MIC was determined using broth microdilution method according to CLSI guidelines. MIC₅₀ and MIC₉₀ were obtained against 38 Pa clinical isolates with tobramycin (TOB), amikacin, polymyxin B, and colistin as comparators.

The spontaneous resistance frequency was calculated as the number of colonies on drug-containing plates divided by the number of colonies on drug-free plates.

Mice rendered neutropenic with cyclophosphamide were infected through nasal instillation with Pa (~5*10⁵ CFU/mouse). Animals were treated with nebulized MRX-8 in saline 10 mg/ml for 15, 30, and 45 min 2 hours post infection, with TOB as control. Bacterial load in lungs before and 24 hours after treatment was numerated through plating lung homogenate onto agar plates and recording the colony counts after incubation.

Results:

Minimum inhibitory concentration (MIC) against Pa

Agent	MIC (mg/L)(n=38)	
	MIC ₅₀	MIC ₉₀
MRX-8	1	2

Tobramycin	1	>32
Amikacin	8	>32
Polymyxin B	1	2
Colistin	2	2

MRX-8 spontaneous resistance frequency against Pa at 2x and 8x MIC agar concentrations ranged 2.7×10^{-8} to 1.7×10^{-6} .

MRX-8 efficacy was tested in mice against clinical isolates of TOB-sensitive and TOB-resistant. Within 24 hours post infection of PAE0026 (TOB MIC>32 mg/L) and PAE4039 (TOB MIC=0.5 mg/L), bacterial load in mouse lungs increased in the vehicle control groups. Nebulized MRX-8 treatment 15 to 45 minutes significantly decreased bacterial load in mouse lungs compared to the vehicle control groups against both TOB-sensitive and TOB-resistant isolates, and the efficacy increased with increasing treatment duration. In the model with TOB resistant infection MRX-8 treatment for 45 min decreased bacterial load in the lungs by 2.8 logCFU/lung reduction, while nebulized TOB treatment saw an increase of the bacteria with 2.6 logCFU/lung increase.

Conclusions:

MRX-8 demonstrated potent *in vitro* activity against Pa including drug resistance isolates. In mouse models with Pa lung infections of both TOB-sensitive and TOB-resistant isolates, nebulized MRX-8 demonstrated bactericidal activity.

Conflict of interest(s) (if any – not included in the 500 words):

The authors have no conflict of interest to declare.

[16.02] Eosinophilic Bronchiectasis: prevalence, severity and predictive features. A cohort study.

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Background/Aims: Bronchiectasis (BE) is traditionally characterized by neutrophilic inflammation, but eosinophilic bronchiectasis (EB) has recently emerged. Data about prevalence, clinical and disease severity are lacking. This study aims to assess EB prevalence, compare EB versus non-EB, evaluate Type-2 (T2) high endotype in BE (T2-high EB) versus non-T2-high EB, and identify EB predictors.

Methods: We conducted a prospective study involving 153 BE patients. Data collected included clinical, radiological, and microbiological findings. BE severity was assessed using the Bronchiectasis Severity Index (BSI), FACED, E-FACED, and Bronchiectasis Aetiology and Comorbidity Index (BACI). EB was defined by blood eosinophils count (BEC) ≥ 300 cells/ μ L, and T2-high EB by BEC ≥ 300 cells/ μ L with fractional exhaled nitric oxide (FeNO) ≥ 25 ppb.

Results: The prevalence of EB was 27%, and T2-high EB was 20%. EB patients exhibited poorer lung function and more severe radiologic features, higher BSI ($P=0.001$), FACED ($P=0.002$), E-FACED ($P=0.02$), BACI ($P=0.001$), and experienced more exacerbations ($P=0.0002$), compared to non-EB patients. T2-high EB patients showed worse BSI ($P=0.01$), FACED ($P=0.004$), E-FACED ($P=0.03$), as well as lower FEV₁% ($P=0.03$), FVC% ($P=0.02$), FEF₂₅₋₇₅% ($P=0.02$), compared with non-T2-high EB patients. BEC was positively correlated with BSI ($r=0.33$, $P=0.002$), exacerbations ($r=0.38$, $P<0.0001$), FACED ($r=0.42$, $P<0.0001$), mMRC ($r=0.43$, $P<0.0001$), while FEV₁ (L) and FEF₂₅₋₇₅ (L) showed inverse correlation ($r=-0.30$, $P=0.0002$ and $r=-0.31$, $P=0.0002$, respectively). Logistic regression identified PA colonization (OR 3.92), dyspnoea (OR 2.53), and exacerbations (OR 1.27) as predictors of EB, with a predictive accuracy of 79%.

Conclusions: EB represents a distinct endotype. Dyspnoea, exacerbations and PA colonization may predict EB, emphasizing the importance of early detection for improved outcomes.

Conflict of interest(s) (if any – not included in the 500 words): No conflict of interest

[16.03] Healthcare utilization and health disparities for patients with non-cystic fibrosis bronchiectasis in the United States

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Background

Health disparities are well-documented among patients with pulmonary diseases in the US, with patients of lower socioeconomic status experiencing worse outcomes. The aim of this study was to describe health disparities and differences in healthcare utilization in the US among Medicare-insured patients with non-cystic fibrosis bronchiectasis (NCFBE) to assess the need for system- and community-based interventions.

Methods

This retrospective study used claims data from the 100% Medicare Fee-For-Service database from Jan-2015 to Dec-2021. Patients with NCFBE were identified by the presence of: ≥ 2 outpatient claims (≥ 30 and ≤ 365 days apart) with a bronchiectasis diagnosis code; ≥ 1 claim for a CT scan followed by ≥ 2 outpatient claims ≤ 365 days apart (one ≤ 60 days from the CT scan) with a bronchiectasis diagnosis code; or ≥ 1 inpatient claim with a bronchiectasis diagnosis code with patients with cystic fibrosis excluded. Demographic and clinical characteristics were stratified by income status (qualified for Medicare Part D Low-Income Subsidy status [LIS] versus those who did not). Exacerbations were defined as an inpatient claim with primary diagnosis of bronchiectasis, or an outpatient claim with a bronchiectasis diagnosis code in any position followed by an intravenous antibiotic claim or prescription for an oral antibiotic within 7 days. Summary statistics included means and standard deviations for continuous variables, and percentages for categorical variables, with differences assessed by Chi-squared or independent t-tests.

Results

In total, 120,251 patients with NCFBE were identified, of whom 21,343 (17.7%) qualified for Medicare LIS. Mean age of patients with versus without LIS was 71.8 years and 77.4 years, respectively ($P < 0.001$). Entitlement to Medicare differed between patients with and without LIS, determined by old age and survivors' insurance (55.8% versus 89.9%, $P < 0.001$) and disability benefit (43.1% versus 9.9%, $P < 0.001$). Likewise, 85.9% of patients with LIS were eligible for Medicaid compared with 0.0% of patients without LIS. Demographic differences between groups included 8.4% of patients with LIS living in a neighborhood with no primary care shortage versus 12.9% of patients without LIS ($P < 0.001$; **Table**). Higher proportions of patients with LIS were Black, Asian, Hispanic/Latino, or North American Native (overall $P < 0.001$). Patients with LIS had a mean (SD) Deyo-Charlson Comorbidity Index score of 3.88 (2.72) (versus 3.15 [2.40] without, $P < 0.001$), and more frequently had comorbidities including asthma, COPD, tobacco dependence, anxiety, depression, congestive heart failure, and diabetes (**Table**). Prescription patterns post-index suggested potentially greater use of short- and long-acting bronchodilators. More patients with LIS than without had ≥ 1 exacerbation and ≥ 1 fill for an antibiotic, with a shorter survival-adjusted time to first antibiotic (**Table**).

Conclusions

Patients with NCFBE who qualified for Medicare LIS differed from patients without LIS across demographics known to impact health inequities, including race/ethnicity and housing. Additionally, they more frequently had comorbidities, such as asthma and COPD, also known to be impacted by social environment. Subsequently, exacerbation diagnosis and antibiotic prescription rates were higher in patients with LIS. Additional research is needed to better understand healthcare disparities among patients with NCFBE to support the development of local, regional, and national interventions for equitable care.

Table. Demographics, social determinants of health, comorbidities, and treatment patterns in patients by Medicare low-income subsidy (LIS) qualification

	Qualify for LIS N = 21,343	Do not qualify for LIS N = 98,908	P-value
Baseline Demographics			
Age, years, mean (SD)	71.8 (13.4)	77.4 (7.4)	<0.001
Female Sex, %	68.3%	71.3%	<0.001
Original Reason for Entitlement, %			
Old age and survivors' insurance (OASI)	55.8%	89.9%	<0.001
Disability insurance benefit (DIB)	43.1%	9.9%	<0.001
Dual Eligible (both Medicare and Medicaid) ^a	85.9%	0.0%	<0.001
Race/Ethnicity, %			<0.001
White	62.3%	92.4%	
Black	11.5%	2.7%	
Asian	13.1%	1.4%	
Hispanic or Latino	6.8%	0.3%	
North American Native or Other Pacific Islander	1.5%	0.2%	
Unknown	4.8%	3.0%	
Census Division ^b , %			
Middle Atlantic	17.1%	16.1%	<0.001
South Atlantic	18.9%	24.5%	<0.001
East North Central	10.9%	12.7%	<0.001
Pacific	21.1%	12.6%	<0.001
Social Determinants of Health^c			
Home property type: single-family dwelling, mean (SD)	73.5% (22.1%)	78.0% (17.5%)	-
Language: speaking English not well or not at all, mean (SD)	5.9% (7.8%)	2.6% (3.7%)	-
Having no vehicle, mean (SD)	11.5% (14.7%)	7.1% (10.4%)	-
Living below the federal poverty level, mean (SD)	14.1% (7.8%)	10.1% (5.9%)	-
Primary care shortage area, %			<0.001
Full area shortage	4.6%	3.2%	
Partial area shortage	87.0%	83.8%	
No shortage	8.4%	12.9%	
Baseline Clinical Characteristics			
Deyo-Charlson Comorbidity Index Score, mean (SD)	3.88 (2.72)	3.15 (2.40)	<0.001
Respiratory Comorbidities, %			
Asthma	31.7%	27.3%	<0.001
COPD	55.5%	41.8%	<0.001
Tobacco dependence	14.0%	5.3%	<0.001
Pulmonary fibrosis	12.8%	11.2%	<0.001
Other Comorbidities, %			
Anxiety	28.1%	20.3%	<0.001
Congestive heart failure	20.4%	13.6%	<0.001
Depression	26.5%	16.9%	<0.001
Diabetes	34.6%	20.6%	<0.001
Exacerbations Post-Index^d			
>1 Bronchitis/Emphysema Exacerbation, %	44.0%	28.0%	<0.001

Conflicts of Interest:

This study was funded by Insmmed Incorporated.

Joseph Tkacz and Laura Moore-Schiltz are employees of Inovalon, a paid consultant for Insmmed Incorporated.

Maitreyee Mohanty, Joseph Feliciano, and Melanie Lauterio are employees and shareholders of Insmmed Incorporated.

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Medical writing support was provided by Rosie Morley, PhD of Envision Pharma Group, and funded by Insmmed Incorporated.

[16.04] Association between lung function and bronchiectasis exacerbations in patients with non-cystic fibrosis bronchiectasis

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Background

Non-cystic fibrosis bronchiectasis (NCFBE) is a chronic and progressive inflammatory lung disease characterized by exacerbations and lung damage. The study aim was to assess the association between exacerbations (including subsequent exacerbations) and lung function decline in patients with NCFBE.

Methods

This retrospective cohort study used Optum's Market Clarity Integrated Claims and Clinical database from 01 Jan 2017 to 31 Mar 2021. Patients ≥ 12 years old were identified as having NCFBE if they had ≥ 2 outpatient claims with an NCFBE diagnosis ≥ 30 days apart, or ≥ 1 inpatient claim with an NCFBE diagnosis. Index date was date of the first claim with NCFBE diagnosis. Patients had ≥ 12 months continuous enrollment before (baseline), and ≥ 24 months after (follow-up), index date. Lung function status was assessed during baseline and follow-up and was categorized into normal ($FEV_1 \geq 80\%$ of predicted), mild ($50\% \leq FEV_1$ predicted $< 80\%$), moderate-to-severe ($30\% \leq FEV_1$ predicted $< 50\%$), or very severe ($FEV_1 < 30\%$ predicted) status. Exacerbations were assessed at follow-up and were defined using diagnosis codes for NCFBE with exacerbation, NCFBE-specific utilization (inpatient or emergency room), antibiotic treatment, and related symptoms (eg, hemoptysis, purulent sputum, or shortness of breath). Descriptive statistics are presented, with differences between groups assessed using univariate Pearson Chi-square test for binary measures or two-sample t-test for continuous measures.

Results

Of 12,018 patients included, 912 had FEV_1 assessments during baseline and 615 had FEV_1 assessments during baseline and follow-up. Patients in a lung function status category with a lower $FEV_1\%$ predicted during baseline were more likely to be in a category with lower $FEV_1\%$ predicted during follow-up (**Table**). Similarly, a larger proportion of patients in a lung function status category with a lower $FEV_1\%$ predicted during baseline experienced any exacerbation during follow-up and experienced exacerbations leading to hospitalizations, or with acute respiratory failure, or intravenous antimicrobial therapy during follow-up (**Table**).

Conclusions

Lung function status categories with a lower FEV₁% predicted (mild, moderate-to-severe and very severe) were associated with NCFBE exacerbations and a sustained worsening of patient lung function and disease status during follow-up. Exacerbations add to the burden on patients with NCFBE, highlighting the need for more effective treatment options.

Table. Lung Function Status and NCFBE Exacerbations During Follow-up by Baseline Lung Function Status

	Lung function status during baseline ^a			
	Normal (n=425)	Mild (n=340)	Moderate-to-severe (n=113)	Very severe (n=34)
Average FEV₁% predicted				
During baseline, n, mean (SD)	425 100.9 (18.7)	340 67.1 (9.1)*	113 42.2 (9.1)*	34 22.7 (6.1)*
During follow-up, n, mean (SD)	290 97.5 (19.3)	216 68.6 (15.6)*	88 48.3 (17.9)*	21 28.9 (16.3)*
First six months of follow-up	206 98.7 (21.1)	152 67.4 (12.5)*	63 48.1 (18.5)*	21 24.2 (9.0)*
Second six months of follow-up	160 100.2 (19.1)	125 68.1 (14.0)*	52 48.3 (19.5)*	13 27.5 (14.3)*
Third six months of follow-up	157 98.0 (22.1)	123 68.9 (13.7)*	47 45.7 (19.3)*	14 34.2 (25.7)*
Fourth six months of follow-up	152 97.6 (21.0)	102 69.6 (24.5)*	47 50.1 (22.6)*	15 37.0 (28.4)*
Lung function status at first follow-up visit with FEV₁% predicted, n	290	216	88	21
Normal, n (%) patients	257 (88.6)	23 (10.6)*	7 (8.0)*	0 (0.0)*
Mild, n (%) patients	28 (9.7)	182 (84.3)*	11 (12.5)	0 (0.0)
Moderate-to-severe, n (%) patients	5 (1.7)	10 (4.6)	68 (77.3)*	4 (19.0)*
Very severe, n (%) patients	0 (0.0)	1 (0.5)	2 (2.3)*	17 (81.0)*
Exacerbations during follow-up, n	425	340	113	34
Total per year, mean (SD)	0.5 (1.0)	0.7 (1.1)*	0.7 (1.2)	0.9 (1.3)
Any exacerbation, n (%) patients	157 (36.9)	169 (49.7)*	56 (49.6)*	20 (58.8)*
Exacerbations requiring hospitalizations, or with acute respiratory failure, or intravenous antimicrobial therapy, n (%) patients	18 (4.2)	28 (8.2)*	20 (17.7)*	8 (23.5)*

* Indicates $P < 0.05$ compared with 0 exacerbations at baseline, or normal lung function at baseline, by univariate Pearson Chi-square test for binary measures or two-sample t-test for continuous measures. FEV₁, forced expiratory volume in the first second; NCFBE, non-cystic fibrosis bronchiectasis.

Conflicts of Interest

This study was funded by Insmed Incorporated.

Ruxana Sadikot has no conflicts of interest to declare.

Phani Veeranki and Nnaemeka U Odo are employees of Optum, a paid consultant for Insmed Incorporated.

Phani Veeranki is a shareholder of Optum.

Maitreyee Mohanty, Joseph Feliciano, and Marko Obradovic are employees and shareholders of Insmed Incorporated.

Medical writing support was provided by Rosie Morley, PhD of Envision Pharma Group, and funded by Insmed Incorporated.

[16.05] Significance of *Aspergillus* sensitization in non-cystic fibrosis bronchiectasis

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Background/Aims: *Aspergillus* sensitization (AS) is associated with poor lung function in patients with cystic fibrosis and bronchial asthma. However, the significance of AS in non-CF bronchiectasis remains unclear. Our primary objective was to evaluate the lung function and the severity of bronchiectasis in those with and without AS.

Methods: We performed a retrospective analysis of patients with non-CF bronchiectasis. We performed investigations per the ERS guidelines to ascertain the underlying etiology. We also performed tracheal mucosal biopsy or whole exome sequencing in selected patients. We excluded patients with underlying asthma or allergic bronchopulmonary aspergillosis. We retrieved the following information: spirometry, chest CT, complete blood count, serum *Aspergillus fumigatus* specific IgE, sweat chloride, serum immunoglobulin levels, and sputum cultures. AS was defined in those with *A.fumigatus*-specific IgE ≥ 0.35 kUA/L. Data are presented as number (percentage), mean $\pm$ standard deviation (SD), or 95% confidence intervals (CI). The differences between continuous and categorical variables were analyzed using the Mann-Whitney U or chi-square tests. We performed a multivariable logistic regression analysis to evaluate if AS was associated with poor lung function (FEV1 <50% predicted). A p-value <0.05 was considered statistically significant.

Results: We included 190 patients with bronchiectasis. The mean $\pm$ standard deviation age of the study population (103 [54.2%] women) was 43 $\pm$ 15 years. The mean (95% CI) duration of symptoms was 5.9 (4.5-6.7) years. We could identify a cause of bronchiectasis in 156 patients (post-tuberculous [n=128], primary ciliary dyskinesia [n=8], common-variable immunodeficiency [n=3], Macleod's syndrome [n=6] and others. The mean (95% CI) segments involved by bronchiectasis was 6 (5-7). The mean (95% CI) serum *A.fumigatus*-specific IgE was 1.8 (0.7-3) kUA/L.

Sixty-one (32.1%) patients had AS. Patients with AS had significantly higher mean serum levels of total IgE (1337 vs. 277, p<0.001) and were more likely to have TB as the underlying cause of bronchiectasis. We found no difference in the FACED score or *Pseudomonas* colonization between the two groups. We found no difference in the mean FEV1 (1.6 vs. 1.6 liters) and FVC (2.1 vs. 2.2 liters) between those with or without AS. Spirometry was normal in 36 (18.9%) patients, while obstruction and restriction were seen in 93 (48.9%) and 61 (32.1%) patients, respectively.

On a multivariable logistic regression analysis, AS was not associated with severe lung function after adjusting for the underlying cause of bronchiectasis, duration of symptoms, extensive bronchiectasis, and blood eosinophilia.

Conclusions: We found AS in one-third of patients with non-CF bronchiectasis. However, AS was not associated with poor lung function on spirometry.

Conflict of interest(s) (if any – not included in the 500 words): None

[16.06] The Healthy Lungs Follow up Study: Respiratory health ten years after LRTI hospitalisation as an infant

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Background: The Healthy Lungs Study (2010-2014) at Kidz First Hospital in South Auckland New Zealand enrolled 403 children under two with severe lower respiratory tract infections. They were randomly assigned to 'intervention' or 'control' groups. At the final two-year assessment, significant respiratory morbidity was recorded in both groups. (Byrnes CA Thorax. 2020 Apr;75(4):298-305). These children aged 10-13 years can now receive a comprehensive respiratory assessment.

Aim: To describe the prevalence of respiratory disease at 10-13 years of age, for the first 100 children seen as part of the Healthy Lungs Follow-Up study (HRC 20/1184).

Method: The first 100 children (of 206) are described without analysing by intervention. Participants had a clinical review, including respiratory symptoms, respiratory examination, health questionnaires, and spirometry. A non-contrast chest CT scan was performed during inspiration for all children who consented and attended (73). Two blinded radiologists scored the scans using the modified Bhalla score.

Results: The mean age was 11.5 years (range 10.26 – 12.90). Almost all participants were of Māori (24%) or Pasifika (69%) ethnicity, and over half (66%) live in the 20% poorest quintile. Only 41% of the children seen in the follow-up had a normal respiratory clinical review (100% completed), normal lung function (87% completed) and a normal CT scan (73 % completed). Respiratory symptoms were common; 14% with wet cough and 7% wheezy. In those with acceptable spirometry (87), the FEV1 z-score was low (<1.64SD) for 13.8% and 5.7% had a positive bronchodilator response. Thirty-six percent had a BMI greater than the 99.6th centile. Only 37% of the cohort had a normal chest CT scan. and the mean modified Bhalla score was 24.7 (range 17 – 27). A further 22 children had mild bronchial dilatation on their chest CT scan but no clinical history consistent with bronchiectasis. Overall, 34% had asthma and 12% had bronchiectasis. Forty-two children required a referral to at least one health service for review of a clinical problem.

Conclusion: Children admitted with an early respiratory infection should be considered high risk for development of chronic respiratory disease. Regular follow-up, awareness and recognition of chronic symptoms, early diagnosis and prompt initiation of management are all important aspects to improve to prevent poor long-term respiratory outcomes.

Conflict of interest(s) (if any – not included in the 500 words): nil

[16.07] The Koira4Rukahukahu: Lungs4Life model of care-early identification of chronic lung disease

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Background: New Zealand Maaori and Pasifika children are over-represented in hospitalisations for lower respiratory tract infections (LRTIs) in early life often with repeat admissions and development of chronic lung disease including bronchiectasis. Previous studies in this population suggest that 5-7% of those admitted <2 y with severe LRTI will go on to develop bronchiectasis. The Koira4Rukahukahu:Lungs4Life community model of care has been developed to reduce these inequities and has been implemented in Counties Manukau since June 2021. Te Whatu Ora Counties Manukau Health is a health district in Auckland New Zealand with a population of 600,000, 37% living in high deprivation areas and a birth cohort of over 8000 including 35% Pasifika and 20% Maaori infants.

Aims: To review the processes and outcomes of the Lungs4Life programme at Te Whatu Ora Counties Manukau district in Auckland New Zealand from June 2021 until February 2024.

Methods: Tamariki are enrolled in the Lungs4Life programme if <2 years age, have ≥ 3 admissions with LRTIs or there is clinical concern by a paediatrician of ongoing respiratory morbidity. Baseline demographics are recorded. Community nursing assessments are then performed at 30 days, 3 months 12 months 2 year and 5 years. with data from each entered onto a REDCap database and open communication with families through email and cell phone. Lungs4Life Nurse Practitioners and Paediatricians perform secondary and tertiary care respiratory and other reviews as required. A retrospective review of the REDcap database was performed for all data from June 2021 to February 2024

Results: 177 children were enrolled in the Lungs4Life programme with 62 Maaori, 96 Pacific, 10 European, 6 Asian, and 3 other. Sixty-six percent live in the lowest deprivation quintile and 47% live in poor housing conditions. Smoke exposure occurs in 30%. 75% of tamariki are up to date with their immunisations at enrolment. To date 24 have been treated for chronic cough with antibiotics, 38 have been commenced on asthma preventative treatment, 22 have been diagnosed as aspiration or awaiting assessment, 5 have been diagnosed with Bronchiectasis and 4 are awaiting a chest CT scan. 99 children have been referred to secondary/tertiary care. Many other health issues have been identified for whaanau including poorly controlled eczema, obstructive sleep apnoea, and developmental delays. Ability to maintain contact these urban families who have very limited resources in has been an ongoing challenge.

Conclusion

The high number of tamariki enrolled onto the programme highlights the burden of respiratory morbidity for this group. The high numbers and difficulties in contact have presented challenges in achieving timely assessment. Ongoing evaluation will provide insights into the health needs of a cohort of children at high risk of respiratory disease. It will

directly inform programme delivery and suggest changes required to keep it sustainable and helpful to whaanau.

Conflict of interest(s) : nil

[17.01] Utilizing Continuous Cough Monitoring to Evaluate Bronchiectasis Therapy

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Background/Aims: Cough, a significant symptom of bronchiectasis, is frequently addressed with multimodal interventions aimed at enhancing airway clearance. Recently, the advent of acoustic cough monitors has enabled continuous passive monitoring of cough in patients. In this pilot study, we utilized Hyfe's CoughTracker to demonstrate the feasibility and effectiveness of various techniques for inducing and reducing coughing.

Methods: Patients admitted to the National Jewish Health bronchiectasis program participated in a standard evaluation and treatment regimen while their coughing was continuously monitored using a dedicated mobile phone running the AI-powered continuous cough monitoring Hyfe app (version 1.8.0(1)). The presence and activities of the respiratory therapist, as well as the types of therapies administered, were recorded. For each patient, cough patterns were charted alongside therapeutic interventions. Visual assessments were conducted to identify associations between changes in cough frequency and therapeutic activities, and overall trends in cough patterns were analyzed.

Results: Nine patients were enrolled in the study. Continuous data were obtained for five patients, who exhibited cough rates exceeding four coughs per hour on the first day. Within the first 24 hours, cough counts for these five patients ranged from 224 to 887. All patients experienced a reduction in coughing during the first four days of treatment, with decreases ranging from 43% to 78%. No consistent relationship was observed between Aerobika, High Frequency Chest Wall Oscillation (HFCW), and Volara therapy and increased coughing. One patient showed a significant increase in cough frequency following hypertonic saline sputum induction. Figure 1, left panel shows the daily average of hourly cough counts in bronchiectasis patients with significant cough over the course of their airway clearance program. Figure 1, right panel: cough monitoring results displayed in hourly increments showing the timing of cough inducing interventions including: hypertonic saline sputum induction (blue), Aerobika combined with hypertonic saline (purple), and vest trials (green).

Conclusions: This is the first report demonstrating the feasibility of continuous cough monitoring to assess the clinical impact of bronchiectasis therapy. The average cough rate significantly decreased in all patients, indicating that the airway clearance protocol at National Jewish Health effectively reduces coughing rapidly. The effects of specific cough-inducing procedures varied between devices and patients. Analysis of the patient monitored for the longest period revealed an increase in cough during hypertonic saline inhalation, followed by a reduction in the subsequent 2 to 4 hours.

If confirmed in larger studies, continuous passive cough monitoring could be a valuable tool for identifying patients with high cough rates, personalizing the selection of the most effective interventions, and demonstrating to patients the benefits of adhering to airway clearance programs.

Conflict of interest(s) (if any – not included in the 500 words): MR, PMS and MG are employees and own equity in Hyfe Inc. CLD is a scientific advisor to Hyfe Inc.

[17.02] Sputum Microbiota correlates with metabolome and clinical outcomes in Asthma-Bronchiectasis Overlap

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Background/Aims:

Co-existing bronchiectasis and asthma (Asthma-Bronchiectasis Overlap, ABO) is common in practice. We aimed to investigate the microbiota and metabolome of adults with ABO (including its subtypes), and determine the relevance with clinical characteristics, inflammatory endotypes and exacerbation risks.

Methods:

In this prospective cohort study (between May 2018 and August 2023), we recruited adults with ABO (N=99), asthma (N=61) and bronchiectasis (N=87). At baseline, patients underwent comprehensive assessments and sputum collection. We profiled microbiota via 16S rRNA sequencing and metabolome via liquid chromatography/mass spectrometry. Patients were followed-up to record exacerbations.

Results:

Microbiota composition and metabolites separated among asthma, ABO and bronchiectasis, and between eosinophilic and non-eosinophilic ABO at steady-state. Baseline Shannon-Wiener diversity index (SWDI) of microbiota was highest in asthma, followed by ABO. Both *Pseudomonadaceae* and *Rothia* best discriminated ABO from asthma and bronchiectasis. Microbiota compositions correlated with bronchiectasis severity and airflow limitation. More microbiota interactions were identified in ABO than in asthma and bronchiectasis, as did in non-eosinophilic ABO than in eosinophilic ABO. ABO patients with low SWDI with sputum eosinophilia or those with high SWDI without sputum eosinophilia exhibited shorter time to the first exacerbation ($P<0.05$). We identified some significant correlations between 15 differential genera and 50 differential metabolites. Except for *Enterobacteriaceae* (negative correlation), the relative abundance of most genera yielded correlated positively with tryptophan metabolism.

Conclusions:

Integrated microbiota and metabolome profiles, together with eosinophilic inflammatory endotyping, may inform exacerbation risk stratification and personalized management of ABO.

Conflict of interest(s) (if any – not included in the 500 words):

The authors declared no conflict of interest with any financial organization regarding the material discussed in the manuscript.

[17.03] Exploring the Intersection of Bronchiectasis and Sarcoidosis: A Clinical Case Study

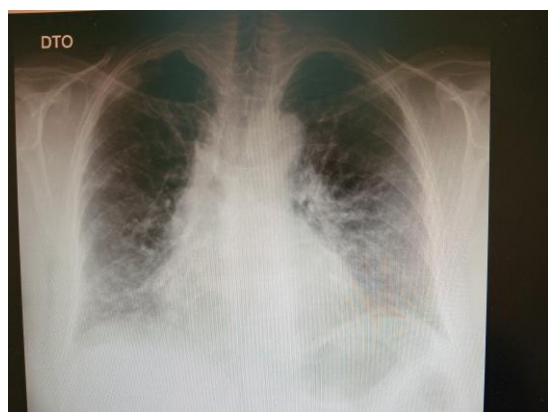
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Bronchiectasis is a permanent dilation and abnormal widening of the bronchi that usually occurs in the context of airway inflammation. Sarcoidosis is a disease that causes inflammation and granulomas in various organs, especially the lungs. Sarcoidosis can cause bronchiectasis by damaging the lung tissue and causing scarring, fibrosis and/or blockage of the airways. Bronchiectasis due to sarcoidosis is rare but can lead to serious complications such as respiratory failure.

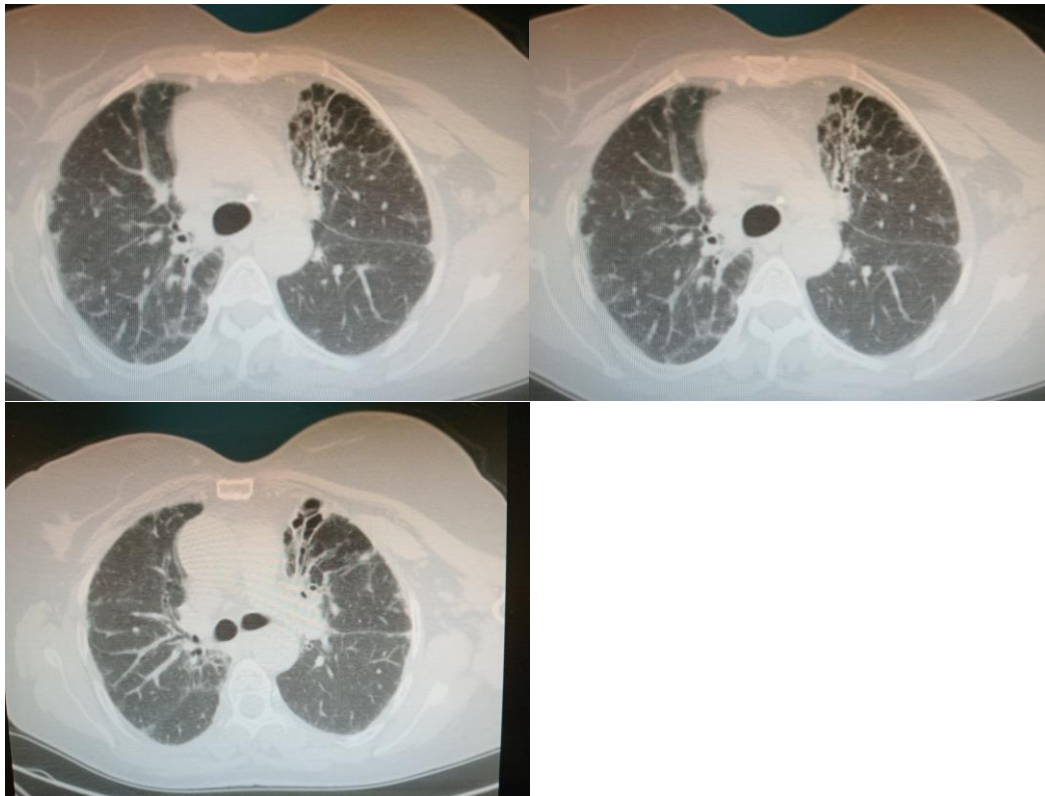
We present the clinical case of a 57-year-old woman diagnosed with hypertension, dyslipidemia, hyperuricemia and recurrent urinary infections, medicated with beta-blocker, ACE inhibitor, statin and aspirin, who sought clinical care due to dyspnea, chronic productive cough with 5 months of evolution and recent onset of cervical lymphadenopathy. She is unaware of any problems in her childhood, denies weight loss, fever, night sweats, syncope or lipothymia and has never been a smoker. She tends to cough most days and has one to two significant lung infections per year.

Initial screening blood tests revealed no abnormalities. Lung auscultation showed coarse crackles, especially in the upper thirds of the lungs, and cardiac auscultation showed no changes. Cervical adenopathy biopsy revealed chronic necrotizing granulomatous lymphadenitis. The x-ray (image 1):



revealed a bilateral hilar lymphadenopathy, well-defined opacities at the hilum of the lungs, with a butterfly-wing appearance, alongside with diffuse reticular opacities throughout the lung fields, suggesting interstitial lung disease.

The Computed tomography (image 2, 3 and 4):



showed fibro scar densifications of the lingular segment, atelectasis and cylindrical bronchiectasis of the upper lobes. No masses or consolidations. The patient was diagnosed with diffuse pulmonary fibrosis of unknown etiology and bronchial lavage, bronchoalveolar lavage and bronchial aspirate were requested. These tests revealed lymphocytic alveolitis with a CD4/CD8 ratio of 4.353, positive aspirate for pneumococci and negative cytology for malignancy. After undergoing antibiotic therapy, the user was advised to consult a pulmonologist, where she maintains clinical follow-up, currently suspecting a diagnosis of sarcoidosis, in the fibrotic phase.

In conclusion, the presented clinical case highlights the intricate interplay between different respiratory conditions. Bronchiectasis, characterized by permanent dilation of the bronchi, can be induced by sarcoidosis, a systemic disease known for its inflammatory and granulomatous effects, particularly in the lungs. The case underscores the importance of thorough investigation in patients presenting with respiratory symptoms, as the underlying etiology may be multifaceted and require specialized care. Through diligent examination and diagnostic testing, healthcare professionals can guide appropriate management strategies, aiming to mitigate complications and improve patient outcomes.

[17.04] Multimorbidity and clinical outcomes in bronchiectasis : data from the EMBARC registry

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Background/Aims: Patients with bronchiectasis are frequently elderly and have other associated conditions. The relationship between bronchiectasis and non-respiratory multimorbidity has not been previously investigated.

Methods: The EMBARC registry is a prospective observational cohort of patients enrolled 2015-2022. Co-morbid illnesses were recorded at baseline. Multimorbidity was defined as >1 non-respiratory co-morbidity. Follow-up for up to 5 years was used to identify the relationship between each additional morbidity and future outcomes.

Results: 16963 patients with 28 European countries were included. 6139 (36.2%) had multimorbidity and the most common co-morbidity was cardiovascular 5510 (32.5%). Each additional morbidity was associated with increased respiratory symptoms (mean difference - 2.29 points, 95%CI -2.55 to -2.03, p<0.0001), an increased risk of exacerbations (rate ratio

1.10, 95%CI 1.09-1.12, $p<0.0001$, adjusted for BSI RR 1.03, 95%CI 1.02-1.05, $p<0.0001$), and increased hospitalization (RR 1.28, 95%CI 1.25-1.31, $p<0.0001$, adjusted for BSI, RR 1.10, 95%CI 1.08-1.13, $p<0.0001$). Each additional morbidity increased the risk of death (HR 1.35, 95%CI 1.31-1.39, $p<0.0001$, BSI adjusted HR 1.23, 95%CI 1.19-1.27, $p<0.0001$).

Conclusions: Non-respiratory multimorbidity such as cardiovascular disease, diabetes, psychiatric conditions, renal and neoplastic diseases are associated with an increased risk of exacerbation, severe exacerbations and mortality in bronchiectasis.

[17.05] The impact of a specialist physiotherapist in the Leeds Adult Bronchiectasis Service.

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Background/Aims:

The British Thoracic Society guideline for bronchiectasis in adults (2019) recommends review by a specialist respiratory physiotherapist and advise the prescription of airway clearance techniques to improve sputum clearance, reduce symptoms and reduce future exacerbation risk. In clinical practice, however, long waits from referral to assessment and treatment can be a barrier to commencement and subsequent ongoing engagement with optimised airway clearance.

To address this, the Leeds bronchiectasis service underwent a pathway redesign to include access to a specialist physiotherapist for all new patients (NP) at the time of their first appointment with the medical team. The physiotherapist provided respiratory assessment, treatment and education of airway clearance, breathlessness management and exercise advice.

This was in addition to the existing weekly bronchiectasis physiotherapy outpatient clinic.

Methods:

A retrospective service evaluation was performed comparing data relative to the 6 months prior and after the remodelling and development of the service. Total number of new patients attending clinic, referral date to physiotherapy and the date of that physiotherapy review were collected.

Results:

In the 6 months prior to the change in service a total of 31 new patients were assessed in the service, with 13 (42%) referred for assessment and treatment by physiotherapy. In the 6 months after the introduction of the specialist physiotherapist into the Bronchiectasis clinic, a total of 37 new patients were seen in clinic, 26 (70%) of whom were referred, and 25 seen simultaneously by the specialist physiotherapist. Reasons for not being referred included patients being stable and not requiring ongoing secondary care or already having an established airway clearance routine. The waiting time from referral to specialist physiotherapy review was reduced from 23 to 0 weeks. An increase in total physiotherapy contacts (NP and follow-ups) was also noted in the 6 months after service remodelling (141 vs 40).

Conclusions:

Ease of access to a specialist respiratory physiotherapist has increased the number of physiotherapy referrals, significantly decreased wait time, and made the service more efficient. Information on the clinical impact of these changes and patient satisfaction is presently being collected.

Conflict of interest(s) (if any – not included in the 500 words):

No conflict of interest.

[17.06] Adherence to respiratory physiotherapy in patients with bronchiectasis: a multicenter preliminary prospective study.

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Background/Aims:

Respiratory physiotherapy (RT) improves physical performance and quality of life in individuals with bronchiectasis and can modify the course of the disease by reducing the number of exacerbations. Although adherence to prescribed treatment is crucial to reach these important functional outcomes, often patients with chronic respiratory conditions are not compliant to the prescribed RT program. Aim of this study is to assess adherence to RT in patients with bronchiectasis and evaluate factors that can implement or reduce adherence.

Methods:

Continuous adult and stable bronchiectasis patients, with an optimized RT program, were enrolled during RT visits at the outpatient clinic of the IRCCS Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano and IRCCS Humanitas Research Hospital from 11/03/2024 to 31/05/2024. Adherence in the different domains of RT (airway clearance, nasal irrigation, physical activity, physical exercise and inhaled therapy) was measured with a previously developed questionnaire, that evaluates both patient-reported adherence to the prescribed treatments and the practical skills in the prescribed RT techniques assessed by a respiratory physiotherapist. The maximum global score is 5 (complete adherence and good practical skills), the minimum is 0; a score <4 was considered low adherence in this study. Demographic and clinical data of the subjects were recorded and compared among the adherent (global score ≥ 4) and non-adherent (global score <4) group, using T Test or Chi-squared test.

Results:

70 patients were enrolled [15(21%) males, mean age 64.8 (13.3)]. The global score for adherence to RT was 3.93 (1.03) with 23 (33%) subjects in the non-adherent group and 47 (67%) in the adherent group. Nasal irrigation and airway clearance techniques showed globally less adherence than inhaled therapy. Subjects of the adherent group experienced a significant higher number of exacerbations in the previous 12 months than the non-adherent ones (2.09 (1.53) *versus* 1.13 (1.52) p value 0.017). No significant differences among the two groups were found in age, sex, BMI, bronchiectasis severity index and number of activities prescribed.

Conclusions:

Form this preliminary data, adherence to RT in subjects with bronchiectasis has to be implemented and more attention should be paid to patients experiencing frequent exacerbations. More studies are needed to investigate clinical, social, and demographical factors that can predict low adherence in this patient population.

Conflict of interest(s) (if any – not included in the 500 words):

No conflict of interest for this work

[17.07] Asthma assessment in bronchiectasis (BE): preliminary results

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Background/Aims:

According to recent EMBARC data, up to 31% of BE patients have a reported diagnosis of asthma, both as comorbidity or as cause of BE. Unfortunately, no standard definition of the association asthma + BE is available. The aim of our study is to evaluate the presence of asthma symptoms, hyperreactivity, allergy and blood eosinophils in BE without known airways comorbidities.

Methods:

We included 55 patients with stable BE, 70% women, mean age 59 year old.

They underwent clinical evaluation with investigation of specific asthma symptoms, spirometry plus post-bronchodilator (PBD) reversibility test and FeNO (cut off ≥ 25 ppb), blood testing for peripheral eosinophils (elevated if $>300/\text{mm}^3$), total IgE and Phadiatop.

Results:

Average FEV1 was 80.4%; PBD test was performed in 37 patients and results were analyzed comparing 1991 and 2022 ERS/ATS criteria: 3 patients had a positive PBD according to both definitions; 2 more had positive PBD according to only one definition. One patient presented paradoxical PBD.

In the whole cohort, mean FEV1 PBD change was 4.6% of preBD FEV1% and 3.3% of predicted value.

FeNO was ≥ 25 in 13/54 patients (24%; mean level 20.3 ppb, min <5 , max 90 ppb).

Peripheral eosinophilia was confirmed in 6/44 patients (mean value 170, median 100); IgE were < 150 in 90.2% of the cohort (37/41); only in one case IgE were elevated (788 IU/ml). Mean level 78.7 IU/ml, median 29.3, SD 141.

Phadiatop was positive in 8/38 (21%).

Regarding symptoms, of 49 responders, 90% (44) reported having had one or more symptoms during their life: cough 78% (38), wheezing 51% (25), dyspnoea 45% (22), chest tightness 31% (15). Symptoms appeared or worsened with viral infection in 70% (31), varied in intensity and/or overtime in 57% (25), were worse at night or on waking on 41% (18), and were triggered by exercise or external conditions in 39% (17).

FeNO level (ppb) showed a positive correlation with FEV1% ($p=0.01$) and, curiously, negative correlation with absolute number of leukocytes ($p=0.032$) and neutrophils

($p=0,032$). Increased FeNO (≥ 25) had positive correlation with eosinophilia ($p=0.002$) and a positive trend according to IgE levels ($p=0,07$).

PBD results and positive Phadiatop did not correlate with any variable.

By applying GINA criteria, we identified 3 patients with a combination of positive PBD, wheezing and other symptoms compatibles with asthma, while 4 patients presented elevated FeNO, peripheral eosinophilia and compatible symptoms altogether; two of them had positive Phadiatop, none positive PBD.

Conclusions:

According to our preliminary data, the combination of clinical, functional and laboratory variables allowed a possible diagnosis of asthma in only 7/44 cases (16%). In addition, our data confirm the correlation of FeNO with peripheral eosinophilia in BE patients.

A bigger sample size is required to confirm these results, and further tests, such as methacoline, sputum cell count, quality of life questionnaires, chronic rhinosinusitis workout, could allow a better comprehension of asthma and asthmatic features in BE patients.

Conflict of interest(s) (if any – not included in the 500 words):

None of the authors has conflicts of interest to declare related with this original work.

[18.01] Treatment outcomes and clinical characteristics of people with tuberculosis/non-tuberculous mycobacteria coinfection between 2015-2021 in Ghana, a retrospective observational study

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Background/Aims:

The importance of non-tuberculous mycobacteria pulmonary disease (NTM-PD) is gradually being recognised, with many sub-Saharan African (SSA) countries increasingly reporting NTM isolation in sputum samples of presumed tuberculosis (TB) patients. There is, however, little documentation on TB/NTM coinfection and no existing guidelines. Thus, our study sought to elaborate on the clinical characteristics of such patients, the common NTM isolated and treatment outcomes of the TB management.

Methods:

We retrospectively analysed the medical records of all confirmed/presumed drug-resistant (DR-)TB patients who had an NTM isolated from a respiratory sample at baseline, diagnosed at the Eastern Regional Hospital laboratory covering twelve regions of Ghana between 2015 and 2021. Smear microscopy, culture using MGIT and drug-susceptibility testing were performed on all sputum samples. All isolated probable NTMs were stored at -20°C and later identified using GenoType CM/AS (Bruker, Germany) and Sanger sequencing of 16sRNA and *rpoB* genes. The medical records of patients were assessed for their clinical characteristics and DR-TB outcomes.

Results:

A total of 908 patients produced 2133 samples over seven years. 756/2133 (35%) and 1377/2133 (65%) samples were submitted for diagnosis and follow-up, respectively. 41 patients were identified with NTM (53 species), 14 of whom had NTM at baseline. All 14 patients had Xpert/MTB results of MTB detected and rifampicin resistance detected, a TB/NTM coinfection diagnosis. Of the 14, 12 (85%) were male, 9 (64%) had previous TB and 2 (14%) were HIV positive. We isolated *Mycobacterium intracellulare* in 10 (71%), *M. fortuitum* in 3 (21%) and *M. abscessus complex* in 1 (7%). Medical records of 11/14 patients were retrieved. All patients were initiated on a DR-TB regimen as per national guidelines. No specific NTM-targeted therapy was initiated. Of these, 7 (64%) had a favourable DR-TB treatment outcome, while 4 had repetitive NTM isolates of the same species during DR-TB treatment.

Conclusions:

We present the first dataset of documented DR-TB/NTM coinfection in Ghana and potentially SSA. Favourable DR-TB outcome — based on microbiological definitions — was noted among the investigated patients, even for those who had multiple NTM of the same species isolated from their sputum. However, it was not possible to determine the clinical relevance of repetitive NTM isolation, requiring further investigation of patients with post-TB treatment and persistent clinical symptoms.

Conflict of interest(s) (if any – not included in the 500 words):

Elizabeth Tabitha Abbew is a PhD Student receiving research funds under DGD Scholarship in Belgium.

[18.02] Assessing the therapeutic potential of DosRS in *M. avium*

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Background: Rapidly-growing non-tuberculous mycobacteria (NTM) of the *Mycobacterium abscessus* complex (MABSC) and slowly-growing NTM of the *M. avium* complex (MAC) have emerged as important human pathogens globally and are linked to an increasing number of pulmonary infections among patients with structural lung disease such as COPD, bronchiectasis, and cystic fibrosis. The low cure rate of currently available treatment regimens (despite a minimum of 12 months of antibiotic therapy), notable side effects, and frequent bacterial re-emergence associated with these regimens highlights the need for alternative approaches to treat NTM infections. In particular, therapies capable of killing persistent drug tolerant bacilli are essential.

We have previously identified orally available antimalarial synthetic peroxides targeting the DosRS two component system (TCS) of MABSC. These drugs inhibited biofilm formation, bacterial survival under hypoxia and drug tolerance *in vitro* and showed efficacy *in vivo*. Here, we set out to assess the therapeutic potential of MAC DosRS and test the efficacy of synthetic peroxides compounds in these slowly-growing mycobacteria.

Methods: We deleted the *dosRS* operon from *M. avium* subsp. *hominissuis* MAH11 and analyzed the phenotypic characteristics of the absence of the TCS. We performed RNA sequencing to delineate the genes under control of DosRS. We assessed the contribution of DosRS to the ability of this NTM to survive under hypoxic conditions, form biofilms, develop phenotypic drug tolerance *in vitro* and for survival *in vivo* in mice. Finally, we determined if treatment with synthetic peroxides phenocopied disruption of *dosRS* in *M. avium* *in vitro*.

Results: We determined both oxygen depletion and nitric oxide were activators of *dosR* and genes in the DosRS regulon. Our RNA sequencing results allowed us to identify a small subset of genes induced under hypoxic conditions and belonging to the DosRS regulon. Survival under hypoxic conditions was severely affected in *M. avium* Δ *dosRS*, in particular at acidic pH. Moreover, the absence of DosRS rendered *M. avium* grown under hypoxic conditions more susceptible to drugs currently used in the clinic for treatment of MAC infections. Surprisingly, biofilm formation was not dependent on DosRS in MAC. *M. avium* Δ *dosRS* was not attenuated *in vivo* in BALB/c mice when compared to *M. avium* WT. Finally, we identified a subset of synthetic peroxides that inhibited *M. avium* biofilm formation, induction of DosRS regulon and had bactericidal activity *in vitro*.

Conclusions: MAC DosRS is required to survive stresses commonly encountered during infection (low oxygen and nitric oxide) and to enter a drug tolerant, non-replicative state by inducing a small subset of genes. We identified synthetic peroxides inhibiting DosRS and are currently working on assessing their therapeutic efficacy *in vivo* alone or in combination with standard of care drugs. Repurposing these agents provides a much needed opportunity for innovative combination chemotherapy that could be available in the foreseeable future for patients with MAC infections.

[18.03] What care should people with NTM expect to receive? Developing UK national standards of care

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Background/Aims: Non-tuberculous mycobacteria (NTM) were until recently not regarded as an important cause of human disease. High-quality information on their management is limited, and clinicians may have little experience of providing care to people with NTM disease. Despite guidelines describing the recommended management of NTM-pulmonary disease being available, recent work by NTM Network UK has identified considerable variation in practice across the UK National Health Service (NHS). A Standard of Care is different to a guideline and reflects the level at which the average, prudent provider would practice. It can help services achieve the delivery of consistent, standardised, high-quality care, and so improve the experience for people with NTM disease. Here we describe the development of UK NTM Standards of Care.

Methods: In February 2022, a call for volunteers was put out through the UK clinical-research group NTM Network UK and the patient association NTM Patient Care UK to develop NTM Standards of Care. Requests for support were also made to professional bodies and stakeholder organisations. Following the first meeting of the multidisciplinary Steering Committee in June 2022, where the Standard's structure and its development process were mapped out, 83 people were allocated to nine Working Groups, each dedicated to a specific aspect of NTM care. These were chaired by a recognised expert with administrative and scientific support provided by NTM Network UK. The Working Groups drafted Quality Statements covering the range of care required by people living with NTM disease together with measurable indicators of good practice. An international clinical advisory board provided external oversight.

Results: Following review by the Steering Committee in April 2023, the nine initial section drafts were reduced to six: Person-centred care, Presentation and diagnosis of NTM disease, Treatment decisions and multidisciplinary support, Monitoring and review, Well-being and prevention, and Research and education. Feedback on the draft Standards was sought from all relevant stakeholders, including people with NTM disease, service providers, commissioners and professional bodies, with the public consultation opening in January 2024. The Standards of Care were circulated for endorsement by Professional Bodies whose members provide care for people living with NTM disease in May 2024. They will be launched in July 2024.

Conclusions: We have developed what we believe to be the first national Standards of Care for people with NTM. The process itself has emphasised the need for a more rapid diagnostic process together with a simplified healthcare journey - both of which can improve patient experience and may offer cost and resource savings. The proposed metrics enable NTM services to benchmark themselves and so identify their specific strengths and needs. The Standards also provide a reference point against which the quality of local NTM disease care can be assessed, and offer a framework to inform and support commissioning

decisions within the NHS. Ultimately, it is intended that implementation of these Standards will help people with NTM disease achieve their best possible health outcomes.

Conflict of interest(s): None

[18.04] Clinical Efficacy of Serum Anti-glycopeptidolipid-core IgA Antibody Test for Screening Nontuberculous Mycobacterial Infection in Bronchiectasis: Data from the EMBARC–BRIDGE study

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Background/Aims:

Serum anti-glycopeptidolipid (GPL) core immunoglobulin A (IgA) antibody test has been proposed as a diagnostic tool for *Mycobacterium avium* complex pulmonary diseases. Cross-reactivity with other non-tuberculous mycobacteria (NTM), including *M. abscessus* complex, indicates that it may have a role as a broader screening test for NTM pulmonary disease (NTM-PD). As NTM is believed to be underdiagnosed in patients with bronchiectasis, this study aimed to evaluate whether the serum anti-GPL core IgA antibody test can be used to screen for NTM-PD in bronchiectasis.

Methods:

A prospective cohort of 240 patients with stable bronchiectasis was enrolled from seven European centers in the United Kingdom, Italy, Spain, Belgium, the Netherlands, and Germany as part of the EMBARC–BRIDGE study (NCT03791086). A control cohort of 42 patients without any underlying lung disease was also recruited. Study participants were divided into those without NTM infection, those with NTM isolation, and those with NTM-PD. The levels of serum IgA antibodies against the GPL core were measured using an enzyme immunoassay kit, and receiver operating characteristics curve analysis was conducted to evaluate the accuracy of the antibody level in screening for NTM-PD.

Results:

Of the 282 patients, 151 (53.6%) were female and the median age was 68 years. Anti-GPL-core IgA antibody levels (mean $\pm$ SD) were 0.2 ± 0.2 U/mL in patients without NTM infection

(n=238), 0.4 ± 0.3 in patients with NTM isolation which are incompatible with the ATS/IDSA diagnostic criteria for NTM-PD (n=18) and 4.4 ± 6.8 in NTM-PD (n=26) ($P=0.0001$). Antibody levels showed excellent accuracy in identifying patients with NTM-PD (area under the curve 0.885, 95% CI 0.799–0.971) in all study participants and also showed excellent discrimination of patients with NTM-PD from those with NTM isolation who did not meet the ATS/IDSA diagnostic criteria for NTM-PD (0.816, 0.687–0.945).

Conclusions:

The anti-GPL-core IgA antibody demonstrated excellent efficacy in screening for NTM-PD in a large bronchiectasis cohort.

Conflict of interest(s) (if any – not included in the 500 words):

This research was funded by the European Respiratory Society through the EMBARC3 consortium. EMBARC3 is supported by project partners Armata, AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Grifols, Insmed, Janssen, Lifearc, and Zambon. JDC is supported by the Asthma and Lung UK Chair of Respiratory Research.

[18.05] Baseline Characteristics and Symptom Burden of Patients With Newly Diagnosed or Recurrent MAC Enrolled in the ARISE Study, a Double-Blind, Active-Comparator Trial to Validate PRO Instruments

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Background/Aims:

Mycobacterium avium complex (MAC), a leading cause of nontuberculous mycobacterial lung disease (LD), is associated with significant respiratory symptoms and considerable all-cause mortality. There are limited data characterizing the symptom burden of patients with newly diagnosed or recurrent MACLD. ARISE (NCT04677543) was a global clinical trial designed to contribute to the validation of patient-reported outcome (PRO) instruments, such as the Respiratory Domain (RD) from the Quality of Life-Bronchiectasis (QOL-B) instrument, and evaluate secondary microbiological endpoints and safety in patients with newly diagnosed or recurrent MACLD. We report the baseline characteristics and symptom burden of the ARISE study population.

Methods:

Enrolled patients (aged ≥ 18 years) had newly diagnosed or recurrent (second or third) non-cavitary MACLD and had not initiated antibiotic treatment for their current MAC infection. Patients with any pulmonary cavity ≥ 2 cm in diameter, current smokers, or those with a history of >3 MAC lung infections, refractory disease, or relapsed MAC infection were excluded. QOL-B RD score was required to average ≤ 85 between screening and baseline. Comprehensive clinical data, including demographics, comorbidities, and history of prior MACLD were collected at baseline. The QOL-B assesses symptoms based on eight domains (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perception and Treatment Burden), and was used to measure symptom burden in the ARISE population. Each domain is scored from 0 to 100, with a higher score corresponding to fewer symptoms.

Results:

Patients (N=99) from 12 countries enrolled in ARISE from December 2020 to October 2022. Patients had a median age of 69.0 years and most were aged ≥ 65 years (67.7%). Patients were predominately white (80.8%) and female (77.8%). For most patients (72.7%), this was their first diagnosis of MAC infection. Among patients with a history of prior MAC infections, the mean time since their previous infection was 2.86 years. MAC species isolated at baseline were *Mycobacterium intracellulare* (43.4%) and *M. avium* (32.3%) followed by other speciated (23.2%) and unspicated (6.1%) MAC. Most patients reported having a comorbid respiratory disorder, with bronchiectasis (49.5%), asthma (21.2%), and chronic obstructive

pulmonary disease (16.2%) most frequently reported. Median FEV₁ was 1.875 liters. For each domain of the QOL-B, the mean [SD] and median scores were, respectively: Emotional Functioning: 76.4 [20.4], 75.0; Role Functioning: 65.3 [21.0], 66.7; Respiratory Symptoms (comprising 9 items): 65.0 [15.3], 66.7; Social Functioning: 58.0 [25.1], 58.3; Physical Functioning: 56.9 [28.9], 60.0; Vitality: 48.7 [20.7], 44.4; and Health Perception: 41.3 [21.3], 41.7.

Conclusions:

In ARISE, chronic comorbid respiratory disease was common in patients with new or recurrent MACLD, and overall, patients were representative of a real-world patient population with MACLD. In ARISE, substantial disease burden at the time physicians initiate MACLD treatment is demonstrated through high burden seen across Respiratory Symptoms, Social and Physical Functioning, and Vitality and Health Perception domains of the QOL-B.

Conflict of interest(s) (if any – not included in the 500 words):

This study was funded by Insmed Incorporated. Kevin Mange, Dayton W. Yuen, Monika Ciesielska, Mariam Hassan, and Marie-Laure Nevoret are employees and shareholders of Insmed Incorporated. Luigi Ruffo Codecasa reports consultant fees by Cepheid and DiaSorin. Korkut Avsar reports lecturing fees from Insmed Incorporated. Dario Andrisani has no conflicts of interest to declare. Pamela J McShane is an advisory board member for Boehringer Ingelheim's Airleaf trial and Insmed's ASPEN trial. She is also a PI for clinical trials with the following pharmaceutical companies: Insmed: ASPEN, 416; Boehringer Ingelheim: Airleaf; Paratek: oral omadacycline; AN2 Therapeutics: Epetraborole; Renovian: ARINA-1; Redhill; Spero; Armata. Mordechai R Kramer has no conflicts of interest to declare. Shahrukh Kureishy has no conflicts of interest to declare. Medical writing support was provided by Bronagh Murray, PhD of Envision Pharma Group, and funded by Insmed Incorporated.

[18.06] Treatment regimens and outcomes of *M. simiae*- lung infection- A retrospective multicenter study

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Background/Aims:

Mycobacterium simiae is a species of non-Tuberculous mycobacteria (NTM) endemic to the Middle East. *M. simiae* is increasingly recognized as pathogenic and causing non-Tuberculous mycobacteria pulmonary disease (NTM-pd). However, treatment regimens and outcomes are poorly established. Our aim was to document clinical features, treatment regimens and long- term outcomes in patients treated for *M. simiae* NTM-pd.

Methods:

A retrospective multicenter study including patients meeting established criteria for NTM-pd caused by *M. simiae* and starting anti-mycobacterial treatment. We invited all infectious disease and pulmonary centers in Israel as well as select international centers who had published on *M. simiae* NTM to participate in data collection. We documented clinical and radiologic features, treatment regimens and outcomes.

Results:

Thirty-one patients filled criteria for NTM-pd and initiated treatment, average age- 62±15 years. Twenty-three patients had bronchiectasis and twelve had COPD. Seven patients were immune deficient. Twenty patients presented with weight loss and/or fever, and fourteen patients had a cavity on CT scan. Drug sensitivities were determined by broth microdilution for sixteen patients, with sensitivities (according to CSLI) to amikacin (15/16), clarithromycin (16/16), moxifloxacin (12/13), trimethoprim/sulfamethoxazole (12/16). Treatment courses included regular airway clearance in eighteen patients. Treatment included a macrolide (30/31 patients), intravenous amikacin in twelve patients, inhaled amikacin in seven and inhaled liposomal amikacin in three. Trimethoprim/sulfamethoxazole was used in 21 patients, a quinolone in eighteen, and clofazimine in nine. Fifteen patients had treatment change due to adverse effects. Eradication was achieved in twelve, of them two had a relapse. During follow up, thirteen patients had a clinical improvement, eight stabilized and ten deteriorated, of which five patients died. Tomographic features were improved in thirteen patients, stabilized in eight and worsened in ten. No factor was identified as correlated with desirable treatment outcomes.

Conclusions:

simiae lung disease is difficult to treat, with frequent treatment failure. It is imperative to adopt new drugs and drug regimens for this rare but difficult infection.

Conflict of interest(s) (if any – not included in the 500 words):

Not relevant.

[18.07] Developing quantitative molecular diagnostics for non-tuberculous mycobacteria

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Background/Aims:

Non-tuberculous mycobacteria (NTM) can cause infections in people with underlying respiratory conditions and this is also known as NTM pulmonary disease (PD). Such infections are mainly associated with *Mycobacterium abscessus* (MAB) and *M. avium* complex (MAC) species, which make up 90% of NTM-PD cases in the UK. Given the rarity of these infections, these do not tend to be suspected in primary care and their diagnosis is lengthy. NTM infections are also associated with long treatment regimens and unpleasant side effects.

Current standard of care for detecting and monitoring bacterial respiratory pathogens relies on sputum culture, which is lengthy, variable in accuracy and non-quantitative. Time to detection through culture methods is particularly long for NTM. Rapid diagnostics are therefore urgently needed. LifeArc scientists are currently developing quantitative molecular assays that detect NTM in sputum. Following consultations with experts in the field, we are focusing on assays that target MAB and MAC.

Methods:

We are developing RNA- and qPCR-based diagnostics for the detection and/or monitoring of NTM species in patient sputum as a proxy measure of bacterial load. The assay turnaround time from sample to result is ~4 hours. Following MAB and MAC assay development, we have evaluated their performance by determining the following analytical characteristics: intra-assay precision, repeatability, linearity, limit of detection (LOD) and limit of quantification (LOQ). MAB and MAC assays were also tested on RNA extracted from frozen NTM-PD patient sputum samples (n=15; Ellis *et al*, 2023). Three of these were MAB culture positive whereas two of these were MAC culture positive. The remainder of the samples were negative by culture for MAB or MAC.

Results:

Table 1: Summary of analytical performance for MAB and MAC assays (MAB: *M. abscessus*; MAC: *M. avium* complex; CV: coefficient of variation; rxn: reaction)

Analytical performance	Assay	
	MAB	MAC
Intra-assay precision	CV $\leq$ 50%	
Repeatability	CV $\leq$ 25%	
Linearity	$1.4 \times 10^7 - 9.6 \times 10^2$ copies/rxn (deviation $\leq 30\% $)	$4.4 \times 10^7 - 2 \times 10^2$ copies/rxn (deviation $\leq 30\% $)
Limit of detection	64 copies/rxn	
Limit of quantification	1024 copies/rxn (CV 40%)	2048 copies/rxn (CV 40%)

Preliminary results on clinical samples showed concordance between culture results and those obtained with our assays. Sputum samples that were culture positive were positive by molecular analysis. MAC was however detected in two samples from a patient with known NTM-PD but negative culture results. Multiple MAC culture positive samples preceding and following these negative culture results suggest that molecular results represent increased sensitivity rather than a false positive result.

Conclusions:

Analytical performance results for our quantitative NTM assays demonstrate their robustness, e.g. measures of precision (intra-assay and repeatability) showed reproducibility of results using the same samples. In addition, preliminary results using these assays to detect NTM species in patient sputum samples showed correlation with those obtained by culture and a potential for increased sensitivity.

We ultimately envisage that our NTM molecular assays will enable quicker and more reproducible NTM detection than the current standard of care. Importantly, quantitative detection will allow for patients with NTM-PD to be monitored for treatment response therefore facilitating improved treatment decision-making.

Conflict of interest(s) (if any – not included in the 500 words): None.

[19.01] Efficacy of Dry Powder Tigecycline in Pulmonary *Mycobacterium abscessus*: Insights from In Vivo Studies

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Background/Aims:

Tigecycline, the first tetracycline with a glycyl moiety, demonstrates efficacy against pulmonary *Mycobacterium abscessus* (*MAB*); however, its intravenous administration often leads to adverse effects that limit treatment duration and patient compliance. While tigecycline holds potential as a first-line therapy for pulmonary *MAB* and as a backbone for new combination regimens, novel routes of administration, formulations, and analogs are required to improve its therapeutic index. We hypothesize that tigecycline is effective and well-tolerated as inhaled therapy for pulmonary *MAB* infections.

Methods:

Spray-dried powder formulations were prepared using a Buchi-B290 spray dryer. Subsequently, optimal dosing regimens for tigecycline treatment via intrapulmonary aerosol were determined in GM-CSF knockout (KO) mice with pulmonary *MAB* infection (strain ATCC 19977).

Results:

Treatment with intrapulmonary aerosols of dry powder tigecycline (1mg/dose) for 8 or 28 days in GM-CSF KO mice with acute or chronic pulmonary *MAB* infections resulted in a significant decrease (over 1000 or 500-fold, respectively) in lung bacterial burden compared to untreated mice. Mice tolerated the administration of dry powder tigecycline formulations well, with no observed adverse effects.

Conclusions:

Preliminary in vivo analyses demonstrate the potential of spray-dried tigecycline formulations as promising candidates for the treatment of *MAB* lung infections. Our ultimate goal is to develop a multidrug regimen for pulmonary *MAB* that includes inhaled tigecycline therapy.

Conflict of interest(s) (if any – not included in the 500 words):

This study received funding from the National Institutes of Health (R01AI155922). The authors declare no other commercial interests

[19.02] *M. avium* versus *M. intracellulare* versus *M. chimaera* pulmonary disease: data from the IRENE Registry

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Abstract

Background: International guidelines for the management of *Mycobacterium avium* complex (MAC) pulmonary disease (PD) recommend a similar approach in case of *M. avium*, *M. intracellulare* or *M. chimaera* isolation. However, some experiences suggested possible different characteristics and clinical outcomes of patients suffering from PD due to different MAC species.

Aim: To explore disease characteristics and clinical outcomes of patients suffering from *M. avium* versus *M. intracellulare* versus *M. chimaera* PD.

Methods: This was a secondary analysis of the IRENE registry, an Italian, observational, prospective cohort study of adults (≥ 18 years) with non-tuberculous mycobacteria pulmonary infection enrolled from 2017 to date across 79 centers in Italy. Patients diagnosed with MAC-PD according to the 2020 ATS/ERS/ESCMID/IDSA Guidelines were included in the present analysis. Patients presenting with coinfection due to different mycobacteria as well as those lacking a clear MAC species identification were excluded. Three study groups were considered: patients suffering from *M. avium*, *M. intracellulare* and *M. chimaera* PD.

Results: Among 705 MAC-PD patients, 347 (49.2%) had *M. avium*, 284 (40.3%) had *M. intracellulare* and 74 (10.5%) had *M. chimaera* pulmonary disease. The overall median (IQR) age of the cohort was 70 (60-76) years, with females representing 75% of total study population. Demographics, comorbidities as well as radiological and microbiological features of the three study groups are depicted in Table 1. *M. chimaera* patients were more likely to be male ($p=0.003$) and have asthma ($p=0.006$). No statistically significant differences in terms of signs and symptoms at MAC-PD were observed among the three study groups. Significant radiological differences detected among the three study groups included a higher prevalence of patients with large cavities and fibro-cavitary disease in the *M. intracellulare* group in comparison to the other two ($p=0.017$ and $p=0.038$, respectively). The prevalence of bronchiectasis significantly varied among the three groups (76.1% in *M. avium*, 81.3% in *M. intracellulare*, and 67.6% in *M. chimaera* cases; $p=0.031$). No differences in terms of adherence to international guidelines for MAC-PD treatment were observed among the three study groups. Clinical outcomes, including microbiological cure, recurrence, treatment halted and mortality as per NTM-NET definitions, and refractory disease as defined by latest 2020 Guidelines were not different across the three study groups, see Table 1.

Conclusions: No differences in clinical outcomes have been recognized among patients suffering from pulmonary diseases due to different MAC species.

TABLE 1

Variable	<i>M. avium</i> Pulmonary Disease (N=347)	<i>M. intracellulare</i> Pulmonary Disease (N=284)	<i>M. chimaera</i> Pulmonary Disease (N=74)	P value
DEMOGRAPHICS				
Female sex	271 (78.1%)	214 (75.4%)	44 (59.5%)	0.003
Age (years)	69 (60-76)	69 (61.3 - 75)	76.5 (56.8 – 75.3)	0.537
BMI	20.8 (18.9 – 23.0)	20.8 (18.9 – 23.2)	21.2 (18.8 – 24.1)	0.596
Ethnicity (White European)	338 (97.4%)	272 (95.8%)	74 (100%)	0.798
Current or former smoker	148 (42.7%)	127 (44.7%)	40 (50.1%)	0.201
FEV ₁ (% predicted)	87.3 (70.2 – 99.2)	88.6 (72.3 – 103.4)	89.6 (74.3 – 107.3)	0.421
COMORBIDITIES				
Any respiratory comorbidity	298 (85.9%)	251 (88.4%)	66 (89.2%)	0.560
COPD	55 (15.9%)	47 (16.5%)	20 (27.0%)	0.063
Asthma	26 (7.5%)	18 (6.3%)	13 (17.6%)	0.006
Bronchiectasis	264 (76.1%)	241 (81.3%)	50 (67.6%)	0.031
Chronic Rhinosinusitis	20 (5.8%)	13 (4.6%)	10 (13.5%)	0.016
Any Cardiovascular comorbidity	141 (40.6%)	119 (41.9%)	32 (43.2%)	0.897
Diabetes	14 (4.0%)	10 (3.5%)	8 (10.8%)	0.022
Mitral Valve prolapse	11 (3.2%)	10 (3.5%)	3 (4.1%)	0.921
Other Cardiovascular diseases	20 (5.8%)	32 (11.3%)	9 (12.2%)	0.190
Immunosuppression	50 (14.4%)	33 (11.6%)	14 (18.9%)	0.237
Active neoplastic disease	20 (5.8%)	14 (4.9%)	7 (9.5%)	0.332

[19.03] Proteomic differences in bronchiectasis patients with and without nontuberculous mycobacterial lung disease.

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Background/Aims:

Pulmonary disease from *Mycobacteria avium* complex (MAC) frequently complicates the clinical course of bronchiectasis patients. It would be helpful from the clinical care perspective to identify host cellular features that allow bronchiectasis patients to foster MAC infection. Extracellular vesicles (EVs) are involved in intercellular communication. They are representative of the physiologic state of the cell and may provide insight into NTM susceptibility. The aim of this study is to compare EV proteomics in bronchiectasis patients with and without MAC pulmonary infection.

Methods:

Patients with bronchiectasis diagnosed by radiographic criteria and clinical symptoms were prospectively enrolled in the study. The study took place at the University of Texas Health Science Center at Tyler and was approved by the local institutional review board. All patients provided consent. EVs from plasma were isolated using size exclusion chromatography. Following EV lysis, EV proteins were digested using trypsin and subjected to liquid chromatography–mass spectrometry based proteomic analysis. Orthogonal partial least-squares – discriminant analysis (OPLS-DA) and computation of variable importance in projection (VIP) scores for each protein was performed using R programming language. The pathway enrichment analysis was performed using GprofileR.

Results:

A total of 29 bronchiectasis patients were included: 16 with MAC lung disease and 13 with no MAC infection. Demographic and culture data is shown in Table 1. Across the 29 patient samples, 168 proteins were quantified. MAC negative and positive samples clustered separately, suggesting that EVs from both categories harbored distinct proteome (Figure 1a). Fifty proteins exhibited a VIP score >1 on OPLS-DA analysis. The differential expression of these proteins is shown in the heat map (Figure 1b). Notably, matrix proteins involved in innate immune system (e.g., integrin beta-1, prenylcysteine oxidase 1, and sorcin) and mucus characteristics (e.g., mucin-5AC and mucin-5B) were upregulated in patients with MAC infection.

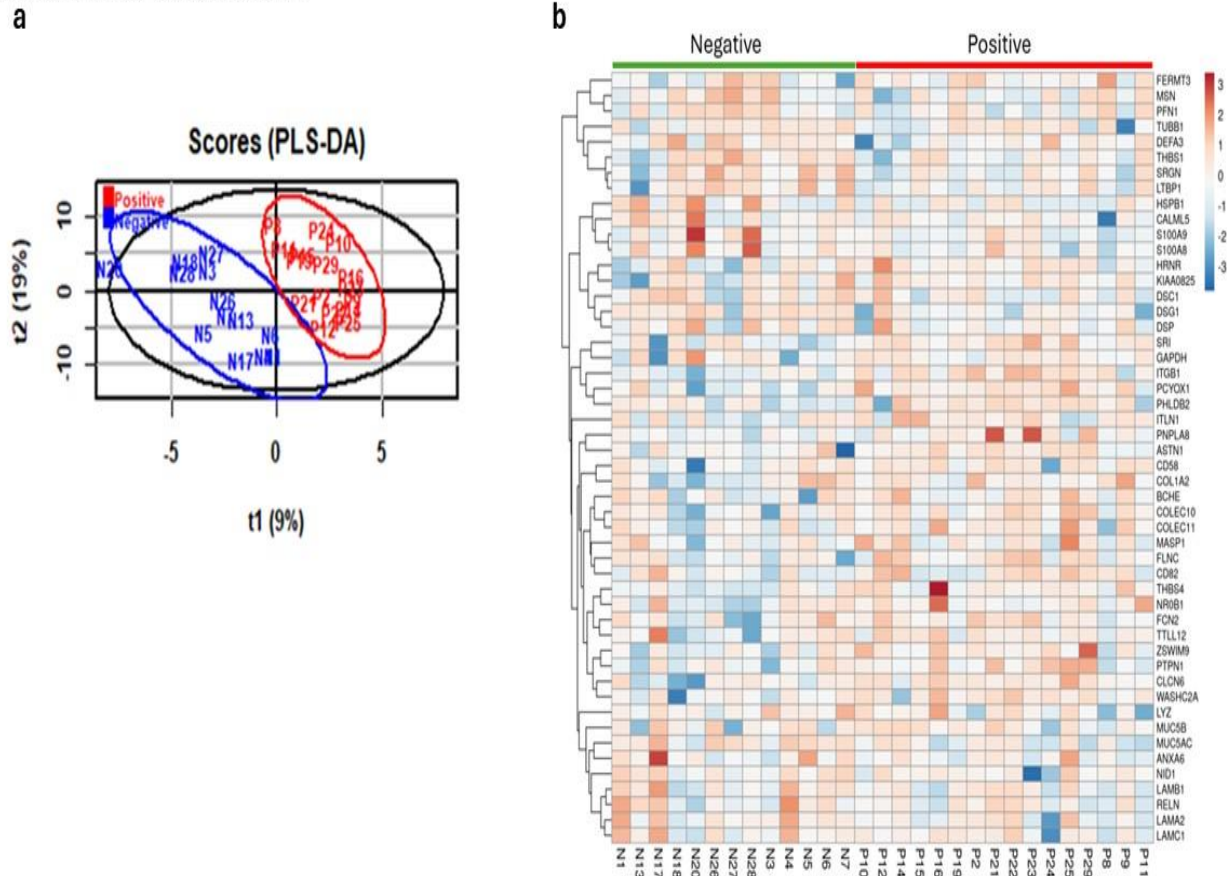
Conclusions:

Bronchiectasis patients with MAC infection have an altered EV profile enriched in proteins involved in host defense mechanisms. The exact role of these proteins has yet to be explored but they could serve as potential targets for therapeutic strategies in MAC lung disease.

Table 1. Demographics and AFB culture data in patients with and without MAC lung disease

	MAC lung disease (n=10)
Mean age (SD)	70 (9.4)
Female (%)	94.7%
White race	79.0%
Never smokers	73.7%
Average number of sputum AFB cultures in the year of consent	6.8
Average number of positive sputum AFB cultures for MAC in the year of consent	6.1

Figure 1. Extracellular vesicles (EVs) distribution and associated proteins in the entire patient cohort.
a. Clusters of EVs in patients with MAC lung infection (red) and in patients without MAC infection (blue)
b. Heat map of EV proteins with variable importance in projection (VIP) score >1 in orthogonal partial least-squares – discriminant analysis. “Positive” refers to patients with MAC infection. “Negative” refers to patients with no MAC infection



[19.04] Recovery and identification of *Mycobacterium abscessus* and *Mycobacterium avium* complex from home environmental samples of patients with nontuberculous mycobacterial lung disease

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Background/Aims:

Nontuberculous mycobacteria (NTM) are indigenous inhabitants of soil and municipal water. It is suspected that patients with NTM lung disease (pwNTM LD) acquire the infection through extended exposure to household environments. The objective of this study is to compare the strain of NTM grown from household samples with correlating sputum culture.

Methods:

A total of 25 participants (24 pwNTM LD, 1 control) have been enrolled in this study and received home environmental sampling kits. All participants have bronchiectasis defined by HRCT and clinical symptoms; pwNTM LD fit ATS/ERS/ESCMID/IDSA criteria. Each kit contained 3 swabs, one each to sample a household kitchen faucet, showerhead, and dust, as well as a vial to collect garden soil. Environmental samples were cultured for NTM using previously identified methods. Recovered isolates were identified to the species level via sequencing a segment of the RNA polymerase beta subunit (*rpoB*) gene. Sputum was obtained for acid-fast bacilli culture (AFB) coincident with administration of environmental kits. Sputum samples were cultured in 7H9 broth and 7H11 agar media. If the environmental NTM ID matched to the respiratory ID, the two were considered a matched pair.

Results:

Of the 25 pwNTM LD, *Mycobacterium avium* complex (MAC) infection was most prevalent (19/25, 76%), followed by *M. abscessus* (3/25, 12%). Both MAC and *M. abscessus* were present in 3/25 (12%) of patients. Twenty NTM isolates representing eight different NTM species were identified from 9/25 kits (36%). *M. abscessus* was the most frequently recovered (6/20, 30%) followed by *M. mucogenicum* (3/20, 15%), *M. rhodesiae* (2/20, 10%) and including single isolates of *M. avium* and *M. chelonae*, and three non-pathogenic environmental NTM species and novel isolates. For two pwNTM LD and *M. abscessus* infection, viable environmental *M. abscessus* was recovered from their showerhead and soil, respectively. *M. abscessus* was also recovered from the control participant's kitchen sink. For a third pwNTM with MAC infection environmental *M. avium* was recovered from their kitchen sink. An additional 36 kits are pending culture results.

Conclusions:

We have recovered *M. abscessus* and MAC from the environments of homes of patients with those infections. Whole genome sequencing will be performed on the three matched environmental and respiratory NTM pairs and other future pairs to study single nucleotide

polymorphism variations, study antibiotic resistance, understand differences in isolate virulence, and improve epidemiological surveillance.

Conflict of interest(s) (if any – not included in the 500 words):

The authors have no conflicts of interest related to this study

[19.05] A clinically-relevant animal model of *Mycobacterium avium* complex pulmonary infection

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Background/Aims:

Mycobacterium avium complex (MAC) is driving a global rise in pulmonary disease (MAC-PD) characterised by chronic infection and immune-mediated lung damage. Animal models are important for screening novel therapeutic strategies, but these remain poorly characterised.

Through testing several combinations of mouse species and MAC isolates in chronic lung infection, we aimed to generate an animal model with clinically-relevant features of MAC-PD, including chronic bacterial infection, histological lung injury and impaired pulmonary function

Methods:

Six-week-old female balb/c or C3HeB/FeJ mice were infected intratracheally with a clinical isolate of MAC (MAC2285R, National Institute of Allergy and Infectious Diseases) or a reference strain (MAC101 or MAC104, both ATCC). Whole body plethysmography (WBP) was performed weekly to measure changes in pulmonary function (Buxco WBP system). Mice were culled at 4-weekly intervals post-infection until week 20. Lungs were harvested for counting colony-forming units (CFUs) and histological examination. Data was analysed by 2-way ANOVA comparing isolate and time, or by unpaired t-test on area under the curve (AUC).

Results:

Intratracheal infection with a high-dose inoculum of all three MAC strains successfully established lung infection in C3HeB/FeJ and balb/c mice. Balb/c mice infected with MAC101 developed proliferative bacterial infection over 20 weeks ($p < 0.05$), associated with progressive inflammatory lung damage (Figure 1A+B). WBP changes were consistent with increased respiratory effort (minute volume) and bronchoconstriction (enhanced pause) ($p < 0.05$) (Figure 1C+D). MAC104 infection generated a similar but less severe response in balb/c mice, whereas MAC2285R was cleared with only mild injury on histology.

In contrast, C3HeB/FeJ mice exhibited stable, chronic infection with all three MAC isolates, but developed negligible histological lung disease. WBP showed evidence of increased respiratory effort, but no bronchoconstriction.

Conclusions:

Chronic MAC-PD with stable bacterial burden, severe inflammatory disease and impaired pulmonary function can be modelled in balb/c mice using MAC101 strain. This model can facilitate the screening of novel antimicrobial and host-directed therapies for MAC-PD.

Conflict of interest(s) (if any – not included in the 500 words):

This work was funded by a travel scholarship from the Dowager Countess Eleanor Peel Trust (UK) and project grants from the NIH (RO1-TGC Award for AI155922 and Project Number 1S10OD030263-01).

[19.06] The Long and Winding Road: Three-year Mortality Following Prescription of Multi-drug Antibiotic Treatment for Mycobacterium avium complex Pulmonary Disease in United States Medicare Beneficiaries with Bronchiectasis

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Background/Aims:

Mycobacterium avium complex (MAC) increasingly cause chronic pulmonary infections. Treatment is complicated, typically requiring 3-5 antibiotics for 18-24 months. Epidemiologic data have demonstrated increased mortality among people with MAC pulmonary disease (MAC-PD) compared to age-matched cohorts without MAC-PD; however data are limited regarding a survival benefit with specific regimens. Although guideline-based therapy (GBT) is recognized as the most effective regimen, published data demonstrate poor adherence to treatment guidelines. We conducted an analysis of 3-year mortality following prescriptions for MAC-PD therapies among United States (U.S.) Medicare beneficiaries with bronchiectasis.

Methods:

Our source population was beneficiaries aged 65 years and older with bronchiectasis (ICD9-CM 494.0, 494.1) in U.S. Medicare data (Jan2006-Dec2014), excluding cystic fibrosis, human immunodeficiency virus, or a history of organ transplant. We limited our cohort to new MAC-PD therapy users, requiring at least 12 months of Medicare coverage without evidence of MAC-PD therapy. MAC-PD therapy was defined as a prescription of a ≥ 60 day-supply of an antibiotic regimen containing a macrolide (azithromycin or clarithromycin) plus ≥ 1 of the following: rifamycin, ethambutol, fluoroquinolone, or intravenous/inhaled amikacin. GBT was defined by the American Thoracic Society/Infectious Disease Society of America 2007 guidelines and included a macrolide, ethambutol and a rifamycin. Using Cox proportional hazard models, we evaluated time-to-death up to 3 years after MAC-PD therapy start between the following groups in an intention-to-treat analysis: 1)GBT vs. non-GBT; 2)azithromycin-ethambutol-rifampin (AZI-EMB-RIF) vs. clarithromycin-ethambutol-rifabutin (CLARI-EMB-RFB); 3)macrolide-ethambutol-rifamycin (3-drug) vs. macrolide-ethambutol (2-drug). We calculated adjusted hazard ratios (aHR) and 95% confidence intervals (95%CI). Beneficiaries were censored at death or end of study period (12/31/2014), whichever occurred earlier.

Results:

We identified 4,820 new users of MAC-PD therapy. Mean age was 77.8 years (standard deviation [sd] 6.1). Most were female (76.1%) and non-Hispanic White (87.6%) (Table1). Overall 866 (17.9%) were deceased at 3 years.

Median duration of therapy was 198 (IQR 108.5,354.0) days and 145 (IQR 88.0,274.5) days for GBT and non-GBT, respectively. Of 3,040 (63.1%) beneficiaries prescribed GBT, 472 (15.5%) were deceased at 3 years compared to 394 (22.1%) of 1,780 (36.9%) prescribed non-GBT (aHR 0.81 [95%CI 0.71-0.93]) (Figure1). Of 1,809 (37.5%) beneficiaries prescribed

AZI-EMB-RIF, 88 (4.9%) were deceased at a mean of 209 (sd87.8) days. Only 125 (2.6%) were prescribed CLARI-EMB-RFB, of whom 12 (9.6%) were deceased at a mean of 217 (sd88.8) days. Three-year-mortality was not statistically different comparing CLARI-EMB-RFB vs. AZI-EMB-RIF, (aHR 1.21 [95%CI 0.80-1.84]). Of 3,040 beneficiaries prescribed 3-drug regimens, 472 (15.6%) were deceased at 3 years compared to 150 (22.0%) of 682 prescribed 2-drug regimens (aHR 0.87 [95%CI 0.72-1.05]) (Figure2).

Conclusions:

Among Medicare beneficiaries with bronchiectasis newly prescribed MAC-PD therapy, adjusted 3-year-mortality was higher in those prescribed non-GBT regimens compared to GBT regimens. There were no statistically significant differences in mortality comparing AZI-EMB-RIF vs. CLARI-EMB-RFB, or 3-drug vs. 2-drug regimens. Limitations exist in evaluating mortality from claims data, including MAC-PD disease severity. More data are needed regarding differential mortality by antibiotic regimen in MAC-PD, however this analysis provides ongoing support for GBT.

Conflict of interest(s) (if any – not included in the 500 words):

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[19.07] In Vitro Activity of Novel Leucyl-tRNA Synthetase Inhibitor Against *Mycobacterium Avium* Complex

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Background/Aims:

The prevalence of non-tuberculous mycobacterial pulmonary disease (NTM-PD) worldwide has increased in recent years. *Mycobacterium avium* complex (MAC) is the most common NTM-PD pathogen. The current treatment of MAC-PD includes multiple antibiotics for several months, which are associated with frequent and serious adverse effects. Therefore, there is a significant need for more efficacious and safer drugs to treat MAC-PD. The goal of this study was to evaluate the *in vitro* anti-MAC activity of MRX-6038, a novel synthetic Leucyl-tRNA synthetase inhibitor, and the resistance in *M. avium* isolates.

Methods:

Minimum inhibitory concentration (MIC) was determined using broth microdilution method according to CLSI guidelines. MIC₅₀ and MIC₉₀ were obtained against 50 MAC clinical isolates with clarithromycin as the control. Among the 50 tested, 25 isolates were non-clarithromycin susceptible.

The spontaneous resistance frequency was calculated as the number of colonies on drug-containing plates divided by the number of colonies on drug-free plates.

Results:

MRX-6038 MIC (mg/L) against MAC

Species (number of isolates)	MIC range	MIC ₅₀	MIC ₉₀
MAC (50)			
MRX-6038	0.25->8	2	8
Clarithromycin	<0.03125->8	8	>8
MAC CLR non-susceptible (25)			
MRX-6038	0.25->8	4	8
Clarithromycin	>8		
<i>M. avium</i> (20)			
MRX-6038	0.25->8	1	2
Clarithromycin	<0.03125->8	8	>8
<i>M. intracellulare</i> (23)			

MRX-6038	1-8	4	8
Clarithromycin	0.5->8	>8	>8
<i>M. chimaera</i> (7)			
MRX-6038	1-8	4	8
Clarithromycin	0.125->8	>8	>8

MRX-6038 at 2 to 8 × MIC (MIC = 8 mg/L in agar) concentrations the spontaneous resistance frequency in *M. avium* ranged 7.8×10^{-8} to 3.8×10^{-8} . When MRX-6038 was combined with clarithromycin, rifabutin, amikacin, and ethambutol, the resistance frequency was greatly reduced to below 6.5×10^{-11} .

Conclusions:

MRX-6038 demonstrated potent *in vitro* activity against different MAC isolates including isolates not susceptible to clarithromycin. Further studies are warranted for the development of MRX-6038 for the treatment of MAC-PD.

Conflict of interest(s) (if any – not included in the 500 words):

The authors have no conflict of interest to declare.

[19.08] In vitro and In vivo activity of a novel Leucyl-tRNA synthetase inhibitor against *Mycobacterium abscessus*

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Background/Aims:

The incidence and prevalence of pulmonary disease caused by nontuberculous mycobacteria (NTM) are increasing globally. *Mycobacterium abscessus* complex (MABC) is the second most common NTM causing pulmonary disease (PD) in the USA and East Asia. Treatment for MABC-PD is challenging because of the high frequency of mutational and acquired resistance to different antibiotics. The goal of this study was to evaluate the *in vitro* and *in vivo* activity of MRX-6038, a novel synthetic Leucyl-tRNA synthetase inhibitor, and its oral prodrug MRX-5 against MABC.

Methods:

Minimum inhibitory concentration (MIC) was determined using broth microdilution method according to CLSI guidelines. MIC₅₀ and MIC₉₀ were obtained against MABC clinical isolates with clarithromycin (CLR) as the positive control.

The spontaneous resistance frequency was calculated as the number of colonies on drug-containing plates divided by the number of colonies on drug-free plates.

BALB/c mice rendered neutropenic with intraperitoneal cyclophosphamide were infected through nasal instillation with *M. abscessus* ~10⁶ CFU/mouse. Mice were treated with oral MRX-5 once daily at 10, 20 and 40 mg/kg for 2 weeks, with clarithromycin as positive control. Bacterial loads in lungs before and after treatment were numerated through plating lung homogenate onto agar plates and recording the colony counts after incubation.

Results:

MRX-6038 MIC (mg/L) against MABC

Species (number of isolates)	MIC range	MIC ₅₀	MIC ₉₀
MABC (50)			
MRX-6038	0.125-0.5	0.25	0.5
Clarithromycin	0.0625->8	0.5	4
<i>M. abscessus</i> (32)			
MRX-6038	0.125-0.5	0.25	0.5
Clarithromycin	0.0625->8	1	4
<i>M. abscessus</i> , CLR non-susceptible (7)			
MRX-6038	0.125-0.5	0.25	0.5
Clarithromycin	4->8	4	>8
<i>M. massiliense</i> (16)			

<i>M. bolletii</i> (2)	MRX-6038	0.125-0.5	0.25	0.5
	Clarithromycin	0.0625-1	0.125	1
	MRX-6038	0.25	-	-
	Clarithromycin	0.25	-	-

MRX-6038 at 2 to 8 × MIC (agar MIC = 1 mg/L) concentrations the spontaneous resistance frequency in *M. abscessus* ranged 3.1×10^{-8} to 2.0×10^{-8} . When MRX-6038 was combined with clarithromycin, rifabutin, amikacin, and ethambutol, the resistance frequency was greatly reduced to below 2.9×10^{-10} .

Two isolates were tested for *in vivo* efficacy against *M. abscessus* in mouse lung infection models, clinical isolate MAB0002 (CLR MIC=0.125 mg/L) and ATCC 19977 (CLR MIC=8 mg/L). Oral MRX-5 treatment reduced bacterial load in lungs with a dose response in both models. After 14 days 10 to 40 mg/kg MRX-5 oral once daily the average bacterial count reduction relative to the vehicle control was 1.9 to 3.4 logCFU/lung reduction against isolate MAB0002 and 1.4 to 2.0 logCFU/lung reduction against ATCC 19977. CLR at 200 mg/kg daily as positive control was used in both animal studies.

Conclusions:

MRX-6038 and its oral prodrug MRX-5 demonstrated potent activity against *M. abscessus* in *in vitro* and *in vivo* animal infection studies. Further investigation is warranted for the development of MRX-6038/MRX-5 as treatment for MABC-PD.

Conflict of interest(s) (if any – not included in the 500 words):

The authors have no conflict of interest to declare

[20.01] Standardising transfer to adult services for patients with primary ciliary dyskinesia (PCD)

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Background/Aims:

Healthcare systems differ internationally with many mechanisms of transfer to adult services. For rare diseases like primary ciliary dyskinesia (PCD) requiring specialised diagnosis and care, adequate and disease-specific handover contributes to optimal transition and prevents patients from having to undergo repeat diagnostic testing which is expensive and uncomfortable.

Standardised, good transition empowers young people, giving them the knowledge and skills to manage their condition, supports the clinical teams, reduces the risk of being lost to follow-up, and increases chances of staying well in young adulthood. We aimed to create a standardised form for PCD patients transferring to adult services to meet the needs of patients and clinicians, irrespective of healthcare system. This would be to be used alongside a formal transition programme such as Ready Steady Go, which has already been translated into many languages and is used widely throughout the network.

Methods:

An international, multidisciplinary working group (WG) of 9 PCD experts from the BEAT-PCD Network and 2 patient representatives was established. It comprised of adult and paediatric professionals to represent the main priorities in PCD diagnosis and care, who discussed and selected the form content. When necessary, we consulted with experts outside the WG. We revised several drafts, refining content and structure. We circulated the form within PCD support groups for additional suggestions and adapted as necessary.

The WG included professionals and patients from across our international network and from high and low resource healthcare settings. Organising meetings with participants from South America, Europe and Australia proved to be achievable but challenging. Goodwill and shared passion to improve outcomes for young people is what made this possible.

Results:

We developed a standardised clinical form for PCD patients transferring to adult services. It includes a short, comprehensive patient history with diagnostic information and recent investigations acting as a clinical status overview for the adult team. It incorporates essential

aspects of PCD education and an 'all about me' section to be completed by the patient. The form will be translated, piloted in different clinics, and adapted as necessary, before finalising.

Conclusions:

A standardised transfer form may improve outcomes for young people with PCD, reducing the need for repeat investigations and empowering them in their care.

Conflict of interest(s) (if any – not included in the 500 words):

[20.02] Treatment of cystic fibrosis can reverse cystic as well as cylindrical bronchiectasis

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Treatment of cystic fibrosis can reverse cystic as well as cylindrical bronchiectasis

Middleton PG, Keatley LR, Bishop JR, Lazarus R, Prasad R, Thompson CS.

Bronchiectasis and Cystic Fibrosis Service, Respiratory & Sleep Medicine, Westmead Hospital NSW AUSTRALIA

Background:

Bronchiectasis is described as the permanent dilatation of the airways on high resolution CT scan. Changes include cylindrical bronchiectasis, dilated airways which have lost their normal tapering, varicose bronchiectasis with focal areas of dilatation and cystic bronchiectasis, progressive airway dilatation ending in large cysts, considered the most severe form of bronchiectasis. Most current treatments aim to delay progression of bronchiectasis, with reversal of these changes previously thought unlikely. We now present a fourth case of bronchiectasis reversing with highly effective modulator therapy for cystic fibrosis.

Aims:

This case report aims to highlight the non-permanence of changes of bronchiectasis, previously thought to be irreversible.

Results:

A 27 year old woman (F508del / F508del) with cystic fibrosis and moderately obstructed spirometry [FEV₁, 63%; FVC, 76%] and baseline CT scan shown in Figure 1. She was commenced on elexacaftor + tezacaftor + ivacaftor (Trikafta/Kaftrio) therapy and noted a significant improvement in sputum production, shortness of breath and overall quality of life within 2-weeks of commencing therapy. After 12 months of therapy her lung function had improved with FEV₁ 81%; FVC 93%. Repeat HRCT showed dramatic improvement in cylindrical, varicose and cystic changes – in particular the cystic change at the apex of the right lung had resolved (Figure 2).

Conclusions:

This case highlights the apparent reversal of cystic bronchiectasis. The novel finding of elexacaftor + tezacaftor + ivacaftor therapy improving all components of bronchiectasis reflects the first time that medicine has been able to “switch off” the underlying

pathophysiological cause of bronchiectasis. Reversal of bronchiectasis in adults with one defined aetiology raises hope for new management and treatment strategies.

Conflict of interest:

PGM was a Chief Investigator in the studies of elexacaftor + tezacaftor + ivacaftor sponsored by Vertex.

[20.03] Evaluating Concordance and Clinical Outcomes in Kartagener Syndrome and Primary Ciliary Dyskinesia

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Background/Aims:

Kartagener syndrome (hereafter KaS) is widely recognised as a characteristic phenotype of Primary Ciliary Dyskinesia (PCD). While KaS can be too broadly labelled based on clinical findings, PCD might be too narrowly confirmed through electron microscopy or genetic diagnostics, leading to potential discrepancies between these two diagnoses. This study aims to evaluate the concordance between KaS and PCD diagnoses in patients labelled with either condition, and to investigate the differences in clinical progression and lung function between those with PCD but not KaS, and vice versa.

Methods:

A review of medical charts was conducted for individuals diagnosed with "Primary Ciliary Dyskinesia", "Kartagener Syndrome", or "Dextrocardia" at Seoul National University Hospital, South Korea, since the year 2000. This review collected data on electron microscopy results, genetic test outcomes, chest imaging findings, instances of haemoptysis, identification of nontuberculous mycobacterium (NTM) and *Pseudomonas* species, and last pulmonary function test results. Patients were defined as having definite PCD if pathogenic variants were observed in genetic testing or if ciliary structural abnormalities were found in electron microscopy. Those with dextrocardia and either sinusitis or bronchiectasis were classified as probable KaS; if both were present, the diagnosis was definite KaS.

Results:

Seventy-four individuals were enrolled, with sixty deemed potential subjects for PCD or KaS. Based on available data, 27 were classified as definite PCD and 22 as probable KaS (including 13 with definite KaS), but only four met the definite criteria for both PCD and KaS. Among the 46 individuals with definite PCD and/or probable KaS, bronchiectasis was observed in 40, of whom 13 were identified with NTM or *Pseudomonas* species, and 7 underwent embolization for bronchial bleeding. Pulmonary function tests were available for 36 out of 46 individuals, showing a median (interquartile range, IQR) FVC predicted percentage (%pred) of 82.5 (68.75–88.5), FEV1%pred of 73 (50 – 87.25), and FEV1/FVC(%) of 73.5 (65.75 – 82). There was no significant difference in NTM/pseudomonas identification frequency between Group 1 (PCD without KaS) and Group 2 (KaS without definite PCD), with six instances each; however, the frequency of embolic intervention for bleeding was higher in Group 1 (five instances vs. one in Group 2). No significant difference was observed between Group 1 and Group 2 in FVC%pred, FEV1%pred, and FEV1/FVC(%) (Wilcoxon rank sum test, $p=0.683$, 0.750 , and 0.467 , respectively).

Conclusions:

Despite the diagnostic challenges, PCD and KaS demonstrate a spectrum of differences. While there may not be a significant difference in lung function, the clinical progression, including bleeding events, can differ, highlighting the need to monitor for sinusitis and

bronchiectasis in PCD, and to confirm accurate PCD diagnosis in cases of KaS.

Conflict of interest(s) (if any – not included in the 500 words):

nothing to declar

[20.04] Looking for new biomarkers in bronchiectasis (BE): sputum Alpha1 antitrypsin (AAT), Neutrophil Elastase activity (NE) and secretory leucocyte protease inhibitor (SLPI) and their role in BE airways.

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Background/Aims:

In the age of precision medicine, biomarkers and therapeutic targets play a fundamental role.

The aim of our study is to describe the role of some key proteases and antiproteases in BE airways and their potential as BE biomarkers.

Methods:

We collected spontaneous sputum, blood and clinical data from stable BE patients. AAT, SLPI, and NE levels were measured in sputum supernatant using ELISA.

Also, AAT was measured in blood with nephelometry to calculate the sputum-to-blood ratio (SBAAT).

Results:

We included 76 patients, 70% women, mean age 61±16, mean FEV1 84.6±25.5%; 31% moderate and 20% severe according to FACED scores.

NE had an inverse correlation with FEV1 (liters $r=-0.278$, $p=0.030$; FEV1%, $r=-0.399$, $p=0.001$), FVC% ($r=-0.398$, $p=0.002$) and a positive correlation with *Pseudomonas aeruginosa* (PA) infection ($r=0.340$; $p=0.007$) and severity (mild vs severe FACED, $r=3.50$, $p=0.035$).

In contrast, SLPI had positive correlation with FEV1% ($r=0.340$, $p=0.009$) and cystic BE ($p=0.007$), negative correlation with PA ($r=0.340$; $p=0.007$) and FACED (mild vs severe, $r=3.50$, $p=0.035$).

Consistently, negative correlation was found between NE and SLPI ($r=-0.454$; $p<0.001$).

AAT levels in blood and sputum did not correlate with clinical, functional or radiological variables, nor with the other biomarkers; however, a higher SBAAT was found in patients with higher Reiff scores (>6 ; $p<0.001$).

Conclusions:

Increased NE and reduced SLPI in BE patients are associated with worse lung function, severity, and chronic PA, confirming them as potential biomarkers of disease activity. Patients with greater radiological impairment exhibit an elevated sputum-to-blood AAT gradient.

Conflict of interest(s) (if any – not included in the 500 words):

The research was financed by a Grifols research grant to Vall d'Hebron Institut de Recerca; the work of C. Pons is financially supported as part of this research grant. The remaining authors have no conflicts of interest to declare related to this original work.

[21.01] Nontuberculous Mycobacteria Isolation: Impact of Inhaled Mucolytic Therapy in Patients with Bronchiectasis

Shoshana Zha¹; Martin leong¹; Amanda Brunton²; Cynthia Fenton¹; Kunal Jakharia³; Choate Radmila⁴; Kevin Winthrop⁵; Mark Metersky⁶; Meghan Marmor⁷; Ashwin Basavaraj⁸; Neeta Thakur¹

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Background/Aims: Bronchiectasis is a progressive disease that causes unremitting respiratory symptoms and places individuals at risk for chronic airway infection. Nontuberculous mycobacterium (NTM) are environmental organisms that can accumulate in airways and mucus, providing a niche for infection. Therapeutic measures for bronchiectasis are complex given different presenting pathologies, however, the commonly recommended treatment is airway clearance. Inhaled mucolytics are a common adjunct therapy in the regimen in the United States to reduce mucus viscosity. The aim of this study is to elucidate if prescription of inhaled mucolytics reduces the risk of NTM pulmonary infection (NTM-PI) in bronchiectasis.

Methods: Two cohorts of adults with bronchiectasis were analyzed. The first was a retrospective cohort who received care at University of California San Francisco from 2014 to 2024 (UCSF). Patients were included if they had 2 or more ICD codes for bronchiectasis at least 1 month apart, at least a year of data, and excluded if a history of cystic fibrosis, HIV, or solid organ transplantation. The second was the US Bronchiectasis and NTM Research Registry (BRR), a prospective national cohort established in 2008. Patients were included if they had a diagnosis of bronchiectasis, documented sputum result at follow-up, and excluded if a diagnosis of NTM-PI or positive respiratory culture at baseline. Chi-square and t-tests were used to assess frequency and mean differences across groups for continuous and categorical variables, respectively. We fit a logistic regression model controlling for age, BMI, and gender to assess the association of mucolytic prescription on the presence of NTM in follow-up respiratory culture.

Results: 1818 individuals were identified in the UCSF (510 or 28.1% prescribed mucolytic) and 330 from the BRR (225 or 68.2% prescribed mucolytic) cohorts. The majority were prescribed saline as the mucolytic in both (94% and 82%, respectively). Cohort characteristics differed across multiple demographics, including female gender (68.3% versus 79.5%, $P<0.001$), mean age (70.9 versus 68.0, $P=0.013$), as well as race, ethnicity, and insurance coverage (**Table 1**). The presence of NTM was lower in the UCSF than BRR cohort (10.8% versus 32.1%, respectively, $P<0.001$). In UCSF, those who self-identified as Asian or Black were less likely to be prescribed mucolytic, without a difference noted in BRR. Further, in UCSF those who were prescribed mucolytics were younger (mean age difference 4 years, $p<0.001$) and more likely to have commercial insurance. Using the prospective BRR cohort, those prescribed mucolytic had a lower odds of positive follow-up respiratory culture for NTM, but this did not meet statistical significance (OR 0.64, 95% CI 0.385-1.06, $P=0.083$).

Conclusion: Our study found differences in prescribing practices of inhaled mucolytics across various demographics. With a small sample size, there was a marginal reduction in

the odds of developing NTM-PI when prescribed mucolytic, with ongoing evaluation of time to positivity in the larger cohort. Further studies are required to understand which, if any, component of airway clearance is most effective in preventing the development of NTM-PI in those with bronchiectasis.

TABLE University of California-San Francisco (UCSF)					Bronchiectasis and NTM Research Registry (BRR)				Overall UCSF vs BRR (P-value)
<i>Prescription of Inhaled Mucolytics</i>	Overall (N=1818)	Not Prescribed (N=1308)	Prescribed (N=510)	P-Value	Overall (N=330)	Not Prescribed (N=105)	Prescribed (N=225)	P-Value	
Gender									
Female	1242 (68.3%)	885 (67.7%)	357 (70.0%)	0.328	262 (80.1%)	84 (81.6%)	178 (79.5%)	0.66	<0.001
Age, Years (Mean (IQR))	70.9 [66.0 - 83.0]	73.9 [67.8 - 84.0]	68.9 [63.0 - 80.0]	<0.001	68.0 [60.0-74.0]	66.0 [59.0-74.0]	68.0 [60.0-74.0]	0.715	0.013
BMI, Lowest (Mean (SD))	21.3 (4.7)	21.6 (4.9)	20.6 (4.2)	0.015	23.7 (4.8)	23.2 (3.3)	23.8 (5.0)	0.989	0.03
Race/Ethnicity									<0.001
White	1126 (61.9%)	787 (60.2%)	339 (66.5%)	0.015	296 (91.9%)	92 (90.2%)	204 (92.7%)	0.438	
Asian	353 (19.4%)	266 (30.3%)	98 (17.8%)	<0.001	10 (3.1%)	5 (4.9%)	5 (2.3%)	0.298	
Black	73 (4.0%)	64 (4.9%)	9 (1.8%)	0.004	8 (2.5%)	2 (2.0%)	6 (2.7%)	0.681	
Other ¹ , Declined, or Unknown	166 (14.6%)	191 (14.6%)	75 (14.7%)	1	8 (2.5%)	3 (2.9%)	5 (2.3%)	0.712	
Hispanic	139 (7.6%)	98 (7.5%)	41 (8.0%)	0.798	13 (4.1%)	5 (5.2%)	8 (3.6%)	0.546	
Insurance²				<0.001				0.359	<0.001
PPO/Private	264 (14.5%)	152 (11.6%)	112 (22.0%)		140 (42.9%)	49 (47.6%)	91 (40.8%)		
Medicare	837 (46.0%)	589 (45.0%)	248 (48.6%)		166 (50.9%)	46 (44.7%)	120 (53.8%)		
Medi-cal or state-program	122 (6.7%)	87 (6.7%)	35 (6.9%)		12 (3.7%)	4 (3.9%)	8 (3.6%)		
Medi-Medi	258 (14.2%)	195 (14.9%)	63 (12.4%)		NA	NA	NA		
ICS Prescribed (Any)	639 (35.1%)	400 (30.6%)	239 (46.9%)	<0.001	121 (37.1%)	27 (26.2%)	94 (42.2%)	0.006	0.525
Vest Prescribed (Any)	101 (5.6%)	12 (0.9%)	89 (17.5%)	<0.001	60 (28.6%)	6 (11.1%)	54 (35.1%)	0.001	<0.001
NTM in Follow-up Culture³	197 (10.8%)	74 (5.7%)	123 (24.1%)	<0.001	106 (32.1%)	40 (38.1%)	66 (29.3%)	0.112	<0.001

BMI = body mass index, FEV = forced expiratory volume, ICS = inhaled corticosteroid, IQR = interquartile range,

NTM = nontuberculous mycobacteria, SD = standard deviation

¹Other includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or Other

²Primary insurance coverage

³Defined as at least one positive culture

Conflict of interest(s) (if any – not included in the 500 words):

S Zha: consultant Insmed, Genentech; K Winthrop has grant funding from Insmed, Paratek, AN2, Renovion, Spero, Mannkind and Consulting for Insmed, Paratek, AN2, Renovion, Spero, Mannkind; M Metersky has grant funding from Insmed and Consulting for Insmed, Boehringer Ingelheim, Tactile; A Basavaraj Consulting for Tactile, Insmed, Baxter, Physio-Assist, Zambon, Dymedso. K Jakharia, R Choate, A Brunton, and M Marmor have no conflicts to report.

[21.02] A new model of outpatient respiratory physiotherapy for bronchiectasis patients: strength and limitations.

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Background/Aims:

During COVID-19 pandemic, the tertiary bronchiectasis program of our hospital, which included outpatient pulmonology and respiratory physiotherapy (RP) visits, was suppressed for almost two. In 2022, at the reopening of the outpatient clinic, we implemented a new model of RP practice and organization, aimed at optimizing the use of resources and professionals and improving the efficiency of care for patients. The purpose of this preliminary study was to assess feasibility and efficiency of this model.

Methods:

The implemented RP model was developed, based on clinical practice, experts' opinion, and review of the current data available from the literature and tested from 01.12.2022 to 31.03.2024. The main purpose of this new model of care was the classification of patients after the first assessment according to specific clinical criteria, to identify active and/or severe patients, with highest clinical needs, and to determine accordingly frequencies of follow-up. The RP agenda was scheduled with specific slots for first assessments and emergencies, as well as for virtual and in presence follow-up. Relevant data about patients' classification and number of visits supplied were recorded and analyzed.

Results:

The new schedule required the work of a specialized part-time respiratory physiotherapist for 4 days/week. During the study period 594 visits were performed and 362 patients were treated; 206 of them were follow-up, whereas 156 were naïve from RP. In the study period, 115 patients received 2 visits and 53 more than 2 visits (up to 5). On average 10 patients/month did not show up or cancelled the visit. The wait list for RP was about 3 months and it was very difficult to keep emergency slots free seen the important number of patients accessing the program. After the first assessment, 154 (43%) patients were classified as mild, 120 (33%) as moderate, 75 (21%) as severe and active, and 13 (4%) as severe and inactive. Among the patients that received more than 1 treatment during the study period, 61 (36.3%) improved and 15 (8.9%) worsened their severity status, according to the proposed classification.

Conclusions:

This new RP organization model along with its patients' clinical classification was feasible and useful to identify bronchiectasis subjects with more needs. In the next future, the proposed classification could be a useful tool to recognize a cohort of patients who can benefit more of a prompt access to physiotherapy assessment.

Conflict of interest(s) (if any – not included in the 500 words):

Authors declare no conflict of interests for the present work.

[21.03] A Laboratory Evaluation of Nebulizers for the Delivery of Solution Medications for Mucus Clearance – How Does the Nebulizer Type and Mode of Action Impact the Respirable Delivery Profile

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Background/Aims:

Failure to expectorate mucus resulting in progressive airway damage is the hallmark of bronchiectasis. Inhaled mucolytics are often added to the airway clearance regimen, but an added time burden is recognized. The aim of this study was to evaluate the efficacy of small volume nebulizers to deliver solution aerosols in a size likely to reach the lower airways and aid in mucus expectoration.

Methods:

The breath enhanced PARI LC SPRINT Nebulizer / Vios Compressor and the AeroEclipse* XL BAN* Nebulizer (AEXL) / Ombra* Compressor, the later tested in both breath actuated mode as well as continuous mode, were evaluated where each nebulizer was filled with 4ml of salbutamol to act as a measurable surrogate to saline or other solution. An adult tidal breathing waveform (tidal volume = 500mL; duty cycle = 33 %; breaths/minute = 13) was delivered by breathing simulator (ASL 5000). Treatment time was determined by placing a filter at the nebulizer mouthpiece to capture emitted aerosol at minute intervals until onset of sputter. A laser diffractometer was used to determine the volume median diameter (VMD) as well as the fraction of delivered medication that was <4.7 microns (fine droplet fraction, FDF). Fine droplet mass (FDM<4.7µm) was determined as the product of mass recovered from the filter and FDF<4.7µm.

Results:

Graph Attached

Conclusions:

In this example study, the caregiver has the option of completing treatment with AeroEclipse* XL BAN* Nebulizer in continuous mode in 11 mins and getting similar fine droplet mass to the LC SPRINT or they could run for 2 minutes longer with the LC SPRINT and get a little more delivery. With the AeroEclipse* XL BAN* Nebulizer in breath actuated mode, they could conserve medication, avoid fugitive emissions and either stop treatment early to produce similar delivery to the two continuous nebulizers or run to sputter and deliver the highest fine particle mass of all.

Conflict of interest(s) (if any – not included in the 500 words):

Judy Schloss and Dominic Coppolo are affiliated with Monaghan Medical Corporation (US)

Jason Suggett, Mark Nagel and Cathy Doyle are affiliated with Trudell Medical International (Canada)

[21.04] Quality of life in bronchiectasis: physiotherapy with High flow nasal cannula

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Background. Bronchiectasis is the consequence of chronic bronchial inflammation, inappropriate mucus clearance, bacterial colonization, and recurrent or chronic infection.

Humidified and heated high flow therapy (HFT) is a type of non-invasive respiratory therapy, usually delivered through a nasal cannula interface (HFNC). It delivers heated and humidified air, with a stable fraction of inspired oxygen at flow rates up to 60 l/min. HFT has several physiologic effects, such as humidification and improved mucociliary clearance, washout of dead space, and alveolar recruitment, representing a valid therapy for various respiratory diseases. It represents a promising approach for bronchiectasis non-related to cystic fibrosis (NCFB) because HFT improves mucociliary clearance and airway inflammation potentially reducing recurrent infection and exacerbation rate.

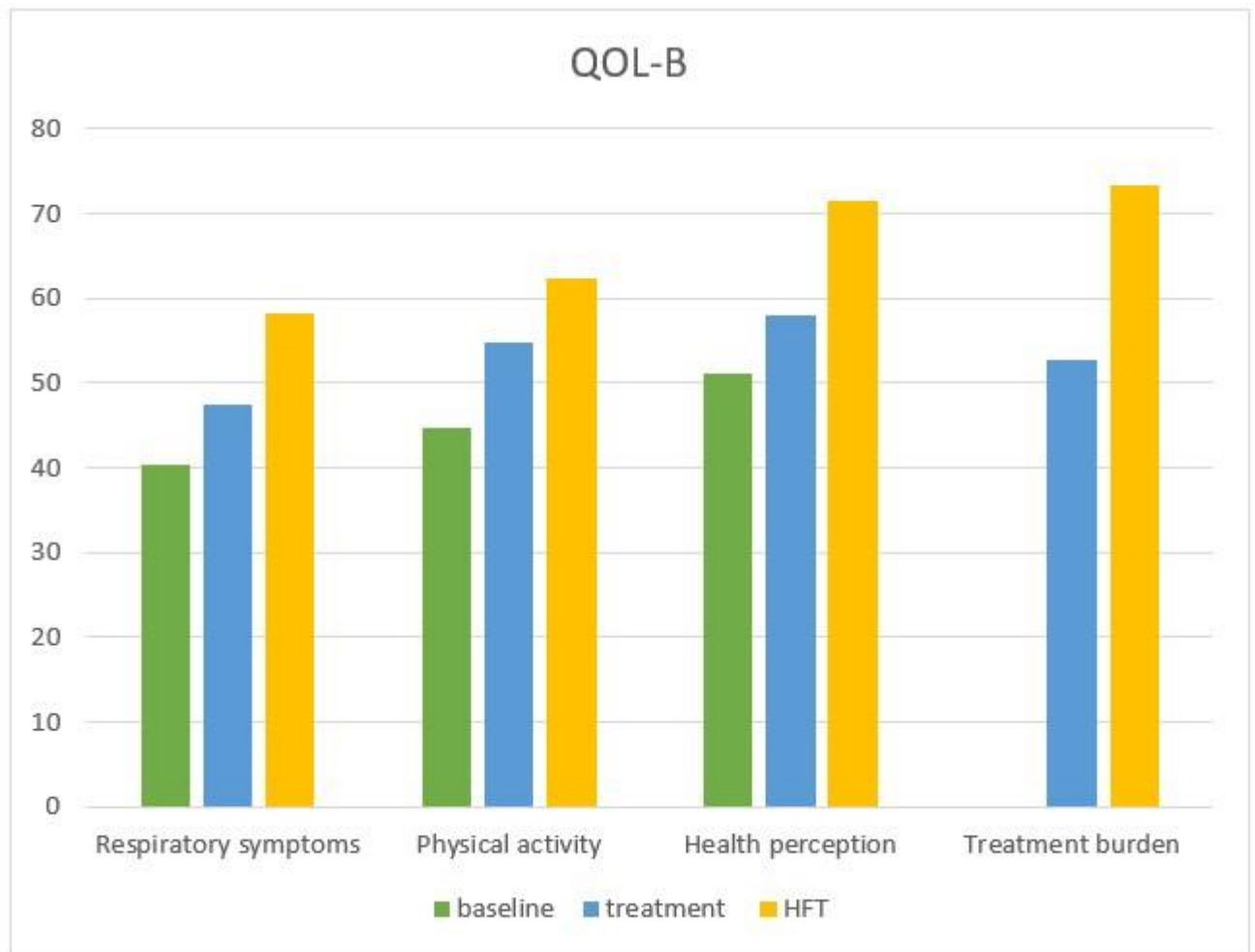
The aim of the study was to describe the quality of life in all-causes adult bronchiectasis with frequent exacerbations and/or hospitalizations, before and after HFT.

Methods. 20 adult severe bronchiectasis were enrolled. Bronchiectasis was diagnosed with high resolution computed tomography (HRCT) of the chest performed within twelve months before enrollment. All patients showed a severe clinical syndrome characterized by 2 or more exacerbations in the last year and/or at least 1 hospital admission caused by bronchiectasis. HFNC was set in our outpatient clinic, and all subjects were trained to autonomously continue at home. Quality of life was assessed by the Quality of Life-Bronchiectasis (QOL-B), at baseline, after standard treatment and physiotherapy (12 months) and after HFT (24 months). 20 patients received HFNC at home. The QOL-B is a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related quality of life for patients with non-cystic fibrosis (CF) bronchiectasis. It contains 37 items on 8 domains (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden). Each domain is scored with a 0- to 100-point scale; higher scores indicate better quality of life. The mean score of QOL-B were compared with a t-test. A p-value < 0.05 was considered statistically significant.

Results. 20 adult patients were enrolled, 7/20 females. Age ranged between 21 and 92 years, the median age was 63 (interquartile range [IQR] 56 – 76). The etiology of bronchiectasis is respiratory tract infection (45%), COPD related (26%) and congenital (22%). The flow setting ranged between 35 and 60 L/min. the temperature setting ranged between 31 and 37 °C. The humidification ranged between 51 and 74%.

The respiratory symptoms domain scored a mean of 40.4±22.4 at baseline, 47.5±24.6 after treatment and 58.1±27.8 after HFT (mean difference +17.7, *p* 0.032, 95% CI 1.539 - 33.861). The physical activity domain scored a mean of 44.7±26.9 at baseline, 54.8±26.9 after treatment and 62.3±19.7 after HFT (mean difference +17.6, *p* 0.023, 95% CI 2.507 - 32.693). The health perception was scored with a mean of 51.2±23.2 at baseline, 58±21.6 after treatment and 71.5±25.4 after HFT (mean difference +20.3, *p* 0.012, 95% CI 4.728 - 35.872).

The treatment burden was not applicable at baseline. The mean score was 52.7 ± 30.4 after treatment and 73.4 ± 25.1 after HFT (mean difference $+20.7$, p 0.024, 95% CI 2.854 - 38.546).



Conclusions. HFT impacts quality of life in adult severe bronchiectasis patients. A long term autonomous therapy improves treatment burden.

[21.05] Combination therapy (OPEP and Nebulizer) to provide focus to mucus clearance – results from a lab study using hypertonic saline

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Background/Aims:

Management of excess mucus is a major treatment goal for bronchiectasis patients. Inhaled nebulized mucolytics such as hypertonic saline are often used with other modalities, such as Oscillating Positive Expiratory Pressure (OPEP) devices. The treatment time burden is significant and therefore being able to combine therapies offers potential benefits to the patient in terms of reduced treatment duration. This study evaluated the medication delivery performance of hypertonic saline when delivered via a nebulizer with breath actuated technology (inhalation) attached to an OPEP device (exhalation).

Methods:

An AeroEclipse* XL BAN* Nebulizer / Ombrac* Compressor (TMI) was connected to an Aerobika* OPEP device (TMI), n=5. A 4ml fill of hypertonic saline (7% NaCl) was delivered through the combination system and a laser diffractometer used to determine the volume median diameter (VMD) as well as the fraction of delivered medication that was <4.7 microns (fine particle fraction, FPF). Treatment time was also determined when operating the combination therapy using an adult USP breathing pattern.

Results:

	VMD (µm mean, sd)	FPF (%) mean, sd)	Treatment time
AeroEclipse* XL BAN* Nebulizer / Aerobika* OPEP device	2.57 +/- 0.04	81.6 +/- 0.5	18 mins

Conclusions:

A typical treatment time for a single session of OPEP therapy is approximately 15 mins. This laboratory study showed that with combination therapy there was a similar time associated with the completion of OPEP therapy and nebulized hypertonic saline, with more than 80% of the delivered medication being in the respirable droplet size range to work therapeutically in the lung. It has also previously been reported that such combination of these devices did not appreciably change the respirable mass delivered using the nebulizer alone.¹

In addition to providing the benefit of treatment time savings, this combination of devices reduces both medication wastage / fugitive emissions and has the potential to provide dual benefits of airway clearance compared to only performing one individual therapy.

Given the efficiency of hypertonic saline delivery demonstrated in the study, as well as the good degree of alignment between ideal OPEP therapy time and nebulizer run time, this type of combination therapy should be considered to reduce the burden of therapy and for mucus management in bronchiectasis patients.

1. M Nagel, et al. Pediatric Pulmonology 2019;54(S2):183.

Conflict of interest(s) (if any – not included in the 500 words):

I work in a medical / scientific capacity for a medical device company

[21.06] The Use of Oscillation and Lung Expansion Therapy with the Volara™ System in Respiratory Diseases in Canada: A Case Series

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Background/Aims: The Volara™ System represents a pioneering solution designed to facilitate the mobilization of secretions, promote lung expansion therapy, and address pulmonary atelectasis treatment and prevention. Oscillation and lung expansion (OLE) therapy, a key feature of the Volara™ System, offers versatile application in both acute care and home environments. It caters to patients with various conditions necessitating airway clearance therapy such as cystic fibrosis [CF], chronic obstructive pulmonary disease [COPD], Bronchiectasis, neuromuscular disease [NMD] and others. While these devices have been used worldwide, it has only recently obtained approval in Canada. Herein, we report a series of cases at our centre to evaluate feasibility of the Volara™ System.

Methods: We enrolled a cohort of patients from Nov 2022 to April 2024 to utilize the Volara™ System. The population of interest was patients with suppurative lung diseases receiving OLE by the Volara™ System. Patients were enrolled at our quaternary care centre with a diagnosis of CF or bronchiectasis. They were enrolled at time of hospitalization and were seen twice daily by a chest physiotherapist who offered the Volara™ System as a form of therapy.

Results: During the pilot project period, four patients were enrolled and consented to the use of the Volara™ System. Two were individuals with cystic fibrosis, and two were those with hypoxic respiratory failure from lung cancer. The first was an 18-year-old male with advanced lung disease from CF and progressive respiratory failure, presenting to our center and requiring ICU admission. Lung transplantation was considered, but in an attempt to mitigate intubation, the Volara™ System was sought out, given its positive benefits in other countries but not yet used in Canada. The patient derived both radiologic and symptomatic benefits, enabling transfer out of the ICU and eventual discharge. The second was a 33-year-old male with advanced lung disease from CF, who presented with hypoxic respiratory failure and again derived benefit, both radiologically and symptomatically, from the Volara™ System. Given the observed benefits, we sought to expand our findings beyond CF and enrolled two patients admitted to the respiratory service with lung cancer, including a 72-year-old female who was able to titrate down from Optiflow 70% FiO₂ to supplemental nasal oxygen through nasal prongs within four days of using the Volara™ System. Finally, the last patient, a 65-year-old male, used the Volara™ System with modest efficacy in terms of imaging and symptoms.

Conclusions: Oscillation and lung expansion therapy use in the hospital may be associated with improvement in clinical outcomes in patients with chronic respiratory disease in Canada and represents a promising new therapeutic approach in this cohort.

Conflict of interest(s) (if any – not included in the 500 words): CST and CS report funding for this study from Baxter.

BACKCOVER