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Early View

Invited review

Research highlights from the 2023 European Respiratory Society International Congress: Assembly 5 - Airway Diseases

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Research highlights from the 2023 European Respiratory Society International Congress: Assembly 5 - Airway Diseases

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Take home message: Novel mechanisms of disease progression and exacerbations of airway diseases, together with superior disease models can be used to develop disease management and novel therapies. This year's congress saw several advancements in this regard.

Abstract

In this review, early career and senior members of assembly 5 (airway diseases) aimed to present key recent findings pertinent to airway diseases presented during European Respiratory Society (ERS) congress 2023 in Milan, with a particular focus on asthma, chronic obstructive pulmonary disease (COPD), chronic cough, and bronchiectasis. During this year's Congress, an increased number of symposia, workshops, and abstract presentations were organized. Seven hundred and thirty-nine abstracts were submitted for Assembly 5 and the majority of these, were presented by early career members. These data highlight the increased interest in this group of respiratory diseases.

Introduction

European Respiratory Society (ERS) International Congress 2023 hosted in Milan, Italy, portrayed the latest advances in respiratory medicine and basic science. Research was reported over five days as oral presentations, hot topics, workshops, and symposiums. Assembly 5, focusing on airway diseases: asthma, chronic obstructive pulmonary disease (COPD), chronic cough (CC) and bronchiectasis, was supported by 688 members attending the congress. Of the 739 abstracts submitted for Assembly 5, an impressive 451 were presented by early career members, with an equal proportion of males and females. As done in previous years [1–3], in this review, early career members of assembly 5 summarise highlights of the research presented and discussed during the congress.

COPD

Early diagnosis, exacerbations, and "pre-COPD"

Patients with typical symptoms not fulfilling current COPD definitions are summarised under the term "pre-COPD". The Lancet Commission 2022 statement paved the way for a more pragmatic mindset about non-linear lung function trajectories, non-smoking aetiologies and earlier diagnosis (Figure 1) [4]. This is closely associated with the well-known insensitivity of basic spirometry [5]. A Copenhagen cohort study demonstrated that the presence of pre-COPD in young adults is an important risk factor for the later development of COPD [6]. Their heterogenous definition included chronic bronchitis, preserved ratio impaired spirometry (PRISm) or early airflow limitation ($FEV_1/FVC <$ lower limit of normal (LLN)). The NOVELTY study, focusing on long-term outcomes, found comparable mortality for patients with GOLD I/II stages and PRISm, with still considerable event rates in pre-COPD. Likewise, lung function decline was similar between pre-COPD and Global Initiative for Chronic Obstructive Lung Disease (GOLD) I/II [7]. Quantitative chest tomography (CT) has become more accepted in this context. Swedish real-life data demonstrated that it is possible to detect typical COPD features within individuals with evidence of pre-COPD using CT [8]. An

obstructive lung disease cohort study showed that cannabis use was associated with quantitative CT measures reflecting emphysema, airway inflammation, and vascular pruning, independent of tobacco use [9].

Small airway dysfunction as assessed by oscillometry has also been increasingly investigated [10]. With "the silent zone" finally being heard [11], a whole session was dedicated to available insights into the small airways in COPD [12, 13]. Considerable short-term impact of heated tobacco products, e-cigarettes and combustible cigarettes to vascular and small airway dysfunction was reported [14]. The London COPD Cohort reported the association of lung function decline and biophysical components of mucus and the pulmonary microbiome [15]. Authors demonstrated an emerging mucus-microbiome signature which was characterised by increased mucin expression and presence of colonising proteobacteria, including *Achromobacter,* which has been associated with FEV_1 decline elsewhere in a recent multi-cohort analysis [16]. The pulmonary microbiome in COPD received attention with respect to prediction of treatment response, whereby a loss of bacterial diversity and a high gammaproteobacteria:firmicutes ratio may be discriminative in terms of exacerbation reduction, in response to Astegolimab [17].

Exacerbations are known to be the main drivers for lung function decline, loss of quality of life (QoL), and mortality [18–20]. Although exacerbation rates decreased during the SARS-CoV-2, they remain a public health problem approaching pre-pandemic levels again [21]. Single inhaler triple therapy has been demonstrated to be highly effective in reducing exacerbations [18, 22, 23]. GOLD 2023 recommends that COPD patients on inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) should be stepped up to ICS/LABA/long acting muscarinic antagonist (LAMA) or switched to LABA/LAMA in patients with a history of exacerbations or major symptoms, respectively [24]. Post-hoc analyses from the KRONOS randomized clinical trial (RCT) suggest that in COPD patients who remain symptomatic on ICS/LABA, a greater benefit may be observed from a step up to ICS/LAMA/LABA, rather than switch to LAMA/LABA [25]. Additionally, airway smooth muscle area was shown to predict ICS response in the HISTORIC study in patients receiving triple therapy

[26]. Cardiovascular events are increasingly recognised as the main driver of COPD mortality and represent an opportunity for addressing a treatable trait [27]. EXACOS-CV revealed a >10-fold increased risk for these detrimental events depending on exacerbation severity. Risk remains elevated for at least 1 year after a severe COPD exacerbation [28]. IMPACT data demonstrated that ECG-derived parameters can identify COPD patients at risk for adverse cardiopulmonary outcomes. Increased Cardiac Infarction Injury Score (CIIS) and right heart dysfunction predicts benefit from triple therapy [29].

Future directions and novel approaches

Dupilumab, was demonstrated to reduce exacerbations, improve lung function and QoL in eosinophilic COPD [30]. Dual phosphodiesterase (PDE)3/4 inhibitor Ensifentrine (ENHANCE-1 RCT) showed a reduction in exacerbations in patients on non-dual-bronchodilator and non-triple-therapies [31, 32]. Several compounds which inhibit interleukin (IL-)33 signaling (Itepekimab, Tozorakimab, Astegolimab), are in clinical development with the most pronounced effects observed in ex-smokers with evidence of intra-epithelial eosinophil infiltration [33, 34]. Interestingly, IL-33 was shown to be upregulated in the small airways within areas of epithelial remodeling [17, 35]. Innovations also included non-pharmacological interventions. In chronic bronchitis, 6-month results from RheOx real-world registry study indicate improvement after Rheoplasty in symptoms (COPD Assessment Test, CAT) and QoL, whilst also demonstrating that Rheoplasty is a safe procedure [36]. Environmental considerations were a central theme at this year's congress. Lifestyle interventions can effectively reduce personal particulate matter $(PM)_{2.5}$ exposure improving the QoL and symptoms of COPD patients [37]. Individual exposure to several air pollutants can be reliably tracked using a wearable device placed at the wrist, as demonstrated in a study conducted locally in Milan [38]. Finally, the environmental impact of inhaled therapies had been discussed controversially. A novel propellant for extra-fine ICS/LABA/LAMA therapy was demonstrated to be bioequivalent with

existing formulations. This data supports therapeutic equivalence while at the same time allowing considerable reductions in the carbon footprint of pressurised metered dose inhalers (pMDIs) [39].

Basic Science Research in COPD

Particulate matter derived from pollution and cigarette smoke was also a focus of basic science research at ERS 2023. Co-culture of macrophages with a BEAS-2B cell line exposed to particulate matter, resulted in increased cytochrome P450 family 1 subfamily B member 1 (*CYP1B1*) and disrupted TP53 and ARG2 epithelial cell gene expression, which are involved in cell cycle and repair [40]. Alterations in macrophage phenotype by carbon, also lead to an increase in cell diameter and increased levels of cluster of differentiation (CD)206 [41]. Particulate matter reduces ITIH4 gene expression, which is correlated with emphysema development, leading to an increase in c-Jun NH2-terminal kinase (*JNK*) signaling [42].

Mechanisms of senescence in COPD were discussed at this year's congress. Leucine-rich repeat containing G-protein coupled-receptor 6 (LGR6) was quantified in COPD and idiopathic pulmonary fibrosis (IPF) lung tissue. LRG6 was upregulated in epithelial progenitors and may contribute to senescence in fibrotic areas of lung tissue in COPD patients [43]. Other polymorphisms are associated with clinically relevant outcomes such as responsiveness to triple therapy (FKBP5) and early onset of COPD (Hedgehog pathway) [44, 45]. Bulk RNA sequencing and proteomics analysis of broncho alveolar lavage (BAL) revealed associations between dysregulated iron metabolism and neutrophilic inflammation in COPD [46]. Polymorphisms in the iron regulatory gene, IREB2, were also shown to be associated with decreased FEV_1 and diffusing capacity of the lungs for carbon monoxide (DLCO) percentage of predicted [47]. MicroRNA (miR)-149-3p was shown to be a key regulator of cellular senescence induced by cigarette smoke [48]. Senolytics (Dasatinib and Quercetin) reduced levels of senescence markers such as p16 while increasing epithelial barrier integrity in ALI cultures of COPD patients but not of healthy non-smoking individuals [49].

Accurate cellular models of the bronchial epithelium have been generated using induced pluripotent stem cells (iPSC), with existing models progressed to include sensory nerves [50]. The addition of both sensory neurons and Schwann cells derived from iPSC resulted in the formation of mature neurons capable of producing axons and Calcitonin Gene Related Peptide (CGRP). The therapeutic potential of iPSC in repairing the bronchial epithelium has been investigated [51]. Bronchial biopsies were cultured and mechanically disrupted to model injury. Both smoker and COPD bronchial epithelial cells showed incomplete repair after injury. iPSC were generated from blood and cultured to produce lung progenitor cells, which then demonstrated complete repair of the bronchial epithelium. P63+ lung progenitor cells were used in a clinical trial to regenerate the lung epithelium [52]. Cell transplantation resulted in increased DLCO % predicted. iPSCs also have the potential to act as therapeutics themselves by aiding cellular repair in the lungs of patients [53, 54].

There has also been an emerging interest in extracellular vesicles (EVs) and in their use as delivery of therapeutics [55]. A molecule of small EVs derived from airway epithelial cells, miR-142-3p, attenuated skeletal muscle dysfunction in COPD [56]. Lipofibroblast-derived vesicles were shown to suppress inflammation when lipofibroblasts were treated with a metabolic modulator, Rosiglitazone [57].

Take-home messages: There is increasing evidence that the current definition of COPD does not represent the whole complexity of the disease. Improvements in refining phenotyping, identification of endotypes and awareness of risk factors other than tobacco smoking are needed. Multi-omic datasets in COPD have increased our understanding of pathophysiological mechanisms of COPD (Figure 2). The mechanisms that drive exacerbations are particularly important given their effect on hospitalisations and mortality. These insights, combined with the development of better pre-clinical models of disease can be used to inform the development of therapeutics.

Asthma

Novelties in the management of asthma

New insights in small airway dysfunction in asthma were presented during the Congress. An unbiased cluster analysis of the Atlantis study demonstrated 4 asthma clusters, with either central airway (cluster 1, neutrophilic), both central and distal airway (cluster 4, severe eosinophilic) involvement, or normal lung function (clusters 2,3) [58]. A radiomics algorithm, based on CT detected ventilation defects towards posterior and the lung base, correlated with small airway dysfunction and identified patients at risk for exacerbations [59]. From a clinical perspective, a smart digital spacer-based education program could identify poor inhaler adherence and technique in primary care asthma and reduce inhaler technique errors (-26%) compared to usual care (+15%), in a feasibility trial [60]. Several clinical studies of severe asthma were presented during the Congress. Although lowering the dose of ICS under biological therapy is recommended [61], limited evidence supports this approach [62] and several researchers sought to address this paradigm in their presentations. The SHAMAL study (phase 4 RCT) showed ICS can be safely reduced up to low dose when asthma is optimally controlled under Benralizumab, without loss of asthma control or worsening lung function. In contrast, ICS as reliever only strategy did worsen lung function [63]. ICS dose reduction was achieved during treatment with Tezepelumab in DESTINATION as compared to placebo (15% vs 10% of patients reduced from high to medium, 22% vs 15 % from medium to low), without loss of lung function [64]. In another study, patients on biologics were found to underreport the reduction of ICS to healthcare professionals, highlighting the importance of openly discussing ICS use and dose reductions by clinicians [65]. From the MESILICO study, histologic evidence of improvement in airway remodeling was found after 6 months of Mepolizumab treatment. Another biopsy study showed submucosal eosinophils at baseline to predict remission on anti-IL-5 biological therapy, better than a type 2 (T2) inflammatory score; T2 scores were derived using a combined score of FeNO (≥50, 25-50 and <25ppb, scoring 3, 2 and 1 respectively) and blood eosinophil count (≥300, 150-300 and

<150, scoring 3, 2 and 1 respectively) [66]. Real-world studies showed remission is achievable in 20-40% of patients and durable with current available biological therapies [67]. Different definitions are used: clinical remission consisting of good asthma control, absence of exacerbations and no maintenance oral corticosteroids (OCS); discretionary combined with lung function remission (normal or personal best FEV_1). A post-hoc analysis of DESTINATION showed the ability to reach remission in a broad population over the range of biomarkers with Tezepelumab as compared to placebo [68]. The DESTINATION extension study showed that improvements in biomarkers, asthma symptoms and lung function gradually decrease after stopping Tezepelumab [69].

Comorbidities have been considered with respect to treatment response, specifically OCS use in asthma. In REALITI-A, patients with depression or anxiety had higher exacerbation rates, maintenance OCS use and worse Asthma Control Questionnaire (ACQ) scores compared to those without after 2 years of Mepolizumab [70]. Furthermore, a post-hoc analysis of the REal worlD Effectiveness and Safety of Mepolizumab (REDES) RCT demonstrated that reduction in OCS daily dose whilst on Mepolizumab was lower in asthmatics with concomitant bronchiectasis, compared to those without [71]. Elsewhere, OCS-dependent patients on anti-IL-5/5Ra biologics were shown to lose weight in a real-world setting [72].

Promising targets for pharmacological treatment

Receptor for advanced glycation end-products (RAGE) is required for allergen-induced release of IL-33, accumulation of ILC2s, and upregulation of IL-5 and IL-13. An ongoing phase 1/2a trial, ARO-RAGE showed reductions in soluble RAGE in BAL fluid and serum of asthmatics [73]. Adermastat, a Matrix MetalloProteinases (MMP)-12 inhibitor, attenuated late allergen-induced asthmatic response in mild allergic asthma [74]. Another phase 1 trial showed good tolerability and safety of LQ036, (inhaled IL-4Rα antagonist) [75]. A single dose of a novel anti-Thymic stromal lymphopoietin (TSLP)/anti-IL-13 biologic molecule improved small airway dysfunction in asthma [76]. A novel inhaled PDE4 inhibitor, Tanimilast, was demonstrated to modulate inflammation both alone and in

combination with ICS in both T2 and non-T2 asthma phenotypes. In fact the use of Tanimilast, resulted in a significant decrease of T2, type-1 (T1) and type-17 (T17) cytokines [77].

The evaluation of anti-IL-6 as a potential new drug for patients with non-eosinophilic IL-6 high asthma was also reported: higher local airway IL-6/sIL-6Rα signaling in asthma patients with low sputum eosinophils is the rationale for these targets [78].

Novel immunological mechanisms in asthma pathogenesis

Single cell transcriptomics has been used to demonstrate novel epithelial: immune cell crosstalk in asthma, for example between goblet cells and CD4+ cells which may be mediated via MHC II, providing a plausible mechanism for potentiating inflammatory responses in asthma [79].

Obese and overweight asthma patients are challenging to treat optimally, and many suffer from poor asthma control [80]. It was reported that alterations in the CD8+ terminally differentiated effector memory expressing CD45 (TEMRA) cell and innate lymphoid cells (ILC) 2 compartments in overweight and obese individuals with asthma, serve to immunologically distinguish these groups [81]. ILC2s are an important source of T2 cytokine production in asthma and therefore may present as a promising therapeutic target. Zinc has been shown to promote T2 cytokine production by ILC2s, thereby acting as a potential target for modulation of ILC2 activity [82]. A significant effect of Mepolizumab on the function of eosinophils was reported: the number and activation status of eosinophils in peripheral blood was decreased by Mepolizumab treatment. This treatment also induced a transition of inflammatory subsets of eosinophils to resident eosinophils (with regulatory properties) [83]. While for Benralizumab treatment, the response of innate immunity mediated by natural killer cells seemed to be a good marker. Benralizumab in fact, shifted NK cell phenotypes towards maturity [84].

The effect of in vitro azithromycin treatment on epithelial antiviral immunity was also reported, augmenting bronchial epithelial cells' antiviral response [85].

Non-Type 2 asthma

The T2 inflammatory phenotype in asthma is characterised by an eosinophilic/Th2 inflammatory pattern. Conversely, a non-T2 phenotype of asthma is becoming increasingly recognized and identified by a neutrophilic/paucigranulocytic inflammatory infiltrate with associated cytokines [86]. A combination of the effect of corticosteroid treatments and the non-specific nature of asthma symptoms defines non-T2 asthmatics. Recently Th1-Th17 and Treg-related cytokines were demonstrated to have similar levels in T2 high and T2 low asthmatic patients [87].

Some thromboxane and prostaglandin metabolites are associated with persistent symptoms in non T2 asthmatic patients independently from obesity [88]. Urine eicosanoid concentrations increase with asthma severity and they are differentially associated with clinical phenotypes of asthma. In this study, high concentrations of LTE4 and PGD2 metabolites were associated with lower lung function and increased amounts of exhaled nitric oxide and eosinophil markers in blood and sputum [89]. Using metabolomics, several novel metabolites associated with blood neutrophils that may prove useful for stratifying non-T2 asthmatics were analyzed. Of these, the ratio of dihydroceramide and sphingosines to glucocorticoids seemed to be the most significant in characterizing non-T2-driven asthma [90].

Changes in serum Chitinase-3-like protein 1 (YKL-40) negatively correlated with changes in annual FEV_1. Serum YKL-40 can be a biomarker of neutrophilic airway inflammation [91, 92]. Neutrophilic airway inflammation seemed to be a driver of inflammatory processes in these patients. Sub-acute exposure to house dust mites (HDM) and diesel exhaust particles was associated with neutrophil extracellular trap formation [93].

Take home messages: Management and treatment of asthma, especially severe asthma, seemed to be the crucial points in the field of asthma. Several novel monoclonal antibodies will be available in the future, and the molecular and immunological characteristics of the patients as well as the presence of

comorbidities could support clinicians in the right choice. Different studies in basic and clinical research on non-T2 asthma were reported.

Chronic Cough

Cough is a protective reflex that can be triggered by various stimuli. When cough persists for more than eight weeks, it is termed CC. The features and treatment of CC were extensively discussed during the 2023 ERS Congress, underscoring the increasing significance and interest in this condition.

Pathophysiology and definitions

The definitions of several subtypes of CC have been discussed and confirmed. Refractory chronic cough (RCC) is characterized by a persistent cough that continues despite receiving appropriate treatment; unexplained chronic cough (UCC) refers to a persistent cough that cannot be attributed to any underlying condition, even after a comprehensive evaluation [94].

The genesis of a cough originates from the activation of a complex reflex arc. It commences with the stimulation of receptors, distributed throughout various airway regions. Receptors located in the larynx and tracheobronchial branches can be triggered by mechanical and chemical stimuli [95] such as cation channel heat, capsaicin, citric acid, and derivatives of arachidonic acid, elicit the cough reflex by activating vanilloid receptors known as TRPV1[96]. The involvement of both the central and peripheral nervous systems has been extensively examined as the primary drivers of CC, essentially treating CC as a neurological disorder and a potential target for therapeutic intervention.

A novel paradigm called Cough Hypersensitivity Syndrome (CHS): is characterized by CC triggered by low-level exposures to thermal, mechanical, or chemical stimuli [97, 98]. The concept of the "exposome" is noteworthy because it emphasizes the pivotal role of the environment in the development and aggravation of respiratory conditions [99].

Management

CC significantly affects multiple facets of a patient's quality of life including chronic pain [100], anxiety and depression [101, 102], and urinary incontinence [103, 104]. The correlation between CC and urinary incontinence has been described: this condition typically manifests as leaks occurring during coughing episodes [105]. Moreover, an analysis of emotions associated with CC using the Discrete Emotions Questionnaire (DEQ), revealed that anger and anxiety are emotions frequently associated with CC, particularly in women [106].

The initial diagnostic steps for CC involve taking a thorough medical history, which includes inquiries about the cough's history, and cardiac, gastrointestinal, and nasal symptoms, as well as assessing ACE inhibitor use and exposure to smoke or environmental irritants. Diagnostic tests such as spirometry with a bronchodilator test, methacholine challenge test, chest X-ray, and a complete blood count are recommended when CC is suspected [105, 107]. The initial approach focuses on identifying and addressing potential triggers and treating any underlying conditions that may be causing the cough: if it persists further evaluations should be undertaken to determine the presence of unexplained or refractory CC. In such cases, a trial with neuromodulator therapy is suggested [105, 107].

Treatments

Managing CC can be a complex task, necessitating a personalized treatment approach. The latest ERS guidelines emphasize the importance of identifying a likely cause for CC and implementing tailored therapy targeted at either resolving the underlying pathology or addressing the pathological mechanisms driving it [105].

CC remains a prevalent issue with limited treatment options, and discussions surrounding its management have been extensive. Furthermore, Notably, there are currently no approved therapies for refractory CC, except in Japan and Switzerland where Gefapixant is approved [108]. Table 1 summarizes current and future therapeutic opportunities. The safety and efficacy of Gefapixant, a selective inhibitor of P2X3, was tested in patients with either short (<1 year) or long (>1 year)

duration of refractory/unexplained CC [109]. The analysis revealed that regardless of the duration of CC, there was a similar and favorable response to Gefapixant treatment.

Camlipixant is a selective inhibitor of P2X3 receptors implicated in the neuronal hyperreflexia of the airways [110]. The SOOTHE study indicates that Camlipixant is effective in reducing cough frequency over a 24-hour period and in enhancing the quality of life of CC patients. The most common adverse events reported are related to taste disturbances [111].

Neurokinin 1 (NK-1) and N-methyl-D-aspartic acid (NMDA), as well as peripheral receptors like P2X3, NaV, and TRPM8, play a role in the hyperreflexia observed in CC. Research into modulating these receptors could provide new avenues for the treatment of CC (table 1).

An intriguing perspective regarding the actual impact of the placebo effect in randomized controlled trial (RCTs) for CC. It is noteworthy that RCT arms often demonstrate significant improvement in CC symptoms, prompting the suggestion to include a "no treatment group" in future studies to better understand this phenomenon.

Take home messages: CC is a complex condition associated with a spectrum of conditions that reduce the quality of life significantly. Promising novel treatments, such as P2X3 receptor antagonists, could be a valid therapeutic option to reduce the 24-hour cough frequency and to improve the quality of life.

Bronchiectasis

Non-Cystic Fibrosis bronchiectasis

At this year's congress, a total of 4 sessions were centered around bronchiectasis with 32 presentations, 109 abstracts, and 97 posters. Bronchiectasis is defined as a clinical syndrome, characterized by abnormal bronchial dilatation that can be identified on high-resolution computed tomography scan [112]. From the clinical perspective, the patient presents with productive cough and recurrent lower airway infections [113]. Most of the research interest is focused on registries and

cohorts to learn more about the etiology, diagnostics treatments, and outcomes of this not-uncommon disease.

Novel findings from EMBARC

Some of the posters presented at ERS were based on the data from the European Bronchiectasis Registry (EMBARC) and the cohorts derived from this registry. A study of the metabolomic profile of patients with bronchiectasis showed that peripheral blood eosinophils have a difference in pathways including metabolism of purine, nicotinate and nicotinamide, among others [114].

There is also interesting information about the genetic diversity of *Pseudomonas aeruginosa* virulence factors in bronchiectasis, using samples from patient at the EMBARC registry. The bacteria's growth and biofilm formation are influenced *in vivo* by different regulatory genes. The effect of these variants on virulence remains to be tested in vivo [115].

Pathophysiology

Regarding the pathogenesis of bronchiectasis, the Cole´s Vicious cycle is an interesting theory. This hypothesis proposes a host-mediated inflammatory response to any foreign material and the bacterium in the airway causes tissue damage resulting in bronchiectasis. It also demonstrates that the airway damage contributes to abnormal mucus clearance and further bacterial colonization [116]. Key pathogens were identified and compared in trials like EMBRACE, BAT, BLESS and the US CNFB registry [117–120]. In Europe, the main pathogen detected was *Haemophilus influenzae*. Whilst in United States of America, the main pathogen is non-tuberculous mycobacteria like *Mycobacterium avium*. Therefore, pathogens isolated form patient with bronchiectasis may depend on the geographic area of residence and should be considered with respect to personalised treatment.

Diagnostics and outcomes

An interesting symposium regarding the controversial issues of bronchiectasis from the perspective of infection and inflammation caught much attention at the congress. It was highlighted that most

research to date is focused on bronchial infection as the main risk factor for bronchiectasis. Approximately 38% of patients with bronchiectasis do not have a bronchial infection as risk factor of the disease [112]. Research presented at this year's congress highlights the importance of understanding inflammatory endotypes present within the disease, as chronic airway inflammation is a pertinent feature [121].

The etiology of bronchiectasis has been explored in the EMBARC study, with the role of inflammation, infection and impaired mucociliary clearance characterized in the early stages of the disease [122]. It has been suggested that most bronchiectasis patients or those in a pre-bronchiectasis state, had clear risk factors to develop the airway disease like genetic predisposition or systemic inflammatory conditions like asthma, allergic bronchopulmonary aspergillosis, rheumatoid arthritis, among others [122, 123].

Treatments

ICS are an option of anti-inflammatory therapy for patients with airway diseases like asthma and COPD. ERS guidelines do not suggest the use of this treatment for bronchiectasis patients [124]. Some research suggested that ICS could induce a reduction in exacerbation frequency in patients with "pure bronchiectasis" and eosinophilia (blood eosinophil count ≥400 cells/μL) [125]. There is also biologic plausibility in utilising macrolides in respiratory disease, such as azithromycin due to the anti-inflammatory effects [126]. It was demonstrated that dipeptidyl peptidase 1 (*DPP-1*) inhibitors reduce neutrophil serine protease activity and this was associated with improvements in clinical outcomes such as exacerbation frequency [127].

Take home messages: As eloquently highlighted by Professor Welte, bronchiectasis has become one of the hot topics of respiratory medicine in this decade. Most research to date has focused on registries and cohorts, which enable us to gain an understanding of the disease. Promising advances in the

understanding of the disease were presented at this year's congress, including the importance of genetic diversity and bronchial infections in bronchiectasis etiology.

Concluding remarks

An increased number of presentations in the field of airway diseases were communicated at the ERS International Congress 2023. Interestingly, advances in several novel treatments were reported. Moreover, increased understanding of the pathogenetic mechanisms of airways diseases were described by several groups from around the world. Further important research in airways disease will be presented at the 2024 ERS International Congress in Vienna (7–11 September).

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Figure captions:

Figure 1. The importance of early diagnosis in COPD

(A) Currently, COPD is diagnosed at a stage when pathological changes are irreversible. This late diagnosis is due to a combination of factors, including the lack of predictive biomarkers, under-recognised clinical symptoms, a long period of disease activity associated with no or minimal symptoms, and reliance on spirometry, an insensitive diagnostic tool. (B) Implementation of a more inclusive diagnosis of COPD allows for the detection of early disease before irreversible pathological changes have occurred and could lead to disease interception. COPD=chronic obstructive pulmonary disease. RCT, randomized controlled trial. Reprinted with permission [4].

Figure 2. A GETomics approach to understanding COPD and other chronic human diseases

The biological effects and clinical outcomes of different gene–environment interactions depend not only on their specific characteristics, but also on a time dimension—ie, the age of the individual at which the interaction occurs and the cumulative history of the individual's previously encountered gene–environment interactions. We propose that future research should take a holistic approach that considers the range of interactions between genes (G) and the environment (E) that occur over an individual's lifespan (time, T) in the context of integrated omics approaches (ie, GETomics) to better understand the pathogenesis of COPD (and probably other chronic human diseases). Examples of environmental factors (the exposome30–33), from conception to death, are represented by orange shading. The positions of different exposures included in the shaded area are not necessarily related to the time axis (arrow) and might occur several times during the lifespan. At different timepoints, these environmental factors interact with the genomic background of the individual through epigenetic and other mechanisms that might be identified through various basic omics approaches. These interactions induce biological responses (endotypes34)—such as innate or acquired immune responses—that modulate organ structure (development, maintenance and repair, ageing) and function. Biomarkers for these endotypes are needed to be able to characterise objectively the pathogenic mechanisms linked to altered lung structure and function. Modulation of organ structure and function, represented here by different lung function trajectories associated with development and ageing, determines long-term phenotypes associated with health and disease, which can be

explored through clinical omics approaches. COPD = chronic obstructive pulmonary disease. Reprinted with permission [128].

Tables

Table 1. Current and future therapeutic options in chronic cough.

Target receptor	Type of receptor	Drug name	Mechanism of action
P2X3	Peripheral receptor	Gefepixant* Eliapixant Sivopixant, Camlipixant	Antagonist
NaV1.7	Peripheral receptor	NTX-1175	Blockers
TRPM8	Peripheral receptor	AX-8	Antagonist
NK-1	Central receptor	Aprepitant, Ovrepitant	Antagonist

*Phase III trial completed

Neurokinin 1 receptor, NK-1; purinoceptor 3, P2X3; Transient receptor potential cation channel subfamily M (melastatin) member 8, TRPM8.

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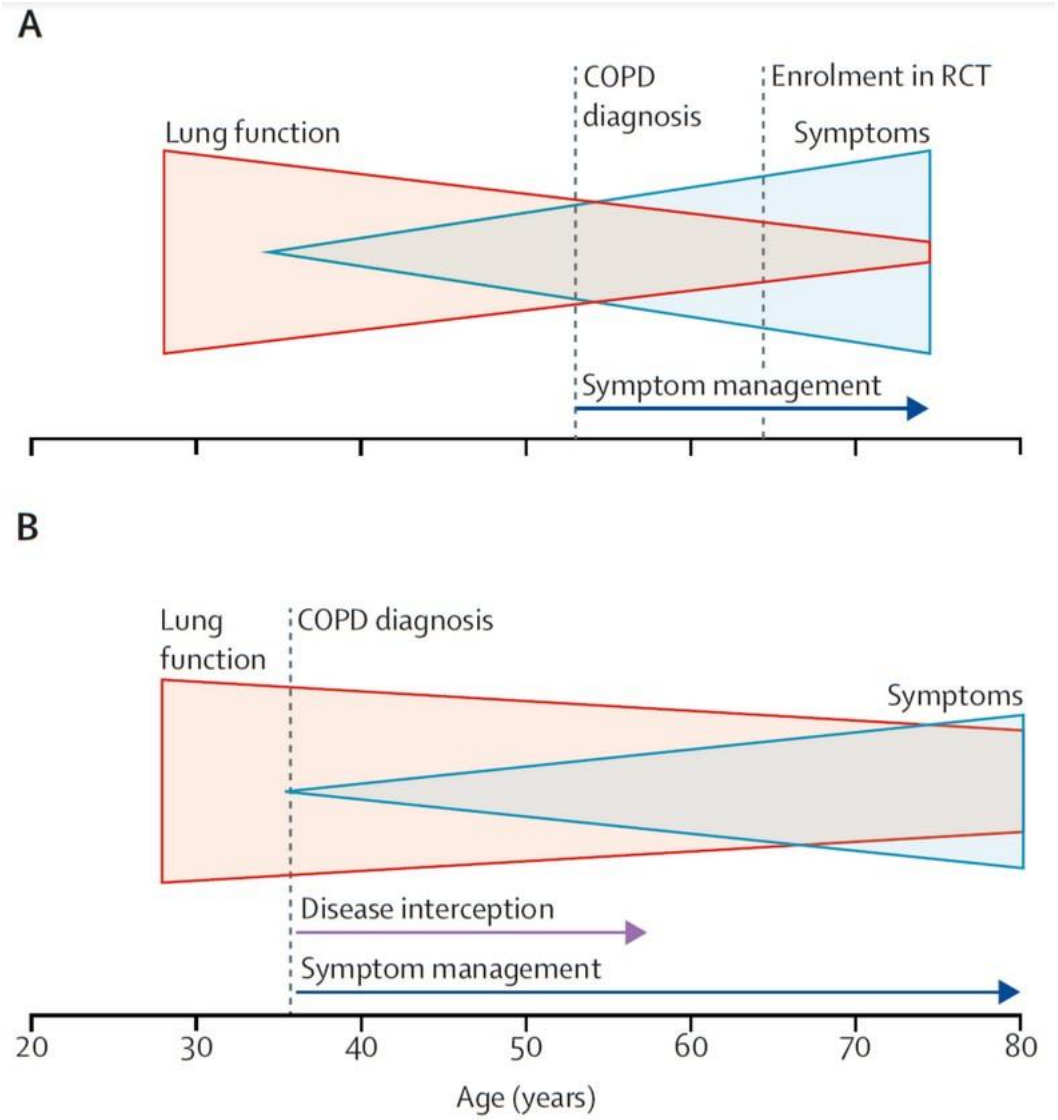

Figure 1

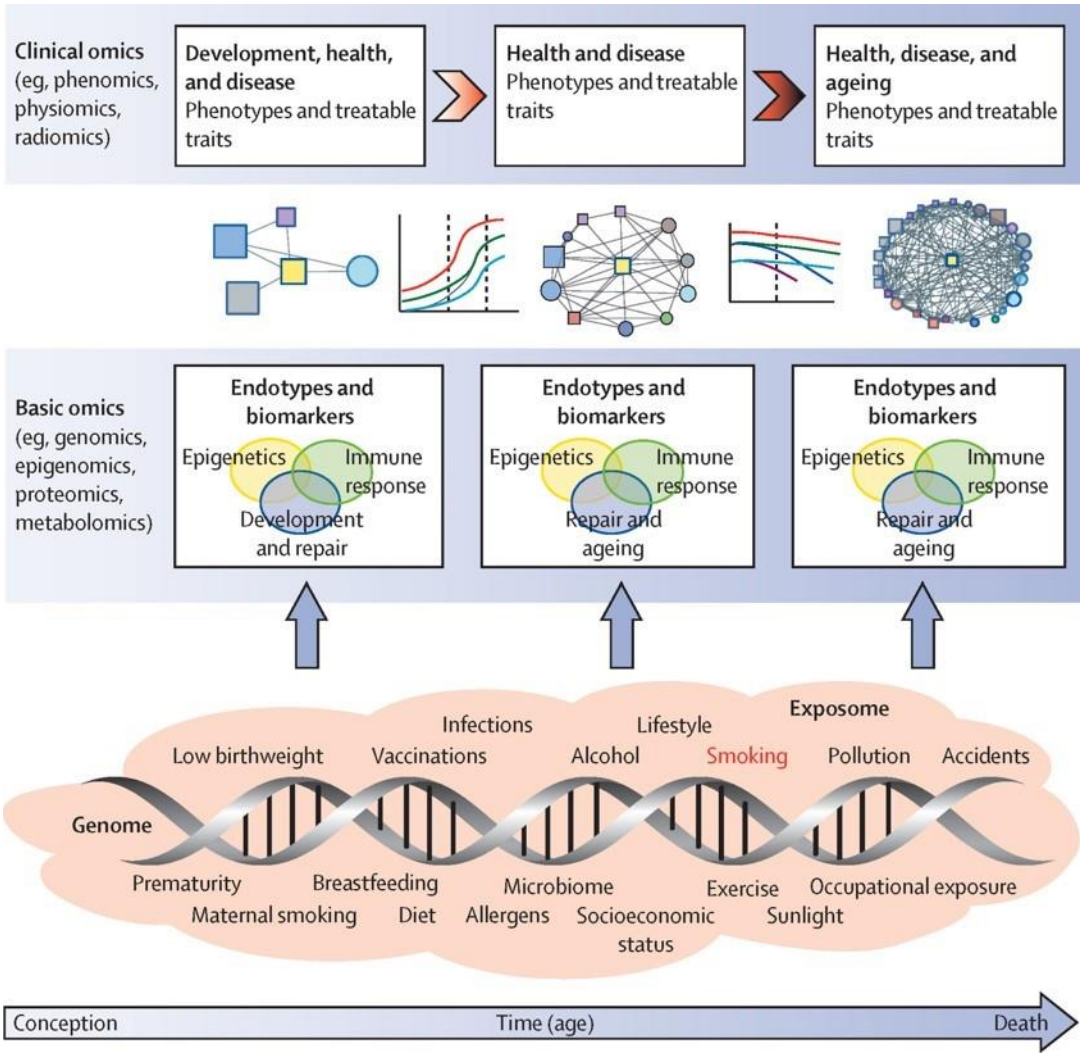

Figure 2