






# ERS International Congress, Madrid, 2019: highlights from the Airway Diseases, Asthma and COPD Assembly

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**ABSTRACT** The European Respiratory Society (ERS) International Congress 2019 in Madrid, Spain, was a platform for scientific discussion of the highest quality scientific research, cutting-edge techniques and innovative new therapies within the respiratory field. This article discusses some of the high-quality research studies presented at that Congress, with a focus on airway diseases, including asthma, COPD, small airways, bronchiectasis and cough, presented through the Airway Diseases, Asthma and COPD Assembly (Assembly 5) of the ERS. The authors establish the key take-home messages of these studies, compare their findings and place them into context of current understanding.



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**This article discusses some of the high-quality research studies presented at #ERSCongress in Madrid, with a particular focus on airway diseases, presented through the Airway Diseases, Asthma and COPD Assembly (Assembly 5) <http://bit.ly/2RpDVvv>**

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## Introduction

Over 22000 delegates from 134 countries attended the 2019 European Respiratory Society (ERS) International Congress in Madrid, Spain, and had the opportunity to participate in more than 420 scientific and educational sessions discussing cutting-edge clinical and scientific advances. Around 20% of the 4440 high-quality research abstracts that were presented at the Congress focused on airway diseases. Similar to those published in previous years [1, 2], this article aims to compare, contrast and critically appraise only some of the research data that were presented during the ERS Congress.

## Asthma

### *Mechanisms and physiology*

The underlying mechanism of asthma is airway inflammation. This heterogeneous condition is a result of genetic predisposition and environmental factors (e.g. allergens) that can affect epithelia, macrophages and dendritic cells, triggering an inflammatory cascade. This can result in non-type 2 (non-T2) neutrophilic inflammation activated by Th1 and Th17 pathways, remodelling involving fibroblast and airway smooth muscle effects, or T2 eosinophilic inflammation (allergic asthma) [3]. Several interesting sessions and symposia aimed to investigate the mechanisms behind the development of asthma the Congress.

Key features of asthma include reversible bronchoconstriction, inflammation and extracellular matrix remodelling. Targets for these were highlighted by several studies at the ERS Congress 2019 in *in vivo* animal and *ex vivo* models. Budesonide-induced decrease of interleukin (IL)-5 production was shown not to affect allergen-induced bronchoconstriction or airway hyperresponsiveness in a novel guinea pig asthma model, recapitulating steroid-resistant asthma [4]. Another study demonstrated that activation of the TRPM3 ion channel in epithelial cells leads to the release of tachykinins that activate the neurokinin (NK) 2 receptor on airway smooth muscle causing bronchoconstriction. This highlighted TRPM3 as a potential novel therapeutic target [5]. In addition, the therapeutic benefit of inhaled calcilytics was described in hyperresponsiveness [6], IgE/Th2 and alarmin-driven airway inflammation [7]. Regarding neutrophilic asthma, inhaled insulin-like growth factor binding protein-3 peptide was reported as novel therapeutic target for severe non-T2 asthma through the modulation of endoplasmic reticulum stress in the lung [8]. Furthermore, as horses naturally develop asthma, unlike conventional research animals, an equine asthma model consisting of decellularised lung scaffolds [9] was proposed as a platform for the study of cell–extracellular matrix interactions and remodelling in asthma [10].

Innovative views on the microbiome and ageing were also explored at the ERS Congress 2019, such as the ALRIgHT project (Applied Lung Bacteria for Health), describing the importance of lung-colonising bacteria after birth for establishing a healthy lung microbiota and for the susceptibility to allergic asthma [11]. Interestingly, *in silico* analysis (Netlogo version 6.1.1) demonstrated a correlation between eotaxin-1 (*CCL11*) levels and asthma severity. This study identified shorter telomeres in subjects, including children, with severe asthma compared to mild asthma and controls, which could be due to *CCL11* promoting superoxide secretion and double-strand breaks, then inducing reduction of telomere length and contributing to an accelerated ageing phenotype [12].

### *Epidemiology*

One aspect in the management of patients with asthma across all age and disease severity spectra that might have been underrepresented in recent years is the role of sex hormones (Hot Topic 432). Menarche and menopause seem to be associated with disease onset and worsening lung function, and perimenstrual asthma could be a disease phenotype that was been reported >30 years ago but not gained much appreciation since [13]. In the data-driven, cluster-based approach of the Severe Asthma Research Program cohort, MOORE *et al.* [14] also identified a “late-onset female obese phenotype with moderate reductions in [forced expiratory volume in 1 s (FEV<sub>1</sub>)]” and the description of sex-related asthma phenotypes as well as sex-specific intervention studies might be a rewarding goal application for the future. In line with this unmet need to better understand sex-specific asthma phenotypes and potential tailored treatment options, therapeutic regimen changes during pregnancy might also be studied in more detail in order to reduce the risk of asthma attacks for both mothers and unborn children [15].

### *Biomarkers*

Although parameters such as blood eosinophil count, fractional exhaled nitric oxide, sputum eosinophil count and total IgE levels have been widely used to determine the type and severity of asthma, more specific biomarkers are still needed to better tailor patient treatments. As highlighted by Kian Fan Chung (Imperial College, London, UK) in a Guidelines Session, the identification of molecular phenotypes in addition to clinical parameters is not only important for the correct diagnosis and management of asthma, but it is also key to identifying patients who would potentially respond to new therapies, especially for T2 severe asthma [3]. Gene set variation analysis [16] of sputum samples from the Unbiased Biomarkers in

Prediction of Respiratory Disease Outcomes cohort identified three transcriptome-associated clusters (TACs): TAC1, driven by T2 eosinophilic asthma mechanisms (IL-33, thymic stromal lymphopoietin (TSLP) receptor and CCR3); TAC2, driven by non-T2 neutrophilic asthma related to the inflammasome, interferon and tumour necrosis factor pathways; and TAC3, driven by non-T2 asthma associated with oxidative stress, ageing or the IL-6 trans-signalling pathway [17, 18]. For patients with low eosinophil counts, who do not benefit from current treatment options, anti-IL6 trans-signalling/receptor inhibition and anti-IL-17 approaches were mentioned as a proof of concept.

Exciting poster discussion sessions revealed TSLP, but not ezrin, as an early biomarker of airway epithelial dysfunction in acute allergic asthma [19]. Although matrix metalloproteases (MMPs) are proposed as biomarkers for asthma severity, as part of the late-breaking abstracts, high serum MMP3 levels were reportedly induced by steroid use, highlighting a need to determine therapeutic effects on new biomarkers [20].

The identification of specific biomarkers brings additional advantages for the detection of asthma phenotypes. Easy-to-use devices measuring exhaled air parameters were highlighted on several occasions as valuable support for the rapid, noninvasive and early detection of asthma, especially in symptomatic children [21]. Molecular biomarkers such as exhaled volatile organic compounds (VOCs) can be detected by electronic nose technology for metabolomic analyses [22] and VOCs measured by gas chromatography–time-of-flight mass spectrometry have been able to discriminate between various asthma inflammatory phenotypes [23]. The Inflammacheck (Exhalation Technology, Cambridge, UK) device could detect exhaled hydrogen peroxide as a marker of lung disease, including mild and severe asthma [24]. Moreover, a late-breaking abstract highlighted that SpiroNose (Breathomix, Reeuwijk, the Netherlands) data obtained by vital capacity manoeuvres provides the highest accuracy in the cross comparison of controls and asthma, COPD and lung cancer patients [25].

### **Exacerbations**

The ERS Congress also hosted sessions on exacerbations. Exacerbation frequency is a relevant clinical outcome in both severe and mild asthma, and its reduction a major therapeutic goal. The recently updated Global Initiative for Asthma strategy document [26] suggests moving away from a short-acting  $\beta_2$ -agonist (SABA)-only treatment paradigm in patients with mild asthma (Hot Topic Session 245). *Post hoc* analyses of the Symbicort Given as Needed in Mild Asthma 1 trial and other studies further substantiate that exacerbation frequency and number of night-time awakenings could be reduced with an inhaled corticosteroid (ICS)/formoterol as needed strategy [27–29]. In a Swedish nationwide drug and patient registry including 365 324 patients considered to be treated for asthma, possible consequences of SABA overuse (three or more canisters with 150 doses) were analysed. Results indicated a dose-dependent relationship between SABA overuse and asthma-related exacerbations irrespective of the underlying controller therapy with ICS [30, 31]. Distinct patient groups, *i.e.* males, adolescents and older patients, were more likely to overuse SABA compared with females and those in the 18–24-year age group [30, 31], and distinct patient beliefs might further amplify the problem [32]. These results emphasise a need for closer monitoring of SABA usage, which might be feasible *via* so called “connected” or “smart” inhalers. The field of digital therapeutics is rapidly emerging and combines remote sensor technology with personalised health behaviour intervention. Several manufacturers already offer sensor devices, mobile applications and cloud-based software but evidence-based results are necessary to support their adoption in daily practice and well-defined guidelines for their development might be necessary [33]. Currently, it is not clear which aspects of digital intervention programmes contribute most to improved symptom control and it may be argued that the mere electronic provision of established tools is not yet a digital intervention [34–37].

### **Asthma guidelines update**

The international ERS/American Thoracic Society (ATS) guidelines on the definition, evaluation and treatment of severe asthma, published in the *European Respiratory Journal* in 2014, is one of the most influential documents in the field of severe asthma in recent years [38]. It is currently referenced by >350 PubMed Central articles and reaches high public attention as one of the top 5% of all research documents scored by Altmetric. Severe asthma is defined as asthma that requires high-dose ICS as well as a second controller (and/or systemic corticosteroid) [38]. As a result of their importance in treatment, several studies investigated the role of ICS in asthma. One particularly interesting study investigated the therapeutic index of three ICS (fluticasone furoate (FF), fluticasone propionate (FP) and budesonide), along with placebo, in an escalated-dose, randomised, incomplete-block, crossover study in 54 asthmatic patients. Interestingly, within the approved dose ranges used for asthma, FF showed a better therapeutic index with more protection against airway hyperresponsiveness and less systemic activity than FP and budesonide [39].

The therapeutic landscape has experienced a paradigm shift, with several novel treatments now being used to treat severe asthma. Three monoclonal antibodies against IL-5 or its receptor have been granted market access: mepolizumab in 2014 [40–42], reslizumab in 2016 [43–46] and benralizumab in 2017 [47–50]. Some of these biologics have shown great potential, with mepolizumab showing significant reductions in exacerbations and use of oral corticosteroids in REALITI-A, a 2-year, “real-world” cohort study of patients with severe eosinophilic asthma; better outcomes than were seen in earlier clinical trials [51]. Just recently, the anti-IL-4/13 receptor antibody dupilumab was also approved for use in patients with severe asthma [52–54]. For scientific evaluation of the body of evidence and clinical guidance of the use of these and other new treatment regimens, a joint ERS/ATS task force was formed in 2017, and subsequently identified and formulated six specific questions using the PICO (Patient Population, Intervention, Comparison and Outcome) format [55]. Questions focus on optimal patient identification for antibody therapies in adulthood and childhood as well as on the use of long-acting muscarinic antagonists (LAMA) and macrolides (*i.e.* azithromycin and clarithromycin) in patients with severe asthma. For the first time, patient representatives were part of the task force and significantly contributed to the Task Force Report (session 44) [3]. While this document integrates the highest level of evidence from placebo-controlled clinical trials, novel perspectives on the clinical trial data and the heterogeneity of the recruited patient populations might be derived from the application of cluster-based asthma phenotypes in *post hoc*, discriminant function-based analyses [55].

## Chronic obstructive pulmonary disease

### *COPD epidemiology and biomarkers*

At the 2019 ERS Congress, many interesting data were presented concerning the epidemiology of COPD. Worldwide, COPD has a prevalence of ~10% and some of the largest countries, including India and China, represent 60–70% of all cases of COPD [56]. The first results of EPISCAN II, which aimed to estimate the prevalence of COPD in the general Spanish population, revealed that COPD remained underdiagnosed in three out of four subjects, and that COPD prevalence among women is rising (prevalence is at 15% in males but already approaching 10% in females). A third of the population was shown to be former smokers and a fifth current smokers, but it is important to note that almost half of these population-based COPD subjects had no smoking history [57]. Cigarette smoke remains to be the key risk factor for the development of COPD [58]; however, there is growing interest in gaining a better understanding of nonsmoking COPD in order to optimise pharmacotherapy in these patients. Besides the harmful effect of cigarette smoke, there is more to understand on the effects of biomass pollution, infections, a history of asthma and other developmental or genetic risk factors. Air pollution may also play a role, and there is a need to investigate the effect of rising electronic cigarette sales on lung development in young people.

COPD remains an umbrella term that groups different clinical entities with multiple causes and it remains important to better understand these causes because they can reveal treatable traits. Alongside offering better disease management strategies, identifying these traits can also yield better treatment options for related pathologies that do not meet the definition of COPD but might share risk factors with it, such as “preserved ratio, impaired spirometry” (PRISm) or chronic cough. Patients with PRISm ( $FEV_1$ /forced vital capacity  $\geq 0.7$  and  $FEV_1 < 80\%$  of predicted) demonstrate an increased all-cause and cardiovascular mortality, with mortality rates similar to COPD [59]. Moreover, one third of PRISm patients transitioned towards COPD over 5 years follow-up. Chronic cough can also present in the absence of COPD but is observed to be a common trait among COPD patients. Around 10% of the COPD individuals from the Copenhagen General Population Study had chronic cough, and demonstrated lower lung function, more symptoms (including wheezing, dyspnoea and chest tightness), and higher levels of C-reactive protein (CRP), fibrinogen, leukocytes, neutrophils and eosinophils in their blood [60]. Systemic inflammation and manifestations remain substantial drivers of the morbidity and mortality burden in COPD.

COPD has been shown to have an adverse effect on the quality of life of sufferers. Among >2000 COPD individuals aged 40–85 years within the Norwegian HUNT Study, symptoms of anxiety were indeed strongly associated with worse health status and increased risk of exacerbations, independent of the severity of disease. In addition, symptoms of depression were associated with increased mortality among these COPD individuals independent of other major comorbidities [61]. These comorbidities or the general decline in resilience (frailty) are important prognostic markers besides lung function, age, sex, body mass index (BMI), degree of dyspnoea and exacerbations in COPD. Cardiac comorbidities are most likely also the reason why cardiac biomarkers, including the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) and troponin T, are such strong predictors of future hospitalisations as well as early and late mortality in patients admitted with COPD exacerbations [62]. However, it is becoming increasingly clear that it is impossible to have one biomarker indicating disease activity in all COPD patients. Therefore, several optimal and clinically useful markers associated with specific mechanisms of

the disease, ideally treatable traits, are increasingly investigated, including higher blood eosinophils for corticosteroid-responsive eosinophilic airway inflammation, CRP for acute (bacterial) exacerbations, and (a combination of) genetic variants, such as  $\alpha_1$ -antitrypsin deficiency, for emphysema. Less fancy, but luckily also less expensive, remains the clinical utility of worsening symptoms, including shortness of breath, chest pain and cough, to indicate increased disease activity, and evaluation of therapy adherence and inhaler technique to indicate poor treatment response.

#### *COPD exacerbations*

Acute exacerbations are largely responsible for the health and socioeconomic burden posed by COPD [63, 64]. While their management remains unchanged for decades, it has become clear that exacerbations are heterogeneous and require a personalised treatment approach [65, 66]. For this reason, diagnostic and prognostic biomarkers were evaluated in high-quality studies presented at the Congress. Blood eosinophils represent one of the most thoroughly evaluated biomarkers in COPD exacerbations. In an observational cohort involving 388 hospitalised patients with COPD exacerbation, KOSTIKAS *et al.* [67] confirmed that higher eosinophil count ( $\geq 2\%$ ) is associated with lower disease severity at presentation and better clinical outcomes (mortality and duration of hospitalisation). However, they also observed a reduced re-exacerbation rate during 1 year of follow-up among patients who presented with higher eosinophils. This contrasts with previous reports, suggesting higher eosinophils are associated with more frequent exacerbations [68]. A *post hoc* analysis of the DYNAGITO trial, involving 7743 patients with a history of exacerbations, did not find an association between blood eosinophil count and risk of future exacerbations either [69]. This controversy may be explained by the sample size, inclusion of patients with no exacerbations and concomitant administration of ICS to the majority of the participants from the newer studies, which significantly impact blood eosinophils in COPD and reduced the exacerbation rate [70].

Several studies evaluated cardiac biomarkers during exacerbations. A longitudinal study of 383 patients with COPD, which captured high-sensitivity troponin during stable disease and 335 episodes of hospitalisation, found troponin to be increased by 40% during exacerbations [71]. Another study assessed the prognostic value of NT-proBNP and troponin T in 176 patients with COPD exacerbations, including 32 with raised NT-proBNP ( $>220 \text{ pmol}\cdot\text{L}^{-1}$ ) and 19 with raised troponin T ( $>50 \text{ ng}\cdot\text{L}^{-1}$ ) at presentation. Both biomarkers were associated with early and late mortality, and future risk of exacerbations and cardiac hospitalisations [72]. A potential limitation of such studies is the poor specificity of the diagnostic criteria of COPD exacerbations [73]. Indeed, it is very challenging to differentiate COPD exacerbations from other pathologies such as episodes of heart failure decompensation [74]. Moreover, both diseases often co-exist. In a real-life observational study of 119 smokers with COPD presenting with acute worsening of their respiratory symptoms, there was poor diagnostic agreement between the emergency and respiratory departments, while a final diagnosis of concomitant COPD exacerbation and heart failure was finally attributed to 40% of the participants [75]. Cardiac magnetic resonance imaging in eight patients with high and 15 patients with normal NT-proBNP during admission with an exacerbation and later, during stable disease, confirmed that biventricular ejection fraction impairment is common during exacerbations [76]. Patients with normal NT-proBNP had a significantly increased right ventricular systolic volume, which may represent a compensatory mechanism. Overall, to interpret the role of cardiac biomarkers in COPD exacerbations, it is crucial to exclude misdiagnosed patients with cardiac decompensation, and to assess carefully for coexisting acute and cardiac pathology.

#### *Long-term home noninvasive ventilation for COPD*

The new ERS guideline on long-term home (LTH) noninvasive ventilation (NIV) for the management of COPD, which was presented during the Congress, issued four conditional recommendations that were based on evidence of low or very low certainty [77]. More specifically, LTH-NIV is recommended for patients with 1) chronic stable hypercapnic COPD or 2) persisting hypercapnia following a life-threatening episode of acute hypercapnic respiratory failure requiring acute NIV. LTH-NIV settings should be titrated aiming to arterial carbon dioxide tension ( $P_{\text{aCO}_2}$ ) (high-intensity NIV). Finally, fixed pressure support, rather than adaptive or autotitrating pressure modes, should be used as the first choice of ventilator mode in patients with COPD using LTH-NIV. These recommendations were based on data from relatively small, nonblinded studies with heterogeneous findings. More recent studies that included patients with higher  $P_{\text{aCO}_2}$  at baseline and used high-intensity LTH-NIV settings achieved better treatment adherence, which resulted in better outcomes [77, 78]. Recognising the absence of adequate, high-quality data that would allow the development of more specific clinical and technical recommendations, this guideline also highlighted several unmet research needs, highlighting the need for high-quality interventional research in this area. Indeed, numerous studies focusing on LTH-NIV were presented during the Congress, including two randomised controlled trials (RCTs) evaluating LTH-NIV initiation at home *versus* in the hospital. These trials involved 608 and 67 patients with stable hypercapnic COPD respectively [79, 80]. Both trials

demonstrated noninferiority of initiating LTH-NIV at home, with regards to the impact of NIV on  $P_{aCO_2}$ . The larger (Dutch) trial also evaluated the cost-effectiveness of the intervention and identified an impressive cost reduction of over €3200 per patient initiating NIV at home [81].

### Small airways

#### *Challenges of assessing small airway disease in asthma and COPD*

Small airways are increasingly being incriminated in asthma and COPD pathophysiology, and the last 5 years have seen several significant research outputs in this field that have highlighted the importance of the small airways in routine clinical practice [82]. In this context, in 2019, the Assembly hosted a postgraduate symposium chaired by Mario Cazzola (University of Rome “Tor Vergata”, Rome, Italy) and Matteo Bonini (University of Trento, Trent, Italy) on small airways to highlight the recent advances in the field with respect to pathophysiology, assessments, treatments and patient-reported outcomes [83]. In an industry symposium, numerous physiological tests, such as oscillometry, body plethysmography and multiple-breath washout (MBW), were shown to evaluate different levels of the airway tree but there has been no homogenised approach validated to assess small airway disease (SAD). The Assessment of Small Airways Involvement in Asthma (ATLANTIS) was the first multinational, large-scale study aiming to determine the optimal approach for characterising SAD. Published in 2019 [84], this study showed that SAD is present across all asthma severities, with an increased prevalence in severe asthma, and a combination of impulse oscillometry (IOS), spirometry and lung volumes was able to delineate two clinically relevant subtypes of mild and severe SAD with asthma.

The 2019 Congress further emphasised that combining spirometry and oscillometry could bring valuable information to improve asthma management and identify phenotypes missed by current tests. As such, some patients were found to be hyperresponsive to mannitol using the forced oscillation technique (FOT) while FEV<sub>1</sub> measurement did not show a response [85]. Using MBW, TRINKMANN *et al.* [86] were able to differentiate between adult healthy controls and asthmatic patients, with some asthmatic patients having normal spirometry but abnormal sulfur hexafluoride MBW readings [87]. Alternatively, previous studies pointed out that SAD could be an early change in asthma prior to spirometric alterations [88]. In a 5-year paediatric cohort, a subset of children with allergic rhinitis seemed to have increased FOT parameters upon allergic rhinitis exacerbation before developing asthma [89, 90].

The notion that assessing SAD could harbour predictive value, and help to identify early stages and distinct phenotypes is also the subject of intense investigation in COPD [91]. Evaluating FOT parameters may have a predictive value in distinguishing COPD patients in Global Initiative for Chronic Obstructive Lung Disease grade 1 from non-COPD controls [92], while MBW parameters were found to be higher in frequent than infrequent COPD exacerbators [93]. A combination of IOS, MBW and spirometry could also help to delineate clusters of COPD phenotypes according to predominant features of emphysema, central obstruction or SAD [94].

While additional studies confirmed the utility of FOT for assessing SAD [95, 96], others did not find a correlation between FOT and other parameters reflecting peripheral airway obstruction [97]. As highlighted by the ATLANTIS study, each single variable is likely to provide different mechanistic insights and this needs further investigation. In the previously mentioned study by GOVE *et al.* [93], only ventilation heterogeneity in the acinar lung zone was different between frequent and infrequent COPD exacerbators, out of 12 parameters tested.

#### *Insights in SAD pathophysiology in asthma and COPD*

Moving away from their conception of as a “quiet zone”, small airways are increasingly recognised as an important site of inflammation and remodelling [98]. BAZAN-SOCHA *et al.* [99] found that fixed airflow limitation and histological signs of airway remodelling correlated better with computed tomography changes in distal than proximal airways in asthmatic patients. Interestingly, those patients had eosinophilia and higher circulating periostin, but also higher blood neutrophils and circulating ADAM33 [100]. Of note, ADAM33 gene polymorphism has already been associated with asthma [101].

The 2019 Congress highlighted the role of the lung microbiome disturbance in airway disease. Determined by bronchoalveolar lavage (BAL) studies, asthmatic patients’ microbiomes seem to differ in relative composition from controls [102]. HUANG *et al.* [103] also demonstrated contrasting gradients of lung bacterial composition relating to measures of small airways obstruction using the Subpopulations and Intermediate Outcome Measures in COPD Study cohort.

With ever-growing concerns, environmental causes of airway disease also received attention at the 2019 Congress. Not only does the common plasticiser dibutyl phthalate appear to exacerbate the early asthmatic

response (EAR) and late asthmatic response (LAR), but it also increases the recruitment of CD206<sup>+</sup> CD163<sup>+</sup> macrophages in the BAL of asthmatic patients [104].

#### *Challenges in delivering therapies to the small airways*

One great challenge is to deliver therapies that can reach the small airways [105]. Extrafine particles (defined as <2.1 µm mass median aerodynamic diameter) [106] seem to improve deposition in the periphery [107]. New single-inhaler, extrafine therapies are being tested, such as in the TRIGGER and TRIMARAN trials in uncontrolled asthma, emphasising the benefit of the addition of LAMA in a subset of patients [108–110]. The associated challenge is to accurately assess their deposition in disease, warranting new pharmacokinetic approaches. Using *in silico* models with functional respiratory imaging, TOPOLE *et al.* [111] simulated a higher peripheral deposition of extrafine beclomethasone/formoterol/glycopyrronium compared to non-extrafine fluticasone. Innovative spatial pharmacokinetics methods were presented, either to estimate drug concentrations at the epithelium lining fluid with better accuracy than BAL [112] or to directly estimate drug free exposure *in situ* using RNAscope (Advanced Cell Diagnostics, Newark, CA, USA) [113].

### Bronchiectasis

Bronchiectasis is a chronic inflammatory lung disease characterised radiologically by the permanent dilation of bronchi, and clinically by persistent cough and sputum production and recurrent respiratory tract infections [114]. It is a heterogeneous disease in terms of its presentation, clinical course and response to treatment. Its pathophysiology is best depicted by the vicious vortex model which demonstrates the interplay driving airway dysfunction, inflammation, infection and remodelling, with each pathophysiological process contributing to all the others [115].

There is an unmet clinical need in bronchiectasis for biomarkers that reflect disease activity or predict treatment responsiveness. CHALMERS *et al.* [116] previously showed that neutrophil elastase can predict disease severity and progression in terms of airway infection and risk of future exacerbations. The group has since developed a novel point-of-care neutrophil elastase assay lateral flow device that can provide assessment of elastase activity from sputum in minutes to identify patients at increasing risk of airway infection and future exacerbations [117]. The group also identified elevated sputum pregnancy zone protein (PZP) in bronchiectasis patients, and showed that elevated levels are associated with disease severity, frequent exacerbations and airway infection in bronchiectasis patients. PZP is released from neutrophils during degranulation and neutrophil extracellular trap (NET) formation, and may therefore provide a novel link between chronic neutrophilic inflammation and impaired host immunity to infection [118]. Sputum heparin-binding protein (HBP), recently implicated as a sputum marker of airway inflammation and bacterial load in cystic fibrosis, was also identified as a potential biomarker of bronchiectasis severity. The effect of HBP on ciliary beat frequency and epithelial integrity in air–liquid interface models of bronchiectasis patients at concentrations found in sputum suggest a potential impact on epithelial defence against infection [119].

Data pertaining to the effect of systemic inflammatory markers in bronchiectasis have been somewhat ambiguous to date. Although it is likely that a sustained level of inflammation does contribute to disease progression and health status, many of these patients have significant comorbidities that could account for this sustained inflammatory effect [120]. Several presentations at the 2019 Congress focused on the predictive ability of systemic inflammatory markers during exacerbations, with CRP shown to be associated with exacerbations and disease severity, with a trend for sputum calprotectin in predicting exacerbations [121]; CRP, white cell count, neutrophils and neutrophil/lymphocyte ratio (NLR) useful in predicting mortality [122]; and CRP an NLR useful in predicting hospitalisations [123]. Platelet aggregation assessed by measurement of soluble platelet selectin was associated with bronchiectasis disease severity in the stable state, although the clinical consequences of this finding are yet to be fully defined [124].

Endotyping bronchiectasis patients may help to determine patient suitability for therapeutic clinical trials and target individualised treatment approaches. Proteomic analysis of sputum and serum of bronchiectasis patients identified three inflammatory endotypes driving disease heterogeneity (airway neutrophilia, systemic inflammation, and eosinophilic and epithelial inflammation) potentially representing different “treatable traits” (with disease severity markedly worse in the neutrophilic group) [125]. Similarly, proteomic and microbiomic analysis suggests that sputum NETs are associated with proteobacteria dysbiosis and loss of microbiome diversity in bronchiectasis; and that bronchiectasis patients, independent of COPD, are predominantly associated with a proteobacteria-dominant microbiome profile with a lower microbiome diversity than COPD patients alone, and a proteomic profile over-represented by a neutrophilic endotype [126, 127].

Respiratory viruses in the context of bronchiectasis have failed to attract much interest to date. Two studies presented at the 2019 Congress suggested that viral analysis of bronchiectasis patients detects viral carriage in 63%, predominantly parainfluenza virus 3, in the Cohort of Asian and Matched European Bronchiectasis [128]. In an Italian study, respiratory viruses were only detected in 13%, with no seasonal differences in detection rates and no associations with chronic bacterial infections [129]. However, those with positive viral detection were noted to have a higher rate of daily sputum production, a history of chronic sinusitis, and a history of frequent exacerbations in the previous year compared to those with negative viral detection. Further work on the role of viruses in bronchiectasis is needed.

Several large, real-life cohort studies were presented using data from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), a prospective dataset from >30 European countries, and lung cancer screening programmes. These included the identification of risk factors for new isolation of *Pseudomonas aeruginosa*, which alongside standard markers of bronchiectasis disease severity, included ICS use, macrolide use, high daily sputum production and management in a nonspecialist centre [130]. Disease severity did not predict new isolation of nontuberculous mycobacteria (NTM), with analysis showing the classical risk factors of female sex, low BMI and older age to be significant on logistic regression, along with ICS use and a history of allergic bronchopulmonary aspergillosis (ABPA) (OR 3.06, 95% 1.01–9.24), suggesting that coexistence of these two conditions is frequent and that ABPA patients should perhaps be screened for NTM infection. ICS are generally only used to treat comorbidities in bronchiectasis, particularly patients with asthma or eosinophilic COPD [131]. Lung cancer screening programmes suggest a pick-up prevalence of ~11% for bronchiectasis, with a coexisting diagnosis of COPD in 48% and a subsequent diagnosis of lung cancer in 7% of bronchiectasis patients [132, 133]. Looking at determinants of survival in bronchiectasis, initial data from EMBARC suggest that symptoms, exacerbations and *P. aeruginosa* infection are potentially modifiable risk factors for death. Given the lower mortality in specialist centres despite high disease severity, management in a specialist centre may improve quality of care and reduce mortality in bronchiectasis [134].

No approved therapies currently exist for bronchiectasis, and many clinical trials have failed to meet their primary endpoints because of heterogeneous treatment responses and the inherent difficulty of identifying patients likely to respond. An RCT of home-based airway clearance showed an improved cough severity with sustained benefit at 12 months follow-up [135]. A study assessing the effects of pulmonary rehabilitation in bronchiectasis showed successful improvements in anxiety and depression with completion of rehabilitation [136]. Several studies focussed on the therapeutic and mechanistic effects of macrolides at the 2019 Congress. Whilst macrolide use was associated with considerable improvements in the Brody and Bhalla radiological scores after 1 year [137], an individual patient data meta-analysis across participants from three RCTs also showed significant improvements in exacerbations and quality of life independent of *P. aeruginosa* infection or baseline exacerbation frequency [138], and an exploratory analysis of inflammatory pathways surprisingly showed that neutrophilic inflammation was lower in *P. aeruginosa* patients versus those without, and that azithromycin did not attenuate inflammatory profiles [139]. A separate study of sputum inflammatory markers after a year of macrolide treatment suggested that, although increasing disease severity and the presence of an exacerbation were reflected by upregulation of proinflammatory markers, azithromycin did not result in attenuation of the baseline inflammatory response in bronchiectasis [140].

Many bronchiectasis treatments are antibiotic-related and thus carry the risk of antibiotic resistance. Multidrug-resistant (MDR) infections are highly prevalent, and associated with frequent use of antibiotics and disease severity [141]. Recent hospitalisation, exacerbation frequency, recent antibiotic use and systemic corticosteroids were found to contribute to MDR in hospitalised patients with an acute exacerbation of bronchiectasis [142]. Strategies to reduce the risk of MDR in bronchiectasis are needed.

Although biomarker development, disease endotyping and the identification of treatable traits are in their infancy in bronchiectasis, they hold therapeutic promise for patients in facilitating a personalised, specialist approach to patient care.

### Airway sensory nerves and cough

Cough is driven by activation of airway sensory nerves housed within the vagus nerve. These nerves, when activated, initiate reflex events such as cough and bronchospasm through a parasympathetic nerve reflex, which are upregulated in airway diseases including asthma and COPD. When cough persists for >8 weeks, the cough is diagnosed as chronic. Chronic cough is an unmet medical need that lowers the quality of life of sufferers [143]. Cough and airway sensory nerves remained a topic of interest at the 2019 Congress, with a well-attended industry-funded session on chronic cough with presentations from leaders in the field, a guidelines update, and a number of symposia and sessions that helped to highlight key developments in the field.



The P2X3 receptor antagonist Gefapixant remains the only cough therapeutic developed in recent years that has shown efficacy, with a phase 1 trial demonstrating a 75% drop in daytime objective cough frequency in patients with treatment-refractory chronic cough [144]. However, patients also developed dysgeusia, which led to some reports of nonadherence. The effects on taste have been attributed to the fact that the antagonist can also cause its effects through the P2X2/3 heterotrimer, which can affect taste perception, as well as the P2X3 homotrimer, which is thought to be responsible for the effect on cough. Data was presented on a novel P2X3 antagonist, S-600918, which was shown to be more selective for P2X3 over the P2X2/3 heterotrimer and was shown to influence daytime objective cough frequency with a minimal effect on taste. However, there was a large effect of the placebo in this trial [145].

Despite the promising effect of Gefapixant, novel targets are also required. A late-breaking abstract highlighted the potential role of a NK1 receptor antagonist in the treatment of chronic cough. Daily administration of 30 mg of the NK1 antagonist orvepitant reduced cough in patients with refractory chronic cough, with higher efficacy in patients with higher cough frequency. However, the placebo in this study also showed a significant effect on cough, and patients exhibited side-effects, including somnolence, indicating that further investigation is required [146].

Cough is often a key symptom of a number of different respiratory diseases, including asthma. Several presentations at the 2019 Congress aimed to look at the characteristics of patients with chronic cough. Mannitol and citric acid cough tests were shown to discriminate chronic cough patients from healthy controls, as patients with chronic cough were more sensitive to both stimuli, and that mannitol challenge could also separate cough in asthmatics, which could be an important challenge test in diagnosis [147]. It was also demonstrated that uncontrolled asthmatic patients had more severe cough, which correlated to symptoms and health status but not to measures of Th2 inflammation, suggesting that further investigation is required to determine the pathways behind the enhanced airway sensory nerve activity seen in disease [148].

The transient receptor potential ankyrin (TRPA)1 ion channel was suggested as a possible target that could account for this upregulation. Although the poster did not focus on cough, the authors were investigating the LAR, an airway reflex initiated following activation of airway sensory nerves [149]. Using a novel, potent and selective TRPA1 antagonist in an ovalbumin-sensitised guinea pig model, it was shown that this reduced both the airway hyperresponsiveness associated with EAR and the LAR by 51% and 36%, respectively, with no effect on inflammatory cell counts [150]. TRPA1 has also been implicated in cough in both animal models and humans [151], suggesting that this could be a key novel target in the upregulation of sensory nerve response in disease.

### Concluding remarks

As demonstrated throughout this article, the ERS International Congress in Madrid highlighted the innovative and exciting novel research developments within the airway disease landscape. With such a large number of submissions and presentations showcased throughout the Congress, this highlights the high level of interest from both basic and clinical researchers for tackling the global problems of asthma and COPD through determining key mechanisms in order to develop novel therapies.

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