5th World Bronchiectasis & NTM Conference
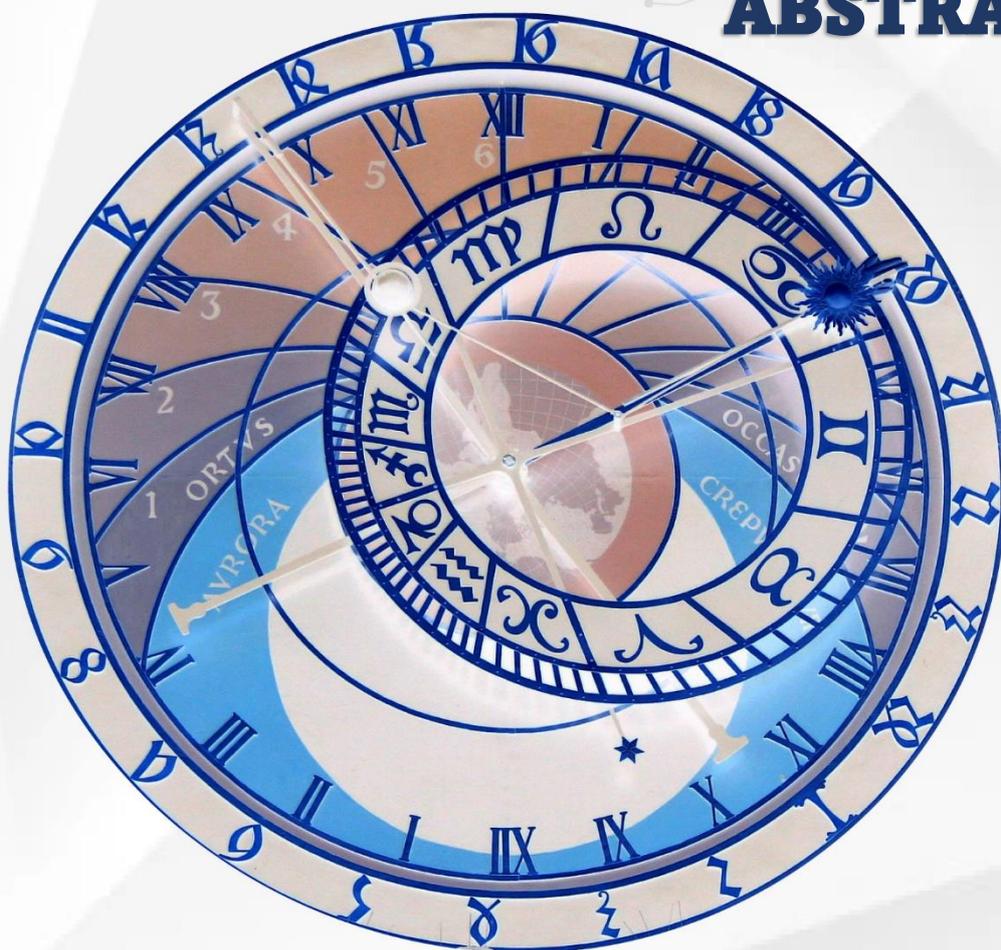
EMBARC
The European Bronchiectasis Registry

ABSTRACT BOOK

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PRAGUE
30 JUNE – 2 JULY 2022

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ABSTRACT BOOK

Please note that the abstract book is ordered per type of presentation. For poster presentations it is ordered per session, per topic and per alphabetical order of the presenter.

The Abstract Book is realized thanks to the educational unrestricted grant of

RISING STARS

RS.1. Sputum microbiome and clinical outcome measures in bronchiectasis: Data from the BRONCH UK Study

Zina Alfahl[1]; Gisli G. Einarsson[2]; J. Stuart Elborn[2]; Deridre F. Gilpin[1]; Katherine O'Neill[2]; Kathryn Ferguson[3]; Adam Hill[4]; Michael R. Loebinger[5]; Mary Carroll[6]; Timothy Gatheral[7]; Anthony De Soyza[8]; James Chalmers[9]; Christopher Johnson[10]; John R. Hurst[11]; Jeremy Brown[12]; Judy M. Bradley[2]; Michael M. Tunney[1]

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Background/Aim:

Characterisation of the airway microbiome may improve our understanding of the natural history of bronchiectasis. This study investigated the changes in bacterial community composition in sputum during clinical stability and following antibiotic treatment for pulmonary exacerbation (PEx).

Methods:

Five subgroups from the multi-centre BRONCH-UK cohort study of adults (n=105) with bronchiectasis were analysed. Group-1: clinically stable patients (n=75) who provided a sputum sample at the first stable visit; Group-2: clinically stable patients (n=44) who provided sputum samples at the first stable visit and one further sample within 12 months; Group-3: PEx patients (n=16) who provided samples at the first stable visit and one further sample within 12 months; Group-4: PEx patients (n=19) who provided paired samples pre- and post-antibiotic treatment and Group-5: clinically stable patients (n=15) who provided four samples (Visit 1, Visit 2, Visit 3 and Visit 4) over a one year period. Some patients met the criteria for more than one group and thus were included in multiple groups for analysis. Clinical outcome measures at the first stable visit included: FEV_1% predicted, lung clearance index (LCI), systemic C-reactive protein (CRP), white cell count (WCC), bronchiectasis severity index (BSI), age, St. George's Respiratory Questionnaire (SGRQ) and Quality of Life-Bronchiectasis questionnaire respiratory symptoms domain (QOL-B- RSS). The V4 region of the bacterial 16S rRNA gene was sequenced using the Illumina HiSeq platform.

Results:

65/105 were female, mean (SD) age 65 (11) years, FEV_1% predicted 69 (19) % and BSI 8.5 (2.7). At the first stable visit (Group 1, n= 75), 27 (36%) of patients were identified as having a microbiome profile dominated by *Streptococcus*, 16 (21.4%) were dominated by *Haemophilus*, 16 (21.4%) by *Pseudomonas* and 16 (21.4%) were dominated by other taxa, including *Veillonella*, *Prevotella*, *Enterobacteriaceae*, *Staphylococcus*, *Actinomyces* and *Moraxella*. No difference was observed in community diversity, richness, evenness and dominance at the first stable visit between patients who remained clinically stable (Group 2, n= 44) and patients who had a PEx (Group 3, n= 16) (p= 0.93, 0.61, 0.48 and 0.98; respectively). Further, no difference was observed in community diversity, richness, evenness and dominance from pre- to post-treatment of a PEx (Group 4, n=19) (p= 0.46, 0.44, 0.71 and 0.58; respectively). For patients who remained clinically stable (Group 5, n=15), no significant change was observed in community diversity, richness, evenness and dominance between Visit 1 and Visit 4 (p=0.45, 0.54, 0.23 and 0.43; respectively). Similarly, no significant change was observed in the Relative Abundance (%) of *Streptococcus*, *Haemophilus* and *Pseudomonas* between Visit 1 and Visit 4 (p= 0.93; 0.58 and 0.12; respectively There was no correlation between the main microbiome ecological indices and demographic/clinical parameters (Age, FEV_1% predicted, LCI, CRP, WCC, BSI, SGRQ and QOL-B RSS) (p>0.05) at the first stable visit.

Conclusion:

Streptococcus, *Haemophilus* and *Pseudomonas* dominate the airways in people with bronchiectasis. Community diversity was stable during periods of clinical stability and did not change following antibiotic treatment of a PEx. No association was observed between changes in the main ecological indices and clinical outcome measures.

RS.2. Rifampicin has no clear role in the standard regimen for M. avium complex lung disease - A hollow-fibre study with genome-wide transcriptional analysis.

Jelmer Raaijmakers[1]; Jodie Schildkraut[1]; Jakko van Ingen[1]

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Background/Aims:

Mycobacterium avium complex (MAC) bacteria are the most frequent causative agents of nontuberculous mycobacterial pulmonary disease (NTM-PD) worldwide. Rifampicin is currently recommended for the treatment of MAC-PD alongside azithromycin and ethambutol. Rifampicin has poor *in vitro* activity against MAC, but is thought to prevent the emergence of macrolide resistance. We evaluated the contribution of rifampicin within the standard therapy of MAC-PD in an intracellular hollow-fibre model. In addition, to study the differences in adaptation to each treatment regimen, we performed RNA sequencing of the bacterial population over time.

Methods:

In an *in vitro* hollow-fibre experiment, epithelial lining fluid pharmacokinetic profiles of either the recommended 3-drug (rifampicin, ethambutol, azithromycin) or a 2-drug (ethambutol, azithromycin) treatment was simulated. THP-1 cells infected with *M. avium* ATCC 700898 were exposed to these regimens for 21 days. On day 0, 3, 7, 14 and 21, samples were drawn to determine bacterial- and THP-1 cell densities and for RNA sequencing. To study the emergence of macrolide resistance, bacterial samples (intra- and extracellular fractions) were inoculated on drug-free and azithromycin (8x MIC) containing 7H10 agar plates. At day 0 and 21, samples were drawn to determine antibiotic concentrations and to generate complete pharmacokinetic profiles.

Results:

The 2- and 3-drug therapies were initially able to maintain bacterial stasis for up to 3 days for both the intra- and extracellular bacterial fractions. After the initial stasis, a rapid regrowth towards the growth control was observed for both therapies from day 7 onwards. This coincided with emergence of a macrolide-resistant subpopulation in both treatment arms. The THP-1 cell concentration (± 8·10^5 cells/ml) remained static over time. RNA sequencing shows that the 2- and 3-drug therapies resulted in a similar transcriptional profile that is only minimally influenced by duration of exposure, although the effect of treatment with 2-drugs was slightly larger.

Conclusions:

Rifampicin did not add to the antimycobacterial effect to a regimen of azithromycin and ethambutol and it did not add to suppression of the emergence of macrolide resistance. RNA sequencing showed that the addition of rifampicin does not greatly alter transcription in comparison to the 2-drug regimen. We believe that the similar transcriptomic profile in the two arms is due to the presence of both azithromycin and host cells, both strongly influencing transcription and likely dominating the stress response with little-to-no additional effect of rifampicin. This questions the role of rifampicin in the currently recommended MAC-PD regimen, particularly in milder manifestations. These findings remain to be confirmed in ongoing clinical trials.

ORAL PRESENTATIONS

OP.1. Characterisation of Ciliary Function in a European Cohort of Bronchiectasis Patients: The EMBARC-BRIDGE cilia study

Bottier Mathieu[1]; Delgado Lilia[1]; Shuttleworth Morven K.[1]; Cant Erin[1]; Perea Lidia[1]; Cassidy Diane M.[1]; Crichton Megan L.[1]; Gallant Stephanie[1]; Aliberti Stefano[2]; Goeminne Pieter C.[3]; Altenburg Josje[4]; Shteinberg Michal[5]; Welte Tobias[6]; Blasi Francesco[7]; Sibila Oriol[8]; Polverino Eva[9]; Hogg Claire[10]; Ollosson Sarah[10]; Loebinger Michael R.[10]; Lorent Natalie[11]; Chalmers James D.[1]; Shoemark Amelia[1]

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Background:

 Impaired mucociliary clearance is central to bronchiectasis pathophysiology. Ciliary dysfunction can be inherited or acquired as a result of chronic inflammation. Cilia function in bronchiectasis is poorly understood with conflicting results in the literature suggesting an increased or decreased ciliary beat frequency (CBF). This work aimed to characterize ciliary function in bronchiectasis in a large prospective international study.

Methods:

153 patients (age = 66.9 ± 13.8 years (mean ± std), 48.7 % female) with bronchiectasis (BE) were recruited to the international observational study EMBARC-BRIDGE (NCT03791086) at 4 European sites (Barcelona, Leuvenondon and Dundee) between August 2019 and March 2022. Patients with a known diagnosis of Primary Ciliary Dyskinesia (PCD) and smokers were excluded. 19 healthy non-smoking controls (age = 27.8 ± 8.5 years, 73.7 % female) were enrolled for comparison. The respiratory epithelium was sampled during a stable disease phase by brushing the nasal inferior turbinate with a modified cytology brush. All subjects included after March 2020 tested negative for *sars-cov-2* on the day of the sampling. Ciliary function was assessed at 37°C by high-speed video microscopy within 4 hours of sampling. Primary nasal epithelial cells were re-differentiated into ciliated epithelium in air-liquid interface cultures and high-speed video microscopy repeated. Ciliary beat parameters, including cilium length, CBF, ciliary beat amplitude, angle, and amplitude per second, were calculated using an in-house developed program.

Results:

 Five patients were newly identified as having PCD. In the remaining 148 individuals, CBF was not different between bronchiectasis patients and healthy donors (BE = 14.5 ± 2.6 Hz, Control = 15.7 ± 4.1 Hz). The ciliary beat amplitude, angle, and amplitude per second were significantly decreased in bronchiectasis compared

to healthy donors' brushings (Fig. 1A). These parameters were rescued to similar values to healthy donors after regeneration of the ciliated epithelium in sterile culture in the presence of antibiotics (penicillin, streptomycin) and steroids (hydrocortisone) (Fig. 1B&C). Exposure of epithelial cells to chronic inflammation (cells cultured with inflammatory cytokines for 3 weeks) resulted in a decrease in ciliary beating efficiency highlighted by a significantly lower ciliary beat amplitude per second after treatment with IL-8, IL-1β and IL-4. Measurement of cilia driven flow by fluorescent beads revealed a correlation with ciliary beat amplitude per second (Spearman r=0.60, p-value <0.0001) highlighting the role of decreased ciliary function in reduced mucociliary clearance.

Conclusions:

There is an impairment of ciliary movement, defined by ciliary beating amplitude per second, in bronchiectasis which relates to impaired mucociliary clearance and can be rescued following culture. We show that in most patients, mucociliary clearance defects are secondary to the effects of the airway environment and are likely to be reversible with anti-inflammatory or anti-microbial treatment.
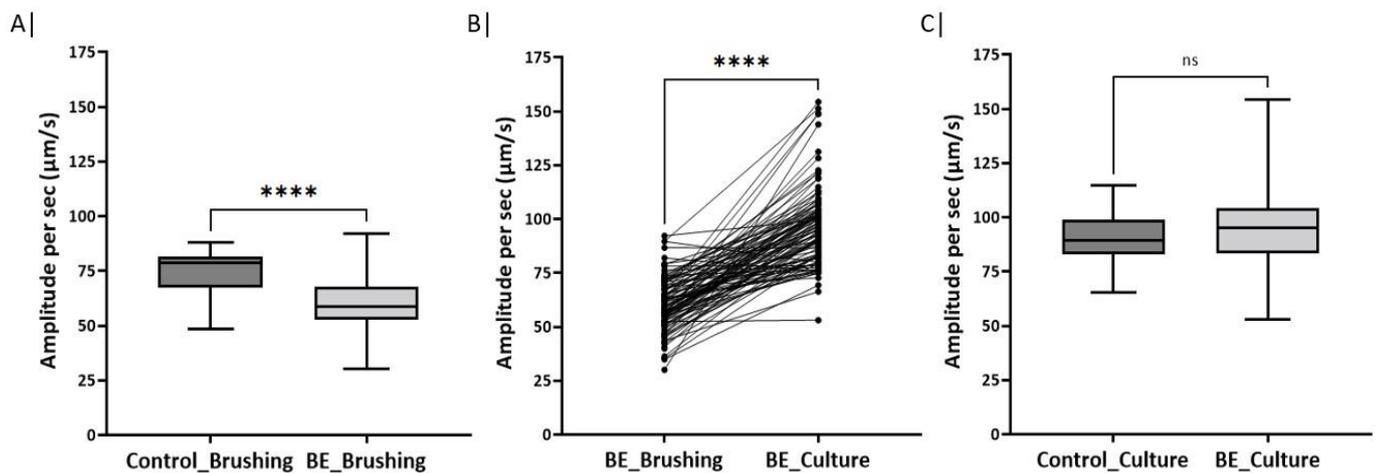
Figure 1 - Cilia function in bronchiectasis. Ciliary beat amplitude per second compared between A| Healthy donors (Control) and bronchiectasis (BE) at brushings (***** p < 0.0001, Mann-Whitney test*). B|Bronchiectasis patients brushings and after culture (***** p < 0.0001, Wilcoxon test*) and C| healthy donors and bronchiectasis patients after culture (*ns non-significant, Mann-Whitney test*).

OP.2. A Th2 endotype in bronchiectasis associated with impaired cilia function

Erin Cant[1]; Mathieu Bottier[1]; Morven Shuttleworth[1]; Lidia Perea[1,2]; Holly Keir[1]; Amy Gilmour[1]; Megan Crichton[1]; Diane Cassidy[1]; Stefano Aliberti[3]; Oriol Sibila[2]; Jeffrey Huang[1]; James Chalmers[1]; Amelia Shoemark[1]

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Background/Aims:

Bronchiectasis is classically associated with neutrophilic inflammation but recent research suggests Th2 inflammation may play a role in a subset of patients. We hypothesised that Th2 cytokines would be associated with severe bronchiectasis and dysfunctional mucociliary clearance.

Methods:

Initially, a cohort of patients with bronchiectasis (n=31), bronchiectasis-COPD association (n=28) and COPD (n=32), provided sputum samples during a period of clinical stability. Sputum cytokines were analysed by ELISA and multiplex assay and principle component analysis (PCA) was used to identify endotypes. Results were then explored in a separate cohort of 275 bronchiectasis patients from the EMBARC BRIDGE study. Primary nasal epithelial cells were cultured at air liquid interface and chronically treated with IL-13, IL-5, or IL-4 with or without the addition of tiotropium bromide (a bronchodilator which also inhibits mucus secretion). Cilia function was evaluated using high speed video microscopy.

Results:

PCA analysis of sputum cytokine concentrations identified a group of patients with inflammatory profiles dominated by cytokines associated with Th2 inflammation including IL-4 and IL-5. In the BRIDGE cohort, using IL-4 in sputum to define this subset, IL-4 concentration was associated with an increase in bronchiectasis severity index (BSI) and a higher frequency of exacerbations. PCA analysis of sputum cytokine concentrations in this cohort confirmed separate clusters defined by Th1 and Th2 cytokines. Treating ciliated epithelial cells for 3 weeks with 10ng/ml IL-4 caused a reduction in the cilia beat frequency and the amplitude per second which was not rescued by treatment with 5μM tiotropium bromide. Three weeks of 10ng/ml IL-13 or 10ng/ml IL-5 treatment did not affect the cilia function.

Conclusions:

We demonstrate in two cohorts that a subset of bronchiectasis patients have elevated Th2 cytokines. IL-4 is associated with worse clinical outcomes which may be associated with impaired mucociliary clearance.

OP.3. Impact of ciprofloxacin treatment on Pseudomonas aeruginosa phenotypes in vitro

Zichuan Li[1]; Ross P. McCleave[1]; Gisli G. Einarsson[2]; Michael R. Loebinger[3]; James D. Chalmers[4]; J. Stuart Elborn[2]; Charles S. Haworth[5]; Michael M. Tunney[1]; Laura J. Sherrard[1]

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Background/Aims:

Pseudomonas aeruginosa (PA) is detected in the airways of 20-40% of people with bronchiectasis and is associated with a worse clinical trajectory. Oral ciprofloxacin is used for eradication of PA and treatment of associated exacerbations and inhaled formulations for long-term use have been developed. The emergence of PA antimicrobial resistance during treatment is a concern. Often development of resistance occurs simultaneously with changes in bacterial fitness.

The aims were to determine (1) how PA evolves phenotypically under treatment with ciprofloxacin *in vitro* and (2) if PA reverts to its baseline phenotype following removal of antibiotic pressure.

Methods:

Four ciprofloxacin-susceptible PA isolates collected from respiratory samples of people with bronchiectasis were included (median MIC: 0.47 mg/L). Three replicates of each isolate were passaged in increasing concentrations of ciprofloxacin for 20 passages using antibiotic gradient plates to evolve resistant lineages. Then the antibiotic pressure was removed for a further 20 passages to assess the stability of evolved phenotypes. The minimum inhibitory concentration (MIC) of ciprofloxacin after each passage was determined by the agar dilution method. The evolution of antibiotic cross-resistance was assessed by disc diffusion. Shifts in swimming and swarming motility and pyocyanin secretion were determined in isolates displaying these phenotypes at baseline. Bacterial growth was determined by monitoring the optical density (OD_{590nm}) over 48 hours and the doubling time and colony density were calculated.

Results:

During experimental evolution of resistance, a stepwise increase in the ciprofloxacin MIC was observed for all 12 lineages. The MIC increased by a median of 9.5-fold across the lineages (MIC_{50}: 256mg/L; MIC_{90}: 2048 mg/L). There was a clear decrease in the MIC of ≥2 doubling dilutions after antibiotic pressure was removed in two evolved lineages of two baseline isolates, but susceptibility was not regained. The remaining evolved lineages had a stable resistant phenotype. Two of four isolates were also susceptible to levofloxacin at baseline and their evolved lineages also developed a stable resistant phenotype over time. Two lineages of one baseline isolate developed multi-drug resistance. A stepwise reduction in swimming and swarming

motility in each evolved lineage of two motile isolates at baseline was observed over time. Each evolved lineage was classed as non-motile after 5-17 passages in ciprofloxacin and motility was not restored after antibiotic pressure was removed. The same trend was observed in pyocyanin production. After 20 passages in ciprofloxacin, pyocyanin was significantly reduced in three lineages of one isolate that produced the pigment at baseline ($p < 0.0001$) and this reduction was maintained following antibiotic removal. Most lineages (n=9/12) showed an increase in the mean doubling time (baseline, 283.6 mins; evolved lineage, 413.4mins) and a significant decrease in colony density ($p < 0.0001$).

Conclusions:

Ciprofloxacin resistance emerged in clinical PA isolates from bronchiectasis. In general, this phenotype was stable after removal of antibiotic pressure and occurred simultaneously with a stable reduction in the virulence traits investigated and growth. Such phenotypic shifts are characteristic of PA adaptation in chronic infections.

OP.4. Preclinical evaluation of a nitric oxide-releasing prodrug as a treatment for chronic Mycobacterium abscessus infections

Mark Schoenfisch[1,2]; Rebecca McDonald[1]; Chris Broberg[2]; Mona Ahonen[1]; John Simons[1]; Diane Ordway[3]

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Background/Aims:

Chronic bacterial infections pose a significant problem for individuals living with bronchiectasis because of the corresponding decrease in lung function. While antibiotic therapies exist to manage some infections, the interventions for non-tuberculosis mycobacteria (NTM) infections are limited. Clearance of NTM infection remains elusive given the biofilm environment at the epithelial lining and poor antibiotic bioavailability. Herein, we describe the preclinical efficacy of a water soluble, nitric oxide (NO)-releasing prodrug, MD3, as a potential treatment for NTM infections.

Methods:

The antimicrobial activity of MD3 was previously demonstrated to be effective both against common bronchiectasis pathogens using classic MIC/MBC/MBEC assays and in an acute model of *M. abscessus* infection in SCID mice. Herein, potential for drug resistance was evaluated using serial passage mutagenesis assays, subjecting *M. abscessus* strains to sub-inhibitory concentrations (25% MIC) of MD3 repeatedly (30 passages). To evaluate MD3 efficacy in a chronic NTM infection model, SCID mice were infected with a bolus of *M. abscessus* intratracheally (IT). The infection proceeded for 28 days, resulting in the formation of granulomas. Animals were then treated with control or MD3 (1-30 mg/kg) once daily, dosed IT, for 28 consecutive days. Animals were sacrificed after the last dose, with surviving bacteria enumerated in the lung, liver, and spleen. Terminal serum samples were also obtained for nitrate (NO_3^-) metabolite analysis.

Results:

Consistent with our prior work with Gram-negative and -positive bacteria, no decrease in antibiotic susceptibility was observed following 30 passages of MD3 in vitro. In the in vivo model, animals sacrificed at Day 2 and Day 28 demonstrate robust *M. abscessus* infection (>10^5 CFU/lung). After 28 days of treatment with negative control, NTM levels rose to 6.5×10^5 CFUs/lung. MD3 pharmacologic activity was NO concentration dependent, wherein in the low doses of 1 and 3 mg/kg/day demonstrated minimal bacterial reductions and the higher doses of 10 and 30 mg/kg/day MD3 reduced the bacterial burden in the lungs by more than 2 logs (>99%). Correspondingly, a dose-dependent increase in serum nitrate was observed between 1 and 30 mg/kg, with 5,546 ng/mL nitrate corresponding to a minimally effective MD3 dose.

Conclusions:

New therapeutic approaches that more effectively penetrate microbial biofilms, do not propagate resistance, and are safe for chronic use are desperately needed to treat NTM infections. The dose-dependent, logarithmic reductions of *M. abscessus* observed following treatment with MD3 in a chronic in vivo model further extends the preclinical evidence for MD3 as an attractive antibiotic alternative.

Conflict of interest(s):

POSTER PRESENTATIONS

STROLLING POSTER SESSION 1OA – IN PRESENCE

1OA.1. Exacerbation rates before and during the COVID-19 pandemic in non-cystic fibrosis bronchiectasis: a retrospective claims study

Annika Åstrand[1]; Steven J. Kiddle[2]; Rohith Siva Ganesh Mudedla[3]; Sanchita Porwal[3]; Kaushik Chafekar[3]; Carlos Seminario[4]; James D. Chalmers[5]; Ioannis Psallidas[6]

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Background/Aims:

Recent evidence suggests that social distancing and lockdown measures may have reduced exacerbation rates in patients with chronic respiratory diseases. The aim of this study was to retrospectively evaluate the impact of lockdowns and social distancing during the Covid-19 pandemic on exacerbation rates in non-cystic fibrosis bronchiectasis (NCFB) in a large US population.
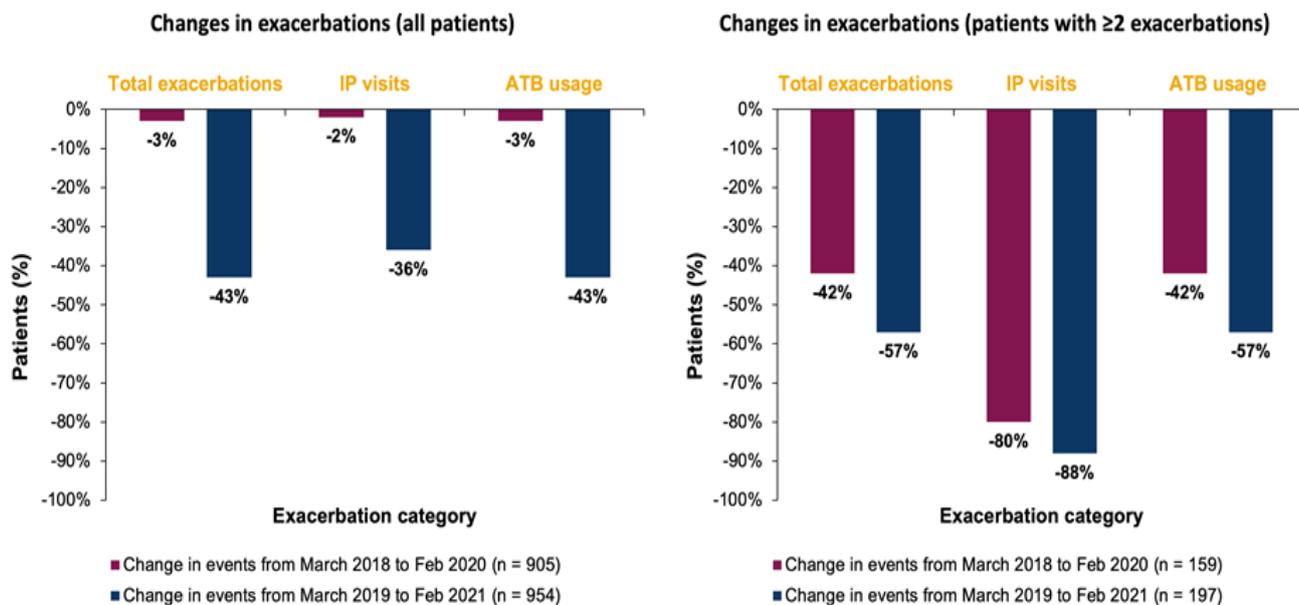
Methods:

Health insurance claims data (March 2018–Feb 2020; March 2019–Feb 2021) from US Optum Clinformatics DataMart, which includes claims covering 68.8 million US patients, were used. NCFB was identified using diagnostic codes within the dataset. Eligible patients had ≥1 NCFB diagnosis code, ≥1 exacerbation in each of the 2 time-windows, and no other respiratory diseases. Descriptive analyses and chi square tests were used to evaluate differences (exacerbations and patients per category) between the 2 time-windows.

Results:

The study included 905 patients in the 2018-2020 evaluation and 954 patients in the 2019-2021 evaluation. Compared to the time-window from 2018-2020, in 2019-2021 fewer patients had an increased exacerbation rate (29% vs 43%) and a greater number had a decreased exacerbation rate (63% vs 45%). Total exacerbations changed by −43% in 2019-2021 vs −3% in 2018-2020, as did inpatient visits (−36% vs −2%) and antibiotic use (−43% vs −3%; **Figure**). Among patients with more frequent exacerbations (≥2 in the previous 12 months), antibiotic usage and exacerbations both decreased by approximately 30% (from -42% to -57%) while the number of in-patient visits decreased by a smaller margin (from -80% to -88%). A higher proportion of patients with exacerbations at baseline had no exacerbations in 2020-2021 (57% vs 39%).

Conclusions:

Real world data demonstrated a significant reduction in exacerbations, treatments and hospitalizations during the pandemic as compared to previous years, potentially due to the reduced exposure to viruses. The effect was more dramatic amongst the patients with fewer exacerbations. Moreover, the analysis showed that previous exacerbations were poor predictors of future exacerbations in patients with NCFB.

Changes in exacerbations (all patients) — Total exacerbations: -3% / -43%; IP visits: -2% / -36%; ATB usage: -3% / -43%. Change in events from March 2018 to Feb 2020 (n = 905); Change in events from March 2019 to Feb 2021 (n = 954).

Changes in exacerbations (patients with ≥2 exacerbations) — Total exacerbations: -42% / -57%; IP visits: -80% / -88%; ATB usage: -42% / -57%. Change in events from March 2018 to Feb 2020 (n = 159); Change in events from March 2019 to Feb 2021 (n = 197).

Conflict of interest(s):

1OA.2 Study design of a Phase II, randomized, double-blind, placebo-controlled trial of a novel cathepsin C inhibitor BI 1291583 in patients with bronchiectasis

James D. Chalmers[1]; Abhya Gupta[2]; Sanjay Haresh Chotirmall[4,3]; April Armstrong[5]; Peter Eickholz[6]; Naoki Hasegawa[7]; Pamela J. McShane[8]; Anne O'Donnell[9]; Michal Shteinberg[10]; Henrik Watz[11]; Anastasia Eleftheraki[2]; Claudia Diefenbach[2]; Wiebke Sauter[2]

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Background/Aims:

In bronchiectasis, uncontrolled release of neutrophil serine proteases damages airways and impairs mucociliary clearance. This contributes to a cycle of recurrent severe infections, lung destruction and disease progression, characterized by frequent pulmonary exacerbations. No approved treatments are currently available to reduce inflammation and tissue destruction in patients with bronchiectasis. Cathepsin C (also known as dipeptidyl peptidase 1) is a cysteine protease responsible for the activation of neutrophil serine proteases such as neutrophil elastase, proteinase 3 and cathepsin G during neutrophil maturation in the bone marrow. BI 1291583 is a potent and selective Cathepsin C inhibitor that may ameliorate neutrophilic inflammation in the lungs. Phase I studies have demonstrated good safety, tolerability and pharmacodynamic potential of BI 1291583 in healthy volunteers. Here, we outline the trial design of a Phase II dose-finding study evaluating the efficacy, safety and tolerability of BI 1291583 in preventing pulmonary exacerbations in patients with bronchiectasis. The trial has been approved by Independent Ethics Committee of the participating centers.

Methods:

In this Phase II, multicenter, double-blind, placebo-controlled, parallel-group trial, 240 patients with bronchiectasis will be randomized in a 2:1:1:2 ratio to receive oral doses once daily of 5mg, 2.5mg or 1mg of BI 1291583 or placebo for up to 48 weeks (Figure). Patients must be 18–85 years old with a diagnosis of bronchiectasis confirmed by computed tomography and currently producing sputum, with a history of at least two exacerbations requiring antibiotic treatment in the past 12 months (or one exacerbation plus severe symptoms, defined by a St. George's Respiratory Questionnaire [SGRQ] symptoms score >40). The main objectives of the study are to evaluate the dose–response relationship and confirm superiority of the 5mg dose over placebo on the primary endpoint: the time to first pulmonary exacerbation. Secondary endpoints include relative change from baseline in sputum neutrophil elastase activity, rate of pulmonary exacerbations, change in SGRQ symptoms score and percent predicted forced expiratory volume in 1 second. Additional exploratory measures of efficacy (including lung function, patient-reported outcomes, exacerbation characteristics, pharmacokinetics and changes over time in biomarkers) will also be assessed.
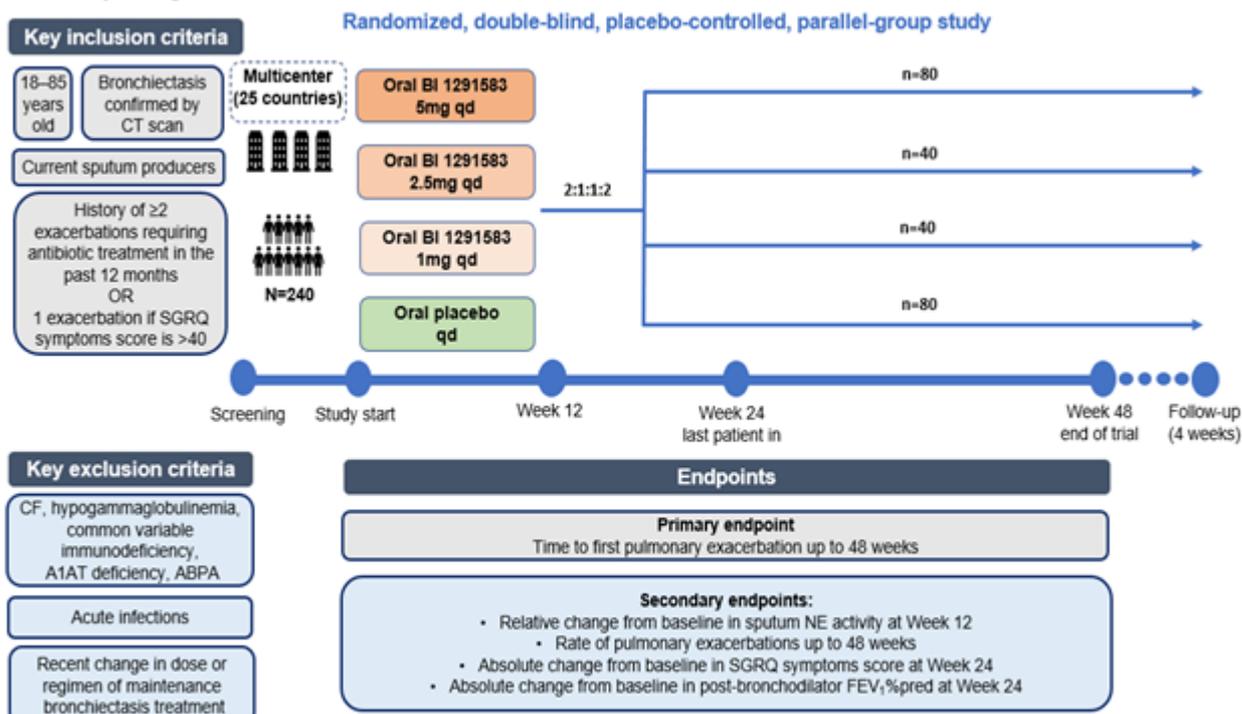
Results:

The trial is expected to start in March 2022, with completion in December 2023.

Conclusions:

Results from this Phase II trial will provide efficacy, safety and dosing evidence of BI 1291583 in preventing pulmonary exacerbations by reducing neutrophilic inflammation in patients with bronchiectasis.

Figure: Study design of Phase II trial of BI 1291583

A1AT, alpha1-antitrypsin; ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; CT, computerized tomography; FEV₁%pred, percent predicted post-bronchodilator forced expiratory volume in 1 second; NE, neutrophil elastase; qd, once daily; SGRQ, St. George's Respiratory Questionnaire.

Conflict of interest(s):

1OA.3 Design of the 52-week Phase 3 MAHALE Study of Benralizumab in Patients with Non-Cystic Fibrosis Bronchiectasis

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Background/Aims:

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic, progressive lung disease associated with inflammation, permanent airway dilatation, and increased susceptibility to infection. There are currently no approved treatments for NCFB. Emerging evidence suggests there are multiple NCFB endotypes, including subtypes defined by the predominant airway inflammatory cells: neutrophils and eosinophils. Approximately 20% of patients have eosinophilic inflammation (NCFB+EI), which may contribute to increased exacerbations. Recent observational studies suggest that treatments targeting eosinophils (EOS) may reduce NCFB symptoms and exacerbations, however, randomized, controlled trials are necessary. Benralizumab is a humanized, afucosylated, anti-interleukin-5 receptor α monoclonal antibody that induces direct, rapid, and near complete depletion of eosinophils in blood and tissue, through antibody-dependent cell-mediated cytotoxicity. The 52-week, phase 3 MAHALE (NCT05006573) study is evaluating the efficacy and safety of benralizumab versus standard-of-care therapy in adults with NCFB+EI. The MAHALE study includes exploratory translational research to confirm the mechanism of action of benralizumab, and to characterise patient phenotypes/endotypes relative to efficacy, in patients with NCFB+EI.

Methods:

This multicentre, randomized, double-blind, placebo-controlled study will enrol ~420 adults with a primary diagnosis of computed tomography (CT)-confirmed NCFB, a documented history of ≥2 exacerbations in the prior 12 months, and without co-morbid asthma or other eosinophilic or respiratory diseases. Patients will be stratified 2:1 by screening blood EOS levels ([bEOS] ≥300 or <300 cells/mL) and will receive either benralizumab or placebo for 52 weeks; patients who complete the double-blind period are eligible for an open-label extension in which all patients will receive benralizumab (**Figure**). The primary endpoint is annualized exacerbation rate in patients with bEOS ≥300 cells/mL. Key secondary endpoints include time to first exacerbation and change from baseline in Quality of Life-Bronchiectasis-Respiratory Symptoms Scale and pre-treatment FEV_1 over 52 weeks. Biomarkers in sputum and blood will be analysed throughout the study. CT scans will be used to characterise the effect of benralizumab on mucus plugging, air trapping, and airway structure by examining the change from baseline to the end of study for these parameters.

Conclusions:

The phase 3 MAHALE study will characterise the efficacy and safety of benralizumab in patients with NCFB while also providing detailed inflammatory, clinical and radiological characterisation of NCFB endotypes.
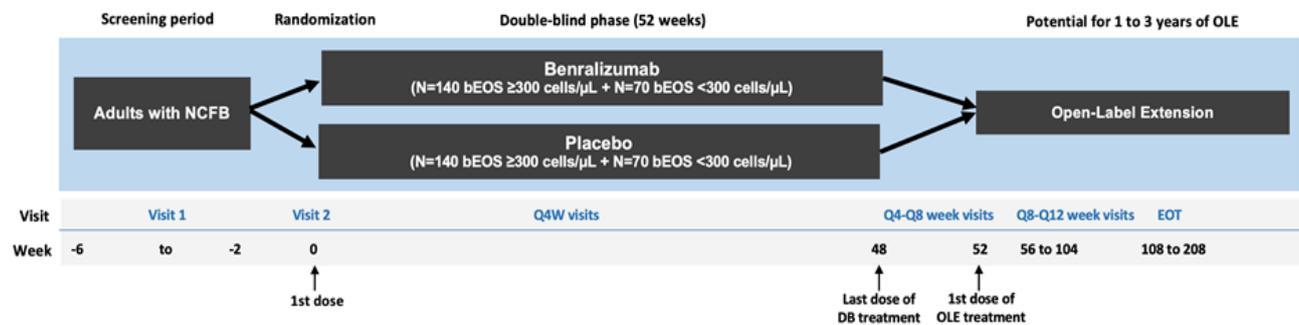
Conflict of interest(s):

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1OA.4. Brensocatib for the Treatment of Non–Cystic Fibrosis Bronchiectasis (NCFBE): Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

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Background/Aims:

Brensocatib is an investigational, small-molecule, orally bioavailable, selective, and reversible dipeptidyl peptidase-1 inhibitor that blocks activation of neutrophil serine proteases, including neutrophil elastase (NE). In a phase 2 study (WILLOW; NCT03218917), brensocatib prolonged time to first exacerbation in patients with NCFBE and reduced sputum NE concentrations in comparison with placebo. This analysis evaluated NNT and NNH using data from WILLOW.

Methods:

WILLOW was a phase 2, randomized, double-blind, placebo-controlled study in which 256 adults with NCFBE were randomized 1:1:1 to receive once-daily brensocatib 10 mg or 25 mg or placebo. The primary endpoint was time to first bronchiectasis exacerbation over 24 weeks, and the key secondary endpoint was rate of exacerbations at week 24. NNT was calculated for the prevention of exacerbations. NNH was assessed for the risk of serious treatment-emergent adverse events (TEAEs), including and excluding exacerbations as safety events. Reciprocal risk difference between brensocatib treatment arms and placebo was calculated for NNT and NNH.

Results:

The proportion of patients with exacerbations at week 24 was lower in groups treated with brensocatib vs placebo, yielding NNTs for exacerbation prevention of 6, 7, and 6 for the 10-mg, 25-mg, and pooled groups, respectively (**Table 1A**). Serious TEAEs across brensocatib treatment groups vs placebo yielded NNHs of −11, −9, and −10, respectively, with negative NNH indicating lower risk of these events vs placebo (**Table 1B**). NNH values excluding exacerbations in the brensocatib 10-mg, 25-mg, and pooled groups compared with placebo were −55, −25, and −34, respectively (**Table 1C**).

Table 1

A. NNTs for exacerbation prevention, proportion with exacerbation at week 24			
Endpoint	Brensocatib, %	Placebo, % (n=87)	NNT
Brensocatib 10 mg, n=82	31.7	48.3	6
Brensocatib 25 mg, n=87	33.3	48.3	7
Brensocatib pooled, n=169	32.5	48.3	6

B. NNHs including exacerbations, proportion with serious TEAEs at week 24			
Endpoint	Brensocatib, %	Placebo, % (n=85)	NNH
Brensocatib 10 mg, n=81	13.6	22.4	−11
Brensocatib 25 mg, n=89	11.2	22.4	−9
Brensocatib pooled, n=170	12.4	22.4	−10

C. NNHs excluding exacerbations, proportion with serious TEAEs at week 24			
Endpoint	Brensocatib, %	Placebo, % (n=85)	NNH
Brensocatib 10 mg, n=81	11.1	12.9	−55
Brensocatib 25 mg, n=89	9.0	12.9	−25
Brensocatib pooled, n=170	10.0	12.9	−34

Conclusions:

NNT and NNH analyses indicate a favorable benefit-risk profile for brensocatib and support it as an advance in the treatment of patients with bronchiectasis. The phase 3 ASPEN trial is ongoing and aims to confirm these findings.

1OA.5. Patient representative engagement and collaboration in the study design of AirleafTM: A multinational Phase 2 trial of a novel cathepsin C inhibitor for the treatment of bronchiectasis

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Background/Aims:

Collaboration with patient representatives (patients, families and carers) before and during the conduct of clinical trials has the potential to improve study design and delivery. Patient representatives can identify potential barriers to study participation, adherence and retention, and support development of potential solutions to those barriers. Such collaboration during trial protocol development and throughout the ongoing trial can lead to a more patient-centred trial with a design and outcomes that better meet patients' needs. Here, we present a patient-centric approach to the design and delivery of Airleaf™, a Phase 2, multinational, randomised, double-blind, placebo-controlled, parallel-group, dose-finding study to assess the efficacy and safety of the novel cathepsin C inhibitor BI 1291583 in adults with bronchiectasis (NCT05238675).

Methods:

Four patient advisory board meetings were held via video conference between September and December 2021 to understand the needs and expectations of patients with bronchiectasis in clinical studies. Seven patient representatives (three patients, one caregiver and three patient organisation representatives who did not have bronchiectasis) advised on elements of Airleaf™, including trial objectives and endpoints, patient communication and trial participation.

Results:

Detailed outcomes from the patient representative advisory board meetings on aspects of Airleaf™ are given in Table 1. Patient representative advice was implemented in the development of the trial name and lay title, the development of patient communication materials on trial participation and rationale for assessments (e.g. specific symptom monitoring), and on drug packaging and labelling. Trial objectives and endpoints were devised in light of the most important symptoms patient representatives reported, and the expected benefits of a new treatment. Similarly, patient representative feedback aided in the design and implementation of trial procedures, including periodontal assessments and patient-reported outcomes, collection of sputum outside of the home environment and modifications to assessments in the event of future COVID-19 restrictions.

Conclusions:

Patient representative input was central to the design of Airleaf™ and will continue to be central during implementation and delivery. Going forward, it is essential that patients have all the information they require to enable successful participation in clinical trials, including rationale for burdensome assessments, leading to trial outputs that are relevant to them and that address important aspects of their disease. Improvements to communications with Airleaf™ trial participants are ongoing, with newsletters planned to keep participants up to date regarding the ongoing trial, and materials to educate patients on the mechanism of action of cathepsin C inhibition. As a result of specific feedback, future trials will aim to feature smaller tablet size and a more patient-friendly device for monitoring specific symptoms.

Table 1. Summary of patient representative advisory board activities and results

Category	Feedback element	Outcome of engagement
Trial objectives and endpoints	Most important symptoms and what a new medicine should offer	Feedback informed primary, secondary and further endpoints, lung function assessment, cough substudy, sputum quantity analysis and QoL PROs
Patient communication	Trial lay title and trial name	Revised to "A study to test whether different doses of BI 1291583 help people with bronchiectasis". Advisors voted for "Airleaf™"
	Pre-trial information flyer, trial guide, welcome letter, dental care guide	Changes made to visual and language elements
	Drug intake card	Changes made to pictogram elements
	Patient card for recording symptoms between site visits	Changes made to lay language describing symptoms
	MoA materials	In development to help patients understand how CatC inhibition works
Concerns about trial participation	Periodontal assessments	May be carried out independently of visit day; historical dental X-rays can be used. Flyer is planned to explain importance of assessments
	Assessment burden	Flexibility of procedures introduced; optional reduction of PK sampling to reduce visit length
	PROs	Onsite staff to review answers for completeness. Advisors

		aided in development of lay language used in visual analogue scale
	COVID-19 safety	During lockdown, site visits may be replaced with remote visits; study drug mailed to home address, if permitted
	Discreet sputum collection outside of the home	Options on collection container: transparent, smaller tube that can be discreetly carried; larger container, but easier to use and not transparent
	Specific symptom monitoring	More patient-friendly tools to be used in future trials
	Tablet size and colour	Tablet size and colour planned to be adjusted for subsequent trials. Adjustment not now possible at Phase 2

CatC, cathepsin C; MoA, mechanism of action; PK, pharmacokinetics; PRO, patient-reported outcome; QoL, quality of life.

Conflict of interest(s):

1OA.6. The Association between Anxiety, Depression, Physical Disease Parameters, and Health-Related Quality of Life in the BronchUK national Bronchiectasis cohort

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Background/Aims:

Bronchiectasis, a chronic lung sepsis syndrome with multi-system components, is increasing in prevalence. Recurrent infections, increased rates of hospitalisation and earlier death indicate the disease's serious consequences. Comorbidities include cardiovascular disease, fatigue and increased rates of psychological morbidity. Understanding the relationship between disease severity, anxiety and depression, and health related quality of life (HRQoL) is limited. It was hypothesised that more severe bronchiectasis as judged by physical disease parameters would be associated with increased rates of anxiety, depression and impaired quality of life.

Methods:

Data on 1442 patients with bronchiectasis from 14 centres across the Bronch-UK study were used. 541 participants were male and 901 were female. The largest age group represented was people aged 50-69 (45.5%). Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS-A and HADS-D); with >or equal to 8 indicating caseness of depression or anxiety. HRQOL was measured using the St. George's Respiratory Questionnaire (SGRQ) and the Quality of Life-Bronchiectasis Questionnaire (QOL-B) and compared to physical disease parameters of the disease, including bronchiectasis severity index (BSI), in univariate and logistic regression multivariate analysis. Significance was set at P<0.01 to adjust for multiple comparisons

Results:

26% of participants had mild, 48% moderate and 26% severe bronchiectasis based on BSI scores. There were significant rates of psychological comorbidity based on HADS scores >or equal to 8; anxiety rates were 31% and depression 20%. HADS-A scores >or equal to 8 were seen in 27% mild cases, 32% moderate cases and 32% of severe bronchiectasis cases; HADS-D ³8 scores were present in 20% mild cases, 45% of moderate cases and 35% of severe bronchiectasis cases respectively. Anxiety symptoms were associated with most notably HRQoL, reduced FEV1%,

MRC dyspnoea scores (all p<0.01) but not BSI scores (p=0.034). Depression scores significantly and positively correlated with BSI (p<0.001) and those with HADS-D >or equal to 8 had significantly worse HRQOL for both SGRQ and QoLB (p<0.001). Anxiety and depression scores were higher in those with a past

diagnosis of anxiety or depression (p<0.001), however many patients (20-30%) with these diagnoses returned normal HADS scores (therefore did not fulfil the criteria for current anxiety or depression). Furthermore 77% of patients with anxiety scores within the clinically significant range had no prior history of anxiety. Similarly, 68% of patients with depression scores within the clinically significant range had no prior history of depression.

In Multivariate logistic regression analysis showed SGRQ symptoms and impacts, QOL-B role, health and emotion and previously diagnosed anxiety were independently associated with HADS-A scores (p<0.05), whereas QOL-B scores on the Health, Role and Emotion correlated with HADS-D scores (p<0.05).

Conclusions:

Anxiety and depression are common in Bronchiectasis. The rates observed are much higher than the 5-10% previously reported for the general UK population. Anxiety and depression increase with disease severity but is common in those who do not have severe bronchiectasis based on the BSI. Clinicians should consider psychological screening and support as part of personalised care regardless of physical disease severity.

Conflict of interest(s):

1OA.7. Bronchiectasis and asthma coexistence; clinical, radiological and bacteriological characteristics of a group of 66 cases

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Background/Aims:

Asthma often coexists with bronchiectasis (BE) and contributes to the disease severity. The aim of this study is to record clinical and laboratory characteristics of patients with both diseases.

Methods:

Patients with Bronchiectasis and asthma were studied prospectively. Etiology of Bronchiectasis was investigated, symptoms, exacerbations/year, hospital admissions, spirometry, microbiology, BSI, eosinophils in blood were recorded. HRCT was used to confirm the diagnosis and grade BE lesions.

Results:

66 patients with the diagnosis of both BE and asthma were studied, 49 women, mean age 60,74 (±11,86), 48 non smokers, mean BMI 27,9 (±4,66). Asthma was the main etiology of BE (62%). The most common symptoms were cough (77%), sputum (71%) and wheezing (19.7%). Additional data are shown in the following table.

Patients (No=66)	Exacerbations /year	Hospitalizations /year	FEV1 (L)	FEV1/FVC	mMRC	No of lobes with BE	BSI	Eos. count
mean ±SD	1.9 ±1.18	0.46 ±0.63	70.9 ±24.2	72.3 ±11.9	0.92 ±0.73	2.74 ±0.92	7.19 ±3.9	306.15 ±263.38
Patients (No=66)	Pseudomonas aer.	All pathogens	Eos. count >300	Biological agents(asthma)	Azithromycin	Nebulized Colistin	Courses of antibiotics	Courses of OCS
No of patients, (%)	12 (18.2%)	17 (25.8%)	20 (30.3%)	12 (18.2%)	28 (42.4%)	11 (16.7%)	60 (90.9%)	9 (13.6%)

BSI was correlated to the number of exacerbations (p=0.017) and the number of hospital admissions (p=0.000).

Conclusions:

Bronchiectasis and asthma coexistence is common, with asthma being the main cause of BE in this population. In a quarter of the patients chronic bronchial infection is present, mainly of Ps. Aeruginosa. The severity of the disease is related to the exacerbations and hospitalizations. Patients need treatment for both diseases.

1OA.8. Microbiome characterization in patients with bronchiectasis and its association with severity and bronchial inflammation. Bronchi-Omics Project

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Background/Aims:

Infection is a key component in the pathophysiology of bronchiectasis (BE). The study of the microbiome offers a higher level of sensitivity and resolution than traditional culture methods. Our objective is to characterize the microbiome in patients with non-cystic fibrosis bronchiectasis (NCFB) and its correlation with relevant clinical variables, bronchial and systemic inflammation.

Methods:

Observational, prospective, and multicentre study involving 9 university hospitals. Clinical data, sputum and blood samples have been collected in stability. The bacterial and fungal microbiome has been determined by amplification and sequencing of 16S rRNA and Internal Transcribed Spacer (ITS). Bronchial inflammatory markers have been analysed by ELISA. Systemic inflammation was measured by C-reactive protein (CPR).

Results:

A total of 165 patients (mean age 63 years, 61% women) were included, of which 153 provided a quality sputum sample for microbiological study. The aetiology of BE is 39% post-infectious, 31% idiopathic, 9% ciliary dyskinesia, 9% asthma and COPD, and 12% other aetiologies. BE severity is mild-moderate in 75% of cases according to the E-FACED and BSI indices. 25% have a high frequency of exacerbations (≥3 exacerbations/year) and 13% have required hospital admission in the previous year.

The analysis of the basal microbiome has detected 14 phyla dominated by Firmicutes and Proteobacteria, and 149 genera, dominated by *Streptococcus*, *Haemophilus* and *Pseudomonas*. Diversity loss is significantly associated with BE severity (p=0.002), airflow obstruction (p<0.001), severe exacerbations (p=0.022), and sputum production (p=0.0003). However, no significant differences have been observed in this microbial diversity depending on the various BE aetiologies. Regarding the presence of dominant genera, the dominance of *Haemophilus* genera is associated with an increase in inflammatory interleukins in sputum, as well as an increase in systemic inflammation measured by CPR, which, however, is not related to variables of severity of the disease. Though, the dominance of the *Pseudomonas* genera is associated with increased levels of neutrophil elastase, and greater severity of BE.

Conclusions:

The characteristics of the respiratory microbiome of patients with NCFB are significantly correlated with clinical markers of disease severity and with bronchial and systemic inflammation.

1OA.9. The need for a remote (virtual) exercise and lifestyle education program in Bronchiectasis and NTM

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Background/Aims:

The COVID-19 pandemic has greatly impacted physical activity levels and positive lifestyle behaviours. Patients with chronic lung disease, particularly, are more vulnerable due to their high risk of developing severe disease. Currently, there are no home-based exercise and education programs, remotely delivered through a virtual platform, available for Bronchiectasis and non-tuberculosis mycobacteria (NTM) patients. As a preliminary step, we reached out to patients and healthcare professionals (HCPs) working within the domain of chronic lung disease to understand their thoughts and experience on this issue.

Methods:

Survey responses were collected via the email databases of NTMir, the Canadian Bronchiectasis-NTM Education & Support Group, and the RESPIPLUS newsletter. A total of 290 North American Bronchiectasis and NTM patients and 18 HCPs working within this domain were surveyed through an online form between December 2021 and February 2022. The survey was constructed with 42 patients and 24 HCP questions. Patients were surveyed regarding their general feelings about exercise programs, their physical activity levels pre- and post-pandemic, their motivation to begin a remotely delivered exercise program through a virtual platform guided by a professional, and their preferences on structure (length, format, group, or individual sessions). HCPs were surveyed for their opinions and motivations towards referring their patients to an exercise and lifestyle program, and their preferences on structure.

Results:

Patients' pre-pandemic physical activity levels were frequent, with 75% of respondents being active 3-4 times/week. However, during the pandemic, 45% of respondents claim they had to reduce their levels of physical activity, and some of which were unable to complete any of their usual physical activities. Despite the reduction, 54% of patient respondents claimed to be motivated to improve their health and decrease their daily symptoms. Delivery of the program via videoconferencing was preferred by 57% of patient respondents; 32% did not have a preference. 93% of patient respondents were confident in using a video-conferencing platform for a remote supervised exercise program. 78% of HCP respondents said that both in-person and online delivery for the program would be their preference for their patients participating.

Conclusions:

Home-based exercise and lifestyle education programs are both feasible and needed to better serve the Bronchiectasis and NTM community and help them find the intrinsic motivation to continue with their physical activities despite the pandemic. Furthermore, increased awareness and confidence in using the Internet as a necessity due to the pandemic has led to a greater acceptance of using online platforms.

1OA.10. Phase I characterization of the novel cathepsin C inhibitor BI 1291583

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Background/Aims:

In patients with chronic airway inflammation (e.g. bronchiectasis), neutrophil proteases that are inadequately controlled by endogenous anti-proteases can damage the distal airways due to excessive proteolysis of the extracellular matrix, increased mucus production and delayed resolution of chronic lung inflammation. The protease cathepsin C (CatC, also known as dipeptidyl peptidase 1) is responsible for the activation of all neutrophil serine proteases during myelopoiesis in bone marrow. Inhibition of CatC is therefore expected to improve protease-antiprotease balance and reduce distal airway destruction; secondary anti-inflammatory and anti-mucus hypersecretory effects may also be expected. We discuss the Phase I characterization of BI 1291583, a novel CatC inhibitor currently undergoing clinical trials.

Methods:

Five Phase I trials of BI 1291583 in healthy subjects are presented (Table 1): (1) 1–40mg single rising-dose (SRD; NCT03414008); (2) multiple-rising dose (MRD) with 1mg and 2.5mg (NCT03868540); (3) a second MRD with 5mg (NCT04866160; 10mg dose investigation ongoing) evaluating safety, tolerability, pharmacokinetics (PK) and pharmacodynamics; (4) relative bioavailability, safety and tolerability of 2 x 7.5mg doses each with and without food (NCT03837964); and (5) relative bioavailability drug–drug interaction of 2.5mg doses with and without the cytochrome 3A enzyme inhibitor itraconazole (NCT03890887). Inhibition of neutrophil elastase activity was assessed in zymosan-stimulated blood as a measure of indirect target engagement. All studies have been approved by the Independent Ethics Committees of the participating centers.

Results:

PK was supra-proportional over the dose range investigated in the SRD trial (n=54), reaching maximum plasma concentration (t_{max}) 6 hours post-dose and declining in a multi-phasic manner. In the first MRD trial (n= 24), steady state was reached after 14 days, with t_{max} at 6–7 hours; preliminary data from the second MRD trial for the 5mg dose (n=12) showed a t_{max} of 6–8 hours. Under both fed and fasted conditions, BI 1291583 PK parameters were generally similar (n=12). BI 1291583 co-administered with multiple doses of itraconazole increased exposures compared with BI 1291583 alone (n=14). In the 2.5mg group, maximum neutrophil elastase activity inhibition of 47.4% was achieved. Overall, adverse events were of mild or moderate intensity, except for two severe events that were unrelated to trial medication.

Conclusions:

BI 1291583 was safe and well tolerated, with no effect of food on systemic exposure. Co-administration of itraconazole resulted in higher exposures of BI 1291583 compared with BI 1291583 alone. A multinational Phase II trial of BI 1291583 in patients with bronchiectasis is planned for March 2022.

Table 1. Summary of Phase I characterization of BI 1291583

Study Type	Study Objective	Study Design	Dosage Regimen	Subj. #	Treatment Duration	Key outcomes
Phase I single rising dose (NCT03414008)	Safety, tolerability, PK and PD	Single-blind, partially randomized, placebo-controlled, parallel group	Placebo 1, 2.5, 5, 10, 20, 30 and 40 mg	54 (8 per dose group, 14 placebo)	Single dose	Supra-proportional PK with multi-phasic decline t_{max} 6 h post-dose $t_{1/2}$ 33.6–60.2 h All AEs were of mild or moderate intensity, except one case of non-drug-related gastrointestinal infection of severe intensity in the 1mg group
Phase I multiple rising dose (NCT03868540)	Safety, tolerability, PK and PD	Single-blind, partially randomized, placebo-controlled parallel group design	1 and 2.5 mg	24 (12 per dose group, 6 placebo)	28 days	t_{max} 6–7 hours Steady state at 14 days All AEs were of mild or moderate intensity
Phase I multiple rising dose (NCT04866160) Note: Investigation for 10mg dose is ongoing	Safety, tolerability, PK and PD	Single-blind, randomized, placebo-controlled parallel group design	5 and 10 mg	24 (12 per dose group, 6 placebo)	28 days	t_{max} 6–8 h All AEs were of mild or moderate intensity Note: Outcomes presented are for 5mg dose only
Phase I food-effect (NCT03837964)	Relative bioavailability (PK), safety	Open-label, randomized, single-dose, two-period,	2 x 7.5 mg	12	Single dose	All PK parameters generally similar

	and tolerability	two-sequence crossover study				in fed vs unfed groups All AEs were unrelated to treatment. All AEs were of mild or moderate intensity, except one severe AE of non-drug-related joint injury
Phase I drug-drug interaction (NCT03890887)	Relative bioavailability (PK) when administered alone or in combination with multiple oral doses of itraconazole	Open-label, two-period, fixed sequence study	2.5 mg BI 1291583, 12 days itraconazole 200 mg (solution) once daily	14	Single dose with multiple oral doses of itraconazole	58% increase in C_{max} 116% increase in AUC_{0-tz} 111% increase in $AUC_{0-\infty}$ All AEs were of mild or moderate intensity

AE, adverse event; AUC_{0-tz}, area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point; $AUC_{0-\infty}$, area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity; C_{max}, maximum measured concentration of the analyte in plasma; h, hour; PD, pharmacodynamics; PK, pharmacokinetics; $t_{1/2}$, terminal half-life of the analyte in plasma; t_{max}, time from dosing to maximum measured concentration of the analyte in plasma.

Conflict of interest(s):

1OA.11. The Association Between Bronchiectasis and Chronic Obstructive Pulmonary Disease: Data From The European Bronchiectasis Registry (EMBARC)

James Chalmers[1]; Eva Polverino[2]; Burgel-P Regis[17]; Charles Haworth[3]; Katerina Dimakou[4]; Michael Loebinger[5]; R. Menendez[15]; Antoni Torres[10]; Tobias Welte[11]; Francesco Blasi[12]; F Ringshausen[14]; Antony De Soyza[13]; Montserrat Vendrell[6]; Amelia Shoemark[1]; J Altenburg[16]; W Boersma[18]; J Stuart Elborn[7]; Stefano Aliberti[8]; Pieter C. Goeminne[9]; Letizia Traversi[2]

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Introduction:

The clinical features of COPD and bronchiectasis are overlapping. An international consensus aimed at standardizing the definition of bronchiectasis and COPD overlap proposed the ROSE criteria. consisting of radiological bronchiectasis(R), obstruction defined by an FEV1/FVC ratio <0.7 (O), symptoms (S) and exposure to a minimum of 10 pack year smoking history (E) to define the assocation. There have been no studies using these standardized criteria to define the bronchiectasis/COPD association or exploring associated outcomes.

Methods:

The European Bronchiectasis Registry (EMBARC) is a prospective observational study of patients with CT confirmed bronchiectasis conducted across more than 30 countries worldwide. Patients with a diagnosis of COPD recorded in the registry (as an aetiology or co-morbidity) were compared to patients without COPD. The ROSE criteria were applied in the dataset to objectively defined COPD-bronchiectasis association and to identify possible under- or over- diagnosis. These objective criteria require a smoking history of at least 10 pack years and the presence of an FEV1/FVC ratio less than 0.7 to be considered COPD/BE association.

Results:

16730 patients were included in the analysis. 4336 patients had a reported diagnosis of COPD. Patients with COPD were older, more likely to be male, with higher BMI, more co-morbidities, higher MRC dyspnoea score and worse lung function (all p<0.0001). Inhaled medications, long term oxygen, and macrolide use were all more common in COPD patients while airway clearance and inhaled antibiotics were less common (p<0.0001). Bronchiectasis was classified as the underlying cause of bronchiectasis by the investigator in 1370 cases (8.2% of all cases).

Among patients with clinician reported COPD, there was a clear relationship between COPD and disease severity. Patients with COPD+bronchiectasis had a higher bronchiectasis severity index (p<0.0001) and a lower QOL-B symptom score (p<0.0001). COPD patients had a higher rate of prior exacerbations (incidence rate ratio- IRR 1.36 95%CI 1.30-1.41) and a higher rate of prior severe exacerbations (IRR 2.10 95%CI 1.98-2.22).

3895/4336 patients with a diagnosis of COPD and 11249/12394 patients without a diagnosis of COPD had complete lung function and pack year smoking data available for analysis. We observed marked overdiagnosis of COPD using the ROSE criteria. Only 3029 (77.8%) of patients with a diagnosis of COPD had an FEV1/FVC ratio <0.7. 2951/3895 (68.1%) had a history of 10 or more pack years. Combining these two parameters the proportion with true COPD was 2157 (55.4%) using the fixed ratio. Compared to patients without COPD, patients meeting Rose criteria had increased risk of severe exacerbations and oral antibiotic treated exacerbations during follow-up (IRR 1.69 95% CI 1.51-1.90 and 1.25 95%CI 1.15-1.35 respectively) but patients with a diagnosis of COPD who did not meet ROSE criteria also had increased risk of severe exacerbations and outpatient exacerbations.

Conclusions:

The label of COPD is often applied to patients without objective evidence of airflow obstruction and smoking. Patients with a clinical label of COPD have poor outcomes irrespective of the presence of these criteria.

Conflict of interest:

STROLLING POSTER SESSION 1OB – IN PRESENCE

1OB.0 Effect of omalizumab on lung function, glucocorticoid use and exacerbations in patients with allergic bronchopulmonary aspergillosis: a systematic review and meta-analysis

J Stuart Elborn[1]; Meiling Jin[2]; Jo A Douglass[3]; Ritesh Agarwal[4]; William J Calhoun[5]; Xavier Jaumont[6]; Slawomir B Lazarewicz[6]; Meng Yan[7]

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Background/Aims:

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease resulting from hypersensitivity to *Aspergillus fumigatus*. ABPA is commonly encountered in patients with asthma or cystic fibrosis (CF) and is associated with high serum total IgE levels. Oral corticosteroids (OCS) are commonly used for the management of ABPA but are not effective in all patients and can progress to chronic corticosteroid dependency, which is associated with several adverse effects. Although biologics such as omalizumab (an anti-IgE therapy) have been used off-label over the past two decades, evidence on the use of omalizumab for ABPA treatment is relatively scarce and is mainly based on small case series and case reports. Thus, this systematic review and meta-analysis was conducted to improve the current understanding of the potential effects of omalizumab in ABPA and to test the hypothesis that treatment with omalizumab results in clinically meaningful improvements in lung function and reduction in exacerbation and use of OCS.

Methods:

A systematic search across standard databases was conducted using specific keywords until May 13, 2021, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered in the PROSPERO database (CRD42021268978). Publications (clinical trials, observational studies, case series, case reports, and conference abstracts [published between May 2020 and April 2021]) evaluating omalizumab as monotherapy ± systemic steroids ± antifungal treatment in patients with ABPA (comorbid with asthma or cystic fibrosis) were included. Data extraction was performed independently by two reviewers, and any discrepancies were resolved by a third reviewer. The effect on FEV_1 (% predicted), OCS-sparing effect and exacerbation reduction were evaluated in patients treated with omalizumab using a random-effects model. Pre-omalizumab measurements served as the control for comparison of effect of omalizumab for single-group analysis.

Results:

Of the 838 identified studies, 49 (n=267) were included in the qualitative synthesis and 14 case series (n=186) in the quantitative meta-analysis (12 retrospective and 2 prospective in design). Treatment with omalizumab for 6 to 54 months resulted in a statistically significant mean improvement in FEV_1 % predicted of 11.85% ([95% CI, 8.15, 15.55], $P<0.01$) compared with baseline. Omalizumab treatment reduced OCS use in 65% of patients (risk difference [RD]: 0.65 [95% CI, 0.46 to 0.84], $P<0.01$), increased the termination of OCS use in 53% of patients (RD: 0.53 [95% CI, 0.26 to 0.80], $P<0.01$) and reduced mean OCS dose by 14.62 mg/day ([95% CI, −19.86 to −9.39]; $P<0.01$) compared with pre-treatment. Furthermore, a significant reduction in the annualised exacerbation rate compared with baseline (mean difference [MD]: −2.09 [95% CI, −3.07 to −1.11], $P<0.01$) was reported in ABPA patients treated with omalizumab for 8.3 to 12 months **(Table)**.

Conclusions:

In patients with ABPA (comorbid with asthma or cystic fibrosis), omalizumab significantly improved FEV_1 and reduced OCS use and annualised exacerbation rate compared with pre-treatment. This systematic review and meta-analysis have given a positive testament that omalizumab is a promising treatment in the management of patients with ABPA. Large RCTs would help confirm these findings.

Table: Effect of omalizumab on lung function (FEV_1 % predicted), glucocorticoid use and exacerbations in patients with ABPA

Outcomes	No. of studies	No. of patients	Treatment duration (months)	Estimated difference – Pre- and post-treatment (95% CI)	P value
Improvement in FEV_1 % predicted	9	120	6 to 54	MD: 11.85 (8.15 to 15.55)	< 0.01
Reduction in OCS use, n	6	65	1 to 19.7	RD: 0.65 (0.46 to 0.84)	< 0.01
Termination of OCS, n	6	58	6 to 54	RD: 0.53 (0.26 to 0.80)	< 0.01
Reduction in OCS dose (mg/day)	5	64	3.7 to 54	MD: −14.62 (−19.86 to −9.39)	< 0.01
Reduction in annualised exacerbation rate, n	3	37	8.3 to 12	MD: −2.09 (−3.07 to −1.11)	< 0.01

ABPA, allergic bronchopulmonary aspergillosis; FEV_1, forced expiratory volume in 1 second; MD, mean difference; OCS, oral corticosteroids; RD, risk difference

Conflict of interest(s):

1OB.1. Prevalence and Causes of Bronchiectasis among high altitude people, HRCT Chest Study.

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Background/Aims:

This study aimed to determine the prevalence and causes resulting in bronchiectasis among patients residing in the high altitude of Nepal. Bronchiectasis has been a common chronic airway inflammatory disease (along with chronic obstructive pulmonary disease (COPD) and asthma) and is often detected by chest imaging. It is one of the important causes of morbidity (usually associated with recurrent infection and related complications) and is usually found to coexist with other underlying pulmonary diseases such as post-tuberculosis, COPD, etc. High-resolution Computed tomography (HRCT) of the lung is proven to be a highly sensitive non-invasive technique for the diagnosis of bronchiectasis.

Methods:

This was an observational, retrospective study conducted in Karnali Academy of Health Sciences (KAHS) Jumla over 6 months period starting from July 2019. Jumla is a mountainous district situated at an altitude of above 2000 meters, in Karnali Province and it accommodates only 2% population of Nepal. All the patients who visited KAHS with a history of cough having excessive sputum production hemoptysis, dyspnea, and repeated history of respiratory infection underwent HRCT chest. HRCT was interpreted by radiologist and pulmonologist independently and findings such as the diameter of the airway, airway having an irregular wall, and lack of tapering were observed. The diagnosis of bronchiectasis was based on chest HRCT. Data were interpreted in frequency, percentage, and standard deviation.

Results:

A total of 20 patients were enrolled in this study over a 6months period with a mean age ±SD (min-max) 61.4 ± 12.02 (31-85) among which 9 (45%) were females and 11 (55%) males. They all had exposure to household air pollution with poor ventilation. The history of smoking was present in 55% of people rest being ex-smoker. The commonest presentation to the hospital was hemoptysis (45%) followed by cough (35%) and dyspnea (20%). As regards the final diagnosis of bronchiectasis found to have the commonest being post-tuberculous bronchiectasis (50%), COPD with bronchiectasis (30%) followed by bronchiectasis solely (20%).

Conclusions:

Bronchiectasis has been a global burden as not much study has been done on this part and its management. In our observational study bronchiectasis was found to be co-existed with other respiratory diseases, common being Post-tuberculosis followed by COPD. HRCT has always been the gold standard for the diagnosis of bronchiectasis and is mostly coexists with underlying disease. Thus, the successful national TB control and awareness program of good hygiene and ventilation could reduce the disease burden of bronchiectasis.

1OB.2. Radiological features and disease severity in patients with bronchiectasis: an observational study

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Background/Aims:

Bronchial dilatation on high resolution CT chest is the gold standard for diagnosis of adult bronchiectasis. Radiological severity scores such as Reiff and Bhalla are validated tools used to assess severity but are rarely utilised in clinical practice and rarely reported by radiologists. Studies have also failed to consistently demonstrate a relationship between radiological severity and clinical severity. The aim of this study was to determine which CT features were associated with disease severity.

Methods:

145 patients enrolled in the EMBARC-BRIDGE study had their baseline CT scans independently reviewed by four respiratory clinicians who were blinded to the clinical data. Each lobe was assessed for the severity of dilatation (cylindrical, varicose and cystic) and presence of; bronchial wall (BW) thickening, mucous plugging (MP), consolidation, cavitation/abscess, emphysema, bullae and mosaicism. An assessment of the presence of diffuse nodularity was made for the whole lung. A modified Reiff (mReiff) score was also calculated for each patient. The radiological findings were linked to corresponding clinical data including the bronchiectasis severity index (BSI), lung function, exacerbation frequency in past 12 months, and QoL-B respiratory domain scores (QoLB-RSS).

Results:

The average age of our cohort was 67.4 and 54.5% (79/145) were female. Mean BSI score at baseline was 5.9. Bronchial wall thickening was the most common finding seen in at least one lobe in 85% of patients. This was followed by nodularity (74%) and consolidation (68%). Mucus plugging was seen in 49% of patients and 32% had radiological emphysema.

The presence of BW thickening, MP, abscess/cavity formation, emphysema and mosaicism had a statistically significant association with lower baseline FEV1% predicted (Table 1). MP was also significantly associated with worse QoLB-RSS at baseline, with the difference between groups greater than the 8 point minimum clinically important difference. Interestingly, none of the radiological features was clearly associated with disease severity using the BSI except the presence of cavitation which was uncommon. (Table 1).

When all of these radiological features were collectively assessed, we found a positive correlation with BSI (r=.254, p=0.002), mMRC score (r=0.19, p= 0.02), prior exacerbation rate (r=0.185, p= 0.03) with the strongest correlation being withFEV1% predicted (r= -0.452, p<0.001). In contrast the mReiff score was only

significantly correlated with FEV1% predicted (r= -0.328, p=0.001). This is despite the mReiff score correlating with the combined features assessed in our study (r=0.418, p<001).

Table 1: Mean differences of severity parameters with radiological features assessed.

		BSI		FEV1%		Exacerbation Hx		QoLB-RSS	
		N	Mean	N	Mean	N	Mean	N	Mean
Nodularity	No	38	5.68	26	103.91	38	1.39	22	65.132
	Yes	107	5.98	65	105.5131	107	2.15	66	63.235
	p	0.398		0.742		0.227		0.609	
BW Thickening	No	22	5.05	17	103.0382	22	1.5	11	59.082
	Yes	123	6.06	75	83.3741	123	2.03	77	64.37
	p	0.134		**0.004**		0.977		0.479	
Mucus Plugging	No	74	5.55	50	96.7094	74	2.07	41	69.346
	Yes	71	6.27	42	75.4581	71	1.83	47	58.791
	p	0.476		**<.001**		0.21		**0.012**	
Abscess/Cavity	No	134	5.75	87	88.5789	134	1.98	82	64.215
	Yes	11	7.82	5	59.67	11	1.64	6	56.8
	p	**0.023**		**0.016**		0.948		0.349	
Bullae	No	138	5.77	86	88.1549	138	1.88	85	63.866
	Yes	7	8.57	6	70.565	7	3.43	3	59.267
	p	0.081		0.184		0.141		0.647	
Emphysema	No	98	5.59	63	91.393	98	1.78	63	65.106
	Yes	47	6.55	29	77.481	47	2.32	25	60.188
	p	0.178		**0.03**		0.093		0.26	
Consolidation	No	46	5.41	30	93.5013	46	1.26	32	63.778
	Yes	99	6.13	62	83.8656	99	2.27	56	63.67
	p	0.146		0.11		0.057		0.903	
Mosaicism	No	123	5.82	78	90.3737	123	1.88	74	63.519
	Yes	22	6.36	14	68.2543	22	2.36	14	64.714
	p	0.4		**0.005**		0.316		0.873	

Conclusions:

Our study suggests that a clinical assessment of selective CT features can be utilised to assess severity in patients with bronchiectasis. Further studies are needed to determine if collectively these features can be converted into a valid scoring tool.

Conflict of interest(s):

1OB.3. Trends in non-Tuberculous mycobacteria isolation in Northern Israel

Razi Even dar[1]; Maya Brodsky[2]; Shifra Ken-Dror[2]; Raya Cohen[1]; Yochai Adir[1]; Michal Shteinberg[1]

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Background/Aims:

The prevalence of non- tuberculous mycobacterial (NTM) infections is rising worldwide. It is undetermined if the prevalence of NTM infections is attributed to certain strains and which underlying conditions predispose to NTM infections. Studies in the United Kingdom (UK) and in Japan have shown that Mycobacteria avium complex (MAC) is a main driver of the increase [1]. Distribution of strains is geographically heterogenic [4], and studies have shown different distribution between coastal and inland zones of the same country. It was suggested that the use of larger water supply systems contributes to the increased isolation rates of MAC species in larger inland cities [2].
Clalit Health Services (CHS) has a central laboratory for mycobacterial infections. This laboratory serves the entire Northern district of Israel, as well as hospitals in the North of Israel (a population of approximately 2 million people). We aimed to assess the distribution of the various NTM strains across time, between 2010 and 2020.

Methods:

All cultures were collected and processed in CHS central laboratory and were positive for NTM between 2010-2020. For each NTM strain, we recorded the absolute number of positive cultures, and the percent of all mycobacterial cultures processed each year. We then examined whether the distribution of various strains remains steady or changes over time.
Until 2017 species were identified using Hain Lifescience GenoType Mycobacterium CM / AS methods, and afterwards using Matrix-Assisted Laser Desorption/Ionization Time Of Flight (MALDI-TOF)

Results:

 A total of 40,328 samples tested for NTM were processed between 2010-2020, of which 2241 (5.5%) were positive for NTM growth. The rate of cultures positive for *M. intracellulare*, as well as *M. simiae* gradually increased (Figure 1), whereas for other strains- percent of positive culture remained stable. The absolute number (but not the percentage) of positive cultures for all strains decreased in 2020, due to a decrease in the number of cultures processed.

Conclusions:

This study demonstrates that the relative incidence of *M. intracellulare* and of *M. simiae* has increased in the past decade in Northern Israel, while others strains remained stable. This trend cannot be solely attributed to increased awareness or improving laboratory methods. We may speculate that crowding of cities may in part explain the increase in the two NTM species.
We are currently reviewing patient files to assess the clinical relevance of the positive NTM strains.

Figure 1. Percentage of cultures with growth of various NTM strains of total samples (2010-2020)
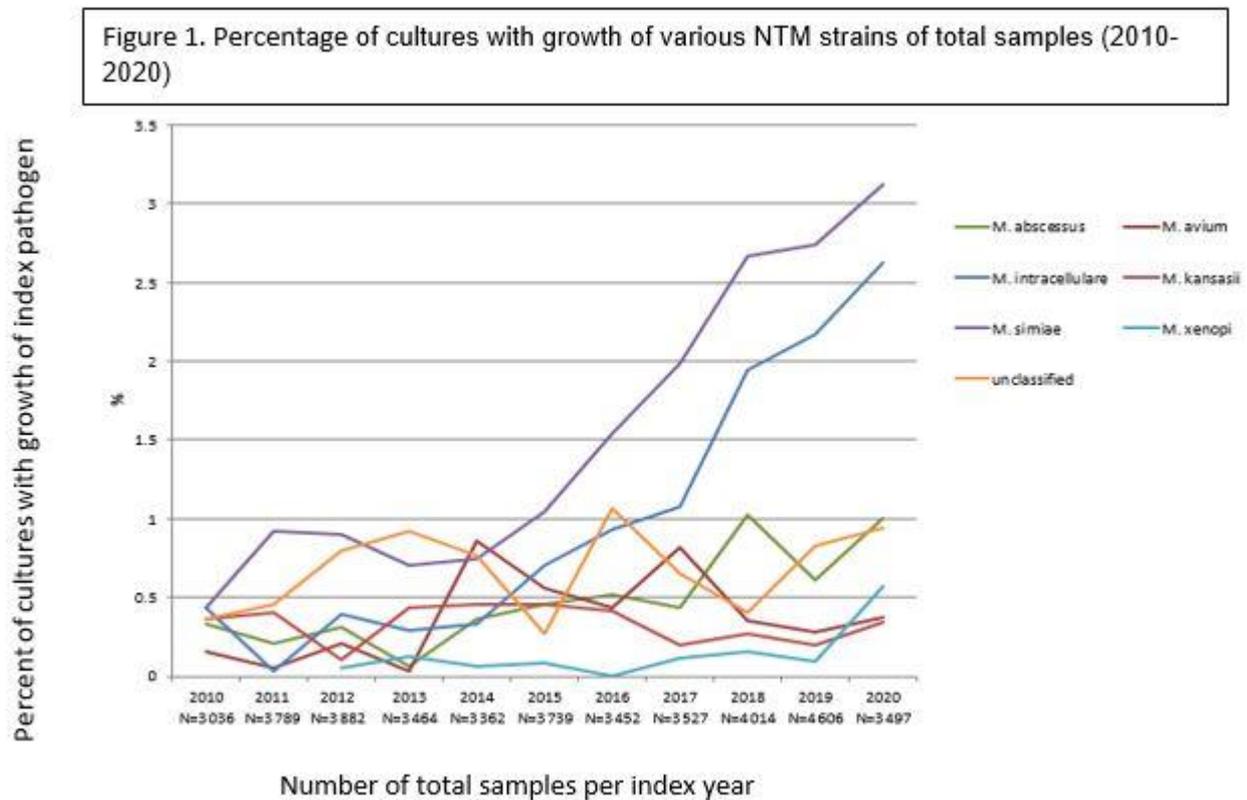
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1OB.4. Development of a brief respiratory symptoms scale for M. avium complex pulmonary disease

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Background/Aims:

Patient-reported outcome (PRO) measures capture key symptoms, daily functioning, and treatment response from the patient's perspective. There is no validated PRO measure for *Mycobacterium avium* complex (MAC) pulmonary disease that measures respiratory symptoms. Approximately 80% of patients with MAC pulmonary disease also have underlying bronchiectasis. Our objective was to use item response theory (IRT) to evaluate, and potentially shorten, an existing respiratory symptom scale (QOL-Bronchiectasis [QOL-B-RSS]) for use in patients with chronic MAC pulmonary disease.

Methods:

This cross-sectional analysis included 197 patients with MAC pulmonary disease completing the 9-item QOL-B-RSS prior to initiating treatment as part of the MAC2v3 pragmatic clinical trial. All patients met ATS/IDSA disease criteria for MAC pulmonary disease, without cavities. First, exploratory factor analysis was used to establish factorial validity by determining whether all items loaded onto a single latent construct. Second, we conducted a series of graded-response IRT models (GRM) to evaluate individual item and overall scale functioning. Both unconstrained and constrained (Rasch) GRMs were specified and model fit was compared with the Bayesian Information Criterion (BIC). We used an iterative process to reduce the item pool to a final scale based on (a) comparisons of item response curves and discrimination estimates, (b) fit to the constrained (Rasch) GRM model to justify summing the items to create a total score, (c) the total test information function being roughly centered on 0, and (d) the final items spanning the facets of the latent trait. Reliability of the final scale was estimated with McDonald's Omega ($\geq$0.70 = adequate reliability).

Results:

Overall, 98 (50%) of patients were <70 years of age, 161 (82%) were female, 159 (81%) had a bronchiectasis diagnosis, and 19 (10%) had a COPD diagnosis. One item, sputum color, was skipped by 16% of patients, showed low discrimination, and was subsequently dropped. Exploratory factor analysis confirmed a single factor model fit the full 8-item scale justifying using all items in a single IRT model. Iterative GRMs resulted in the removal of three items. The "chest pain" item (discrimination 1.01) was dropped first, then "shortness of breath while talking" (0.98), and then "shortness of breath with activity" (1.13). Items remaining at that point had a discrimination that ranged from 1.69-2.71. Fit statistics for the 5-item scale showed that the constrained model fit better than an unconstrained model (BIC=2103.56 vs 2117.01). The retained 5 items include congestion, wheezing, and three cough-related questions. These items met face validity on initial review. McDonalds Omega for the final 5-item scale was .73, showing adequate scale reliability.

Conclusions:

We identified a brief, 5-item NTM Respiratory Symptoms Scale (NTM-RSS5) modified from the QOL-B-RSS in patients with MAC pulmonary disease. This shortened scale retained items with strong discrimination and resulted in an overall scale with balanced test information and adequate scale reliability. With further validation, the NTM-RSS5 could fulfill an unmet need for measures of MAC pulmonary disease progression and treatment response applicable to clinical practice or clinical trials.

Conflict of interest(s):

1OB.5. Nutritional assessment in non-tuberculous mycobacteria pulmonary disease (nutrintm): rationale and study protocol.

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Background:

Non-tuberculous mycobacterial (NTM) pulmonary disease (PD) is an emerging condition with heterogeneous manifestations from both the microbiological and the clinical point of view. Diagnostic and therapeutic guidelines are available but there are still unmet patients' and physicians' needs, including the exams to perform in the nutritional evaluation and intervention to improve health-related QoL and to control gastrointestinal side-effects during antimicrobial therapy, particularly in those with low body mass index and history of weight loss.

Aim of the study:

The aim of the study is to evaluate the nutritional status in patients with non-tuberculous mycobacterial pulmonary disease (NTM-PD) and to provide an initial assessment of the potential impact of the introduction of targeted antibiotic therapy on the nutritional status itself. Specifically, the primary objective is the assessment of the proportion of underweight subjects, i.e. with Body Mass Index (BMI) <18.5 kg/m^2, to confirm that it is significantly higher than that of the general Italian population.

Study Design:

Multicenter Cohort Pilot Observational Study.

Patients and Methods:

Adults with a recent diagnosis of NTM-PD according to the BTS 2017 guidelines will be enrolled (estimated 120 pts). Participation in the study consists of two pneumological visits, as per normal clinical practice, (at the beginning of the study, T1, after 6 months, T3, and at the end of the antimicobacterial antibiotic therapy, T5) in which the collection of past medical history, measurement of oxygen saturation, pulmonary functional tests and 6-minute walking tests will be performed. In addition, nutritional assessments (T2, T4, T6) will be carried out at the same time as the pulmonary visits. Nutritional assessments will include anthropometric measurements, questionnaires on nutritional status and physical activity, performing blood chemistry tests, bioimpedance, dynamometry and gait speed 4 meters, to evaluate body composition and physical performance.

1OB.6. Testing at-risk patients for NTM-PD in current clinical practice: results of an international survey

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Background/Aims:

Non-tuberculous mycobacterial pulmonary disease (NTM-PD) is a rare pulmonary disease that may manifest in patients at risk due to underlying lung disease and/or other risk factors. Guidelines for bronchiectasis and cystic fibrosis address the importance of NTM testing but clinical practice on testing in these and other at-risk groups is largely unknown. The aim was to explore triggers for NTM testing in clinical practice with respect to clinical symptoms, underlying respiratory diseases, and medication use.

Methods:

In total, 455 clinicians (288 respiratory disease specialists, 49 internal medicine specialists, 113 infectious disease specialists, 5 others) from Europe, North America, Australasia and Japan completed the online survey.

Results:

Across the survey, respondents' caseloads varied with 42% having >10, 28% having 6–10 and 29% having 1–5 new patients with NTM every year. Persistent cough was the most reported symptom prior to initiating NTM testing, followed by weight loss and haemoptysis, while gastroesophageal reflux disease was least likely. Respondents were most likely to test patients with non-cystic fibrosis bronchiectasis (NCFBE) (mean 90%) or those with chronic obstructive pulmonary disease (COPD) (mean 64%), and those using immunosuppressants (mean 64%); however, there were large inter-country differences.

In NCFBE, radiological features or clinical symptoms suggestive of infection prompted testing for NTM, while only a minority tested for NTM when initiating macrolide therapy (15%) or at initial NCFBE presentation (24%), despite guideline recommendations.

In COPD, radiological exams or clinical symptoms triggered testing, but inter-country variability exists when considering exacerbations as a prompt to test (min: Japan 23%, max: Canada 78%) and there was limited testing in patients receiving inhaled corticosteroids (9%).

In patients with cystic fibrosis (CF), where NTM testing is recommended annually, 60% of respondents tested for NTM. Of those who test in CF, 50% tested all adults with CF; respondents in Canada and Australia/New Zealand were much more likely to test all adults (71% and 73%, respectively, vs. <50% in other regions).

Use of steroids (oral and inhaled) was the most common prompt for testing (66% of respondents) among clinicians who test for NTM in patients in receipt of specific medications. Few respondents tested those receiving anticancer agents and anti-TNF alpha inhibitors (19% and 10%, respectively). A mean of 4.8 risk factors (range 3.4–5.5) prompted NTM testing; most combinations included symptom(s) and underlying disease, except in Japan where symptoms only were paired together most often. Overall, the most common combinations prompting testing were persistent cough with weight loss or fatigue or bronchiectasis. Other symptoms (e.g., purulent sputum, exacerbations) prompted testing among clinicians with larger NTM patient caseloads.

Conclusions:

These data show that testing for NTM is influenced by underlying disease and presence of clinical/radiological symptoms. However, context is key, and the decision to test for NTM may depend on the overall patient profile, not individual symptoms. Clinical practice varies considerably across geographies and is not always aligned with the existing recommendations for NTM testing in certain patient subgroups. International expert recommendations on which patients should be screened for NTM are warranted.

Conflict of interest(s):

1OB.7. A systematic literature review and meta-analysis of patient risk factors for non-tuberculous mycobacterial pulmonary disease (NTM-PD)

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Background:

Non-tuberculous mycobacteria (NTM) are ubiquitous in the environment and can cause pulmonary disease (NTM-PD). Patients with NTM-PD typically experience reduced lung function, increased morbidity, and substantial reduction in health-related quality of life. NTM-PD is often diagnosed when the disease has become established and is difficult to treat. Understanding risk factors for NTM-PD can prompt testing and initiation of early, effective treatment. Results from a systematic literature review (SLR) and meta-analysis (MA) of the identified risk factors are reported.

Methods:

Electronic searches on Medline and EMBASE were performed in July 2021 to identify publications (2011–2021) reporting attributable risk factors for NTM-PD. Systematic screening of 7,246 citations against agreed inclusion and exclusion criteria identified 99 publications for inclusion in the SLR and were subjected to full data extraction. Of these, 24 publications contained data on attributed risk factors that could be included in the meta-analysis (MA). Patient demographics, NTM species, symptoms identified, risk factors and co-morbidities were recorded, and results were analysed. Due to high heterogeneity in the data, random effect modelling was used for MA which was performed using R based meta package.

Results:

Underlying lung disease was associated with NTM-PD, notably non-cystic fibrosis bronchiectasis (NCFBE), chronic obstructive pulmonary disease (COPD), asthma, and a history of tuberculosis (Table). Use of inhaled corticosteroids and immunosuppressive drugs, specifically anti-tumour necrosis factor alpha (TNFα), were also positively associated as was infection with *P. aeruginosa*. Low body mass index was positively associated with risk of NTM-PD and cardiovascular disease (CVD) was marginally associated. In this analysis lung function (FEV1) as well as macrolide use were not statistically significantly associated with NTM-PD.

Table: MA of identified attributable risk factors

Identified risk factor	No. of studies (n)	Baseline population	Combined OR	95% CI	I^2 (%)
Non-cystic fibrosis bronchiectasis	4	General population Symptoms of TB	21.43	5.90, 77.82	95
History of TB	7	General population Symptoms of TB Rheumatoid arthritis COPD	12.69	2.39, 67.26	99
COPD	8	General population Symptoms of TB Rheumatoid arthritis	6.10	3.96, 9.40	90
Infection with *Pseudomonas aeruginosa*	5	General population COPD CF	5.54	2.72, 11.26	95
Inhaled corticosteroids	4	General population Pulmonary disease	4.46	2.13, 9.35	97
Asthma	4	General population Symptoms of TB	3.73	2.21, 6.27	89
Low BMI (<18 kg/m²)	2	General population COPD	3.04	1.95, 4.73	88
Use of anti-TNFα treatment	2	Rheumatoid arthritis	2.13	1.24, 3.65	0
CVD	2	Rheumatoid arthritis General population	1.73	1.01, 2.97	50
FEV1% of predicted	3	CF	1.01	0.97, 1.05	97
Macrolide use	3	CF	0.80	0.47, 1.39	96

Conclusion:

This is the first SLR and MA to explore a comprehensive range of risk factors predisposing patients to NTM-PD and provides insight into other factors that influence the risk of developing NTM-PD such as comorbid diseases e.g. NCFBE and COPD, and presence of *Pseudomonas* infection, CVD and inhaled steroid use. For BMI it is unclear if low BMI is associated with an increased risk for NTM-PD or if NTM-PD results in reduced weight. However, this MA is limited by a paucity of data regarding the attributable risk for NTM-PD and a high degree of heterogeneity across studies compared. Similarly, some studies are performed in defined patient groups e.g. cystic fibrosis which may not be reflective of data in a more general population. Understanding risk factors, as explored in this MA, may identify patients for NTM testing and further treatment if appropriate.

Conflict of interest(s):

1OB.8. Reduction in Hospitalizations After Initiation of Amikacin Liposome Inhalation Suspension (ALIS): A Retrospective Cohort Study of Patients in Real-World Settings

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Background/Aims:

Mycobacterium avium complex (MAC) lung disease (LD) is a rare infectious disease associated with worsening lung condition, increased mortality, and high rates of hospitalizations. MAC-LD is difficult to treat; 20% to 40% of patients do not respond to conventional guideline-based therapy. In 2018, amikacin liposome inhalation suspension (ALIS) became the first therapy approved by FDA for refractory MAC-LD. In clinical trials, addition of ALIS to guideline-based therapy showed evidence of MAC infection elimination in sputum by month 6, which was maintained in most patients through the end of treatment (up to 12 months postconversion). The objective of this study was to assess changes in hospitalizations among patients initiating ALIS in the real-world setting.

Methods:

In this retrospective cohort study the All-Payer Claims Database was used to identify patients receiving ALIS from October 1, 2018 to April 30, 2020. Eligibility criteria included age ≥18 years, with ≥1 pharmacy claim for ALIS, and ≥12 months of continuous enrollment in health plans both before and after ALIS initiation. All-cause and respiratory disease–related hospitalizations (including inpatient stays and hospital emergency department visits leading to hospitalizations) were compared for the 12 months before and after ALIS initiation. Hospitalizations were reported for every 6-month interval of the study period; the 6-months before ALIS initiation was the reference period for statistical comparisons.

Results:

Of the eligible study population, a total of 331 patients with continuous health plan enrollment pre- and post-ALIS initiation formed the analysis population (mean [± SD] age, 64.6±16.0 years; female, 77.9%). Among them, 65.9% and 27.8% had Medicare and commercial plans, respectively. Geographically, patients were from the South (45.9%), the Northeast (22.4%), the West (19.0%), and the North Central US (12.7%). Approximately 45.6% of patients had COPD and 57.1% had bronchiectasis. Hospitalizations occurred in the highest proportion of patients in the 6 months immediately preceding ALIS initiation. A significant reduction in the proportion of patients hospitalized and mean number of hospitalizations per person/6 months were observed after ALIS initiation (**Table**). Compared with the 6 months before ALIS initiation, approximately 28% and 43% fewer patients had respiratory disease–related hospitalizations during months 0 to 6 and 7 to 12 after ALIS initiation follow-up, respectively. The average respiratory disease–related hospitalizations decreased by 43%-44% for both months 0 to 6 and 7 to 12 after ALIS initiation follow-up. A similar trend was observed for all-cause hospitalizations (**Table**).

Table. Hospitalizations Pre- and Post-ALIS Initiation (N=331)						
Hospitalizations	**Baseline (Pre-ALIS)**		**Follow-up (Post-ALIS)**			
	7–12 months	**0–6 months (reference)**	**0–6 months**	**P-value**	**7–12 months**	**P-value**
Proportion of patients with hospitalizations						
All-cause, n(%)	93(28.1)	119(35.9)	88(26.6)	0.0033[a]	76(23.0)	<0.0001[a]
Respiratory disease-related, n(%)	67(20.2)	89(26.9)	64(19.3)	0.0061[a]	51(15.4)	<0.0001[a]
Number of hospitalizations per person per 6 months						
All-cause, mean±SD	0.9±1.4	1.2±1.8	0.7±1.2	0.0002[b]	0.7±1.4	<0.0001[b]
Respiratory disease-related, mean±SD	0.7±1.2	1.0±1.6	0.6±1.0	0.0002[b]	0.6±1.2	0.0001[b]

[a]McNemar's χ^2 test.
[b]Wilcoxon Signed Rank test.

Conclusions:

This study provides the first real-world evidence on the benefits of adding ALIS to the treatment regimen for patients. Significant reductions in both all-cause and respiratory disease-related hospitalizations were observed in the 12 months following ALIS initiation in real world settings.

Conflict of interest(s):

1OB.9 Epidemiology of Non-Tuberculous Mycobacteria in Bologna, Northern Italy, in the last ten years (2012-2021).

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Background/Aims:

The importance of non-tuberculous mycobacteria (NTM) is becoming increasingly evident. Several studies documented an increasing prevalence in NTM-related pulmonary and extra-pulmonary disease worldwide, especially among subjects with progressive lung diseases. Defining NTM epidemiology is challenging as reporting of NTM disease to health authorities is not mandatory in many countries. In addition, NTM isolates are very heterogeneous, since the family consists of more than 170 different species of mycobacteria. Our aim is to describe the epidemiology and demographics of pulmonary and extra-pulmonary NTM infections in a large reference hospital located in Bologna, Northern Italy, in the last ten years.

Methods:

A single-centre, retrospective, observational study performed at IRCCS Azienda Ospedaliero-Universitaria (AOU) of Bologna is described. Inclusion criteria: subjects with at least one NTM isolated on culture between 01 January 2012 and 31 December 2021. All types of specimens have been included. NTM species were identified by the molecular genetic assays Genotype Mycobacterium CM, AS or NTM-DR (Bruker, Germany). The following data have been analyzed: age, sex, nationality, type of specimen and NTM species/subspecies. Trend over time between two different study periods (2012-2016 and 2017-2021) is described. Continuous variables were expressed as median with interquartile range, and categorical variables were expressed as percentage. Comparisons between two time periods were made using Mann Whitney U-test for continuous variables and chi-square test for categorical variables. $p \leq 0.05$ was considered statistically significant. Study was approved by Ethic Committee of Area Vasta Emilia Centro (AVEC), Bologna, Italy (Protocol code n. 616/2021/Oss/AOUBo).

Results:

478 subjects with at least one NTM isolate were identified. Males represented the 50.4% (241/478); median age was 71.2 (IQR 61.0-77.8) years; 16 (3.3%) were pediatric cases (age < 14 years). The majority was represented by native subjects: 448 (93.7%). Respiratory samples constituted the 86.6% of total specimens: bronchoalveolar lavage (62.8%), sputum (31.6%), bronchial aspirate (5.6%). Among study population, 475 (97.3%) subjects had a single NTM isolate, while 13 (2.7%) had two NTM species in the same specimen. A vast heterogeneity of species was documented, with the most common being *M. avium* (150, 30.5%), followed by *M. intracellulare* (129, 26.3%) and *M. gordonae* (54, 11%). NTM epidemiology and study population characteristics are summarized in Table 1. Comparing the two study periods, 217 subjects with NTM were identified between 2012 and 2016, and 261 between 2017 and 2021, showing an increasing trend over time. *M. avium* and *M. intracellulare* were the most common isolates in both periods. *M. chimaera* was isolated only in the second period, as its speciation test became available in 2017. No significant differences between the study population of the two periods were found, as shown in Table 2.

Conclusions:

Our study describes the vast heterogeneity of NTM species, with MAC representing 62% of total isolates. NTM were mostly identified in native, >65 years old subjects, from respiratory samples. An increasing number of NTM isolates in the last 5 years, possibly reflecting a greater attention to NTM disease and better diagnostic capacities, was observed.

Table 1. NTM epidemiology and study population characteristics

Characteristics	Cathegory	Total (478)		Species		Total (N=491)
Type	Monomicrobial	465 (97.3%)		Species	Myc avium	150 (30.5%)
	Polymicrobial	13 (2.7%)			Myc intracellulare	129 (26.3%)
Age, years		71.2 [61.1-77.8]			Myc xenopi	44 (9.0%)
Etnicity	Native	448 (93.7%)			Myc gordonae	54 (11.0%)
	Foreign	30 (6.3%)			Myc fortuitum	23 (4.7%)
Sex	Male	241 (50.4%)			Myc chelonae	14 (2.9%)
	Female	237 (49.6%)			Myc abscessus	12 (2.4%)
Specimen	BL/BAL	260 (54.4%)			Myc kansasii	8 (1.6%)
	Sputum	131 (27.4%)			Myc chimaera	27 (5.5%)
	BA	23 (4.8%)			Myc lentiflavum	9 (1.8%)
	Other	64 (13.4%)			Other	22 (4.5%)

Table 2. Comparison between two periods (2012-2016 vs 2017-2021)

Characteristics	Cathegory	2012-2016 (N=217)	2017-2021 (N=261)	p-value		Species		2012-2016 (N=223)	2017-2021 (N=268)
Type	Monomicrobial	211 (97.2%)	254 (97.3%)	0,672		Species	Myc avium	64 (28,7%)	86 (32.1%)
	Polymicrobial	6 (2.8%)	7 (2.7%)				Myc intracellulare	62 (27.8%)	67 (25.0%)
Age, years		69.7 [57.9-76.7]	72.0 [63.7-79.1]	0,240			Myc xenopi	27 (12.1%)	17 (6.3%)
Etnicity	Native	200 (92.2%)	248 (95,0%)	0,340			Myc gordonae	31 (13.9%)	23 (8.6%)
	Foreign	17 (7.8%)	13 (5.0%)				Myc fortuitum	7 (3.1%)	16 (6.0%)
Sex	Male	113 (52.1%)	128 (49.0%)	0,062			Myc chelonae	11 (4.9%)	3 (1.1%)
	Female	104 (47.9%)	133 (51.0%)				Myc abscessus	5 (2.2%)	7 (2.6%)
Specimen	BL/BAL	106 (48.8%)	154 (59.0%)	0,162			Myc kansasii	4 (1.8%)	4 (1.5%)
	Sputum	59 (27.2%)	72 (27.6%)				Myc chimaera	0 (0,0%)	27 (10.1%)
	BA	15 (6.9%)	8 (3.1%)				Myc lentiflavum	0 (0,0%)	9 (3.4%)
	Other	37 (17.1%)	27 (10.3%)				Other	13 (5,8%)	9 (3.4%)

1OB.10. Clofazimine is a safe and effective replacement for rifampicin in Mycobacterium avium complex pulmonary disease treatment – primary outcomes of the PERC trial

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Background/Aims:

Retrospective studies have suggested clofazimine as a substitute for rifampicin in MAC-PD. The need for an evidence based alternative treatment regimen is great due to toxicity and drug interactions particularly for rifampicin. The aim of this study was to prove non-inferiority of clofazimine-ethambutol-macrolide compared to the standard treatment regimen.

Methods:

A non-blinded single center randomized clinical trial was done from 2016-2020. Forty patients with MAC-PD according to ATS/IDSA diagnostic criteria were included. The primary outcome was culture conversion, which was defined as 3 consecutive negative sputum cultures.

Results:

Baseline characteristics were similar in both groups (table). After 6 months of treatment, patients in both arms had similar sputum culture conversion rates based on intention to treat analysis: 57.9% (11/19) in rifampicin group versus 61.9% (13/21) in the clofazimine group. Five patients in the rifampicin arm and seven patients in the clofazimine arm discontinued the study (26.3% versus 33.3%; p=0.629), mainly due to side effects. Diarrhoea was more frequent in the clofazimine arm (76.2%) versus 36.8%; p=0.012). Arthralgia was more frequent in the rifampicin arm (36.8% vs 4,8%; p=0.011). Qtc prolongation over 500ms was seen in 2 patients in the clofazimine arm with qtc-prolongation at baseline (470 and 471ms). In the rifampicin arm 1 patient had qtc prolongation, likely due to azithromycin.

Conclusions:

A regimen of clofazimine-ethambutol-macrolide is an effective treatment regimen in MAC and has similar cure rates. The frequency of adverse events was similar in both arms, but their nature was different. Clofazimine is thus a good alternative for rifampicin in patients with MAC-PD; this may result from clofazimine itself or increased macrolide exposure in absence of rifampicin. Individual patients characteristics and possible drug interactions should be taken into consideration when choosing an antibiotic regimen for MAC-PD.

Conflict of interest(s):

	Rifampicin (n=19)	Clofazimine (n=21)	P value
Age	61.4±11.2	64.7±10.4	**0.409**
Gender (Male/Female)	7/12	11/10	**0.324**
Radiological manifestation *Nodular bronchiectatic disease*	8 (42.1%)	8 (38.1)	**0.246**
Fibro-cavitary disease	11 (57.9%)	13 (61.9%)	

1V.1. Imaging analysis of sarcopenia in a cohort of stable patients with bronchiectasis

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Background/Aims:

Chronic respiratory diseases are associated with systemic manifestations, characterized by alterations in the different body compartments. Sarcopenia, defined as loss of function and/or muscle mass, is present in diseases such as bronchiectasis. Our objective was to characterize by imaging (ultrasound-elastography and MRI) the degree of sarcopenia in the quadriceps of stable patients with non-cystic fibrosis bronchiectasis.

Methods:

In stable adult patients (n=20) with bronchiectasis and sarcopenia: fat-free mass (FFMI) < 16 kg/m2 (men) and < 15 kg/m2 (women) and quadriceps strength (QMVC) to fat-free mass ratio (QMVC/FFM) < 0.8 and in healthy control subjects (n=10) the architecture and composition of the vastus lateralis (VL) of the non-dominant quadriceps muscle was assessed in a cross-sectional, prospective study. Patients and controls were clinically evaluated [lung and muscle functions, exercise (shuttle test) and general laboratory tests].

Results:

Compared to control subjects, patients exhibited mild airflow obstruction, reduced upper and lower limb muscle strength and body mass index, without any nutritional alterations. In the patients compared to levels in the healthy controls, imaging tests showed a decrease in muscle thickness and pennation angle, while fatty infiltration and edema were increased. Quadriceps strength positively correlated with both exercise capacity (shuttle test) and VL muscle area, whereas negative correlations were observed between age and the variables quadriceps strength, exercise (shuttle), VL elasticity and quadriceps muscle area.

Conclusions:

These data show the presence of radiological alterations in the quadriceps of stable patients with bronchiectasis and sarcopenia without nutritional alterations. Muscle function should be routinely assessed in patients with bronchiectasis and periodic imaging monitoring will allow quantification of the degree of deterioration of the muscle architecture in these patients. These results have clinical implications for exercise training programs in patients with bronchiectasis

1V.2.Viral load analysis of spirometry filters in patients with chronic respiratory disease whilst asymptomatic of acute viral respiratory tract infection.

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Background/Aims:

Clinically significant bronchiectasis is characterised by chronic cough and recurrent exacerbations. The cause of these exacerbations is often assumed to be bacterial in nature, but the role of viruses in these exacerbations is currently poorly understood.

This study aimed to:

- Explore whether viruses could be detected from exhaled breath using standard spirometry filters.
- Assess viral load in clinically stable patients with bronchiectasis chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and asthma.
- Explore whether the asymptomatic detection of respiratory viruses (including COVID-19) was a precursor to the development of symptoms of viral respiratory tract infection.

Methods:

Patients with underlying asthma, COPD, bronchiectasis or ILD were recruited at the time of routine lung function testing in the Respiratory Medicine Department at Concord Hospital. All patients tested negative to COVID-19 RAT and were clinically stable with nil viral infective symptoms. The spirometry filters were frozen immediately after completion of spirometry and processed in batches using a methodology previously published (Mitchell et al 2016). Bronchiectasis patients also provided spontaneously expectorated sputum samples. All samples were evaluated for the presence of severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2), human rhinovirus (RV), parainfluenza-1-virus (PIV1), parainfluenza-2-virus (PIV2), influenza-type-A (FluA), influenza-type-B (FluB) and human metapneumovirus (HMPV) via reverse transcription polymerase chain reaction (RT-PCR) analysis. Bronchiectasis patients were followed up 4-6 weeks after recruitment to complete a short common cold questionnaire assessing for viral infective symptoms during follow-up.

Results:

This study has demonstrated respiratory viruses can be isolated from exhaled breath during pulmonary function testing. This technique is applied in a range of chronic respiratory diseases, highlighting asymptomatic viral carriage in these individuals is highly prevalent, particularly in the bronchiectasis and COPD groups, with 94% of samples analysed detecting at least 1 respiratory virus. The bronchiectasis sputum group displayed significantly greater viral load relative to all other disease groups at the $p < 0.05$ level. When the COPD and bronchiectasis filter groups are combined, significantly greater viral load can be demonstrated relative to the ILD filter group at the $p < 0.05$ level. For the first time, the non-invasive identification of SARS-CoV-2 from exhaled breath on spirometry filters is documented.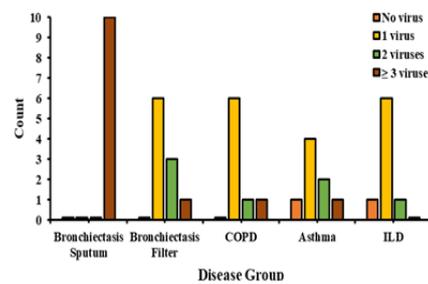 No link between virus type or total number of viruses was found when assessing viral infective symptoms in bronchiectasis patients in the 4-6 week follow up period.

	Bronchiectasis (n = 10)	COPD (n = 8)	Asthma (n = 8)	ILD (n = 8)	p-value
Population Demographics					
Sex *n* Male Female	3 7	6 2	5 3	5 3	0.24[a]
Age *(years), mean (SE)*	67 (3.54)	75 (3.57)	68 (3.13)	69 (5.68)	0.49[b]
Respiratory Function Metrics					
FEV1 *(L), mean (SE)*	1.5 (0.22)	1.56 (0.23)	1.86 (0.31)	2.05 (0.19)	0.37[b]
FVC *(L), mean (SE)*	2.48 (0.28)	3.34 (0.40)	2.90 (0.39)	2.48 (0.26)	0.25[b]
FEV1/FVC *(%), mean (SE)*	59.4 (4.34)	47.3 (5.28)	64.1 (4.94)	83.4* (1.66)	< 0.001[b]

a - Pearson's chi-squared test

b - One-way ANOVA

* - Indicates a statistically significant difference relative to all other disease groups (p < 0.05)

Figure 2. Non-specific total respiratory virus counts identified following PCR for each spirometry filter and sputum sample compared across disease groups ($n = 44$).
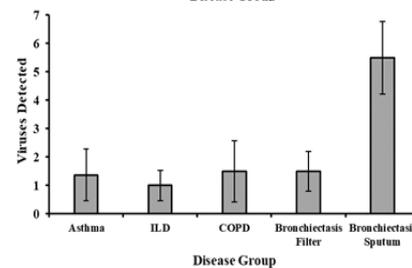
Figure 3. Non-specific mean respiratory virus counts identified following PCR for each spirometry filter and sputum sample compared across disease groups ($n = 44$). Error bars represent ± SD.

Figure 1. Relative distribution of respiratory viruses identified following PCR of spirometry filters and sputum samples in entire study cohort ($n = 44$).
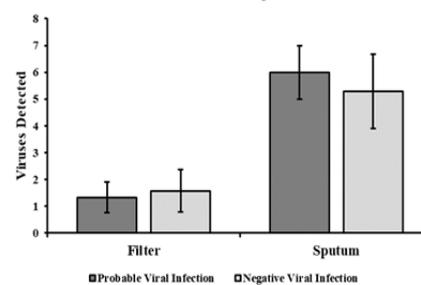
Figure 4. Comparison between mean viral load of bronchiectasis filter and sputum samples for patients determined to have experienced a probable viral infection or no viral infection at 4 - 6 weeks follow up via CCQ data ($n = 10$). Error bars represent ± SD.

Conclusions:

This study demonstrates that respiratory viruses, including COVID-19, can be detected in standard spirometry filters. This unique sampling technique has the potential to serve as a non-invasive monitoring tool for patients with chronic respiratory diseases whereby exacerbations of viral aetiologies are clinically pertinent. The high viral load in clinically stable bronchiectasis samples relative to other disease groups demonstrated in our study supports further enquiry in this area to ascertain the mechanisms of high viral prevalence in these patients and the causal relationships that may exist between the lung microbiome, inflammation, and exacerbations that have been hypothesised in the literature.

1V.3.The relationship between airway Interleukin-1 beta, microbial dysbiosis and mucus hyperconcentration in bronchiectasis: The EMBARC-BRIDGE study

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Background/Aims:

Mucus hyperconcentration and impaired mucociliary clearance are central features of bronchiectasis. Inflammation and infection are believed to be the key mediators of impaired mucociliary clearance. IL-1β is a key regulator of inflammatory responses and directly triggers mucus production and hyperconcentration in cystic fibrosis. The role of IL-1 β in bronchiectasis has not been investigated. The aim of this study was to investigate the relationship between sputum IL-1β levels and disease severity, the microbiome, inflammation, and mucus properties in an international bronchiectasis cohort.

Methods:

Sputum samples from 269 patients with stable bronchiectasis were collected at three European centres (Dundee, Milano, Barcelona) as part of a European observational cohort study NCT03791086. The study was approved by institutional committees on Ethics of experimental and human investigations. IL-1β levels were measured by Meso Scale Discovery (MSD) assay in sputum supernatant. Patients were stratified into two groups according to the IL-1β median value (designated High and Low for analysis). Disease severity was evaluated using the bronchiectasis severity index, microbiome by 16s rRNA sequencing and Th1, Th2 and Th17 inflammatory mediators were evaluated by MSD assay. Mucus properties were determined by rheology in an independent cohort of 51 patients.

Results:

Patients with high sputum IL-1β had more severe disease (Fig.1A), a Proteobacteria dominated microbiome, lower microbial diversity (Fig.1B-D) and significantly higher Th1, Th2 and Th17 inflammatory mediators (TNF-α, IFN-γ, IL-10, IL-4, IL-13, IL-8, resistin, neutrophil elastase, heparin-binding protein) than patients with low sputum IL-1β (all $p<0.0001$). Sputum IL-1β levels also showed linear correlations with all these inflammatory mediators (Fig.1E). IL-1β was related to sputum purulence (84% mucopurulent or purulent in the high group vs 22.2% in the low group; Fig.1F) and increased mucus solid content measured by the percentage of dry weight (Fig.1G) indicative of mucus dehydration. IL-1β was also associated with the viscoelastic properties of mucus. Specifically, it was associated with elastic (G') (rho=0.43, p=0.002), viscous (G'') (rho=0.48, p=0.0004) and complex ($G*$) moduli (rho=0.46, p=0.0006), and with damping factor (rho=0.32, p=0.02) by rheology.

Conclusions:

IL-1β is strongly related to microbial dysbiosis and mucus dehydration in patients with bronchiectasis.

Conflict of interests:

1V.4. Diagnostic value of the Biofire® Filmarray Pneumonia panel compared to conventional sputum culture in patients with an exacerbation of bronchiectasis

Patricia Elena Oscanoa Huamán[1]; Leticia Bueno Freire[2]; Andrea Palomeque[1]; Victoria Alcaraz Serrano[3]; Ruben Lopez Aladid[2]; Nil Vasquez[2]; Nona Rovira-Ribalta[2]; Rosanel Amaro Rodriguez[1]; Laia Fernández-Barat[2]; Antonio Torres Marti[1]

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Background/Aims:

The identification of the etiological agent of bronchiectasis exacerbations (BE) is primordial in order to administrate a proper treatment. Multiplex PCR panels, like BioFire® FilmArray Pneumonia panel (FAPN), are more rapid and sensitive compared to routine cultures in patients with community acquired pneumonia, but the evidence in BE is scarce. The aim of this study was to compare FAPN vs. conventional sputum culture results in patients with BE.

Methods:

We performed a prospective observational study including adult patients with BE at the Hospital Clinic of Barcelona. BE was defined according to the international consensus statement (REF Hill et al). Sputum samples (1 per patient) were collected at the beginning of the BE (before antibiotic treatment) and processed for both microbiological studies, FAPN and conventional sputum culture.

Results:

84 patients were included 69 [59-76] years; 47(56%) females. 47(56%) females. Positive microbiological isolation was found in 72(86%) by FAPN vs 32(38%) by conventional sputum culture (Table 1). 24% of *P. aeruginosa* was underdiagnosed according to conventional sputum culture results. Therefore, the sensitivity and specificity of the FAPN method was 96% and 100% respectively (Table 2).

Conclusions:

Diagnosis using FAPN method allows obtaining quickly, safely and more sensitive and specificity results than conventional sputum culture in BE, especially *P. aeruginosa*. More studies are needed to find out if early detection improves the course of the disease.

Conflict of interest(s):

Table 1. Microbiology of patients with exacerbation of bronchiectasis: sputum culture vs Filmarray pneumoniae panel plus

	TEST	
	SPUTUM (N=84)	FAPN (N=84)
POSITIVE	32 (38%)	72(86%)
NOT APPLICABLE	27(32%)	0 (0%)
NEGATIVE	25 (30%)	12(14%)
MICROBIOLOGICAL ISOLATION:		
P. aeruginosa	23 (27%)	42(50%)
H. Influenzae	2(2%)	8(10%)
Virus	0(0%)	28(33%)
K. Pneumoniae	0(0%)	8(10%)
S. aureus	1(1%)	11(13%)
S. pneumoniae	2(2%)	7(8%)
Mixed *P. aeruginosa* + other	1	22
Mixed non *P. aeruginosa* + other	1	11

Table 2. Sensitivity and Specificity of Filmarray Pneumoniae Panel Plus in patients with exacerbation of bronchiectasis

Se/Sp SOC vs FA in BE exacerbations			
	Colonized	**Non-colonized**	**TOTAL**
POSITIVE FAPN	48	0	48
NEGATIVE FAPN	2	6	8
TOTAL valid	50	6	56
* SOC: Standard of care			
* Extended Gold Standard: Colonized was considered when positive SOC, positive FAPN or positive SOC/FAPN.			
Se FAPN: 96%			
Sp FAPN: 100%			

1V. 5. A Questionnaire to assess adherence to respiratory physiotherapy in patients with bronchiectasis: a preliminary study.

Martina Santambrogio[1]; Veronica Polelli[2]; Matteo Figini[3]; Angela Bellofiore[1,4]; Emilia Privitera[1,4]; Margherita Ori[1]; Stefano Aliberti[2,5]; Francesco Blasi[6,1]

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Background/Aims:

Respiratory physiotherapy (RT), including airway clearance strategies, exercise training, and self-management education, improve physical performance and quality of life in individuals with bronchiectasis, and can modify the course of the disease by reducing the number of exacerbations. Adherence to prescribed treatment is crucial to reach these important functional outcomes. To date, no specific instruments to measure adherence to RT has been developed for people with bronchiectasis. Aim of this study is to preliminary evaluate a Questionnaire developed to assess adherence to RT in patients with bronchiectasis.

Methods:

Reviews of literature and health care practitioners input were used to generate the initial RT Adherence Questionnaire. The Questionnaire is divided into five sections recording and evaluating 1) socio-demographic data; 2) prescribed RT program; 3) patients' self-reported adherence to the prescribed treatment; 4) practical skills in the prescribed RT techniques; 5) reasons for non-adherence. Four specific RT domains were assessed in section 3 and 4 separately: airway clearance strategy, nasal irrigation, physical activity and inhaled therapy. Self-reported adherence was expressed as a percentage of sessions performed in the last month as compared to the prescription (5 possible answers: 0-25%; 25-50%; 50-75%; 75-100%; not prescribed). Practical performances were assessed following pre-established procedures for each technique, in which the different steps were divided in essential or not for a correct performance. Physiotherapists assessed patient performances by reporting for each step whether it was performed correctly or not. Omissions or errors in at least one essential step resulted in a "not correct" technique, while omissions or errors in not essential steps resulted in "partially correct" evaluation. No errors or omissions resulted in a "correct" technique. The maximum global score is 5 (complete adherence and good practical skills), the minimum is 0. The Questionnaire was tested on a small sample of adult bronchiectasis patients, with an optimized RT program, during visits at the outpatient clinic of the IRCCS Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano (Italy) from January 1st to April 30th 2022.

Results:

Twenty-five individuals, meeting the inclusion criteria, were enrolled in this study [mean age 62.8 (16.0); 18 (72%) female]. The most used airway clearance techniques included ELTGOL (16%), and use of positive expiratory pressure (PEP) systems, such as PEP bottle (36%) and PEP mask (24%). The best self- reported adherence was found for the inhaled therapy, followed by the domain of airway clearance techniques (Figure 1A), whereas the better practical skills were observed in nasal irrigation and inhaled technique (Figure 1B). The mean score obtained was 3.73, with 14 subjects (56%) showing scores ≥4.

Conclusions:

Form these preliminary data, the Questionnaire appears to be a useful tool for assessing adherence to RT in subjects with bronchiectasis. Validation of this instrument should be performed with a larger sample of patients.
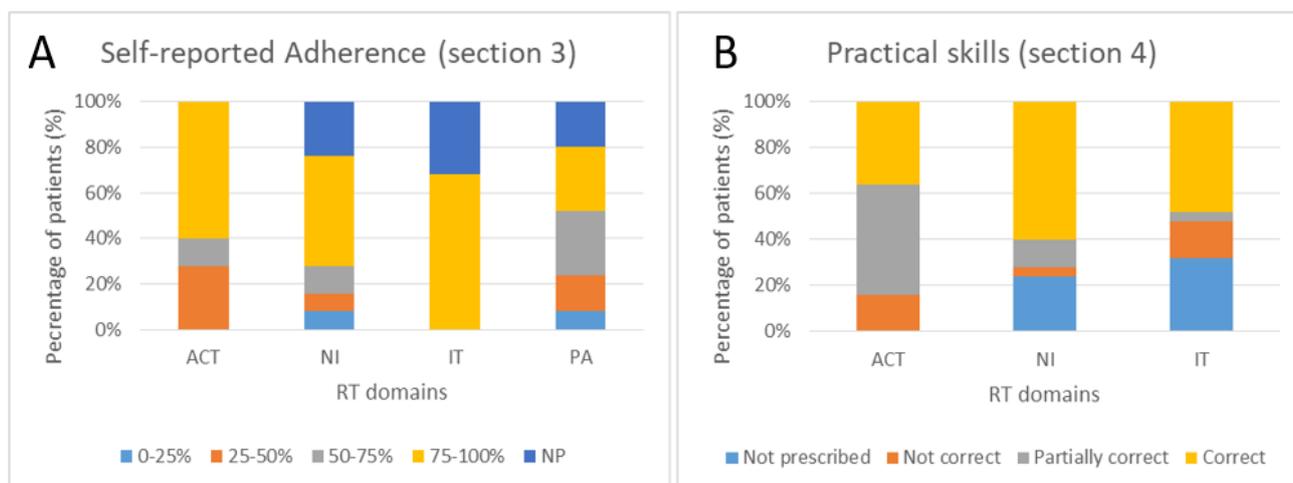
Figure 1- Adherence to RT expressed as self-reported by patients (A) and in terms of practical performance (B) for the different domains of RT. Self-reported adherence is expressed as a percentage of sessions performed in the last month as compared to the prescription.
ACT, airway clearance techniques; IT, inhaled therapy; NI, nasal irrigation; NP, not prescribed; PA, physical activity; RT, respiratory physiotherapy.

1V.6. Multicenter, Pragmatic, Randomized, Controlled Trial to Assess the Efficacy and Safety of Nocturnal Humidification Therapy in Patients With Bronchiectasis: the AIRVO-BX Study

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Background/Aims:

Bronchiectasis is a chronic condition characterized by an abnormal widened airways, mucus retention, cough, daily sputum, and frequent respiratory infections. The management of bronchiectasis includes prevention of exacerbations and lung infections along with airway clearance techniques. Mucus composition and hydration are crucial to allow mucus transport along airways during respiratory physiotherapy. The aim of the present study is to assess the effect of long-term use over-night of myAIRVO2 warm humidification in adults with bronchiectasis who experience at least 3 exacerbations/year still with optimized clinical and respiratory therapies.

Methods:

This is a multicenter, pragmatic, randomized, controlled trial. Consecutive adult patients with radiological evidence of bronchiectasis, daily sputum, presence of at least 3 exacerbations requiring antibiotic therapy during the 12 months prior randomization, the bronchiectasis medical and respiratory therapies optimized according to international guidelines[1] during the 12 months preceding randomization and no changes in therapies that occurred during the 28 days prior randomization were screened during outpatient visits. Exclusion criteria were: 1) COPD or asthma recognized as main diseases; 2) Any other medical condition which can affect patients' safety; 3) Long-term treatment with non-invasive ventilation or continuous positive airway pressure; 4) Tracheostomy; 5) Major haemoptysis during the 6 weeks prior randomization; 6) Cystic fibrosis; 7) Traction bronchiectasis in the context of pulmonary fibrosis; 8) Lung cancer in the last 5 years; 9) Use of drugs that can modify mucus liquid content; 10) Pregnant and brest-feeding women; 11) Being enrolled in other intervention trials during the 12 months prior randomization; 12) Active smoker or ex-smoker.

One hundred and thirty patients will be enrolled and randomized into two groups. The control group continues to receive standard therapy for bronchiectasis according to international guidelines. In addition to their usual therapy, the treatment group receives a myAIRVO2 humidifier at home deliver every day for one year over-night. The gas flow is set between 20 and 30 l/min based on patient preference, temperature is 37°C and, for patients already in long-term oxygen therapy, FiO_2 is regulated according to patient's prescription. Once enrolled in the study, patients are followed up every 3 months with 4 consecutive outpatient visits. The following endpoints will be assessed at the end of the study: exacerbations frequency, quality of life, pulmonary function and, for patients enrolled in the treatment group, myAIRVO2 use, and comfort.

Ethics and dissemination:

The trial protocol was published before study initiation (NCT 04102774). The study was approved by the Ethics Committee of Milano Area 2 (approval ID 792, studio 4309) and subsequently by the local Ethics Committees of the participating sites. Recruitment stared in June 2019. Results of this study will be published in scientific journals and presented at scientific meetings.

Conclusion:

The aim of this trial is to evaluate the effect of nocturnal AIRVO Heated Humidification on exacerbations in Bronchiectasis. This study is open to every center that wants to participate. If interested in participating in the study, please contact the Principal Investigator.

1V.7. Bridging the Gap: A Novel Symptom Diary for Non-Cystic Fibrosis Bronchiectasis (NCFB) Exacerbations

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Background/Aims:

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic lung disease characterized by recurrent infection and inflammation, respiratory symptoms, and exacerbations. Our goals were to understand patient perspectives on NCFB symptoms and to develop a patient-centered, content-valid, daily Bronchiectasis Exacerbation Diary (BED) to monitor key exacerbation symptoms.

Methods:

Content validity of the BED was established through comprehensive qualitative research following FDA guidance, including a targeted literature review, 3 specialist interviews to understand clinical perspectives, and 20 patient concept elicitation/cognitive interviews (4 waves of 5). Patients described their personal experiences with NCFB symptoms and corresponding levels of disturbance and provided input on the clarity of the instructions, response options, and recall period of a draft BED. The BED was modified and finalized based on patient feedback.

Results:

A total of 20 US patients with NCFB were interviewed. Mean (range) patient age was 54 (23-71) years, most were female (85%) and white (85%); all patients (100%) had an NCFB diagnosis for ≥12 months and ≥2 exacerbations in the previous 24 months. Most NCFB symptoms (91%) were identified during the first wave of patient interviews, with saturation reached by wave 3. Most patients felt a 24-hour recall period was appropriate. Cognitive interviews confirmed 6 key symptoms and were used to develop the final 8-item, daily BED (**Figure**).

Conclusions:

Key bronchiectasis symptoms reported by patients were included in the BED. This qualitative research supports the content validity of the BED as a suitable tool for capturing key bronchiectasis exacerbation symptoms associated with exacerbations.

Conflict of interest(s):

1V.8. Morphological aspects of pulmonary nocardiosis

Leonardo Gori[1]; Tomassetti Sara[1]; Puglisi Silvia[2]; Ravaglia Claudia[2]; Ciani Luca[1]; Luzzi Valentina[1]; Giuntoli Leonardo[1]; Marinato Martina[1]; Pasini Valeria[1]; Comin Camilla[1]; Dubini Alessandra[2]; Piciucchi Sara[2]; Cavigli Edoardo[1]; Lavorini Federico[1]; Rosi Elisabetta[1]; Poletti Venerino[2]

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Background/Aims:

Nocardia is an opportunistic pathogen that most frequently affects the lungs.Pulmonary nocardiosis (PN) is an uncommon but potentially life-threatening infection.PN typically occurs in patients with cell-mediated immunosuppressive conditions, but infection may occasionally develop in immunocompetent patients as well.The pathological manifestations of nocardiosis are described as pyogenic or necrotic changes, and the typical pathological feature is suppurative necrosis with abscess formation; therefore, low-density areas or cavities often appears in the lung.

The aim of this study was to describe the pathologic features of pulmonary nocardiosis, focusing on possible novel or under reported features.

Methods:

Retrospective revision (2014–2021) of pathological specimen form lung biopsies, along with clinical and radiological evaluation of PN patients seen at 2 referral university hospitals in Italy (Florence and Forlì).

Results:

Seven patients were included in this study, 4 women and 3 men, median age 59 years. Nocardia was detected in 2 cases by CT-guided needle biopsy, in 4 cases by transbronchial lung cryobiopsy and in 1 case by bronchoalveolar lavage. In 4 cases, BAL was negative, and subsequent biopsy positive. Major risk factors for PN were smoking and previous tuberculosis; all patients were apparently immunocompetent (as defined by normal WBC, Ig tests, no immunosuppressive drug). The most commons species found was *Nocardia abscessus* (5 cases of 7, 71%), 1 case of *Nocardia beiijingsensis* and in 1 case is not specified. The most frequent anatomopathological pattern was organizing pneumonia (4 cases of 6, 66%), 1 bronchiolitis (mixed fibrotic and cellular) and e 1 peribronchial lymphoid infiltrate.

Conclusions:

Our findings on the pathological aspects of pulmonary nocardiosis differ significantly from the literature, in fact we found in 66% of cases organizing pneumonia and other features suggestive of a possible underlying immune-mediated mechanisms not yet identified.

1V.9. A laboratory assessment of nebulized medication delivery through different Oscillating Positive Expiratory Pressure (OPEP) devices – not all devices are the same

Jason Suggett[1]

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Introduction:

Medications to manage care of bronchiectasis and NTM patients are often delivered via a nebulizer, as they are easy to use. OPEP devices are also often used for airway clearance by the same group of patients and the two treatments can be combined allowing medication delivery on inhalation and OPEP therapy on exhalation. This study compares a number of different OPEP / Nebulizer combinations using salbutamol as the modelled medication.

Methods:

Four different OPEP / Nebulizer systems were evaluated. These were: a) AEROBIKA* OPEP with AEROECLIPSE* II BAN* Nebulizer at back of OPEP b) acapella[†] choice OPEP with VixOne[†] nebulizer using t-piece at front of OPEP, c) acapella Choice Blue OPEP with AEROECLIPSE* II BAN* Nebulizer at back of OPEP, and d) acapella[†] Choice Blue OPEP with Salter Labs[†] 8900 nebulizer using t-piece at front of nebulizer.   Medication delivery (total emitted mass until sputter) of salbutamol 2.5mg in 3ml was determined in the lab for each system using a breathing simulator and filter collection at mouthpiece (settings 600ml tidal volume, 1:3 I:E ratio, 2s pause after inhalation).

Results:

The table below reports the medication delivered via each system

Delivery System	Emitted mass of salbutamol (mcg, +/- SD)
AEROBIKA* OPEP / AEROECLIPSE* II BAN* Neb	764 +/- 18
acapella[†] Choice Blue OPEP / AEROECLIPSE* II BAN* Neb	229 +/- 15
acapella[†] choice OPEP / VixOne[†] Neb	248 +/- 25
acapella[†] Choice Blue OPEP / Salter Labs[†] 8900 Neb	214 +/- 8

Conclusions:

The results show that OPEP/Neb combination selection can have a large impact on the amount of drug delivered. The AEROBIKA* OPEP / AEROECLIPSE* breath actuated device combination delivered more than 3x as much salbutamol in a treatment compared to the other combinations. Combining OPEP and nebulizer therapy has advantages in terms of patient efficiencies, convenience, and adherence, however care should be taken to ensure the drug delivery is not compromised.

1V.10 Respiratory physiotherapy in private practice: an audit of clinical practice and quality of life outcomes in patients with bronchiectasis

Mitchell Taylor[1]

[1]*Functional Lungs, Sydney, Australia*

Background:

Bronchiectasis is a disease characterised by excessive mucous production in the airways (1,2). Respiratory physiotherapy (also known as chest physiotherapy) involves implementing a range of physiotherapy techniques to augment mucous clearance from the lungs (3,4). Respiratory Physiotherapy is considered first line therapy in bronchiectasis management however research in this field primarily examines the effect of one individual treatment modality whilst clinically treatment modalities are often implemented synergistically (4)

Aims:

A) To audit the respiratory physiotherapymodalities implemented in the clinical management of bronchiectasis
B) To review the effect of respiratory physiotherapy on quality of life at 1 month post implementation.

Methods:

An audit was conducted on patients with bronchiectasis who presented to a 'Functional Lungs' clinic for an initial physiotherapy assessment between July 2019 and May 2021. Baseline characteristics (see Figure 1), treatments administered and COPD Assessment Test (CAT) QOL scores (baseline and 1 month) were recorded. 50 patients fit the inclusion criteria and information on treatment prescription was recorded for all patients. Of the 50 patients; 2 did not attend a follow up and 5 patients had missing data. 43 patients with CAT QOL scores were analysed at both baseline and at 1 month postimplementation.

Demographics

Patients	50
Sex	M = 18 (36%) F =32 (64%
Age	20-83yrs (Av 63)
Referral Source	
– Resp Physician	46 (88%)
– Self-referral	3 (6%)
– Allied health	1 (2%)
– GP	2 (4%)
Self-reported exacerbations per year	0-6 (average 2.2)

Results:

The frequency of modality administration is listed in Table 2.

Table 2 – Treatment modalities

Therapy	No of patients (%)
Education*	50 (100%)
PEP Therapy(3, 7, 8)	43 (86%)
Inhaler technique review(9)	25 (50%)
Home exercise program(8)	43 (86%)
Nebulised Adjuncts**(10)	9 (18%)
Modified gravity assisted drainage(3)	44 (88%)
Active Cycle of Breathing Technique(3)	12 (24%)
Autogenic Drainage	1 (2%)
Thoracic Mobility	8 (16%)

The average number of modalities implemented in each patient was 4.7 (3-6). See Figure 1.

Figure 1 – No. of modalities implemented
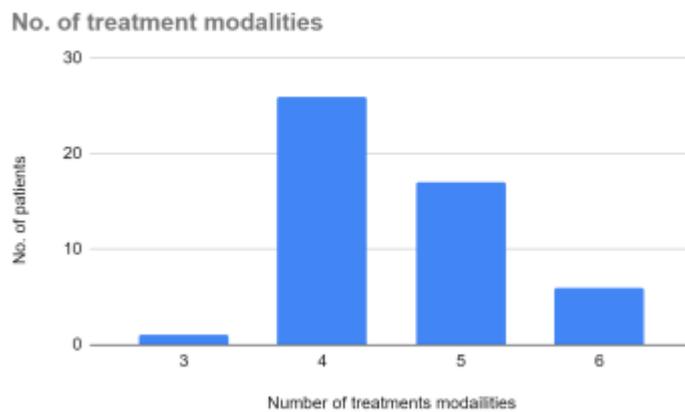
The average reduction in CAT QOL score at 1 months was 7.6points (-1-18). 40/43 (93%) patients improved by the minimal clinically importance difference (MCID) of 3 points.
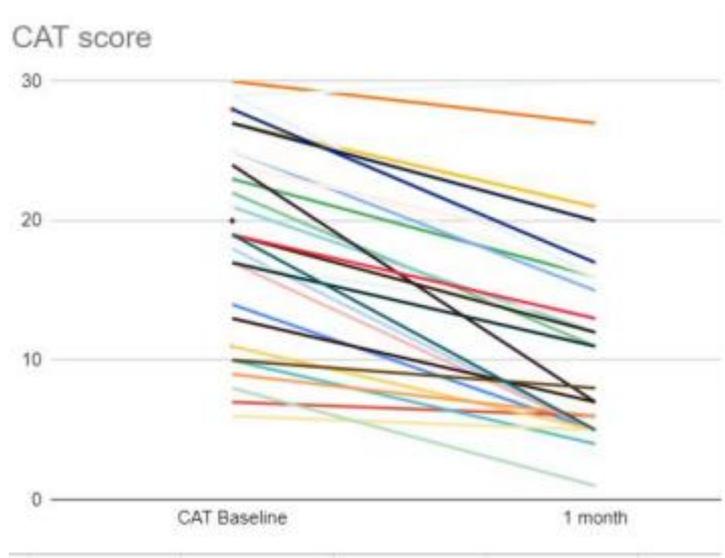
Discussion:

Our data demonstrates real world practice in which multiple airway clearance treatment modalities are used simultaneously in the treatment of bronchiectasis. This is not reflected by current research in which single modalities are examined. There is potential that combined treatments act synergistically and enhance outcomes above current research.

The CAT score is validated in bronchiectasis and correlates with disease severity, exacerbation frequency, FEV1 and exercise tolerance (5,6). Our data demonstrated an average reduction in CAT score of 7.6 which is significantly above the MCID of 3 points. Our data highlights the need for prospective studies into the effect of multi-modal respiratory physiotherapy in bronchiectasis on both qualitative and quantitative outcomes.

Conclusions:

Multiple treatment modalities were implemented within the first month of bronchiectasis treatment. Treatment by a respiratory physiotherapy resulted in a significant reduction in the CAT QOL score.

STROLLING POSTER SESSION 2OA - IN PRESENCE

2OA.1. Effect of glycaemia on lung function in people with bronchiectasis- a retrospective analysis

Marwa Naamneh[1]; Nili Stein[2]; Sameer Qasem[3,1]; Yochai Adir[3,4]; Raya Cohen[3]; Michal Shteinberg[4,3]

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Introduction:

Glycemic control has previously been found to affect lung function in chronic airway diseases such as cystic fibrosis and COPD. In CF, glycemic control is known to directly affect pulmonary outcomes. Proposed mechanisms to the relation include effect on nutrition, as well as airway glycaemia affecting CFTR gene expression(1). The correlation between glycaemia and lung function has not been reported in bronchiectasis to the best of our knowledge.

Our aim was to assess the correlation between glycemic control and pulmonary function (PFTs) in people with bronchiectasis.

Methods/ design:

This study is a retrospective cross sectional study including people with bronchiectasis in Lady Davis Carmel Medical Center in Haifa, Israel, between the years 2012 and 2020. We included patients with available results of HbA1C, and spirometry when stable, performed within 1 year of each other. Correlation between lung function measures and HbA1C were assessed using the Pearson or Spearman correlation, as appropriate. Differences between the two time periods were analyzed using the paired t-test or Wilcoxon sign rank test.

Results:

Of 401 people with bronchiectasis, 116 people had at least two paired HbA1C and spirometry testing within one year and were included. 55% were females, mean (SD) age 65(15) years. 53 (45.7%) have a diagnosis of diabetes mellitus type 2.

At the second, but not at the first time point, there was a weak but statistically significant inverse correlation between HbA1C and FEV1 (**r=-0.20, P=0.033**, figure) and between HbA1C and FVC% (**r=-0.31, p=0.003**). There was no correlation between HbA1C levels and infection with *P. aeruginosa*, NTM, or any airway infection. FEV1 change over the two time points was not associated with HbA1C levels.

Conclusion:

Our findings suggest that glycemic control affects lung function in bronchiectasis. While the mechanisms behind this correlation remain to be explored, our findings suggest that improved glycemic control may be a therapeutic target in bronchiectasis.
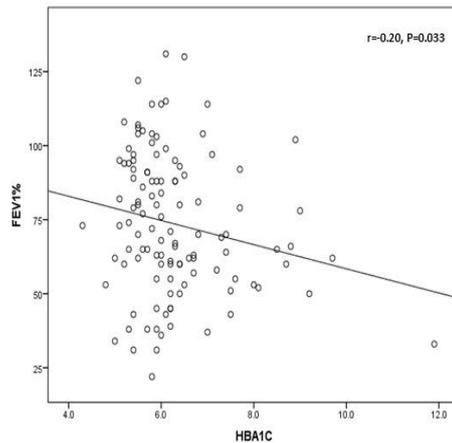
Reference

1. Fei Y, Sun L, Yuan C, Jiang M, Lou Q, Xu Y. CFTR ameliorates high glucose-induced oxidative stress and inflammation by mediating the NF-κB and MAPK signaling pathways in endothelial cells. Int J Mol Med. 2018 Jun;41(6):3501–3508.

2OB.2. In vitro and in vivo characterization of the novel cathepsin C inhibitor BI 1291583

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Background/Aims:

Recurrent pulmonary exacerbations and progression of respiratory symptoms are attributed to damage to the distal airways due to an abundance of neutrophil proteinases that are not adequately inhibited by endogenous anti-proteases, leading to excessive lung tissue proteolysis. The protease cathepsin C (CatC; also known as dipeptidyl peptidase 1) is exclusively responsible for activation of all neutrophil serine proteases (NSP; neutrophil elastase [NE], cathepsin G, proteinase 3 [PR3]) during myelopoiesis in the bone marrow. Inhibition of CatC is therefore expected to improve the protease–antiprotease balance in the lungs of patients with chronic airway inflammation (e.g. bronchiectasis) and to reduce distal airway destruction with possible secondary anti-inflammatory and anti-mucus hypersecretory effects. We discuss the in vitro/in vivo characterization of BI 1291583, a novel CatC inhibitor currently undergoing clinical testing.

Methods:

Enzymatic assays were used to measure the in vitro activity and selectivity of BI 1291583. Since CatC is essential for NSP activation in the bone marrow, the effect of BI 1291583 on the level of active NE was measured in the human myeloid cell line U937. In vivo activity was tested in mice treated orally with BI 1291583 once daily for 12 consecutive days, followed by a lipopolysaccharide challenge via inhalation on Day 12. Neutrophils were collected 4 hours post-challenge from bronchoalveolar lavage fluid, and the activities of NE and PR3 were measured. Compound exposure was measured in bone marrow and plasma. All animal experimentation was conducted in accordance with German national guidelines and legal regulations.

Results:

BI 1291583 is a covalent, fully reversible and potent inhibitor of the enzymatic function of CatC with a half-maximal inhibitory concentration (IC_{50}) of 0.9 nM and a >7000-fold selectivity for CatC versus related cathepsins. BI 1291583 inhibits the production of active NE in U937 cells with an IC_{50} of 0.7 nM. In vivo production of active NE in mice was completely attenuated by BI 1291583 in a dose-dependent manner (effective dose producing 50% inhibition [ED_{50}] = 0.03 mg/kg and 99% inhibition [ED_{99}] = 0.3 mg/kg; Figure). Levels of active PR3 were similarly reduced. Due to its physicochemical properties, BI 1291583 shows over 100 times higher exposure in the bone marrow compared with plasma at efficacious doses (0.1, 0.5 and 5 mg/kg), which may reduce the risk of unwanted effects of inhibiting CatC in the periphery.

Conclusions:

BI 1291583 is a potent and highly selective inhibitor of CatC, which has the potential to ameliorate neutrophilic inflammation and tissue destruction mediated by uncontrolled NSP activity in the airways.

Figure: Neutrophil elastase activity in the lysate of BAL neutrophils from mice treated with BI 1291583
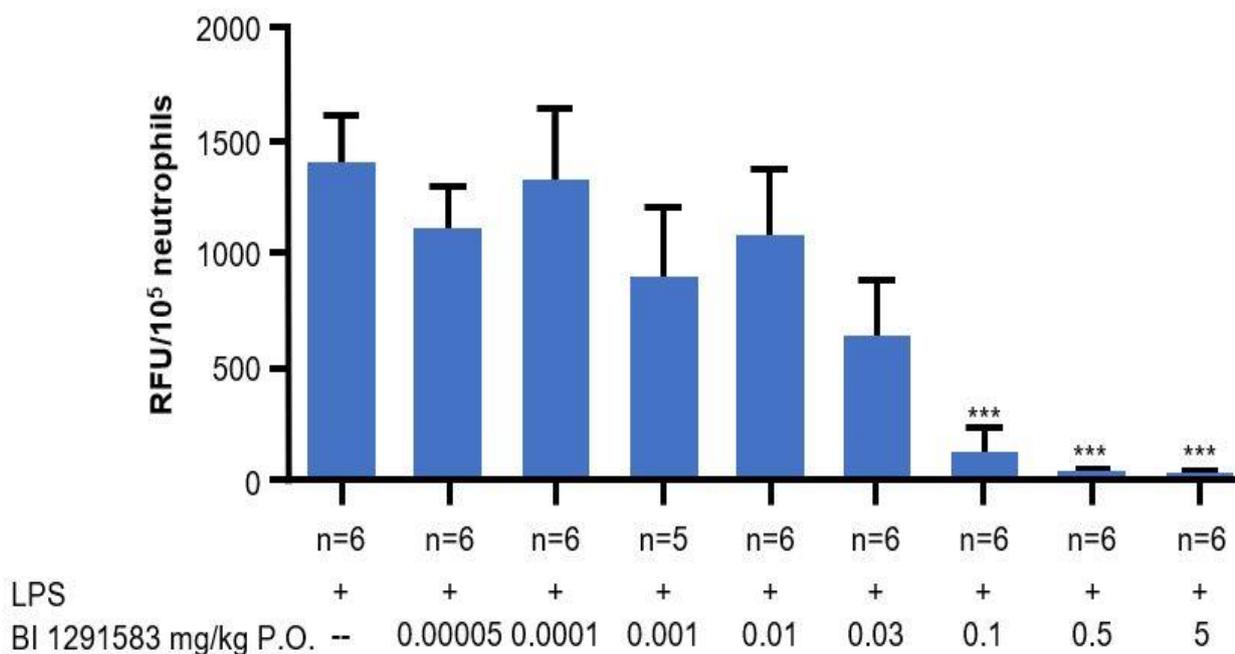
Data are shown as mean ± standard error of mean; ***P<0.001 vs LPS control; NE activity shown as RFU normalized to the number of neutrophils.

BAL, bronchoalveolar lavage; LPS, lipopolysaccharide; P.O., per os (by mouth); RFU, relative fluorescence units.

Conflict of interest(s):

2OA.3. Investigation of exoU in Pseudomonas aeruginosa respiratory infections from people with bronchiectasis

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Background/Aims:

The ExoU protein is a toxin of the type III secretion system of *Pseudomonas aeruginosa* (PA), which can cause acute cytotoxicity and lung injury. Infection of PA harbouring the *exoU* gene has been associated with an increased rate of pulmonary exacerbations in bronchiectasis. In addition, the presence of *exoU* has been associated with higher rates of ciprofloxacin resistance in PA in other infections.

To determine the prevalence of *exoU* in a collection of PA isolates from people with bronchiectasis and investigate its relationship with isolate phenotypic characteristics and patient clinical features.

Methods:

Single PA colonies (n=482) isolated from longitudinal respiratory samples collected from 105 patients (mean: 4.6 isolates/person) enrolled in the iBEST-1 study (NCT02712983) were included. Isolates were screened for *exoU* by PCR and classed as positive or negative for the gene. Susceptibility to eight antibiotics in seven categories was tested by the broth microdilution method and minimum inhibitory concentrations (MICs) were interpreted according to Clinical and Laboratory Standards Institute guidelines. Isolates non-susceptible (resistant or intermediate) to ≥1 antibiotic in ≥3 categories were classified as multi-drug resistant (MDR). Colony morphotype was also recorded as mucoid or non-mucoid. Patients were classed as having infection with PA positive or negative for the *exoU* gene and FEV_1 %predicted and PA total viable count at study baseline were compared.

Results:

Approximately one fifth of isolates (n=109/482; 22.6%) were positive for the *exoU* gene and 31/105 (29.5%) patients had ≥1 isolate positive for *exoU*. Most patients had infection with PA always positive or negative for *exoU* over time (n=97/105; 92.4%). There was no association between PA harbouring *exoU* and ciprofloxacin resistance (positive, n=12/109, 11.0%; negative, n=60/373; 16.1%; p=0.1) as well as no difference in the median ciprofloxacin MIC (positive, 0.5mg/L; negative, 0.5mg/L; p=0.4) or in the rates of MDR (positive, n=14/109, 14.7%; negative, n=40/373, 12.0%; p=0.6) between the groups. There was also no association between harbouring *exoU* and mucoidy (positive, n=41/109, 37.6%; negative, n=169/373, 45.3%; p=0.1). At the patient-level, there was no difference between mean lung function (FEV$_1$: positive, 61.7 %predicted; negative, 61.0 %predicted; p=0.9) nor mean total viable count of PA (positive, 2.9 x10^6 CFU/mL; negative, 3.6 x10^6 CFU/mL; p=0.8) in individuals infected with PA positive or negative for *exoU*.

Conclusions:

In contrast to previous studies, this preliminary data showed that the presence of the *exoU* virulence gene in PA is not associated with increased antibiotic resistance or a worse clinical status in this bronchiectasis cohort.

2OA.4. Prevalence of Breathing Pattern Disorder in a Physiotherapy Bronchiectasis Outpatients Clinic

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Background:

Bronchiectasis is a chronic respiratory condition, characterised by widening of the airways resulting in chronic cough and excessive mucus production. Studies suggest 5 in 1000 people live with bronchiectasis in the UK.

National guidelines recommend all patients are reviewed by a respiratory physiotherapist for education, airway clearance techniques and where appropriate advice on adjuncts (inhaled/oral therapy or exercise).

Breathing Pattern Disorders (BPD) are a set of heterogeneous dysfunctional breathing symptoms that are not always attributable to a specific medical diagnosis. BPD can increase health care utilisation and reduce the quality of life in patients with asthma. Studies show the prevalence of BPD is up to 30% in asthma and up to 40% in patients with Primary Cilia Dyskinesia (PCD). Both asthma and PCD are well recognised co-morbidities in bronchiectasis.

There is a notable lack of research investigating the existence and/or prevalence of BPD in bronchiectasis. There may be a significant proportion of patients with a BPD in the bronchiectasis population, highlighting an unmet need.

Aim:

To investigate the prevalence of BPD in an outpatient physiotherapy bronchiectasis clinic in the UK.

Methods:

All patients were assessed at consecutive predetermined physiotherapy bronchiectasis outpatient clinics between 22/10/21 and 25/2/22. Only patients who attended face-to-face (n = 40/187) were included (Table 1). The Brompton Breathing Pattern Assessment Tool (BPAT) used for assessing BPD could not be conducted via telephone call and it is not validated via video call. Data were recorded and analysed using Excel.

Results:

Forty patients were eligible for inclusion in the observational study. Sixteen (40%) of patients had a confirmed diagnosis of breathing pattern disorder. This was measured subjectively using the Nijmegen questionnaire and objectively using the BPAT. Eight (20%) patients had asthma or COPD as a co-morbid respiratory condition in addition to their bronchiectasis. No patients had both asthma and COPD as co-morbidities. 80% (n =13) of patients with BPD had an MRCD ≥ 3.

Conclusion:

Our study shows bronchiectasis patients are likely to present with clinical signs and symptoms of BPD. Interestingly despite moderate prevalence of BPD in asthma, our study found only 19% of those with asthma as a co-morbidity had confirmed BPD.

Current national bronchiectasis guidelines do not recommend assessment of BPD. Our study suggests the assessment and management of BPD in this population may be beneficial based on the prevalence in this cohort. Further research is needed to better estimate the prevalence of BPD in the bronchiectasis population. This may support the need for guidance on additional physiotherapy training in this specialty.

Table 1.

Data Collected	Options	Results
Age	Years (Median/Range)	73 (43-89)
Sex	Male/Female	F (17/40) M (23/40)
Asthma	Yes/No	8 (20%) 32 (80%)
COPD	Yes/No	8 (20%) 32 (80%)
Breathing Pattern Disorder	**Confirmed by both BPAT & Nijmegen scores**	**16/40 (40%)**
Brompton Breathing Pattern Assessment Tool (BPAT)	Significant score (≥4)	18/40 (45%)
Nijmegen Questionnaire	Significant score (≥23)	19/40 (48%)
Medical Research Council Dyspnoea (MRC) Scale	≥ 3	13/16 (50%)

2OA.5. Bronchiectasis and other imaging changes on thoracic computed tomography (CT) in adult cystic fibrosis (CF) patients in North Macedonia

Sonja Momchilovikj[1,2,3,4]

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Background/Aims:

Most common complication of the lungs in patients with CF are bronchiectasis. If untreated, there will be frequent haemoptysis, significant decline in the lung function and chronic colonization of many opportunistic bacteria.

Methods:

We have monitored 25 adult CF patients (13 male and 12 female) in the Center for CF in the Institute for respiratory diseases in children in Skopje, Republic of North Macedonia. They were divided into younger group (gr.) 17-27 years old (8 patients or 32%), and older gr. 28-45 years old (17 patients or 68%). Spirometry, thoracic CT, sputum samples, occurrence of haemoptysis were analyzed in the period of 1 years (from January to December 2021).

Results:

On thoracic CT we have found bronchiectasis: tubulo-cystic 5 (62%) in younger gr, 9 (53%) in older gr.; cylindrical and saccular 3 (18%) in older gr.; cystic in 2 (25%) in younger gr., 3 (18%) in older gr. Impacted mucus in 6 (35%) in older gr.; hilar and mediastinal lymph nodes in 3 patients (37%) in younger gr. and 7 patients (41%) in older gr.; nodular changes in 2 patients (25%) in younger, 6 (35%) in older gr.; tree in bud in 5 (29%) in older gr.; milk glass-attenuation in 8 patients (4 per group), emphysematous bulls in one older patient. From sputum samples Pseudomonas aeruginosa was isolated in 3 (37%) younger patients, and 9 (53%) in older gr., MRSA-Methicillin-resistant Staphylococcus aureus 2 patients (25%) in younger gr., and one older patient. Both bacteria were found in 2 (25%) in younger and 5 (29%) in older gr. Staphylococcus aureus was found in 2 patients (28%) in older gr. In one younger patient Burkholderia cepacia was isolated. The mean value of the best FEV1 in younger group was 75.3% and 54.3% in older gr. In 2021, mild hemoptysis has occurred in 2 patients (1 per group).

Conclusions:

 Due to frequent pulmonary exacerbations, improper airway clearance, progression of the disease with hemoptysis, we found decline in lung function and chronic colonization of bacteria, with more severe radiological changes in elderly patients.

2OA. 6. Eosinophil Peroxidase is a Proteomic Marker of Bronchiectasis Disease Severity.

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Background/Aims:

Historically, bronchiectasis has been regarded as an exclusively neutrophilic disease; however, recent evidence highlights that ~20% of bronchiectasis patients show evidence of eosinophilic inflammation. While the likelihood of an eosinophilic endotype of bronchiectasis is becoming increasingly apparent, this newly recognised disease endotype has not yet been fully investigated and details regarding a link to disease severity are currently unclear. If eosinophil-targeted therapies (such as inhaled corticosteroids and anti-IL-5 biologics) are to be used in the treatment of bronchiectasis, evidence that eosinophilic inflammation contributes to disease severity and pulmonary exacerbations is important.

As such, the aim of this study was to investigate the link between eosinophilic inflammation and bronchiectasis disease severity.

Methods:

Sputum proteomics was performed in three bronchiectasis patient cohorts from Dundee, UK. Specifically, cohort 1 included patients stratified as 'severe' or 'mild' based on Bronchiectasis Severity Index (BSI), cohort 2 included bronchiectasis patients hospitalised for acute exacerbation and prescribed 14 days intravenous antibiotics, and cohort 3 included clinically stable bronchiectasis patients. Sputum protein profiling of spontaneous sputum was performed using a label-free shotgun proteomic workflow with liquid chromatography-tandem mass spectrometry and proteomic data for key eosinophil inflammatory proteins, Eosinophil Peroxidase (EPX), Major Basic Protein (MBP), Eosinophil Cationic Protein (ECP), Eosinophil-derived Neurotoxin (EDN) and Charcot-Leyden Crystal protein (CLC) were analysed for relationships with key clinical parameters. Data is presented as logged values of peptide intensity.

Results:

40 patients (cohort 1; mild = 20, severe = 20), 20 patients (cohort 2) and 41 patients (cohort 3) were included for analysis. Eosinophil proteins were identified in sputum across all three cohorts, indicating eosinophilic inflammation is present within bronchiectasis patients. Of the eosinophil proteins measured, EPX specifically was significantly elevated in severe disease compared with mild disease ($p = 0.036$, t-test, **Figure 1A**). Furthermore, relationships between EPX and clinical parameters including exacerbations ($p=0.0317$, t-test), severe exacerbations requiring hospitalisation ($p = 0.0098$, t-test, **Figure 1B**) and MRC dyspnoea score ($p = 0.018$, ANOVA) were observed. Correlation analysis confirmed EPX as an eosinophil-specific inflammatory marker, with no correlations observed between EPX and key neutrophilic inflammatory markers including neutrophil elastase ($r = 0.11$, $p = 0.50$, Pearson), azurocidin-1 ($r = 0.19$, $p = $

0.24, Pearson) and myeloperoxidase (r = 0.17, p = 0.29, Pearson). Proteomic data obtained from cohort 3 highlighted that eosinophil protein levels were unchanged following antibiotic treatment.
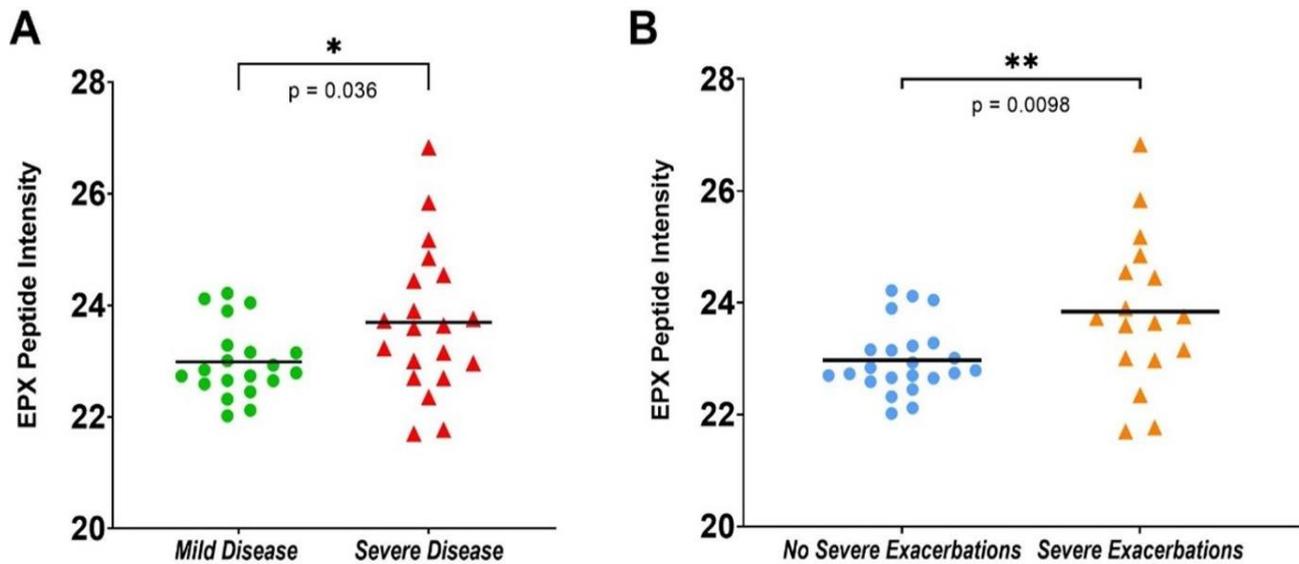
Conclusions:

Eosinophilic inflammation is present within bronchiectasis airways, as confirmed by sputum proteomics, and EPX is associated with bronchiectasis disease severity.

Conflict of interest(s):

This is an encore abstract of 'Proteomic Markers of Eosinophilic Inflammation and Bronchiectasis Disease Severity' due to be presented via poster at the American Thoracic Society Conference 2022.

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2OA.7. Aetiology and Clinical Characteristics of Non-CF Bronchiectasis Cohort in a Middle Eastern Population

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Background/Aims:

Bronchiectasis is a common airway disease characterized by airway dilatation and recurrent infections, leading to respiratory failure in severe cases. It is well known that the aetiology of bronchiectasis varies geographically. However, there is no published data looking at the aetiology of bronchiectasis within the middle eastern population.

Methods:

We performed a retrospective analysis of our bronchiectasis patient register. In particular, recording the clinical and demographic characteristics from their electronic medical records. Quantitative variables are expressed as the median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages. Statistical comparisons between continuous characteristics were carried out using the t-test, and a significant p-value was taken to be less than 0.05.

Results:

In total we analysed 261 records (63% female, 37% male), with a median age of 58 years (IQR 38-71), BMI 25.8(IQR 22-30), FEV1% 65 (IQR 43-79) and FEV1/FVC 76% (67-86).

A total of 93 cases (35.6%) were post-infectious in aetiology (including post-tuberculosis, 28 patients). 55 (21.2%) patients were labelled idiopathic, while PCD was the third most common aetiology with 23 (8.8%) of cases. The breakdown of aetiology is shown in table1 and figure 1.

Pseudomonas was the most common colonizing organism, followed by Haemophilus influenzae and Methicillin-sensitive Staphylococcus aureus. At the time of review, 10 patients had died (median age FEV% and BSI 59,38 and15.5 respectively), all due to respiratory failure, and as expected, all were classed severe on BSI. BSI was available for 109 patients, of which 31(28%) were classed mild, 29(27%) were moderate, and 49 (45%) were classed severe. The median bronchiectasis severity index (BSI) score was 8 (IQR 4-11). On dividing the patients according to obstructive vs restrictive spirometry, we found that patients with FEV1/FVC < 70% had significantly higher BSI (10.1 vs 6.9, p = 0.001) and that 8 out of the 10 deceased patients had FEV1/FVC < 70%.

Conclusions:

In our cohort, post-infectious aetiology seems the most common, with tuberculosis accounting for almost a third of these cases. Unexpectedly PCD appeared to be the 3rd commonest aetiology after post-infectious and idiopathic. Patients with obstructive spirometry seemed to have a worse prognosis than those with restriction.

Table 1: Baseline characteristics

Column1	n	median	(IQR)
Age	261	58	(38-71)
BMI	261	25.8	(22-30)
FEV1%	226	65	(43-79)
FVC%	226	69	(50-82)
FEV1/FVC	226	76	(67-86)
BSI score	109	8	(4-11)

Table 2: Etiology

aetiology	n	%
Post-infectious	93	35.6
Idiopathic	55	21.1
PCD	23	8.8
COPD	21	8.0
Sinobronchial disease	15	5.7
ABPA	12	4.6
CTD	9	3.4
GERD	9	3.4
Immunodeficiency	8	3.1
Others	7	2.7
Aspiration	3	1.1
Rheumatic disease	3	1.1
NTM	3	1.1

Table 3: Bacterial colonization

	n	%
Pseudomonas	85	32.6
H influenzae	24	9.2
MSSA	18	6.9
MRSA	10	3.8
Stenotrophomonas	3	1.1

2OA.8. Rates of Pseudomonas aeruginosa in bronchiectasis patients on long-term ventilation

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Background/Aims:

Bronchiectasis unrelated to Cystic fibrosis (NCFB), is a chronic disease characterised by infective exacerbations. *Pseudomonas aeruginosa (Pa)* is a significant pathogen, increasing both morbidity and mortality. Meta-analysis has previously recorded *Pa* rates in NCFB at 21.4%. National UK guidelines recommend sputum surveillance for *Pa*, and eradication with long term inhaled antipseudomonal antibiotics (i.e. nebulised colistin) or long-term macrolides. Home long-term ventilation (LTV) services manage a diverse number of conditions that cause respiratory failure, including bronchiectasis.

Methods:

Retrospective observational study in a regional LTV population (837 patients), covering North East England and Cumbria, UK. Patients with NCFB were identified via the regional LTV database. The primary outcome was *Pa* isolation. Electronic medical records were accessed recording: *Pa* isolate positive, *Pa* isolate positive in last 24 months, co-pathogens isolated, body mass index (BMI), bronchiectasis aetiology comorbidity index score (BACI), percentage predicted forced expiratory volume (FEV_1), presence of tracheostomy, requirement for long-term oxygen therapy (LTOT) or ambulatory oxygen therapy (AOT) and 1 year mortality rates. LTV support was defined as receiving non-invasive ventilation (NIV) or cough assist.

Results:

Common LTV indications were chronic obstructive pulmonary disease (25%), obesity hypoventilation syndrome and/or obstructive sleep apnoea (19%) and motor neurone disease (6%). 2% of the LTV population received LTV for NCFB (n=17) with mean age 65.7 years, male: female 8:9. Mean BMI 24.3, mean percentage predicted FEV_1 42% and mean BACI 4.4. LTOT was prescribed in 10 patients, none had AOT. Mean time on ventilation was 993 days. One patient was managed on a cough assist device only, 2 patients on dual (cough assist with nocturnal NIV). The remaining 14 patients were managed with nocturnal NIV.

58.8% (n=10) were culture positive for *Pa*. 9 patients (90%) with *Pa* isolates were *Pa*

culture positive before commencing long-term ventilation. The patient who develop *Pa* whilst ventilated had positive isolates after 15 months of NIV. 41.2% of patients were *Pa* positive within the last 24 months. No patients had tracheostomy.

Within the *Pa*

positive cohort the following co-pathogens were isolated (n = number of patients): *Haemophilus influenzae* (n=6), *Streptococcus pneumoniae* (n=5), *Candida* (n=4), *Serratia marcescens* (n=4), *Acinetobacter species* (n=3), *Moraxella catarrhalis* (n=3), *Klebsiella pneumoniae* (n=3), *Proteus Species* (n=2) *Staphylococcus aureus* (n=2), *Stenotrophomonas maltophilia* (n=2), *Enterobacter cloacae* (n=2), *Aspergillus* (n=1) and other diverse bacteria pathogens (n=1).

One year mortality rate was 24% (2 *Pa* positive patients and 2 who had not isolated *Pa*). There was no significant difference (p>0.05) in age, BMI, % predicted FEV_1, and BACI score between the *Pa* isolate positive group and those without *Pa*.

Conclusions:

Bronchiectasis is an infrequent indication for LTV. In this cohort *Pa* is common (58.8%) but not universal. The *Pa* rate likely reflects disease severity, supported by the following data: a wide range of co-pathogens cultured, high frequency of LTOT and mean BACI score indicating 'intermediate risk' (estimated 5 year mortality 11.7%). 1 year mortality rates were significantly higher (24%) suggesting the BACI score may have limited validity within the LTV NCFB.

2OA.9. Multimorbidity in bronchiectasis: a systematic scoping review

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Background/Aims:

Multimorbidity, the coexistence of two or more chronic conditions, has been extensively studied in certain diseases i.e. COPD, but to a lesser extent in non-CF bronchiectasis (NCFB). Significantly, prognostic tools such as the Bronchiectasis and Comorbidity Index incorporate comorbid conditions into their design. We performed a systematic scoping review; summarising the existing literature and identifying gaps.

Method:

A systematic literature search of the electronic databases PubMed, CINAHL, and EMBASE was conducted, performed from inception to end of January 2021. Broad search terms and boolean operators were employed. The studies included were observational, interventional, qualitative, randomised control trials and systematic reviews. The main objective was to identify the prevalence, prognosis, quality of life (QoL) and management of NCFB multimorbidity. The review followed the PRISMA guidelines with key findings analysed descriptively.

Results:

40 studies (200,567 patients) reached the inclusion criteria. Study size ranged from 25 to 57,576; mean age range 30 - 69 years. The majority (68%) were cohort studies. 70% investigated the prognosis of comorbidities and 68% prevalence. 70% analysed multiple comorbidities in NCFB. The most frequent evaluated were COPD (58%), cardiovascular disease (53%) and asthma (40%).

Multimorbidity in BR is common, an international cohort study reported medium number of comorbidities as 4 (IQR= 2-6) (males: females 4: 3). In this scoping review the most prevalent multimorbidities were COPD (range 7.9% - 65.1%, pooled mean 34.9%) and hypertension (range 1.3% - 54.3%, pooled mean 34.3%). The wide range values potentially reflect study heterogenicity. COPD had higher prevalence (mean 34.9%) than the general population (3-5%). Prevalence did not reflect breadth of research; for instance osteoporosis had a mean prevalence of 18.6% but only analysed in 4 studies.Multimorbidity was associated with increased mortality, exacerbation and hospitalisation rates. A cohort study demonstrated increased mortality with increasing comorbidities (HR= 1.17, CI 95%). The median number of morbidities in survivors was 3 vs. 6 for non-survivors. Included studies found associations between increased mortality and COPD, gastro-oesophageal reflux disease (GORD) and rheumatoid arthritis. Cardiovascular disease was a major cause of mortality (16%); 42% of deaths were from a non-respiratory cause.

Increased risk of hospitalisation at one-year was demonstrated for the following comorbidities: heart failure, COPD, and diabetes (p<0.001, p<0.001, p=0.002 respectively). NCFB with asthma increases exacerbation rates (OR 2.6, 95% CI 1.15-5.88; p=0.021) whereas coexisting GORD was associated with both increased exacerbations (p=0.011), and number of hospitalisation (p=0.022).

Three comorbidities were associated with reduced percentage predicted FEV_1; emphysema (34.2% lower, p<0.01), COPD (12.6% lower, p<0.001), and hiatus hernia (15% lower, p=0.02). RA was also associated with decreased FEV_1 (1.19L vs 0.89L).

There is a deficit of research into symptoms, QoL, interactions and management. HRCT diagnosis is not consistent nor mandated and there is no agreed multi-morbidity screening questionnaire.

Conclusions:

Multimorbidity in NCFB is common and associated with adverse outcomes. To date research has focussed on a limited range of comorbidities, and has neglected the impact of multimorbidity on symptom burden, quality of life, and treatment; future research should concentrate here.

2OA.10. Prevalence of T2-High endotype in adults with bronchiectasis in Ukraine

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Background/Aims:

Although it was assumed that neutrophilic inflammation plays a key role in the pathogenesis of bronchiectasis, recent studies indicate the presence of a contribution of eosinophilic inflammation to the severity and progression of the disease, and, in turn, may be one of the "treatable traits". This study aimed to define the prevalence of the T2-High endotype in adults with bronchiectasis in our study population.

Methods:

Patients with confirmed by the HRCT bronchiectasis without comorbid asthma were included in a cross-sectional monocentric study. Prevalence of patients with a T2- high endotype (defined by the presence of either eosinophils blood count ≥300 cells·µL−1 or FeNO ≥ 25 dpp) during a stable state were reported.

Results:

Among 63 Bx patients (51 years, 71.4% women), 8 patients (12.7%) had comorbid asthma and were excluded from further analysis. Among 55 bronchiectasis patients without asthma enrolled in the cross-sectional study, a T2-high endotype was present in 11 patients (17.5%): seven of them (12.7%) had only FeNO ≥ 25 dpp, four (7.3%) – only eosinophils blood count ≥300 cells·µL−1 and only two patients (3.6%) were positive simultaneously by both markers.

Conclusions:

Among bronchiectasis patients without asthma enrolled in the cross-sectional single-center study, a T2-high endotype was defined in 17.5% of them. This rate is lower than in previously published studies which could be explained by the monocentric design of all studies and potential geographical diversity, as well as fewer observations in our study. Nevertheless, further multicentric with larger population studies are needed to assess T2-high endotype as a "treatable trait" in bronchiectasis patients and for the personalization of management.

2OA.11. Prevalence of eosinophilia in two cohorts of bronchiectasis patients with and without asthma

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Background/Aims:

Bronchiectasis (BE) often co-exists with asthma and has overlapping pathophysiology, symptoms and treatable traits. Recognition of eosinophilic airway inflammation in BE is a potential target for steroid and anti-eosinophilic biological therapy. The prevalence of blood eosinophils ≥300/µl in BE patients without asthma was recently reported at ~20%. (Shoemark, AJRCCM 2022) We aimed to assess the prevalence of eosinophilia in two cohorts of BE patients, with and without asthma, and compare patient characteristics between categories of eosinophilia.

Methods:

We assessed baseline characteristics and blood eosinophilia of two cohorts of patients with bronchiectasis, with and without asthma. The first cohort was made up of 82 patients with combined diagnostic codes of bronchiectasis and asthma retrieved from the Erasmus MC and Franciscus Gasthuis&Vlietland in-hospital electronic clinical records. Both diagnoses were verified through assessment of patients' clinical records and radiographic records. The second cohort was derived from the FORZA study (clinicaltrials.gov NCT03846570) and included 34 BE patients without asthma. In this study cohort, asthma was ruled out by bronchodilator reversibility and/or histamine provocation testing. Eosinophilia was categorised into three groups based on multiple measurements of eosinophil counts in peripheral blood; <100, 100-299, and ≥300 cells/µl. Statistical analysis for categorical differences were performed using Pearson Chi-square and ANOVA testing.

Results:

In the cohort of BE with asthma, 52.4% of the patients had had eosinophilia ≥300 cells/µl. In the cohort of BE without asthma, this share was 20.5%. No differences were observed in FACED score, exacerbations, FEV1, inhaled corticosteroid use, *Pseudomonas aeruginosa* or radiological extension. Small statistically significant differences were observed in mMRC in asthmatic patients and BMI in non-asthmatic patients. For full results see Table 1 and Table 2.

Conclusions:

Data from these cohorts showed high blood eosinophil counts in more than half of the patients with a combined diagnosis of BE and asthma. This percentage seems higher than would be expected based on published eosinophil counts for asthma alone (Benson, ERJ 2022). Among bronchiectasis without asthma, one-fifth fell in the category of high eosinophils, which is compatible with European cohorts. Different eosinophilic groups showed no clear associations with typical factors of BE severity.

Bronchiectasis and asthma (n=82)	Blood eosinophil counts			
Characteristics	<100 cells/μL	100-299 cells/μL	≥300 cells/μL	p-value
No. of subjects	6	33	43	
Age, mean	61.3	65.0	60.6	0.516
Sex %female	50% (3/6)	60.6% (20/33)	51.2% (22/43)	0.693
mMRC, mean	0.67	2.06	1.53	0.033
BMI, mean	22.4	25.0	24.2	0.427
BE aetiology (besides asthma)				
- 'Asthma only'	1/6	8/33	9/43	-
- Post-infectious	1/6	9/33	6/43	-
- Idiopathic	3/6	4/33	3/43	-
- CTD	1/6	2/33	0/43	-
- ABPA	0/6	1/33	12/43	-
- Immunodeficiency	0/6	3/33	6/43	-
- PCD	0/6	1/33	1/43	-
- NTM	0/6	1/33	1/43	-
- GERD/aspiration	0/6	3/33	1/43	-
- Other	0/6	1/33	4/43	-
FACED score, mean	1.67	2.27	2.14	0.702
FACED category:				
- Mild	66.7% (4/6)	60.6% (20/33)	60.5% (26/33)	
- Moderate	33.3% (2/6)	21.2% (7/33)	30.2% (13/43)	0.609
- Severe	0% (0/6)	18.2% (6/33)	9.3% (4/43)	
No. exacerbations/y, mean	1.33	1.24	1.02	0.845
"Frequent exacerbators" (≥2/y)	33.3% (2/6)	21.2% (7/33)	20.9% (9/43)	0.789
FEV1%pred	89.9	72.8	70.0	0.152
FER (FEV1/FVC)	0.69	0.62	0.64	0.419
Sputum Pseudomonas aeruginosa	33.3% (2/6)	27.3% (9/33)	23.3% (10/43)	0.835
Inhaled corticosteroid use	100% (6/6)	87.9% (29/33)	95.3% (41/43)	0.359
Eosinophil count cells/μL, mean	60	140	410	0.004
Total IgE kU/L, mean	171.0	119.8	1034.4	0.056
Inhalation allergy (Positive RAST)	33.3% (2/6)	39.4% (13/33)	60.5% (26/43)	0.133
Radiological extension				
- 1-2 lobes affected	33.3% (2/6)	54.5% (18/33)	39.5% (17/43)	0.357
- ≥3 lobes affected	66.7% (4/6)	45.5% (15/33)	60.5% (26/43)	

Table 1. Cohort of patients with bronchiectasis and asthma

Bronchiectasis without asthma (n=34)	Blood eosinophil counts			
Characteristics	<100 cells/μL	100-299 cells/μL	≥300 cells/μL	p-value
No. of subjects	7	20	7	
Age, mean	39.0	54.8	59.3	0.089
Sex %female	85.7% (6/7)	65.0% (13/20)	57.1% (4/7)	0.482
mMRC, mean	1.14	1.25	1.29	0.949
BMI, mean	21.7	23.2	27.1	0.033
BE aetiology				
- Idiopathic	0/7	6/20	1/7	-
- Post-infection	2/7	5/20	2/7	-
- Immunodeficiency	2/7	6/20	1/7	-
- PCD	2/7	1/7	1/7	-
- GERD/aspiration	0/7	0/7	1/7	-
- Other	1/7	2/20	1/7	-
FACED score, mean	0.71	1.50	0.86	0.217
FACED category:				
- Mild	100% (7/7)	75% (15/20)	85.7% (6/7)	
- Moderate	0% (0/7)	25.0% (5/20)	14.3% (1/7)	0.317
- Severe	0% (0/7)	0% (0/20)	0% (0/7)	
No. exacerbations/y, mean	0.71	1.05	1.0	0.834
"Frequent exacerbators" (≥2/y)	28.6% (2/7)	25.0% (5/20)	28.6% (2/7)	0.973
FEV1%pred	86.14	87.45	85.57	0.963
FER (FEV1/FVC)	0.81	0.76	0.71	0.208
Sputum Pseudomonas aeruginosa	28.6% (2/7)	25.0% (5/20)	14.3% (1/7)	0.796
Inhaled corticosteroid use	0% (0/7)	20% (4/20)	0% (0/7)	0.205
Eosinophil count cells/μL, mean	30	150	270	<0.001
Total IgE kU/L, mean	N/A	N/A	N/A	N/A
Inhalation allergy (Positive RAST)	20% (1/5)	16.7% (2/12)	20% (1/5)	0.98
Radiological extension				
- 1-2 lobes affected	71.4 (5/7)	30% (6/20)	57.1% (4/7)	0.121
- ≥3 lobes affected	28.6% (2/7)	70% (14/20)	42.9% (3/7)	

Table 2. Cohort of patients with bronchiectasis without asthma

STROLLING POSTER SESSION 2OB - IN PRESENCE

2OB.1. Sputum Biomarkers and Exacerbations in People with CF

Theodore G Liou[1]; Natalia Argel[2]; Fadi Asfour[1]; Perry S Brown[3]; Barbara A Chatfield[1]; David R Cox[4]; Cori L Daines[5]; Dixie Durham[3]; Jessica A Francis[1]; Barbara Glover[6]; My Helms[1]; Theresa Heynekamp[7]; John R Hoidal[1]; Judy L Jensen[1]; Christiana Kartsonaki[8]; Ruth Keogh[9]; Carol M Kopecky[10]; Noah Lechtzin[11]; Yanping Li[1]; Jerimiah Lysinger[12]; Osmara Molina[5]; Craig Nakamura[6]; Kristyn A Packer[1]; Robert R Paine III[1]; Katie R Poch[10]; Alexander L Quittner[14]; Peggy Radford[2]; Abby J Redway[4]; Scott D Sagel[10]; Rhonda D Szczesniak[15]; Shawna Sprandel[11]; Jennifer L. Taylor Cousar[13]; Jane B. Vroom[1]; Ryan Yoshikawa[7]; John P Clancy[15,16]; J Stuart Elborn[17]; Olivier Kenneth[18]; Frederick R Adler[1]

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Background:

Airway inflammation promotes bronchiectasis and lung injury in cystic fibrosis (CF). Amplification of inflammation underlies pulmonary exacerbations of disease. We hypothesized that sputum inflammatory biomarkers provide explanatory information on the pathophysiology underlying pulmonary exacerbations.

Methods:

We randomly selected stable adolescent and adult patients who were able to produce sputum from nine CF care centers in the Mountain West CF Consortium in the western United States. We collected sputum, measured potential biomarkers of inflammation and prospectively observed time to next exacerbation, our primary outcome. We evaluated relationships between biomarkers, clinical characteristics and outcomes and assessed clinical variables as potential confounders or mediators of explanatory models. Adjusting for confounders and excluding mediators, we assessed associations between the markers and time to next exacerbation using proportional hazard models.

Results:

We enrolled 114 patients [December 8, 2014 to January 16, 2016; 46% male, mean age 28 years (SD 12), mean percent predicted forced expiratory volume in 1 s (FEV_1%) 70 (SD 22)], collected data on clinical variables and measured 24 inflammatory markers from expectorated sputum. All patients had complete follow up to the next pulmonary exacerbation following enrollment, and collectively were representative of the US population with CF.

Half of measured inflammatory markers were plausibly associated with time to next exacerbation. Age, sex and number of prior exacerbations were considered to be confounders and included in proportional hazards modeling of time to next exacerbation. FEV_1% was associated with time to next exacerbation by proportional hazards modeling and was also associated with multiple biomarkers in univariable linear regressions. These findings indicate that FEV_1% is a likely mediator between biomarkers and exacerbation; thus, it was excluded from models. Diabetes status, weight-for-age *z*-score and status of *Pseudomonas aeruginosa* and *Staphylococcus aureus* infections were not clearly confounders or mediators and were excluded.

Three biomarkers of receptor for advanced glycation end products (RAGE) axis inflammation were associated with time to next exacerbation (extracellular newly identified RAGE Hazard Ratio [HR] = 1.35, p = 0.004, soluble RAGE HR = 1.23, p = 0.21). Six biomarkers of neutrophil activity with associations with time to next exacerbation included two indicators of protease activity (neutrophil elastase, HR = 1.19, p = 0.022, matrix metalloproteinase 9, HR 1.20, p = 0.04) and one indicator of reactive oxygen species (myeloperoxidase, HR = 1.30, p = 0.008).

Sensitivity analyses showed that anti-inflammatory treatments including corticosteroids and antibiotics had no significant independent associations nor interactions with the biomarkers in proportional hazards models of time to next exacerbation. The timing of the study meant only 7 patients were using a CFTR modulator, ivacaftor, but no effect of ivacaftor was detected in the models.

Conclusions:

Pulmonary exacerbation biomarkers are part of the RAGE proinflammatory axis or reflect neutrophil activity, specifically implicating protease and oxidative stress injury. Anti-inflammatory treatments and CFTR modulator use in a few patients had no effect on these associations. Development of novel anti-inflammatory agents should consider RAGE axis, protease and oxidant stress antagonists.

2OB.2. Assessing Severity of Chronic Obstructive lung disease (COPD) Using CAT score among high altitude residents of Nepal.

Anusmriti Pal[1]; Manoj Kumar Yadav[2]; Tula Krishna Gupta[1]

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Background/Aims:

The goal of this study was to see if the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT) score was beneficial in determining the severity of COPD patients. It is simple and quick for patients to complete, and it produces a score that reflects the impact of the condition on their health status among Nepalese inhabitants living at high altitudes, as well as looking for the causal elements connected with early and better disease control. GOLD guideline (2013) recommends CAT above other respiratory questionnaires since it is regarded to be a better assessment tool.

Methods:

This was a 6-month cross-sectional study that began in March 2020. All COPD patients who presented to Karnali Academy of Health Sciences in Jumla, Nepal with an acute exacerbation characterized by two out of three symptoms (change in sputum colour, increased shortness of breath, or increased cough) were included. During the admission time, a validated CAT questionnaire in the local language (Nepali) was employed and completed by the patient or patient party. Based on the impact level, the total CAT score was calculated and grouped into four groups. Data were evaluated using descriptive statistics (such as percentage and mean) and Pearson's correlation tests to compare means.

Results:

Considering all 55 patients included in this study 52.7 % were females and all had firewood exposure (100%), in addition to current smoking history which was present more in the high impact group (0.5%). The median number of exacerbations of COPD at 3 months was 2 (Range: 0 – 90) with a median CAT score of 30 (Range: 17 – 37). Based on the individual CAT scores, the patients were categorized into different severity groups. Almost half (47.3 %) were in the high impact group whereas none lay in low impact. The median number of exacerbations was significantly higher in the "very high impact" group compared to other groups (5 vs. 2 and 0, P <0.001). Use of medication was also significantly higher in the "very high impact" group, with significant use of inhalers in form of salbutamol or long-acting bronchodilators in combination with steroid.

Conclusions:

 CAT is a dependable exacerbation severity score that is higher in frequent exacerbates. The "extremely high impact" group had a considerably higher median number of exacerbations than the other groups (5 vs. 2 and 0) respectively with p<0.001. As a result, as a simple tool, it might be utilized in clinical practices in resource-constrained environments like ours to monitor changes in patients' general health status and treatment effectiveness, as well as assist governments in allocating health resources appropriately.

2OB.3. Characteristics of adult PCD patients: a single-center experience.

Chrysavgi Kosti[1]; Antonia Digalaki[1]; Vasilios Tzilas[1]; Sofia Koukidou[1]; Ioannis Tomos[1]; Georgios Hillas[1]; Serafeim Chrysikos[1]; Emmanouela Zervou[1]; Katerina Dimakou[1]

[1]5th Respiratory Department, "Sotiria" Chest Diseases Hospital, Athens, Greece

Background/Aims:

Primary ciliary dyskinesia (PCD) is a heterogeneous genetic disease characterized by motile ciliary dysfunction. Data on adult population remains limited. We herein aim to report the clinical and radiological features of a Greek PCD cohort.

Methods:

We reviewed retrospectively clinical and laboratory information of adult PCD patients from a single reference center for bronchiectasis. Chest HRCTs were scored for bronchiectasis morphology, distribution and associated findings.

Results:

15 PCD patients were studied. Mean (±SD) age was 38 (±18.8), 60% were female and 67% were never-smokers. One third of patients were diagnosed during adulthood. Common clinical features included sinusitis (93.3%), chronic productive cough (86.7%), otitis (33.3%) and fatigue (33.3%). Mean FVC and FEV1 (%pred) were 77.5 (±19.4) and 72.5 (±22.8) respectively. 14 patients isolated at least one pathogen in sputum culture with a high prevalence of pseudomonas aeruginosa (PA) (80%). Analysis of the BSI score revealed mild disease severity in 50%, while severe disease was reported in 21.4%. Mean BSI was 4.6 (±3.2). According to HRCT, all patients exhibited bronchiectasis in ≥3 lobes sparing of apices. Mean Reiff score was 8.7 (±2.7). The most common additional finding was tree-in-bud (86.7%), while situs inversus was identified in one third of patients. Furthermore, we noticed middle lobe cicatrisation atelectasis in 40%. Interestingly, this feature was observed in 80% of patients with chronic PA infection.

Conclusions:

This cohort broadens the clinical and imaging features of adults with PCD. Chronic PA infection may relate to permanent radiological abnormalities.

2OB.4. Genome sequencing reveals underdiagnosis of primary ciliary dyskinesia in bronchiectasis

Amelia Shoemark[1]; Helen Griffin[2]; Gabrielle Wheway[3]; Claire Hogg[5]; Jane S Lucas[3]; Carme Camps[4]; Jenny Taylor[4]; Mary Carroll[3]; Micheal Loebinger[5]; James D Chalmers[1]; Hannah Mitchison[6]; Anthony De Soyza[2]

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Background/Aims:

Bronchiectasis can result from infectious, genetic, immunological and allergic causes. 60-80% cases are idiopathic, but a well-recognised genetic cause is the motile ciliopathy, primary ciliary dyskinesia (PCD). Diagnosis of PCD has management implications including addressing co-morbidities, implementing genetic and fertility counselling and future access to PCD-specific treatments. Diagnostic testing can be complex, however PCD genetic testing is rapidly moving from research into clinical diagnostics and would confirm the cause of bronchiectasis.

Methods:

This observational study used genetic data from bronchiectasis patients recruited to the UK 100,000 Genomes Project and referred for gene panel testing within a tertiary referral centre for PCD and bronchiectasis, as well as data accessed from the British Thoracic Society audit, to investigate whether motile ciliopathies are underdiagnosed in people with bronchiectasis in the UK. Patients referred for genetic testing due to clinical suspicion of PCD were excluded from analysis.

Results:

Pathogenic or likely pathogenic variants were identified in motile ciliopathy genes in 17/142 (12%) individuals by whole genome sequencing. This incidence replicates that of a single centre with access to pathological diagnostic facilities, where 5-10% patients received a PCD diagnosis by gene panel, often linked to normal/inconclusive nasal nitric oxide and cilia functional test results. In 4,898 audited patients with bronchiectasis, <2% were tested for PCD and <1% received genetic testing.

Conclusions:

PCD is underdiagnosed as a cause of bronchiectasis. Increased uptake of genetic testing may help to identify bronchiectasis due to motile ciliopathies and ensure appropriate management.

2OB.5. Development and first results of the BEAT-PCD international Primary Ciliary Dyskinesia gene variant database: CiliaVar

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Background/Aims:

Primary Ciliary Dyskinesia can be diagnosed by bi-allelic pathogenic mutations in one of >50 ciliary genes. ~60% of patients with an identified genetic cause have private mutations not previously reported in another patient. Increasing numbers of variants of unknown significance (VUS, i.e. unknown if they are pathogenic) are identified. As clinical genetic testing is increasingly used for PCD, there is a need to develop a public access resource to identify if variants have previously been reported to be associated with disease.

Our aim was to establish an online open database registering gene mutations and specific combinations of variants causing PCD.

Methods:

A panel of clinicians and geneticists with expertise in PCD identified database fields to link each variant with the associated diagnostic, clinical and genetic evidence supporting pathogenicity. A literature search was conducted to identify published mutations causing PCD. PCD cohort genetic data was entered from 4 pilot genetics centres (London UK, Oslo Norway, Southampton UK and East Jerusalem Palestine). Database curators checked mutation nomenclature and classification of variants was carried out following ACMG guidelines.

Results:

624 papers were identified. Following abstract review 235 papers yielded 1,282 PCD patients. Additionally, 466 PCD cases from a diagnostic centre were entered to pilot the database. 1424 mutations were included in CiliaVar. The majority of mutations (52%) were in 4 genes DNAH5, DNAH11, CCDC39, CCDC40. The most common variants reported are CCDC40: c.248del and DNAI1: c.48+2dupT. 21% of the distinct variants are classified as VUS.

Conclusions:

The online open database CiliaVar will be published as an online open access database in September and will improve access to PCD variant information to improve the diagnosis of PCD

2OB.6. QTc interval prolongation in NTM disease treatment with Azithromycin

Francesco Bindo[1]; Sofia Misuraca[1]; Tommaso Pilocane[1]; Federica Bellino[1]; Margherita Ori[1]; Andrea Gramegna[1]; Luigi Ruffo Codecasa[2]; Maurizio Ferrarese[2]; Francesco Blasi[1]

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Background/Aims:

Nontuberculous mycobacteria (NTM) represent over 190 species and subspecies, some of which can produce disease in humans with underlying conditions and can affect both pulmonary and extrapulmonary sites. Treatment of NTM pulmonary disease varies depending on the species, extent of disease, drug susceptibility results, and underlying comorbidities. Regimens require the use of multiple antimicrobial agents that are often associated with clinically significant adverse reactions and must be administered for prolonged periods. Some NTM drugs, such as azithromycin, might cause delayed ventricular repolarisation, measured by QT prolongation, and predispose the miocardium to re-entrant tachycardias, as torsades-de-pointes, possibly leading to sudden death.
The use of azithromycin is a source of concern in patients with congenital long QT syndrome. In these patients the proper treatment of NTM lung disease might be difficult.

Methods:

Report.
We treated two patients with congenital long QT syndrome and lung disease secondary to Mycobacterium avium complex following the standard regimen (Rifabutin, Ethambutol and Azithromycin for 18-24 months). The patients concluded the treatment without major events after a close follow up.

Results:

Case presentation.
1.   In January 2021 a 70-year-old woman was prescribed with rifabutin (Rbt) 450mg/die, ethambutol (E) 1200mg/die and azithromycin (Azm) 500mg three times a week s econdary to the isolation of m. avium on bronchoalveolar lavage along with signs of radiological progression at the concomitant CT-scan. The patient has suffered from long QT syndrome since 2000. An electrocardiogram with QT calculation was performed every month. Due to gastric intolerance, azithromycin was discontinued after about 2 months and clofazimine was started.
In March 2021 , therapy was suspended due to QT prolongation up to 500 msec and the patient resumed after 15 days with a modified regimen of three times a week. In July 2021, the patient was hospitalized for tako-tsubo syndrome and QT prolongation and antimycobacterial therapy was suspended. A sputum for mycobacteria was performed with negative results.

2. In XXX 2020 a 65 -year-old woman was diagnosed with a MAC lung disease and started with RbtAzmE. She was affected by congenital long QT syndrome associated with a causative mutation in the KCNQ1 gene. Considering the increased risk of cardiac event, the patient underwent a close monitoring with ECG and cardiological evaluations. During the treatment, AZT was well tolerated and after 18 months sputum samples were repeatedly negative for NTM.

Conclusions:

This is the first report of patients with congenital long QT syndrome and NTM lung disease treated with drugs that could prolong the QT interval. Patients with congenital or acquired (?) long QT syndrome can be safely candidate for standard NTM treatment including AZT. The multidisciplinary approach to cardiac and pulmonary outcomes should include close ECG monitoring and discontinuation or modification of the standard therapy as soon as QT values increase.

2OB.8. Feasibility of implementing innovative airway clearance technology at home by telecare in patients with non-cystic fibrosis bronchiectasis

Marlene Murris-Espin[1]; Sylvie Leroy[3]; Marine Mahot[4]; Raphael Abouly[4]; Hughes Gauchez[5]; Sophie Jacques[6]; Jean-Christian Borel[4]; Eloise Joffray[4]; Nathalie Arnol[4]; Laurent Morin[7]; Rebecca Hamidfar[2]

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Background/Aims:

Mucociliary clearance is a cornerstone of management of patients with Non-Cystic Fibrosis Bronchiectasis (NCFB) but regular access to chest physiotherapy facilities can be limited. Easy-to-handle airway clearance device (ACD) could provide patients with homecare bronchial drainage. We hypothesized that telecare could allow efficient remote training and set up of an innovative ACD (SIMEOX, PhysioAssist) in NCFB patients and promote its stand-alone use at home.

Objectives of the study: Primary outcome was to evaluate the 3-month ACD therapy self-adherence (% of patients with an average of 3 or more ACD sessions/week during study follow-up) of NCFB patients after remote training. Secondary outcomes were to assess the feasibility, clinical efficacy, patient satisfaction and safety of combined ACD+telecare solution.

Methods:

Multicentre, prospective, open-label study: An ACD (SIMEOX) was delivered to each patient during inclusion visit at investigative sites for homecare therapy; training in ACD use was carried out remotely with physiotherapist (PT) by telecare (2-5 training sessions during the first two weeks). Thereafter, the PT called the patient every 10 days for motivational reinforcement and collecting any side effects. Adherence was reported on diary card (self-adherence) by patients and transfered on data server via bluetooth tablet (web)

Results:

22 NCFB patients with chronic mucus hypersecretion (CMH) were included: 59% female; age 52(18) years; never smoker 52%; FEV1 74.0(21.8)%; BSI 6.5(3.5), PA colonization 48%; ≥ 3 lobes or cystic bronchiectasis 86%. Etiology: Idiopathic 32%; Post-infective 16%; PCD 16%; ABPA 16%; COPD 5%; others 16%. Comorbidities: Chronic Rhinosinusitis 52%; Asthma 23%; Nasal polyps 11%; COPD 9%; Diabetes 5%; CVD 5%; anxiety/depression 18%.

ITT analysis: 14 patients (64%) were self-adherent (PP+web adherence: 17 patients, 81%). Mean self-adherence of cohort was 3.6(2.3) ACD sessions/week and remained stable over time. After 3 months of therapy, respiratory function did not change but symptoms and quality of life improved: CAT score= -4.2 points; 95%CI [-7.3 ; -1.2], p=0.009; SGRQ-QoL= -6.5; 95%CI [-11.4 ; 1.6], p=0.012, QoL-B-vitality: +0.8 point 95%CI [0.1 ; 1.5], p=0.019 ; QoL-B-social functioning: +1.0 point; 95%CI [0.1 ; 1.9], p=0.038. Patient satisfaction was rated at 8.9 [8.0 ; 10.0] on a 10-points VAS.

4 patients were hospitalized for pulmonary exacerbation but only one stopped ACD therapy temporarily (48h). Few non-serious side effects were reported (4 blood in phlegm, 3 chest pain, 1 GERD), most of them were occasional and resolved rapidly (1-2 weeks) with no discontinuation of therapy.

Conclusions:

NCFB patients with CMH have a high level of adherence to SIMEOX HomeCare therapy and very high satisfaction for its use combined to telecare. This solution seems to be safe and efficient to improve airway clearance. Clinical effectiveness of this procedure in NCFB must be evaluated in a RCT.

Conflict of interest(s):

Physio-Assist was the sponsor of the study

STROLLING POSTER SESSION 2V – VIRTUAL

2V.1. Assessing quantitative PCR method in determining P. aeruginosa bacterial load: Correlation with clinical endpoints in bronchiectasis patients (iBEST study)

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Background/Aims:

In studies that aim to evaluate the efficacy of antibiotics in the treatment of bacterial infection, the reduction in the load of the key pathogens of interest in sputum is usually reported. Although microbial culture is considered the gold standard for quantifying and identifying pathogens in clinical samples, molecular methods, e.g. quantitative PCR (qPCR), can offer a helpful alternative "microbiological endpoint" that can be used in the assessment of antimicrobial agents in clinical trials. First, however, the validity of qPCR as a clinical endpoint needs to be investigated.

Aim: To assess the use of qPCR as a surrogate to the culture-based method and to correlate the effect of change in *Pseudomonas aeruginosa* (PA) load quantified via qPCR with clinical parameters in response to treatment with tobramycin inhalation powder (TIP) in bronchiectasis patients.

Methods:

Sputum samples (n=609) from 105 patients, aged 19-86 years, collected during the iBEST trial were processed. Patients received TIP in three different dosing regimens [3 capsules OD (each containing 28mg of TIP) (84mg-Cohort A), 5 capsules OD (140mg-Cohort B), and 4 capsules BID (224mg-Cohort C)] in a continuous or cyclical regimen, over six months period. The total bacterial load of PA was assessed by quantitative PCR (qPCR) targeting the *opr*L gene. Kruskal-Wallis test was used to compare continuous variables across the groups. The Spearman's rank correlation coefficient (r) was used to measure the association between PA load and continuous variables (e.g. lung function as per cent of predicted FEV1 (ppFEV1) and inflammatory biomarkers).

Results:

Overall, there was a strong positive correlation between methods (e.g. total PA load by qPCR vs. total viable count data (TVC); r=0.74 [p<0.001]). On day 29, there was a significant reduction in the PA load ($\log_{10}$ *oprL* copies/ml) in all treatment cohorts (A, B, and C) when compared to the pooled placebo group (p<0.0001), which corresponded with the TVC data, indicating the efficacy of TIP. There was a significant negative yet weak correlation between ppFEV1 and PA load (r=-0.14, p<0.001). There was a significant positive correlation between PA load and a number of different inflammatory markers, such as Elastase (r=0.33, p<0.001), IL-8 (r=0.37, p<0.001), IL-1β (r=0.46, p<0.001) and Calprotectin (r=0.1, p=0.012), respectively.

Conclusions:

The study compared the results of total PA load by qPCR and TVC and demonstrated significant correlations between the two methods. However, while qPCR represents a valuable tool for quantifying bacterial loads in clinical respiratory samples, cultures should be retained as the reference and the routine technique. The results suggest that an increase in the PA load was correlated with a decline in lung function (ppFEV1) and that an increased burden of PA in sputum was associated with elevated levels of markers of inflammation.

2V.2. Phage Cocktail Powders for Pseudomonas aeruginosa Respiratory Infections

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Background/Aims:

To combat respiratory infections caused by multidrug resistant bacteria, there has been resurgent interest in phage treatment. Inhaled phage therapy as a promising alternative to antibiotics for therapeutic use have been demonstrated in animal models and humans. Unlike antibiotics, phages target narrow host range, thereby the use of phage cocktail over a single phage is often encouraged for phage treatment. In this study, we aim to produce a stable and inhalable dry powder formulation of a phage cocktail by spray-drying process.

Methods:

A phage cocktail powder by spray-drying three *Pseudomonas* phages PEV2 (*podovirus*), PEV1 and PEV20 (both *myovirus*) with lactose (80 wt%) and leucine (20 wt%) as excipients has been produced. The viability of phages before and after spray-drying was determined by a standard plaque assay. The physical and chemical property of powders has been measured in sequence.

Results:

Our results showed that the phages remained reasonably stable in the spray dried powder, with a total 1.3 log loss of phage titre in the phage cocktail powder. The powder contained spherical particles with a small volume median diameter of 1.9 μm (span 1.5) and a moisture content of 3.5 ± 0.2 wt%. The powder was largely amorphous with some crystalline peaks, which were assigned to the excipient leucine, as shown in the X-ray diffraction pattern. When the powder was dispersed using the low- and high-resistance Osmohalers, the fine particle fraction (FPF, wt. % of particles < 5 μm in the aerosols relative to the loaded dose) values were 45.37 ± 0.27% and 62.69 ± 2.1% at the flow rate of 100 and 60 L/min, respectively.

Conclusions:

A *Pseudomonas* phage cocktail dry powder comprising two *myoviruses* and a *podovirus* produced is stable, inhalable, and efficacious in *vitro* combating respiratory diseases. This formulation potentially broadens the host range and reduce the occurrence of resistance in bacteria compared with single phage treatment.

2V.3. Phenotypic characterisation of Pseudomonas aeruginosa isolates from people with bronchiectasis following experimental induction of tobramycin resistance

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Background/Aims:

Persistent *Pseudomonas aeruginosa* (PA) infection occurs in ~30% of people with bronchiectasis and is a major cause of morbidity and mortality. In a recent clinical trial of this patient cohort (iBEST-1), tobramycin inhalation powder (TIP) was investigated as a suppressive treatment. The aims of this study were to determine if (1) tobramycin resistance can be experimentally induced in PA isolates from the iBEST-1 trial; (2) resistance occurs simultaneously with changes in multidrug resistance, growth, and virulence; and (3) the same phenotypic changes are observed in PA collected during the iBEST-1 trial.

Methods:

To induce antibiotic resistance, three replicates (i.e. lineages) of three tobramycin-susceptible PA isolates (Minimum inhibitory concentration [MIC] ≤4mg/L) were exposed to increasing concentrations of tobramycin using antibiotic gradient Müller Hinton Agar (MHA) plates for a maximum of 25 passages or until no further increase in resistance was observed (evolved lineages). A control lineage of each isolate was passaged in parallel in tobramycin-free MHA. To determine if resistance was transient, each evolved lineage was then passaged through MHA containing no antibiotic. MICs were determined using the ETEST® method. Susceptibility against a panel of antibiotics was tested using disc diffusion assays. Growth rates and various virulence traits (flagellar motility, mucoidy, pigment production) were compared in the tobramycin-susceptible ancestral isolates and their evolved lineages. For *in vivo* comparison, these features were also compared in matched iBEST-1 trial patient (n=3) isolates which demonstrated a change in susceptibility (susceptible to resistant) under treatment with TIP.

Results:

Passaging resulted in increased tobramycin MICs for all evolved lineages (n=9) with a median increase in the doubling dilution of 32-fold and all 9 evolved lineages were categorised as resistant. Two evolved lineages of one ancestral isolate exhibited transient resistance. No change in MIC was observed for any of the control lineages. In four evolved lineages (two of three lineages from two ancestral isolates), multidrug resistance developed. As resistance evolved, maximum growth rate decreased (Wilcoxon signed rank test, P=0.004), lag time increased (Wilcoxon signed rank test, P=0.004) and flagellar motility decreased (Wilcoxon signed rank test, swimming: P=0.03; swarming: P=0.03). Two ancestral isolates exhibited a mucoid phenotype, which was lost in each of their three evolved lineages. Overall, there was a decrease in

pyocyanin production (Wilcoxon signed rank test, P=0.02) but no statistically significant difference in pyoverdine production (Wilcoxon signed rank test, P=0.1) was found following tobramycin exposure. In two of three cases, similar phenotypic shifts were observed in matched isolates *in vivo*.

Conclusions:

Tobramycin resistance in PA clinical isolates was experimentally induced and resulted in a decrease in growth and virulence factor production. Some within-patient PA isolates which developed resistance following treatment with TIP demonstrated similar shifts in these phenotypes over time. This indicates that the *in vitro* model might be useful to predict changes that occur concurrently in PA with the emergence of resistance in the patient.

2V.4. Rapid molecular detection of bacterial infection and antimicrobial resistance in bronchiectasis

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Background/Aims:

Infection is a crucial component of the vicious vortex of bronchiectasis. Culture based detection of respiratory pathogens is limited by poor sensitivity and slow turnaround time. Polymerase chain reaction (PCR) or point of care metagenomic sequencing techniques have the potential to provide more rapid and sensitive detection of bacterial pathogens. This study evaluated the detection of bacterial pathogens in patients with bronchiectasis.

Methods:

Patients with bronchiectasis were included in a prospective study conducted at a single tertiary centre (Ninewells Hospital and Medical School, Dundee, UK). Sputum or bronchoalveolar lavage (BAL) samples were obtained and underwent three methods of bacterial detection: conventional culture, the BioFire® FilmArray® Pneumonia Plus Panel (PCR method) according to manufacturers' instructions, and host DNA depletion and nanopore sequencing using the Oxford Nanopore Technologies MinION device.

Results:

40 patients were included, with 34 sputum samples and 6 BAL samples. 19 patients had a clinically significant pathogen identified by culture (47.5%). The most frequent pathogens identified by culture were *Haemophilus influenzae* (9), *Pseudomonas aeruginosa* (4) and *Staphylococcus aureus* (3). In contrast, the PCR method detected pathogens in 24 patients (60%) with a turnaround time of 1 hour. The most frequent pathogen detected by the PCR method was *Haemophilus influenzae* (41.6%). No antimicrobial resistance genes were identified using the PCR method. Point of care metagenomics using nanopore sequencing identified clinically relevant bacterial pathogens in 50% of samples. Clinically relevant pathogens identified included *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Haemophilus influenzae.* Also detected were organisms such as *Veillonella parvula* and *Rothia mucilaginosa,* as well as an extensive number of antibiotic resistance genes associated with tetracycline resistance (tetM) and macrolide resistance (ErmB).

Conclusions:

Molecular diagnostics (PCR and point of care metagenomics) are more rapid and more sensitive than conventional culture in detecting bacterial infection in patients with bronchiectasis.

2V.5. Mycobacterium abscessus infection in a patient with second motor neuron disease and chronic respiratory failure

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Background/Aims:

Mycobacterium abscessus complex (MABSC) is a fast growing, multidrug-resistant, non-tuberculous mycobacterium (NTM), which is a common contaminant of soil and water. MABSC is primarily responsible for chronic lung infections and skin and soft tissue infections (SSTI), but can also cause infections in almost all human organs, particulary in immunocompromised patients. Infections caused by *M. abscessus complex* are difficult to treat due to resistance to antimicrobial drugs. We report the case of a 78 year-old man, admitted to the Pneumology Unit of the "Magna Graecia" University of Catanzaro, suffering from second motor neuron disease, tracheostomized and with dysphagia.

Methods:

In order to search for MABSC, a sample of bronchial aspirate was processed in accordance with national and international guidelines using a decontamination procedure with N-acetyl-l-cysteine-NaOH. The sample was inoculated in BACTEC MGIT 960 (Mycobacteria Growth Indicator Tube) liquid medium and in Löwenstein-Jensen solid medium. Cultures were incubated at 37 ° C for 4 to 6 weeks. Ziehl-Neelsen staining was carried out to detect alcohol-acid fast bacilli (BAAR). A molecular genetic assay for the identification and differentiation of *Mycobacterium tuberculosis complex* and 27 clinically relevant NTM was performed using Genotype Mycobacterium CM VER 2.0 (Hain, Germany). The GeneXpert MTB-Rif assay (Cepheid, USA) was carried out to exclude *M. tuberculosis complex* infection.

Results:

Microscopic examination revealed the presence of BAAR. After 6 days, the MGIT culture tube was positive. The molecular genetic assay confermed the presence of *M. abscessus complex*. In addition, the bronchial aspirate was positive for *Candida parapsilosis, Pseudomonas aeruginosa, Enterobacter cloacae, Acinetobacter baumannii complex* and *Candida albicans*. The galactomannan serum concentration was 2.27 (VN < 0,5 index).

Conclusions:

This case report suggests how early and timely diagnosis might help therapy for the eradication of *M. abscessus* in a critically ill patient.

2V.6. Characteristics of patients with bronchiectasis associated with risk for nontuberculous mycobacterial infection

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Background/Aims:

Diagnosis of nontuberculous mycobacterial (NTM) infection in patients with non-cystic fibrosis bronchiectasis disease (NCFBr) can be challenging as the clinical presentation significantly overlaps with classical bronchiectasis symptoms.

Methods:

We conducted a retrospective cohort study between January 2007 and August 2020 of NCFBr patients who underwent bronchoalveolar lavage (BAL) for a pulmonary exacerbation to determine the contribution of NTM infection to the etiology of the exacerbation.

Results:

During the study period, 771 patients with bronchiectasis disease underwent BAL, with 94 yielding positive NTM cultures. As compared to the overall cohort, patients with positive NTM cultures were more likely to be older (OR= 1.16, 95% CI 1.160-1.066, p<0.008), and female (OR= 1.64, 95% CI 1.02-2.62, p=0.04), with lower BMI (OR= 1.11, 95% CI 1.05-1.18, p<0.001) and with comorbidity of GERD (OR= 1.59, 95% CI 1.01-2.50, p=0.04). Comparison of CT chest imaging among the cohort demonstrated a distribution of bronchiectasis in the patients with NTM infection to involve more than one lobe (OR= 2.02, 95% CI 1.23-3.30, p=0.005), with a predominance for upper lobes (OR= 3.41, 95% CI 2.17-5.37, p<0.0001) and the lingula (OR= 1.98, 95% CI 1.27-3.10, p<0.002).

Conclusions:

NCFBr patients experiencing pulmonary exacerbations with one or more characteristics of older age, female gender, low BMI, and upper lobe predominant disease should be evaluated for potential NTM infection.

2V.7. NTM : The Biggest TB Mimic in an endemic country like India

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Background/Aims:

1)To microbiologically confirm the diagnosis of TB and DRTB

2)To differentiate TB from NTM infections before starting on empirical anti tb drugs in an endemic country like india

Methods:

India is the TB Capital of the world. Around 1 person dies of TB every 8 minutes in the country. Still Today in many parts of interiors of the country, many people are started on anti tb drugs without proper microbiological confirmation of the disease. We did this study in a tier 3 city of the country to prove how NTM is often misdiagnosed and treated like TB which might be one of the reasons of increased drug resistance in the country.

This study was performed at shwas chest hospital nanded, Maharashtra, india from a period of 1st july 2021 to 15th march 2022. We performed bronchoscopy on 50 patients who were sputum negative suspected tb but started on empirical anti tb drugs from outside. We sent the BAL fluid for proper analysis and TB culture. We followed up patients with proper reports and treatment.

Inclusion criteria

All patients between age 10-70 who were diagnosed as TB but had no microbiological evidence for it

Exclusion criteria

Patients with microbiological proven TB

Patients with known malignancy and not willing to undergo bronchoscopy

Results:

 In our study we found out that 09 patients out of 50 had NTM infection proven on culture and were misdiagnosed as TB. Out of 11 2 were mycobacterium abscessus, 2 were mycobacterium chimaera, 2 M Gordonea, 2 M Kansaii, and 1 MAC . All of them were stopeed with anti tb drugs and treated with specific drugs indicated to have a almost complete clinical response and radiological resolution

Conclusions:

In a country like India it is very important to microbiologically diagnose and confirm TB as the man made hazard of DRTB is on rampant rise. NTM is the biggest TB Mimic and is often missed . It is very important to use proper diagnostic modalities to confirm diagnosis before initiating patients on anti tb drugs.

2V.8. Describing the Ear, Nose, and Throat symptom burden in a cohort of Australian patients with Primary Ciliary Dyskinesia

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Background/Aims:

Primary Ciliary Dyskinesia (PCD) is a rare, autosomal-recessive disorder of ciliary motility, characterised by chronic rhinosinusitis (CRS), chronic otitis media with effusion (ChOME), infertility, and recurrent upper and lower respiratory tract infections that eventually lead to bronchiectasis. The ear, nose, and throat (ENT) manifestations of PCD typically occur early in life, are variable but persistent, and significantly affect quality of life. Currently, there are no published studies that demonstrate a reduction in ENT symptom burden with PCD treatment, despite almost all PCD patients having sinonasal or otologic complications. The Sino-Nasal Outcome Test (SNOT-22) is a validated patient-reported outcome measure for CRS symptom severity and impact on quality of life, it is routinely implemented at Concord Hospital's multidisciplinary PCD clinic. The mean clinically important difference (MCID) for total SNOT-22 scores has been demonstrated in previously published metrics to be 9 for surgical management and 8 for medical therapy, while MCID values for rhinologic, extra-nasal rhinologic, ear/facial, psychological, and sleep symptom domain scores have been reported as 3.9, 2.5, 3.3, 3.4, and 2.9 respectively. This study aimed to evaluate changes in the SNOT-22 scores of 24 patients with PCD treated at Concord Hospital since 2015, to assess whether optimal multidisciplinary management lead to a reduction in ENT symptom burden.

Methods:

This study was a single site retrospective medical records audit using Concord Hospital's PCD patient database to review the SNOT-22 scores of 24 patients from 2015 to 2022. Each patient's initial SNOT-22 was taken as their "Baseline", and was compared to the average of their recorded SNOT-22 questionnaires following this.

Data were analysed using the Wilcoxon signed-rank test and paired T-tests. All analyses were performed using SPSS software for Mac. A p-value <0.05 was considered statistically significant.

Results:

Baseline: age 29.5 ± 12.9, 46% male, average initial SNOT-22 score of 42.

Significant improvement in SNOT-22 total (9.0 ± 12.4, p<0.001) and domain scores (Rhinologic: 2.5 ± 4.7, p<0.05; Extra-Nasal Rhinologic: 1.2 ± 2.7, p<0.05; Ear/Facial: 1.9 ± 4.1, p<0.05; Psychological: 3.4 ± 5.7, p<0.05; Sleep: 2.0 ± 4.6, p<0.05) were reported. While this surpasses the MCID for SNOT-22 total scores, none of the average domain changes exceeded their respective MCIDs.

Conclusions:

These results confirmed the efficacy of the multidisciplinary treatment approach to PCD, demonstrating that optimal patient management in a multidisciplinary clinic reduces chronic rhinosinusitis symptom burden and leads to a discernible improvement in quality of life. This may be mediated by a 'global' improvement in ENT symptoms, without any particular symptom group experiencing a meaningful change.

2V. 9. Correlation of genotype, phenotype and ciliary ultrastructure in adults with bronchiectasis, suspected primary ciliary dyskinesia (PCD) and inconclusive genetics

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Background and Aim:

Whole exome sequencing (WES) expedites the complex work-up for primary ciliary dyskinesia (PCD) and has gained importance as a front-line diagnostic in addition to clinical phenotype and nasal nitric oxide. It provides an unequivocal genetic diagnosis in about 70% of patients, with the remainder showing variants of uncertain significance (VUS) or variants in novel PCD candidate genes of uncertain relevance. The aim of our study was to correlate genotype, clinical phenotype and ciliary ultrastructure in adults with CT confirmed bronchiectasis, clinical suspicion of PCD and inconclusive WES panel genetics, using transmission electron microscopy (TEM).

Methods:

All patients had two heterozygous or homozygous VUS in established PCD genes or homozygous likely pathogenic variants in PCD candidate genes of uncertain relevance. Ciliated epithelial cells were obtained by nasal brush biopsy of the inferior nasal meatus. TEM was used to evaluate the ciliary ultrastructure, analyzing over 50 cilia cross sections from different cells in each sample. TEM findings were classified as disease defining class 1 (hallmark) defects, class 2 defects that indicate the diagnosis of PCD in combination with other supporting evidence or normal ultrastructure according to *BEAT PCD TEM Criteria*. In addition to visual analysis of TEM, ciliary images were enhanced by the *PCD Detect Software*, which reduces background by averaging ciliary features.

Results:

Overall, 16 patients with VUS in *CCDC40*, *DNAH1*, *DNAH11* and *DNAI1* (n=2, each), *CCDC39, CCDC103, DNAH5, DNAH5/CCDC40* and *DNAH8/HYDIN* (n=1, each) as well as variants in the candidate genes *DNAH7*, *NEK10* and *NME5* (n=1, each) were recruited. Of those, 15 patients had sufficient sample quality in at least one nasal brush biopsy. Normal ciliary ultrastructure was found in 8 patients with VUS in *DNAH1* and *DNAH11* (n=2, each) as well as *CCDC39, DNAH7, DNAH8/HYDIN a*nd *DNAI1* (n=1, each). In 6 patients with VUS in *CCDC40* (n=3) as well as *DNAI1, CCDC103* and *DNAH5* (n=1, each) we identified a corresponding hallmark defect (outer dynein arm defect or microtublar microtubular disorganization +

inner dynein arm defect, respectively). Moreover, a central complex defect indicated clinical relevance of a homozygous variant found in *NME5*.

Conclusions:

Targeted TEM analysis established the definite diagnosis of PCD and provided valuable supporting evidence for the clinical relevance of novel variants, respectively, in 54% of patients with inconclusive WES panel genetics, considering that even pathogenic variants in *DNAH11* are expected to have normal ultrastructure (7 of 13 subjects with evaluable ultrastructure, excluding subjects with VUS in *DNAH11*). The *PCD Detect Software* proved to be a feasible and useful tool in addition to the visual analysis of TEM.

Conflict of interest:

5th
World Bronchiectasis & NTM Conference

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