ERS International Congress 2022: highlights from the Airway Diseases Assembly

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Early View

Review

Research highlights from the 2022 European Respiratory Society International Congress: Airway diseases

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Research highlights from the 2022 European Respiratory Society International Congress: Airway diseases

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Take home message: In this review, recent advances presented at the #ERScongress in Barcelona, from Assembly 5, are reviewed by Early Career Members and leaders in the field. This review focusses specifically on COPD, asthma, bronchiectasis and chronic cough.

Abstract

The European Respiratory Society (ERS) celebrated the return of an in-person meeting in Barcelona, Spain, after two years of virtual congresses. The congress programme was replete with symposia, skills workshops and abstract presentations from all 14 assemblies, encompassing over 3000 abstracts presented in the form of thematic poster discussion and oral presentations. In this article, highlights from this year's congress (including that from thematic poster sessions, oral presentations and symposia from keynote speakers), presented by Assembly 5: Airway diseases, Asthma, COPD and Chronic Cough, are reviewed by Early Career Members and experts in the field, with the aim of presenting key recent findings in the field**.**

Introduction

This year's European Respiratory Society (ERS) International Congress saw the return of the in-person meeting after two years of virtual congresses. The congress, hosted in Barcelona, Spain, featured a plethora of exciting new research findings from all 14 assemblies. Various symposia, skills workshops and abstract presentations facilitated the dissemination of these novel developments. Assembly 5, focusing on Airway diseases, Asthma, COPD, Chronic Cough, was responsible for 507 posters and several brilliant oral presentations, with 276 (54%) presented by early career members. Here, recent advances presented at the Congress from Assembly 5 are reviewed by Early Career Members and leaders in the field. This review focusses specifically on COPD, asthma, bronchiectasis and chronic cough.

Chronic Obstructive Pulmonary Disease (COPD)

Early diagnosis and evaluation of lung function

At the 2022 ERS Congress, several authors and speakers sought to challenge the traditional paradigm of COPD. A conceptual framework of COPD origin has begun to emerge, which diverges from the traditional view of COPD. The traditional view of COPD is considered to be a tobacco smoking-induced disease prevalent in older males and characterised by an age-related accelerated lung function decline [1, 2]. *Stolz et al* presented the recently published Lancet commission: 'Towards the elimination of COPD' [3], highlighting the requirement for a more objective definition of COPD, earlier intervention and consequently more observational studies and randomised clinical trials (RCTs) in young COPD patients and those with pre-COPD [4].

The use of techniques other than spirometry to detect early changes in airway pathophysiology received much attention. A general population study (Lung, hEart, sociAl, body [LEAD],

n=5646) reported that changes in forced oscillometry technique (FOT) parameters, such as abnormal resistance and reactance, are highly prevalent in subjects with preserved spirometry [5]. The use of oscillometry to detect early small airway dysfunction (SAD), characterised using a threshold of the product of resistance at 5Hz minus resistance at 20Hz (R5-R20) of ≥0.07kPa/L/sec, was described in a multicentre cohort of smokers (n=407) with normal spirometry [6]. The product of R5-R20 is considered to represent resistance of the small airways [7]. Fifteen percent of the cohort had detectable SAD, which was associated with worse lung function including spirometric values (forced expiratory volume in 1 second (FEV_1) % predicted = 98.6 *versus* 105%) and higher symptoms scores (total COPD assessment test (CAT) score = 13.4 *versus* 10.8, a maximum score of 40 indicates more severe impact of COPD [8]) compared to those with no detectable SAD ($p<0.01$ for both comparisons). Furthermore, a post-hoc analysis of the COPDgene study observed distinct phenotypes in susceptible smokers using lung volume measurements, with the ability to distinguish between radiographic-defined emphysema and airway disease [9]. A machine learning approach was utilised in an analysis of the Change in Airway Peripheral Tone in COPD (CAPTO-COPD) cohort (n=90) to describe improved diagnostic accuracy of detecting early disease using advanced tidal-breathing lung function testing [10]. The final model, combining spirometry, body plethysmography, transfer factor of the lung for carbon monoxide (TLCO), oscillometry and multiple breath washout (MBW), had an accuracy of 85% ($k = 77\%$, all $p < 0.01$) in differentiating mild COPD patients and former smoking controls at risk of developing COPD from healthy control subjects.

Collectively these studies highlight the utility of advanced lung function testing in the general population or COPD patient groups to improve early identification or better disease management, respectively; with promising developments in oscillometry, supporting more objective characterisation of disease and earlier diagnosis.

Precision medicine and immunopathology

Precision medicine relies on the identification of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish a given patient from others with similar clinical presentations [11], and a number of potential such characteristics were evaluated at the 2022 Congress.

Higher levels of cough and sputum are associated with worse quality of life, accelerated lung function decline, increased exacerbations and mortality in COPD [12]. However, current COPD treatments fail to address these symptoms. A RCT investigating the efficacy of Icenticaftor (an oral cystic fibrosis transmembrane conductance regulator (CFTR) potentiator) demonstrated improved clinical outcomes including cough and phlegm scores in patients with COPD and chronic bronchitis on triple inhaled therapy [13]. However, the effect size in this study was small and the primary outcome not reached (improvement in FEV_1 after 12 weeks from baseline).

The effect of inhaled corticosteroids (ICS) in COPD was evaluated (reviewed in [14]), with greater effects observed in patients at risk of exacerbations with higher levels of eosinophilic inflammation. A threshold of >100 cells / μL is currently recommended to predict a beneficial ICS response in COPD patients with recurrent exacerbations, despite treatment with long-acting beta agonist/long-acting muscarinic antagonist (LABA/LAMA) [15]. In a post-hoc analysis of The Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) study, the use of either (1) one single baseline blood eosinophil count (BEC) measurement, (2) the maximum (≥200-250 / μL) or (3) median (≥125-150 cells / μL) value of multiple measurements were all found to be discriminatory for predicting ICS response [16]. Previous studies have shown that lower eosinophil counts confer the greatest temporal stability, using blood [17, 18] and tissue [19]. A study of 100 COPD patients reported consistent results

concerning sputum eosinophil counts [20]. The authors found that lower levels of sputum eosinophils (<1%) were stable over 6 months whereas those with higher eosinophil counts (≥1%) were more temporally variable. The Studying Acute Exacerbations and Response (STARR2) multi-centre RCT [21] assessed the utility of BEC to guide oral CS use for COPD exacerbations with treatment failure as the primary outcome. The risk ratio of treatment failure was 0.82 (95% CI 0.54-1.23, p=0.34). Although results for the primary outcome were negative, the authors suggested that eosinophil guided prescription enables better safety in the long term and was not associated with worsened outcomes.

The mucins: MUC5AC and MUC5B are necessary for the formation of airway mucus [22], with longitudinal data from the SPIROMICS cohort demonstrating that increased MUC5AC concentrations, as measured in sputum, were associated with manifestations of COPD including worsened lung function, increased symptoms and increased exacerbation frequency [23]. Assessment of bronchial mucosal biopsies and bronchial wash from COPD patients and healthy controls recruited into the Cohort of Mortality and Inflammation in COPD (COSMIC) cohort, demonstrated that smokers (regardless of airway obstruction) express higher levels of MUC5AC and lower MUC5B compared to never-smokers [24]. Furthermore, elevated levels of interleukin-4 (IL-4), a type 2 (T2) inflammatory mediator, are associated with increased levels of MUC5AC and reduced ciliary function in several respiratory diseases including COPD [25]. These findings suggest that smoking-induced changes in mucus production and clearance are a potential therapeutic target, mediated possibly by T2 cytokine modulation of mucin production. Meanwhile, work presented by *Anderson et al* shows promise in regenerative medicine; by targeting Jagged-1 (a cell surface protein that interacts with the Notch-2 pathway) using Anticalin proteins, epithelial progenitor commitment was redirected from goblet to ciliated cells. In turn, this reduced IL-13-induced mucus trans-differentiation and goblet cell numbers *in vivo* [26].

Several other inflammatory pathways were suggested as therapeutic targets in COPD, including: iron sequestration by bacteria [27] and signalling relating to IL-33, via ST2-dependent and independent (RAGE/EGFR) pathways [28-30], with the expression of membrane ST2 mRNA detected predominantly in mast cells, implicating this particular leukocyte as having a major role [28].

Exacerbations

A presentation by *Singh D* highlighted that mortality in clinical trials of COPD is associated with specific characteristics (possible treatable traits) including cardiovascular disease and frequent exacerbations. Interestingly, a population-based cohort study revealed that COPD exacerbations were associated with an increased risk of a cardiovascular event within one month [31]. This information adds to cumulative evidence that COPD exacerbations are responsible for a large health and socioeconomic burden worldwide [32].

The current definition of a COPD exacerbation, which is subjective (depending on physician treatment decisions) and uninformative regarding pathophysiology, was discussed at the Congress. The recently published Rome proposal, now adopted by GOLD, and the aforementioned Lancet commission highlighted the shortcomings of our current practice [3, 33]. The documents suggest new definitions, diagnostic approaches and standard investigations within an updated classification system. The proposed definitions include, for the first time, assessment of local and systemic inflammation. In addition, new recommendations include assessment of the aetiology of the event i.e. bacterial, viral, environmental or other possible causes. Importantly, both publications propose that the traditional retrospective classification of exacerbations by healthcare resource utilisation is inappropriate and new classification systems should be based on objective characterisation of exacerbations using measured variables at the time of the event, with consideration for the significance of differential

diagnoses. The overall definition of a ‘’COPD exacerbation’’ as an outcome in clinical trials was investigated in a methodological systematic review. Based on a total of 174 different exacerbation definitions, the authors observed a high degree of variability in identification tools across the included studies [34]. Heterogeneity has also been observed in the outcomes assessed in clinical trials of COPD exacerbations management [35]. It is hoped that the ERS COPD exacerbations core outcome set, that was recently published, and presented in the conference will improve the consistency, quality and comparability of clinical trials [36]. A core outcome set is an agreed set of critical outcomes that should be assessed in all future clinical trials. Similar to new proposals for the identification and classification of exacerbations mentioned above, this core outcome set is considerate in terms of resources required, making it both feasible and accessible.

Take home messages: COPD is a heterogenous disease and findings from this year’s congress have furthered our knowledge in the field of biomarkers to facilitate the progression of precision medicine in COPD. Furthermore, key elements of disease heterogeneity which may be addressed as treatable traits in terms of mortality reduction, were considered including frequent exacerbations. Finally, the development of a new definition of a COPD exacerbation and the publication of the ERS COPD exacerbations core outcome set, take consideration of the heterogeneity of COPD and will hopefully lead to prosperous advances in RCTs in relation to exacerbations, but also improve treatment success during acute events.

Asthma

Basic Science Research

Considerable advances in basic science research in asthma were presented at the ERS Congress 2022. Through metagenomic sequencing of the airway microbiome, bacterial infection was identified in the nasal lavage of 21% of patients with severe asthma whereby it was associated with sputum neutrophilia and pro-inflammatory cytokines (such as IL-6 and IL-8). This differed to the microbial composition of bronchoalveolar lavage samples derived from the same patients, suggesting that differences exist between the upper and lower airway microbiome in severe asthmatics [37].

Impaired mucociliary clearance is a well-known feature of asthma. Lower ciliary beat frequency was seen in severe asthma, which did not improve after air-liquid interface cell culture (which mimicked normal respiratory tract epithelia in vitro). The authors suggested that this shows that ciliary dyskinesia may be a primary problem, not secondary to airway inflammation, as the dyskinesia persisted when the cilia were in the non-inflammatory air-liquid interface cell culture [38].

The role of innate lymphoid cells is an emerging area of interest in asthma. Mice lacking innate lymphoid cells (Rag2-/-γC-/-) did not develop airway hyperresponsiveness upon challenge with lipopolysaccharide. Adoptive transfer of innate lymphoid cells into these mice restored airway hyperresponsiveness, implying that innate lymphoid cells are involved in the development of this important feature of asthma [39].

While anti-IL-5 biologics are now well established in the management of severe asthma, some of their mechanistic effects are not fully understood, such as their effect on the airway epithelium. One study presented at the Congress showed that mepolizumab induces gene expression and DNA methylation changes in the nasal airway epithelium, leading to the inhibition of downstream cytokines (such as TNF-α) [40]. Moreover, the role of anti-IL-5

biologics in obesity-related type 2 (T2) asthma was highlighted: BMI positively correlated with T2 biomarkers in sputum, while anti-IL-5 reduced obesity-induced NLRP4 inflammasome activity and steroid-resistant airway hyperresponsiveness [41].

Precision Medicine

Clinical research of biologics in severe asthma played a prominent role at the Congress. Tezepelumab (the monoclonal antibody which targets TSLP, the upstream epithelial cytokine instrumental in T2 inflammation) was of particular interest. The DESTINATION study, which was an extension study of the NAVIGATOR and SOURCE studies, showed that tezepelumab reduced exacerbation rates by 39-58% over a 104-week period (39% reduction in patients who had completed the NAVIGATOR study, 58% reduction in patients who had completed the SOURCE study) [42]. Of note, a post-hoc analysis of the PATHWAY and NAVIGATOR studies showed that tezepelumab reduced exacerbation rates irrespective of BEC: there was a 50% reduction of annual exacerbation rates in patients with blood eosinophils <150cells/μL and not on maintenance oral corticosteroids (OCS) [43]. This raises the possibility that tezepelumab will be an effective therapy for T2-low asthma, for which new therapies are urgently needed. Moreover, over three times as many patients on tezepelumab achieved clinical remission compared to placebo (12.7% vs 4.4%), with remission being defined based on various parameters, such as Asthma Control Questionnaire (ACQ-6) score ≤0.75 at 52 weeks [44].

Other biologics were discussed at the ERS Congress 2022. In a national Danish study, 58% of patients on a biologic achieved remission (defined as no exacerbations nor OCS use in the last 52 weeks); increased T2 biomarkers (e.g. BEC) and shorter disease duration predicted remission [45]. The VOYAGE study showed that dupilimab reduced exacerbations rates in children aged 6-11 years old who were on medium-dose or high-dose inhaled corticosteroid

(ICS) therapy and resulted in a significant increase in FEV_1 in the medium-dose ICS group [46]. Interestingly, in the dupilimab group, exacerbation rates were not associated with baseline FeNO nor blood eosinophils, though these biomarkers were associated with FEV_1 improvement [47]. The Liberty Asthma Excursion study (a 52-week extension of VOYAGE) showed reductions in exacerbations were maintained in 6-11 year old children with T2 asthma (blood eosinophils ≥150cell/μl or FeNO ≥20ppb) [48].

Some future targets for biologics were also presented. IL-33 is another upstream epithelial cytokine in the T2 pathway and is released in a reduced form (IL-33red). Tozorakimab binds to IL-33red and inhibited ST2-dependent inflammation (a clinical trial is ongoing [49]) [50]. Furthermore, anti-IL-17 reduced levels of pro-inflammatory cytokines (such as IL-17 and IL-2) in mice treated with ovalbumin and porcine pancreatic elastase (which acted as a model for asthma-COPD overlap) - this highlights the potential of anti-IL-17 in this disease entity [51].

Multi-Disciplinary Management

The importance of a multi-disciplinary approach to asthma management was highlighted at this year's Congress. A digital medicine programme carried out in pharmacies (including pharmacist-led medication counselling and use of digital health apps) resulted in improved Asthma Control Test (ACT) scores and an average annual cost saving of €465 per patient, possibly through improved medication adherence and inhaler technique [52]. Pharmacist-led programmes like this may be helpful in countries with particularly over-stretched primary care services. A model for multidisciplinary management of T2 diseases of the upper- and lower-airways was presented (featuring respiratory physicians, ENT specialists and dermatologists) [53]. In addition, the first questionnaire assessing global airways disease symptoms (the STARR-15) was presented [54]. This led to the introduction of the ULANC (Upper and Lower Airways Northern European Consensus) group, which is a multidisciplinary European

consortium, who are aiming to improve the management of comorbid ENT conditions (such as chronic rhinosinusitis with nasal polyposis) in asthma.

Take home messages: Ciliary dyskinesia and innate lymphoid cell-driven airway hyperresponsiveness may play important roles in asthma development and progression. Tezepelumab is an important new biologic in the management of T2-high and T2-low asthma. Multi-disciplinary management of asthma and comorbidities in asthma is crucial.

Chronic Cough

Cough is a vagal reflex activated by multiple chemical and mechanical triggers, representing a pivotal symptom in many airway diseases. The term "chronic cough" (CC) defines the presence of recurrent cough episodes lasting more than 8 weeks in adults [55]. During the 2022 ERS Congress, CC features and pathophysiology were extensively discussed, with many abstracts and lectures from expert researchers in this field.

Pathophysiology

NEuroCOUGH network aims to develop new understandings on CC, creating a wide European registry and specific specialist-oriented standardized protocols [56]. Starting from a Delphi survey among clinicians of 57 specialist centres from 19 countries, the panel reached consensus on 15 statements concerning the duties of cough specialist centres, the minimum number of assessments required for CC evaluation, the importance of multidisciplinary teams and the need for specific speciality training on this topic [57].

An interesting aspect of CC pathophysiology comes from its relationship with chronic pain. These two entities frequently co-exist [58], probably due to their intrinsic similarities. CC and chronic pain share common neuronal pathways [59], as well as a similar cortical activation after the exposure to a trigger [60]. Moreover, the terms "hypertussia" (excessive cough response evoked by a tussive stimulus) and "allotussia" (cough response after a non-tussive stimulus) resembles chronic pain words "hyperalgesia" and "allodynia", as proof of the intimate bond between this two entities [61]. Moreover, recent evidence suggested that allotussia could be detected even using hypotonic solutions [62], probably due to ATP release via TRPV4 receptors [63, 64].

Several abstracts elucidated the role of CC as prognostic factor in the general population. Data from the Copenhagen General Population Study highlighted how productive CC (defined in presence of affirmative responses to specific questions on cough with mucus production for 8 weeks or 3 consecutive months in a year) is not only frequently associated with several respiratory symptoms, but is also a strong predictor for COPD exacerbations (HR=7.19, CI 4.29-12.04), acute pneumonia (HR=2.9, CI 2.23-3.75) and all-cause mortality (HR=2.06, CI 1.61-2.65) [65] . CC seems also to be related to an accelerated FEV_1 decline over time, regardless of smoke history or COPD diagnosis [66]. Since we still lack a pathophysiologic explanation for the relationship between CC and worse clinical outcomes, some authors described several approaches to solve this problem. The proteomic profile of Particles in Exhaled Air (PExA) in patients with non-productive CC revealed proteins related to inflammation, immune response and cellular adhesion processes [67].

Interestingly, women with asthma showed an increased sensitivity to capsaicin when treated with oral contraceptive during the luteal phase, suggesting a potential role of sex hormones in CC development [68]. Another interesting topic is the connection between gastric-oesophageal diseases and CC. Patients with CC are frequently affected by a certain degree of oesophageal dysmotility, even in absence of a clear gastroesophageal reflux disease (GERD) [69]. Furthermore, in presence of a hiatal hernia, its size seem be related to cough intensity and duration [70].

Management and Diagnosis

The perception of CC among healthcare professionals is of paramount importance for its correct management. Data from a Canadian survey among primary care physicians and specialists revealed that CC definition is clinically applied in one third of cases, addressing asthma, GERD, and upper airway diseases as possible causes [71]. Unfortunately, terms like

Refractory CC (RCC), Unexplained CC or Cough Hypersensitivity Syndrome are less frequently used. Not surprisingly, the low familiarity of primary care physicians with ERS and CHEST guidelines could affect CC management [72]; dedicated training on this topic could fix this issue. Finally, while several CC treatments are frequently prescribed (inhaled or nasal corticosteroids, bronchodilators, proton pump inhibitors), there are a large number of patients lost during follow up, both in primary and secondary care [73]. This problem can be extremely burdensome, especially in patients with a significant psychological impact due to CC persistence. In fact, anxiety, depression and psychological distress frequently develop along with CC, due to various psychopathological mechanisms (less emotional stability, less extraversion, less openness to experiences) [74]. Additionally, up to 11% of patients with CC and psychiatric disorders reported suicidal ideations, especially in patients under 50 years old and with a worse cough severity [75].

Two main diagnostic tools have been described during the ERS congress: database algorithms and portable devices. The CC algorithm was created starting from the Optum Clinformatics Data Mart database, profiling patients with the use of an ICD-based "cough event" definition and with the application of several exclusion criteria. After the use of this algorithm, 25.8% of patients were classified as "probable", 35.9% as "possible" and 38.3% as "unlikely" for RCC [76].

Portable devices represent a good choice for a rapid, non-invasive cough assessment. The device SIVA-P3 is a new wearable audio and movement recorder, able to detect cough after being positioned around patient's chest. This device has shown not only good sensitivity (84-87%) and specificity (99.9%) compared to a human listener, but the majority of the enrolled patients also found the device comfortable to wear [77]. Another example of a portable device is the Hyfe acoustic artificial intelligence system, worn on the wrist. *Gabaldon-Figueira* and colleagues presented some interesting case studies, using this device, illustrating that cough

monitoring is an important part of remote care, with indication that it may be used to complement smoking cessation programmes, improve medication adherence and improve monitoring of stochastic cough data [78]. However, 12% of patients complained of some kind of discomfort with this device, highlighting a possible limitation of wearable tools, especially for long-term use. A possible alternative comes from bedside recorders, able to track respiratory rate and cough without causing wearer discomfort for the patient. Using the Albus Home RD, the authors demonstrated a good interclass correlation between this system (ICC = 0.99; 95%CI = 0.98-0.99; $p < 0.001$) and two different human listeners (ICC 0.98, 0.99 respectively), proving the reliability of this device in cough assessment and monitoring [79].

Treatment

The activation of ATP-gated channel P2X3 is considered a crucial element in RCC pathophysiology, since its activation is intimately bonded with the increase in airway afferent sensitivity. The SOOTHE trial investigated the effects of the P2X3 antagonist BLU-5937 on patients with RCC. Two different populations were randomized, one with an awake cough frequency ≥ 25 and an exploratory cohort with ≥10 to <25 cough episodes/hour. Except for a higher male proportion in the exploratory population, the two groups revealed no substantial differences in anthropometric features, pulmonary function or cough duration and severity [80]. BLU-5937 12.5 mg, 50mg or 200 mg BID administration improved 24h cough frequency after 28 days of treatment (respectively -21.1%, $p = 0.098$; -34.4%, $p = 0.003$; -34.4%, $p = 0.003$), as well as awake cough frequency (-18.8%, $p = 0.0167$ -32.9%, $p = 0.008$ and -34.1%, $p = 0.007$) [81]. Taste alterations, a common adverse effect of P2X3 antagonist, were rarely observed in the treatment arm, being frequently self-limiting and with no loss of taste reported [82].

A more common off-label treatment for RCC is slow-release Morphine Sulphate. Real world data suggest a good response in almost half of treated patients, while 25% of them showed no variation or a worsening of CC [83]. However, reported opioids-related side effects are frequent, forcing 15% of patients to stop their chronic treatment [83].

Take home messages: CC shares specific pathophysiologic mechanisms with chronic pain, being also influenced by many factors such as mucus production, GERD with hiatal hernia and psychiatric disorders. Despite CC perception among physicians could be limited, some diagnostic efforts have been made, especially considering non-invasive portable devices. New emerging treatments for CC, such as P2X3 antagonist, could represent a valuable therapeutic choice to reduce patients' burden for this disease.

Bronchiectasis

Bronchiectasis is defined radiologically as abnormal widening and thickening of the bronchi with an irregular wall, lack of tapering and/or visibility of the airway in the periphery of the lung [84]. Bronchiectasis is considered a markedly heterogeneous disease with different aetiologies, different microbial and inflammatory profiles that may contribute to different clinical outcomes, disease progression and diverse responses to treatment [85]. Therefore, recent research in bronchiectasis has focused on developing strategies to identify underlying aetiologies of the disease, the impact of overlap syndromes, diversity of the airway microbiome and its interactions, the local and systemic inflammatory responses and assessing the impact of these key aspects on clinical outcomes and prognosis. At the ERS Congress 2022, we had the opportunity to broaden our knowledge on these topics that will help us to stratify patients based on their endotype and clinical phenotype to support the use of personalised medicine [86].

Aetiology of bronchiectasis and the clinical impact of overlaps

Despite the development of a standard aetiology algorithm [87], the number of idiopathic cases in cohorts from European countries is still very high in bronchiectasis. The detection of alpha1 antitrypsin deficiency (A1ATD) is included in the algorithm, with an analysis of the European Alpha-1 antitrypsin Deficiency Research Collaboration (EARCO) database identifying bronchiectasis in almost 30% of people, with A1ATD being more frequently detected in those with emphysema (37% of A1ATD patients with emphysema) [88]. This finding supports consideration of A1ATD as possible aetiology in bronchiectasis patients, particularly in men with smoking history, and the need for further investigation into the impact of both diseases on prognosis and management [88].

Another possible cause for underdiagnosis of bronchiectasis is motile ciliopathies, with diagnostic tests not always currently feasible for clinical practice. Late diagnosis of primary

ciliary dyskinesia (PCD) is associated with more rapid lung function decline and risk of chronic *Pseudomonas aeruginosa* infection; such patients may benefit from a multidisciplinary team in a PCD referral centre and therefore early diagnosis is a priority [89]. Diagnosis of PCD in patients with normal ultrastructure is arduous, especially if they present elevated nasal nitric oxide production, high residual ciliary motility and absence of laterality defects. In this cases, the use of genetic testing is required leading to a PCD diagnosis. [90]. *Shoemark et al*, identified pathogenic, or likely pathogenic, variants in motile ciliopathy genes in 12% of cases from a UK cohort of people with bronchiectasis without suspicion of PCD, demonstrating that PCD may be underdiagnosed if genetic testing is not included in the aetiology algorithm of bronchiectasis [91].

The coexistence of bronchiectasis and other comorbidities is frequently associated with a greater symptom burden, coupled with worse clinical outcomes and prognosis [92-94]. The coexistence of bronchiectasis and COPD is the most studied to date and a definition of COPD-bronchiectasis association emerged in 2021 under the acronym of `ROSE` [95]. *Dolliver et al*, evaluated this definition, enrolling 1610 patients from COPDGene cohort and demonstrated that patients who meet the ROSE definition presented higher risk of exacerbations and mortality than those with COPD or bronchiectasis alone [96].

The respiratory microbiome and resistome

Microbial dysbiosis in bronchiectasis activates host-immune and inflammatory responses and is associated with poor prognosis. Loss of Alpha-Diversity is associated with disease severity, worse lung function, severe exacerbations and increased sputum production [97]. Respiratory microbiomes dominated by *Pseudomonas*- and *Aspergillus*- colonisation are associated with a higher frequency of exacerbations and greater disease severity compared to other microbiome profiles in bronchiectasis [97, 98]. *Haemophilus*-dominant profiles are associated with an

increase in airway inflammation (e.g. IL-1β) but not with heightened disease severity [97]. Not surprisingly, the United States Bronchiectasis and nontuberculous mycobacterial Research Registry (BRR) confirmed the association between rates of exacerbations and the *P. aeruginosa* infection in bronchiectasis, in a large cohort of nearly 3000 patients [99]. Chronic infection with *P. aeruginosa* is included in disease specific - severity assessment tools and is often detected as a relevant variable when performing cluster analysis to identify possible endotypes / phenotypes [100]. However, the potential role of other pathogens and microbial interactions across organ systems remains unclear.

Respiratory commensals are frequently considered innocuous but in the presence of dysbiosis, their expansion may contribute to pathogenesis. *Li et al*, demonstrated that the presence of *Neisseria* promotes airway inflammation and loss of epithelia integrity [101, 102]. Furthermore, presence of *Neisseria* in the lung microbiome is associated with worse clinical outcomes in bronchiectasis, corroborating their pathobiont role. Similarly, a clinical profile of patients' disease characterised by frequent exacerbations, worse radiological features and more severe disease seems to be associated to a dysregulated ´gut-lung´ axis characterised by the presence of lung *Pseudomonas*, gut *Bacteroides* and gut *Saccharomyces* [103, 104].

Patients with bronchiectasis are exposed to multiple and long-term courses of antibiotics; thus, a better understanding of the resistome may help to explore the mechanisms underlying the emergence of antibiotic resistance in this population. The respiratory resistome appears to be stable over time, even during exacerbations. Similar findings were observed in cystic fibrosis [105], supporting the hypothesis that the use of antibiotics had a minor effect on the respiratory microbiome and the changes in microbiome composition may be more related to a complex long-term process [106]. Moreover, the resistome profile may also be related to poor clinical outcomes in bronchiectasis, such as exacerbation frequency and lung function. Moreover, the resistome may be associated with geographical origin of the patient. Therefore, the combined

analysis of microbiome and resistome would help predict and manage long-term bacterial resistance and enable the implementation of individualised antibiotic therapy in bronchiectasis [106].

Inflammatory endotypes

Peripheral blood neutrophils show prolonged survival and delayed apoptosis in bronchiectasis [107], perpetuating the vicious cycle /vortex model of bronchiectasis pathogenesis, where airway dysfunction, airway inflammation, infection and structural damage are linked [108]. W*ang et al,* demonstrated that patients with a blood neutrophil count above 4990 cells/μL exhibit more severe disease, worse lung function and nutritional status [109]. Likewise, a profile of airway inflammation, characterised by increased expression of IL-8, IL-1β, neutrophil elastase and matrix metalloproteinases, is associated with poor biophysical properties of sputum (e.g., increased mucus solid content and poor visco-elastic properties), worse lung function and radiological severity in bronchiectasis [110]. These findings were confirmed by *Perea et al*, who evaluated the inflammasome in 269 patients with stable bronchiectasis [111]. The main findings suggest that inflammasome activation aligns with increased expression of caspase-1, and that ensuing elevations in levels of IL-1 β are associated with impaired mucociliary clearance as a consequence of pathological mechanisms such as abnormal mucus properties, sputum purulence and ciliary beat dysfunction. Efforts should now be directed to implement these biomarkers into clinical practice, such as the colour of sputum that it is proposed as a biomarker of the visco-elastic properties of sputum in bronchiectasis [112].

Take home message: Efforts to identify the underlying cause of bronchiectasis or the co-existence of other diseases should be encouraged in clinical practice, as prognosis may be different, and management may require different approaches. A combined analysis of the

microbiome, resistome and inflammasome would be aligned with the vortex model of bronchiectasis and help to implement individualised therapy in bronchiectasis.

Concluding remarks

The ERS International Congress 2022 showed that research in airways disease has gone from strength to strength since the COVID-19 pandemic, with the respiratory community capitalising on lessons learnt from the past two years. Of note, ongoing efforts to attain personalised medicine in airways disease will hopefully lead to improved patient outcomes. Moreover, continued international collaboration in airways research will only serve to enrich this work. Further important research in airways disease will be presented at the ERS International Congress 2023 in Milan (9-13 September).

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Declarations

Dr Bossios A declares honoraria for Advisory Board Meetings from GSK, AstraZeneca, Teva, Novartis and Sanofi, is a member of the steering committee of SHARP, secretary of Assembly 5 (airway diseases, asthma, COPD and chronic cough) European Respiratory Society and vice-chair of Nordic Severe Asthma Network (NSAN). Dr Braunstahl G-J reports attending advisory boards for GlaxoSmithKline, Novartis, AstraZeneca, Boehringer Ingelheim and Sanofi, honoraria from Novartis, AstraZeneca, Chiesi, GlaxoSmithKline, Teva and ALK Abello, participated in research with GlaxoSmithKline, Chiesi, AstraZeneca, ALK Abello, Novartis and Teva and attended international conferences with Novartis and Teva, Dr Gotera C declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or

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