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Clinical highlights from the 2016 European Respiratory Society International Congress

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ABSTRACT This article contains highlights and a selection of the scientific advances from the European Respiratory Society (ERS) Clinical Assembly (Assembly 1) and its six respective groups (Groups 1.1–1.6) that were presented at the 2016 ERS International Congress in London, UK. The most relevant topics for clinicians will be discussed, covering a wide range of areas including clinical problems, rehabilitation and chronic care, thoracic imaging, interventional pulmonology, diffuse and parenchymal lung diseases, and general practice and primary care. In this comprehensive review, the newest research and actual data will be discussed and put into perspective.



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Group 1.1: Clinical Problems

The majority of sessions in the field of Clinical Problems were focused on asthma and chronic obstructive pulmonary disease (COPD), while a small number of presentations addressed rare lung diseases.

Chronic obstructive pulmonary disease

The potential role of eosinophils as biomarkers/phenotypic markers in COPD is controversial and a number of studies presented at the 2016 European Respiratory Society (ERS) International Congress explored the correlation of eosinophils with COPD phenotypes and disease severity. GEORGE *et al.* [1] examined 256 COPD patients with and without eosinophilia, defined by a cut-off of 200 eosinophils per mL, concluding that eosinophilic and noneosinophilic COPD have similar clinical and physiological characteristics, and cannot be distinguished by quantitative computed tomography (CT)-derived measures of emphysema or airway remodelling. Another study, by ZYSMAN *et al.* [2], compared the clinical features and mortality rate between COPD patients with >2% and <2% blood eosinophils in a cohort of 458 COPD patients, showing no difference in symptoms, lung function, exacerbation rates or 3-year mortality rates. Interestingly, the authors reported a higher and significant frequency of diabetes in the >2% eosinophils group, a finding that may warrant further investigations. Similarly, in a study by MARIN TRIGO *et al.* [3], 303 COPD patients from three different eosinophil cut-off level groups (<200, <300 and <400 eosinophils per μ L) did not present any differences in lung function decline, median annual exacerbation frequency or mortality.

A number of presentations addressed less frequently discussed aspects of the clinical management of COPD. While poor nutritional status and weight loss are associated with poor survival in COPD, little is known of the impact of recent nutritional intake on prognosis. In a survey based on the nutritionDay initiative, a multinational registry in 56 countries, 31% of 5518 hospitalised COPD patients were reported to have eaten less than half of what they normally eat during the week before the survey [4]. All-cause mortality was significantly increased ($p < 0.001$) in these patients compared to those with normal food intake, highlighting the relevance of simple measures such as monitoring food intake in the management of hospitalised COPD patients. A study by FURIAN *et al.* [5] on cerebral hypoxia measured by near-infrared spectroscopy showed persistent arterial hypoxaemia and cerebral tissue deoxygenation in lowlanders with COPD travelling to 2590 m, linked to reduced barometric pressure and high-altitude periodic breathing. The risk of cerebral hypoxia was higher in COPD patients with nocturnal hypoxaemia in the lowlands, a finding that may have implications for the clinical management of COPD during flights.

COPD management could be improved by identifying patients with severe COPD who are at increased risk of exacerbations and several presentations focused on risk factors for future exacerbations. In a *post hoc* analysis of the Wisdom study, a 12-month, randomised, parallel-group study, 2291 patients with severe to very severe COPD and history of exacerbations received 18 μ g tiotropium, 100 μ g salmeterol and 1000 μ g fluticasone propionate for 6 weeks, followed by inhaled corticosteroids (ICS) for 12 weeks [6]. ICS treatment at screening and two previous courses of antibiotics or steroids significantly increased the risk of exacerbations, while higher baseline forced expiratory volume in 1 s (FEV₁), Global Initiative for Chronic Obstructive Lung Disease (GOLD) C versus GOLD D and taking xanthines at screening were associated with decreased risk. The effects of treatment escalation to ICS/long-acting muscarinic antagonist (LAMA)/long-acting β_2 -agonist (LABA) triple therapy following an exacerbation were presented in an observational study by TAVARES *et al.* [7] based on the Quebec Provincial Health Insurance administrative database. From the database, 19198 (49.5%) of COPD patients without a preceding moderate or severe exacerbation treated regularly with LAMA, LABA or LAMA/LABA experienced COPD exacerbations, and only 1136 (5.9%) of them were escalated to triple therapy following an exacerbation episode as recommended by the Canadian Thoracic Society guidelines. Increased exacerbations, emergency department visits and concomitant medication use were significantly higher in patients who were not escalated as compared to those who received triple therapy. The management of COPD according to GOLD recommendations or to phenotypic approaches was studied in stable COPD patients from 11 countries from Central and Eastern Europe in the frame of the POPE study [8]. The authors found out up to 45% of patients received triple therapy with LAMA/LABA/ICS, and ICS were not prescribed in line with GOLD recommendations, being overprescribed in 38% of the participants, including half of the nonexacerbators.

Asthma-COPD overlap syndrome

The asthma-COPD overlap syndrome (ACOS) is still a controversial topic, and some interesting data on its prevalence and characteristics were presented. CAILLAUD *et al.* [9] analysed a large cohort of COPD patients and observed that up to 13% of them had a diagnosis of asthma before the age of 40 years. These patients had lower tobacco exposure, were more frequently obese and suffered from atopic disease compared to the rest of COPD patients, but no differences in disease severity (dyspnoea, quality of life, exacerbations or comorbidities) or mortality were observed. BACKMAN *et al.* [10] found 29% ACOS in a cohort of 2055 patients with asthma. Patients with ACOS were older, more frequently men and had more

respiratory symptoms than asthma patients. A study conducted in the Netherlands [11] addressed the impact of different ACOS definitions on prevalence, characteristics and clinical outcomes in 864 patients registered as having asthma and COPD in a population-based cohort. Six different definitions of ACOS were used, based on different combinations of registry-reported ACOS, self-reported ACOS, lung function data (FEV₁/forced vital capacity (FVC) <0.7) and exhaled nitric oxide fraction. The prevalence of ACOS varied from 2.1% to 38.2% depending on the definition used, with higher prevalence rates detected by definitions that including lung function in addition to registry or self-reported ACOS.

α₁-Antitrypsin deficiency

α₁-Antitrypsin deficiency (α₁-ATD) remains often underdiagnosed and in some countries, its prevalence is not yet well known. A study that evaluated the population tested for *α₁-ATD* by a reference laboratory in Portugal over 9 years [12] found a prevalence of 9.5% of Pi*ZZ individuals. Up to 3.5% of individuals had a rare variant and four new alleles were identified during the study period. DUK *et al.* [13] observed that the prevalence of Pi*F and Pi*I alleles in patients with chronic respiratory disorders in Poland were higher than in other European studies. Interestingly, the allele Pi*Mmalton, which is the most prevalent rare variant in the south of Europe, was not detected. Regarding treatment, the RAPID trial showed recently that augmentation therapy can reduce the mean decline in lung density compared to placebo. A subanalysis observed that the proportion of patients with a slow lung tissue decline was higher in the group treated with augmentation therapy and moreover, after switching to active treatment, there was a progressive shift from fast to slow decliners [14].

Group 1.2: Pulmonary Rehabilitation and Chronic Care

The abstracts presented in the field of pulmonary rehabilitation and chronic care addressed the full scope of Group 1.2, including the methodology of patient assessment, new treatment modalities, alternative target populations and outcome evaluation.

While pulmonary rehabilitation is defined as a comprehensive intervention addressing multiple facets of chronic lung disease, extensive facilities and programmes may not be available in many care settings. In a case-control study, PALMER *et al.* [15] observed that exercise training in a community setting with minimal equipment had similar benefits regarding muscle strength, exercise performance and health status to training in a gym setting with specialist aerobic and resistance equipment. This suggests that training with less advanced equipment may be useful to enhance access for COPD patients who cannot participate in traditional exercise training models. KALTSAKAS *et al.* [16] compared the effects home telerehabilitation and traditional outpatient hospital-based pulmonary rehabilitation on acute exacerbations of COPD. They reported that both interventions significantly reduced these events with no between-group difference, thereby increasing our understanding of the potential of this alternative pulmonary rehabilitation model.

VAN DE BOOL *et al.* [17] investigated the effects of COPD specific nutritional supplementation in addition to exercise training in patients with moderate disease. While muscle mass and function and cycling endurance increased with exercise training, nutritional supplementation resulted in additional effects on respiratory muscle strength and physical activity.

BENJAMIN *et al.* [18] presented the results of a prospective randomised controlled study of the effects of exercise training in patients with pulmonary arterial hypertension. Low-dose exercise training for 4–7 days per week significantly improved peak oxygen uptake per kilogram, cardiac index, mean pulmonary arterial pressure, 6-min walk distance (6MWD) and quality of life. JAROSCH *et al.* [19] investigated the effects of inpatient pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis (IPF). They reported improvements in psychological symptoms, health status and walking distance that were largely sustained after 3 months.

MADDOCKS *et al.* [20] highlighted the relevance of physical frailty in COPD as an independent predictor for dropout during pulmonary rehabilitation but also showed that pulmonary rehabilitation can reverse this phenotype. Although structural and metabolic abnormalities in skeletal muscle are well recognised in COPD, these changes have hardly been investigated in other chronic lung diseases. BALAÑA *et al.* [21] reported skeletal muscle dysfunction in a cohort of patients with non-cystic fibrosis bronchiectasis. However, these patients did not depict changes in the *vastus lateralis* muscle structure. This suggests that different chronic lung diseases affect the skeletal muscle compartment in different ways.

With regard to chronic care, GONZALEZ-BERMEJO *et al.* [22] investigated whether early diaphragm pacing can delay the need for noninvasive ventilation in patients with amyotrophic lateral sclerosis (ALS). Contrary to what may have been expected, active diaphragm stimulation resulted in reduced ventilation-free and overall survival compared to sham stimulation, indicating that this intervention is contraindicated in ALS patients with moderate respiratory involvement.

Group 1.3: Chest Imaging

At the 2016 ERS International Congress, interesting data concerning several promising imaging techniques for a wide variety of diseases were presented.

One of the emphases of presentations dealt with COPD and emphysema. FISK *et al.* [23] used fluorodeoxyglucose (FDG) positron emission tomography as a marker for pulmonary inflammation in stable COPD patients and correlated the whole-lung FDG uptake to blood values of fibrinogen. They showed that fibrinogen could be used as a biomarker to stratify and monitor pulmonary inflammation in COPD patients. Airway remodelling is an essential feature of COPD and asthma. GÓRSKA *et al.* [24] evaluated measurements of airway remodelling by CT and endobronchial ultrasound (EBUS) in patients with mild to moderate asthma and COPD showing that in mild disease, bronchial wall thickness does not differ between these diseases and hence may not reflect the degree of airflow limitation. Moreover, they showed that EBUS is feasible in the evaluation of airway remodelling.

Inhalation of bronchodilators LAMA and LABA may improve dyspnoea in COPD patients. TAKEMURA *et al.* [25] evaluated cross-sectional area (CSA) of small pulmonary vessels by CT examination before and after inhalation of bronchodilators, showing that CSA increased after inhalation and that bronchodilators thus may improve dyspnoea by enhancement of pulmonary blood flow. Bronchial dilatation may occur in COPD but also in nonsmoking populations without cardiopulmonary disease. DIAZ *et al.* [26] examined bronchoarterial ratio by CT as a surrogate for bronchiectasis in never-smokers. They found a good relation to lung function measurements regardless of the body size; however, using a fixed ratio to define bronchiectasis may not be always appropriate. HOFFMANN *et al.* [27] examined reproducibility and sex differences of the normal human airway tree by CT analysis. Over 1 year, all airway measurements remained stable; however, luminal diameter and wall thickness showed significant differences between females and males. SMITH *et al.* [28] evaluated large-airway morphometry by CT among symptomatic smokers with preserved pulmonary function and with COPD. They found that symptomatic smokers with preserved pulmonary function have thick large-airway walls relative to total airway area, a distinct phenotype when compared to smokers with COPD.

A few more innovative presentations focused on lung fibrosis. VILLETTI *et al.* [29] performed a comparative longitudinal study of bleomycin-induced lung fibrosis progression in C57Bl/6 mice using micro-CT coupled with histology. Micro-CT can quantify disease progression longitudinally, reducing the variability and number of animals used. WEATHERLEY *et al.* [30] investigated baseline reproducibility and clinical significance of ^3He diffusion-weighted magnetic resonance (MRI) imaging metrics in patients with IPF, indicating that alveolar microstructural changes accompany interstitial thickening in IPF. PRASSE *et al.* [31] presented a study with the new tracer ^{68}Ga -pentixafor, which identifies CXCR4 expression in IPF, may have the ability to monitor disease activity and may predict response to pirfenidone treatment in IPF.

TERZIKHAN *et al.* [32] presented data from the Rotterdam study evaluating mortality risk by measuring pulmonary artery to aorta ratio (PA/A) in COPD and general population patients. They found increased mortality associated with greater PA/A values in both populations.

Finally, TUBMAN *et al.* [33] performed analysis of right atrial size in patients with pulmonary arterial hypertension (PAH) before and after therapy by means of MRI. Change in minimal atrial volume predicted mortality and maybe of value in the serial evaluation of patients after therapy of PAH.

Group 1.4: Interventional Pulmonology

The field of interventional pulmonology is constantly evolving and thus expanding the range of endoscopic approaches in various pulmonary diseases. Key topics covered at the 2016 International Congress were the innovative diagnostic technologies in patients with lung cancer or interstitial lung diseases and the role of bronchoscopy in patients with emphysema.

A needle technique (EBUS-guided transbronchial needle aspiration (TBNA) and/or endoscopic ultrasound-guided fine-needle aspiration) is recommended as a best first test for an accurate mediastinal lymph node staging in lung cancer patients [34]. However, negative cytological results cannot sufficiently exclude mediastinal lymph node involvement. To increase the negative predictive value, new technologies related to EBUS-TBNA were examined. Needle-based confocal laser endomicroscopy (nCLE) provides high-resolution imaging within the lung. In the first *in vivo* study in mediastinal lesions, four lymph nodes were examined by nCLE followed by cytological aspiration [35]. The mean nuclear size of clusters of cells assessed by nCLE and cytological images were similar, and differed between reactive nodes, metastatic nodes and malignant tumours. Hence, nCLE seems to differentiate reactive from malignant nodes.

Another technology that aims improvement of mediastinal staging assessed by EBUS is the three-dimensional (3D) EBUS that is performed by using electromagnetic (EM) navigated EBUS [36]. After identification of

targeted mediastinal lymph nodes in the computed tomography of four patients, a prototype EBUS bronchoscope with an EM tracking sensor was used for visualisation of the targeted lymph nodes. Within 4–8 s, 100–200 two-dimensional EBUS images were acquired and used for 3D volume reconstruction. The diagnostic yield of TBNA that was guided by EM navigated EBUS and 3D EBUS was found to be 81.3%.

A further key topic was transbronchial cryobiopsy, which due to larger samples and good tissue quality without crush artefacts, is particularly helpful in histological diagnosis of interstitial lung diseases, in which forceps biopsies often fail [37, 38]. One multicentre prospective study evaluated the feasibility, safety and potential role of transbronchial cryobiopsy in the diagnosis of diffuse lung infiltrates in 17 mechanically ventilated patients [39]. In 88%, the histology obtained by cryobiopsy led to changes in the therapeutic management. In one patient, massive bleeding occurred after cryobiopsy, requiring selective intubation. The association of transbronchial cryobiopsies with an increased risk of bleeding was also confirmed in a prospective, randomised, controlled multicentre trial, in which 370 patients with interstitial lung disease underwent cryobiopsy [40]. The rate of clinically relevant or severe bleeding following cryobiopsies was significantly higher compared to the forceps biopsies (15.9% *versus* 4.1%, $p < 0.05$).

Another key topic was endoscopic lung volume reduction, which presents an effective therapy in patients with severe emphysema. The impact of emphysema distribution on outcome following valve, was analysed in the multicentre prospective IMPACT trial [41]. Here, 93 patients with severe homogeneous emphysema and absent collateral ventilation were randomly assigned to receive valve therapy or standard care. At 3 months, changes in efficacy parameters were significantly greater in the valve therapy group than in the standard care group, thus demonstrating that valve therapy is also an effective treatment in patients with homogeneous emphysema.

To date, valve therapy was primarily considered a symptom-modifying treatment, as so far, there have been only two small studies demonstrating a survival benefit in patients who were effectively treated by valves [42, 43]. One retrospective analysis presented at the International Congress evaluated the impact of valve therapy on survival in 449 patients [44]. Patients who developed a lobar atelectasis following valve implantation had a significant survival benefit compared to patients without atelectasis (5-year survival rate 63.5% *versus* 43.9%, $p = 0.009$), thus demonstrating the positive impact of effective valve therapy on survival.

Endoscopic coil therapy presents an effective therapy in patients with severe hyperinflation [45]. However, meaningful predictors for successful coil treatment are still missing. That is why one retrospective analysis aimed to determine predictors of positive treatment outcome following coil therapy [46]. The distribution of low-attenuation clusters and vascular volumetry predict the response to coil treatment. Furthermore, lower 6-min walk test scores, lower FEV₁ values and larger total lung capacity values were significantly associated with greater improvement following coil therapy.

Group 1.5: Diffuse Parenchymal Lung Disease

Pirfenidone and nintedanib, the two antifibrotic “arrows” in our quiver, will hopefully constitute cardinal parts of the management of IPF. A substantial amount of data was presented during the ERS International Congress in London concerning the effect of the antifibrotic drugs on quality of life and symptoms [47]. Early diagnosis and treatment may improve prognosis of IPF patients, and great effort should be focused on the commencement of therapy as soon as possible following diagnosis [48], as asymptomatic disease for >5 years and misdiagnosing are common [49].

Interestingly, emerging data support the role of pirfenidone in patients with more severely altered lung function [50], while continued treatment with pirfenidone may confer benefit to patients with IPF who experienced a 6MWD decline $\geq 15\%$ within the first 6 months of treatment [51]. Based on experience with pirfenidone, BALESTRO *et al.* [52] suggest that patients with a rapid pre-treatment progression profile seem to have a more favourable FVC decline rate in comparison with slowly progressing patients. In subgroup analyses of pooled data from the INPULSIS trials, nintedanib slowed disease progression irrespective of CPI (Composite Physiologic Index) [53] or the level of gas exchange impairment at baseline [54]. Importantly, there are data suggesting that the combination of nintedanib with pirfenidone is quite safe and tolerable [55].

Moreover, attempts were made to shed light on the possible side-effects of the drugs; the reasons for intolerance and ways to overcome them were proposed [56, 57]. Great emphasis was laid upon the role of the patient in treatment choices and disease management, both at the phase of diagnosis and at the palliative stage. The role of the caregivers was also pointed out [57, 58].

Regarding the diagnosis of usual interstitial pneumonia (UIP), the team from Royal Brompton Hospital (London) pointed out that inter-multidisciplinary team agreement is poor on decisions to biopsy and management strategy [59], making the diagnosis of definite UIP still not easy even if the guidelines are followed, leading clinicians to refer more and more patients for surgical biopsy [60]. However, a similar mortality to

lobectomy for lung cancer with surgical lung biopsy for interstitial lung disease was supported [61]. Lastly, volumetric CT analysis emerges as a useful tool for predicting mortality in IPF [62], and interventional transbronchial biopsy methods were presented and compared regarding the risk profile [40].

Group 1.6: General Practice and Primary Care

For many clinicians, especially those from, or working closely with, primary care, the 2016 Congress started on Saturday, September 3, with the Primary Care Day. This whole-day event followed the theme “Challenging times” and was well attended by >500 delegates. The Primary Care Day emphasised the challenging tasks of getting the correct diagnosis, managing our patients with multimorbidity when guidelines are disease-specific, and having made a diagnosis and management plan, improving adherence to treatment. These key challenges were echoed throughout the primary care-focused sessions at the ERS Congress in London.

Diagnosis and assessment

Correct diagnosis of airways diseases remains challenging but with good organisational structures, this is both feasible and affordable, argued Thys van der Molen in the Primary Care Day opening lecture in which he described the asthma/COPD service in the Netherlands.

In a primary care oral presentation, JORDAN *et al.* [63] described how selecting COPD patients who will benefit most from, for example, pulmonary rehabilitation can be facilitated by using the ADO (age, dyspnoea, obstruction) index. Using two UK COPD cohorts (n>7000), they estimated that increasing uptake of pulmonary rehabilitation in patients with high ADO scores could reduce acute COPD admissions by 19%, equating to an approximately GBP 38 million reduction in hospital admission costs. In the same session, SŁOK *et al.* [64] presented their randomised controlled trial of the Burden of Disease Tool, which uses balloons to display the patient’s profile. They were able to improve the health status of primary and secondary care patients by implementing this innovative tool by structured assessment and facilitating discussion, and thereby improving individualised management.

CHAMBERLAIN *et al.* [65] described a research programme using smartphone apps to facilitate accurate assessment and interpretation of pulmonary sounds offering the prospect of widespread use in low- and middle-income countries in the years to come.

Multimorbidity and end-of-life care

General practitioners see the broad range of diseases within individual patients and Ioanna Tsiligianni suggested that the term “multimorbidity” seemed to be more appropriate than “comorbidity” in asthma and COPD. Patients with multimorbidity including COPD generate more healthcare costs than those without COPD, as shown in a poster reporting a large Swedish study comparing >17000 COPD *versus* >84000 non-COPD patients [66]. The International Primary Care Respiratory Group UNLOCK (Uncovering and Noting Long-term Outcomes in COPD and Asthma to Enhance Knowledge) consortium presented an international comparison of the negative effects of multimorbidity on quality of life in patients with COPD [67] and multimorbid patients with COPD were found to have a higher prevalence of exacerbations (5.9% *versus* 4.0%) in >16000 primary care patients. RUSSELL *et al.* [68] assessed the effect of COPD medication on other diseases including diabetic patients, showing ICS reduced glycaemic control in patients having both diabetes mellitus and COPD. This study echoes the discussion at the Primary Care Day that there is a need to provide clinicians with more guidance on how to treat respiratory disease in the presence of other diseases.

In a symposium on end-of-life care, the importance of communication was emphasised by all the speakers. In a moving description of caring for his wife who had died with respiratory disease, a lay speaker recruited through the European Lung Foundation highlighted the need to open discussion about prognosis and enable care planning from an early stage in a life-threatening disease, a theme that was echoed in talks from specialists in primary palliative care, communication skills, respiratory nursing and intensive care.

Adherence and inhalation technique

During the Primary Care Day, Rob Horne provided the audience with an overview of the poor adherence to regular inhaled medication (as low as 30%) and practical tips for addressing the challenge in routine clinical practice. A useful model is the Necessity-Concerns framework that highlights the trade-off patients make before deciding whether (or not) to take medications. Clinicians need to be aware of the disconnect between patient-reported and clinician estimates of ICS side-effects. For example, doctors estimate that 10% of asthma patients have a sore mouth or throat while 46% of patients report this side-effect [69]. He advised clinicians to look for the combination of low adherence with poor control, as these are the patients most in need of intervention. Reflecting the (lack of) necessity argument, in their poster on reasons for nonadherence in Indian patients, JAMAL *et al.* [79] identified that the commonest misconception was not

needing medications when they were symptom free, followed by forgetfulness or social embarrassment. Unfortunately, even when patients are adherent to medications, inhalation technique is poor in more than half of people in the Swedish TIE study [71]. Only 28% of the patients reported having received information on correct inhalation instruction in the last year. Encouragingly, KLIJN *et al.* [72] found, in a systematic review of education on inhalation technique, that many interventions are effective, but highlighted the need for frequent reinforcement of the education. With the rise of electronic monitors connected to inhalers to monitor patients' adherence and inhalation technique, a new era has started and in future conferences new interventions will certainly be reported.

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