Early Career Members at the Lung Science Conference and the Sleep and Breathing Conference 2019

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Early career forum

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Lung Science Conference 2019

The European Respiratory Society (ERS) Lung Science Conference (LSC) is the basic science conference of the ERS and it takes place every March in Estoril, Portugal. It is important to note that, particularly at this conference, there is a lot of emphasis on the inclusion and development of Early Career Members. For example, each session is chaired by one Early Career Member together with a more senior scientist; there are 40 travel bursaries to enable abstract authors to attend the conference; there is a mentorship lunch session; and every year the Early Career Member Committee (ECMC) organises a specifically dedicated Early Career Member career development session on the Saturday afternoon. Thus, there are many reasons for Early Career Members to attend this conference but, for those who could not attend, we will describe here the scientific highlights of the LSC 2019 on the topic "Mechanisms of acute exacerbation of respiratory disease".

Triggers of acute exacerbations

The LSC opening session this year focused on different triggers of acute exacerbations in lung disease. Guy Brusselle (Ghent, Belgium) kicked off the session with an extensive overview of pollutant-induced acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD). The respiratory health effects of air pollution consist, among others, of increased mortality, increased frequency of symptomatic asthma attacks and increased incidence of upper and lower respiratory tract infections. The most important sources of air pollution are transportation and traffic, and combustion processes such as electricity generation. A meta-analysis by Orellano *et al*. [1] showed that there is a significant association between air pollutants and moderate to severe asthma exacerbations. So far, the main processes of how air pollution could contribute to asthma exacerbations are oxidative stress, airway remodelling and inflammation, and sensitisation to allergens. After discussion of the potential mechanisms, Guy Brusselle stressed that prevention of exposure to air pollution is very important and that there are several initiatives in place, such as the "Healthy Lungs for Life" campaign (www.europeanlung.org/en/projects-and-research/projects/healthy-lungs-for-life/about/ers/elf/), which raises the awareness for the importance of healthy lungs and clean air.

Next, in a short oral presentation selected from the submitted abstracts, Akhilesh Jha (London, UK) presented his work on the use of a synthetic single-stranded RNA analogue (R848) to study the effect of allergy and asthma on the nasal mucosal innate immune response. Nasal administration of R848 in healthy non-allergic subjects, subjects with allergic rhinitis and subjects with allergic asthma was well tolerated without any evidence of systemic immune activation. Interestingly, asthmatic subjects showed an increase in expression of interferon-stimulated

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The Lung Science Conference and the Sleep and Breathing Conference 2019 brought together leading experts in the field to discuss the latest cutting-edge science, as well as various career development opportunities for early career members http://bit.ly/2XNX6V6

genes in the nasal mucosa compared to healthy subjects. The next speaker, Antje Prasse (Hannover, Germany), discussed the immune mechanisms and inflammation in pulmonary fibrosis and acute exacerbation. The diagnosis of idiopathic pulmonary fibrosis (IPF) exacerbations has proven to be quite challenging, as performing a bronchoscopy may do more harm than good and can lead to further acceleration of the exacerbation. The risk of acute exacerbations appears to differ between patients and the underlying mechanisms are currently under investigation. Antje Prasse discussed her recent study in which they identified a bronchoalveolar lavage cell transcriptome profile that was associated with increased mortality in IPF patients, and from which they consequently developed a gene expression signature predictive of mortality [2]. Interestingly, they observed that genes associated with mortality were highly enriched for those expressed in airway basal cells and this may suggest an unexpected role for these cells in the pathogenesis of IPF. The winner of this year's award for the best oral presentation of a selected abstract, Matthew Loxham (Southampton, UK), summarised his findings of novel cellular effects induced by ultrafine particulate matter (UFPM) from an underground railway station. Exposure of primary bronchial epithelial cells to UFPM showed that transcriptional responses were time dependent, with alterations in genes associated with epithelial maintenance at 6 h post exposure, whereas at 24 h post exposure alterations in genes related to redox homeostasis and metal binding were observed.

In the second part of the session "Triggers of acute exacerbations", Nahal Mansouri (Boston, MA, USA) presented her abstract on the potential therapeutic effect of mesenchymal stem cell-exosomes (MEx) in an experimental model of bleomycin-induced pulmonary fibrosis. MEx treatment in the lung was able to both prevent and reverse the development of pulmonary fibrosis. Interestingly, she reported that the beneficial actions of MEx are mediated *via* modulation of the monocyte phenotype in both the lung and the bone marrow. Niki Ubags (Lausanne, Switzerland) next discussed the involvement of inter-organ interactions in acute exacerbations. Diet-induced alterations of the gut microbiome can either alleviate (high-fibre diet) or exacerbate (low-fibre diet) experimental allergic airway inflammation in mice [3]. The alterations in gut microbiome composition can lead to changes in short chain fatty acids, which can consequently act upon dendritic cell haematopoiesis in the bone marrow. In addition, the importance of the skin microbiome in immune and barrier maturation in early life and consequent development of the atopic march was discussed. Pierre-Marie Boutanquoi (Dijon, France) provided an overview of his work on TRIM33 (tripartite motif containing 33) in fibrogenesis during the last oral abstract presentation of this session. TRIM33 was found to be upregulated in the lungs of IPF patients compared to control, and these findings were recapitulated in an experimental model of lung fibrosis. Induction of pulmonary fibrosis in conditional TRIM33 knock-out mice (specifically in haematopoietic cells) showed increased disease severity and increased transforming growth factor (TGF)-β levels in the lung, suggesting that TRIM33 may play a key role in lung fibrosis.

The microbiome and acute exacerbations

Since the recognition that even healthy lungs are not sterile [4], the microbiome has been implicated as a key player in maintaining pulmonary homeostasis and initiating disease. It appears to be of particular importance at the beginning of life, and Debby Bogaert (Edinburgh, UK) described the composition and development of normal nasopharyngeal microbiota in a cohort of 112 Dutch infants. Those who experienced a higher number of respiratory tract infections in the first year of life could be identified within the first month as characterised by decreased microbial community stability, early enrichment of *Moraxella* and later enrichment of *Neisseria* and *Prevotella* spp. [5]. With potential implications for public health interventions, independent factors associated with the aberrant development of a healthy microbiome included delivery by Caesarean section, infant feeding and recent antibiotic use.

In IPF too, the role of the microbiome in the lower airways is increasingly gaining attention. Accordingly, Philip Molyneaux (London, UK) explained that it seems to be less diverse, more abundant and persistent. Whilst clinicians attempt to differentiate exacerbations as infective or non-infective using traditional culture techniques, the 6-month mortality is still 50% in both groups. Acute exacerbations are associated with an outgrowth of proteobacterial species (also seen in COPD patients after rhinovirus challenge) and gut-associated bacteria, with the latter implicating a role of aspiration as a trigger [6]. The airway microbiome is different between stable disease and during exacerbations, thus highlighting the benefits of serial sampling in the same patient to identify causative pathogens.

The microbiome is also altered in cystic fibrosis (CF) exacerbations, as discussed by Marcus Mall (Berlin, Germany), who explained that molecular-based techniques have extended the range of causative pathogens beyond the usual suspects of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Burkholderia cepacia*. Patients with CF exacerbations have a decline in their lung function and the local microbiota can be an important trigger. He presented results of the CFMATTERS trial (www.cfmatters.eu), in which patients with acute exacerbations were managed with a third microbiome-directed antibiotic in addition to a standard regimen of ceftazidime and tobramycin. The trial did not demonstrate any difference in

forced expiratory volume in 1 s or time to second exacerbation in the active arm. This highlights the need to better understand the associations between airway microbiota and clinical disease, which can be further complicated by host factors such as age and severity of lung disease. Further detail on the lung microbiome and its role in health and disease can be accessed in a recently released ERS *Monograph* [7].

At the end of the session, an early-career oral presentation by Sally Yunsun Kim (London, UK) described a novel *ex vivo* approach to investigate lung injury and repair, which are aberrant in diseases such as COPD and IPF. Wingless/Integrase I (Wnt) signalling plays a key role in lung epithelial development and alveolar epithelial cell function in disease, and augmentation of this pathway may drive tissue repair. Data using murine precision-cut lung slices were presented to demonstrate that Wnt5a treatment increased expression of pro-surfactant protein C (a marker for alveolar epithelial type II cells and an early repair response), highlighting its utility in studying lung injury and repair.

Pathophysiology of acute exacerbation

The session of the LSC on the pathophysiology of acute exacerbation contained three very different multidisciplinary talks describing acute exacerbations from the angles of various diseases, such as asthma, COPD and CF. Interestingly, it also touched upon patient data, treatment aspects and various animal models mimicking acute exacerbations.

It was opened by Thomas Marichal (Liège, Belgium) showing the relationship between host DNA and exacerbations in type 2 allergic asthma. During rhinovirus infection, host double-stranded DNA (dsDNA) is released through neutrophil extracellular trap formation. Host DNA was demonstrated to promote allergic type 2 immunity through stimulation of dendritic cell migration, T-helper cell type 2 (Th2) responses, IgE production and allergic airway inflammation. Through a study of 23 asthma patients, he demonstrated that rhinovirus infection induces dsDNA release, which strongly correlated with exacerbation severity in type 2 immune-mediated asthma [8]. This work may represent potential therapeutic targets for rhinovirus-induced asthma exacerbations.

James Chalmers (Dundee, UK) discussed the role of the lung microbiome in bronchiectasis. At the phylum level, the microbiota appears to be largely dominated by either the presence of proteobacteria or firmicutes, with correlations between proteobacteria dysbiosis, disease severity and neutrophilic inflammation. Studies indicate that some patients suffer from a loss of microbiome diversity during an exacerbation, but that exacerbations are highly heterogeneous events with no consistent microbiome change associated with exacerbation. Individual patients show remarkable stability of the microbiome over time. Antibiotic treatment is the mainstay of therapy for bronchiectasis but does not work for all patients. New data were presented from an analysis of a randomised controlled trial of inhaled antibiotics [9], showing that patients only responded with an improvement in symptoms if they had a high baseline bacterial load of Gram-negative pathogens.

Next, Mirjam Roffel (Groningen, the Netherlands) showed, in a short oral presentation, the association between the microRNA miR-223-3p and airway inflammation in asthma and COPD. Patients with asthma and COPD both had significantly higher levels of miR-223-3p compared with controls. Additionally, she showed that patients with asthma demonstrated a positive correlation between miR-223-3p and eosinophils, whereas COPD patients had a positive correlation between miR-223-3p and neutrophils. The session was concluded by another short oral presentation based on a selected abstract by Eliza Tsitoura (Heraklion, Greece), who discussed her work on the expression of the microRNA Let7c, which is required for the differentiation of alternatively activated macrophages. She found that Let7c was significantly lower in patients with IPF compared with other interstitial lung diseases, and that low Let7c levels are significantly associated with lower survival in patients.

Philip Hansbro (Newcastle, Australia) started the second part of this session by talking about cellular mechanisms underlying steroid-refractory asthma. Various animal models were presented, where a classical ovalbumin model was used to create allergic inflammation and was characterised by increased airway hyperresponsiveness and elevated eosinophil counts. However, the introduction of respiratory tract infection using *Chlamydia muridarum*, *Haemophilus influenzae*, influenza (H1N1) or respiratory syncytial virus, following ovalbumin challenge, induced pathophysiology in allergic mice. In this exacerbation model, they could not reverse the exacerbation by steroid treatment, showing intervention resistance. Steroid resistance was however restored in a miR-21 knock-down [10]. An additional insight was that loss of asthma control was associated with significant NLRP3 inflammasome staining in macrophages and epithelial cells. The NLRP3 inflammasome has been demonstrated to play an important role in activation of mature interleukin (IL)-1β [11, 12], a cytokine that was frequently mentioned throughout various sessions during this year's LSC.

Christopher Brightling (London, UK) gave an overview of the mechanisms of acute exacerbations in COPD. He presented the day-to-day variation of COPD exacerbation markers presented as biological clusters [13]. When observing the total colony-forming units of bacteria in the airways at exacerbation, not only did they increase in total numbers but also the diversity of colonising bacteria was increased. *Haemophilus influenzae*

presented as the major species at baseline, while other species colonised and took over at exacerbation. The quantitative PCR bacterial load correlated with tumour necrosis factor-α and IL-1β [14]. Interventional studies involving azithromycin showed that this can reduce the COPD exacerbations, which leads to discussion about personalised therapy. Which patients should be targeted by using macrolide treatment? If we search for certain biomarkers, would sputum eosinophils be a good predictor? Data about the use of an anti-IL-5 receptor antibody in a COPD cohort were presented, where decreased blood and sputum eosinophilia have been seen [15]. Lastly, Christopher Brightling introduced the technique of breathomics, where a device is used to collect breath biomarkers for infection and inflammation, which could also be used to identify bacterial load.

The last talk of the session was held by Aurélie Crabbé (Ghent, Belgium), presenting her data from their *in vitro* models of CF. It is a known fact that CF patients suffer from chronic colonisation of the airways by certain bacteria and, due to this, antibiotic treatment is difficult to manage. Antibiotic resistance and tolerance are observed, due to biofilm formation by the bacteria. Also, the microbiome influences the efficacy of any medication that is administered. An RNA sequencing approach was employed to study the influence of multispecies *versus* single species occurrence on the basis of biofilm formation. The most prominent genes that were of interest were associated with the cell wall of the bacteria. To confirm and build further on these findings, transmission electron microscopy was used to study the cell wall composition of the bacteria. Interestingly, in a state of antibiotic resistance, the cell wall thickness was increased in cultures where multispecies biofilms were produced [16]. The phenomenon of antibiotic and bacterial interaction was observed from the opposite view as well. Not only did the microbiome affect antibiotic resistance and efficacy, but antibiotic treatment also had an impact on the diversity of the bacterial community. Furthermore, colonising *Pseudomonas aeruginosa* was able to downregulate IL-1β, IL-8 and IL-6, *via* the interferon regulatory factor and NF-κB pathways. These events were studied in three-dimensional lung epithelial cell cultures [17].

Early-career delegates session: how to advance your career

Next to the great science presented in Estoril, as in previous years, the Saturday afternoon was dedicated to the career development of Early Career Member delegates. The topic of the LSC 2019 ECMC session was "How to advance your career" and the session included four talks covering career opportunities in academia and industry, with the aim of helping young researchers to boost their careers.

The session was opened by Sabine Bartel (Groningen, the Netherlands), who is the current ECMC representative for Assembly 3. She provided an overview of ECMC vision and mission as well as opportunities for Early Career Members to engage with ERS activities. Her talk was followed by Gunilla Westergren-Thorssen (Lund, Sweden), Director of Wallenberg Centre for Molecular Medicine at Lund University, who presented an example of a successful academic model, aiming to strengthen the research field in Sweden. She emphasised that an important step is to support young researchers by providing junior research groups with attractive start-up packages. She also indicated that the objective of the tenure track system is to provide career and leadership support to young group leaders, who are expected to be the future leaders, by offering mentorship programmes as well as various seminars and workshops.

Darcy Wagner (Lund, Sweden), a recently successfully recruited junior group leader within this programme, talked about challenges she has faced along the way to become an associate senior lecturer at Lund University. She emphasised that everybody in academia encounters numerous rejections of papers and grant proposals, but what really matters is to learn how to handle rejections, learn from the feedback you are given and to continue trying. She added that she owes her success to "perseverance, hard work and creative problem solving". Darcy Wagner ended her presentation with three take-home messages: "Sometimes you need to fail really big until you succeed", "Find good mentors and keep them", and "Don't strive to be like your mentor, as they already exist, but be you".

After a discussion about career paths in academia, Sorif Uddin (Biberach, Germany), head of *in vivo* pharmacology at Boehringer Ingelheim, presented his view from the industry perspective on tips for a successful entry into industry. His first point was "Understand what you want to do and then find someone who will pay you to do it". The second step he mentioned was to make sure that your CV stands out from the crowd, as a CV is your marketing document and its very first impression will determine whether you will be considered for an interview or not. Therefore, he recommended emphasising one's skills and abilities according to the position you are applying for. He stated that the criteria for making a hiring decision after the interview is based on the applicants' scientific potential and enthusiasm for the future role, their presentation and leadership skills, as well as whether they fit into the team. Therefore, his advice was: "Be authentic at the interview and don't try to be someone you are not, as people will see through it".

The Early Career Member career development session ended with a presentation from Marc Kästle (Biberach, Germany), who described the interview process from the perspective of a successful industry applicant. He once again stressed that a well-written CV and a thorough preparation for the interview are essential in achieving your goal.

He advised customising your CV for every job you are applying to. According to him, the second important part is the preparation for the interview, where the applicant should be able to show good scientific, presentation and communication skills as well as knowledge about the company and what you would bring to the company as an employee. He ended his talk with three questions an applicant should be able to answer before coming to an interview: "Do I really want the job? Why do I want the job? Why am I the best candidate for the job?"

The session was concluded with an interactive discussion with the audience and the presenters and was followed by a networking event over drinks and snacks, where Early Career Members had the opportunity to interact with the speakers and other members.

In conclusion, the LSC in 2019 was a big success, where great science was presented along with a lot of career development opportunities for ERS Early Career Members. We can only highly recommend this meeting and encourage all Early Career Members to be part of this conference next year!

Sleep and Breathing Conference 2019

Next to the LSC, another exciting event of the ERS took place in April in Marseille, France, namely the Sleep and Breathing Conference, which is organised by the ERS and the European Sleep Research Society. Just like the LSC, this conference also provided a unique opportunity to Early Career Members to network with professionals in the field and in the following sections we highlight a couple of sessions from this conference.

Clinical assessment and comorbidities of sleep disorders

In the poster discussion session on clinical assessment and comorbidities of sleep disorders, the studies presented were focused on novel diagnostic techniques, aiming to provide a more accurate diagnosis of sleep disorders, and on conditions that may co-exist with obstructive sleep apnoea (OSA), such as cardiometabolic disease and chronic lung disease.

In the novel diagnostics section, Sunil Kumar (Zurich, Switzerland) described the development of a noninvasive method of sleep staging that utilises cardiorespiratory signals and body movements to identify sleep stages. The random forest technique was used in the development phase. A total of 13 night signals captured in healthy subjects was used to train the system. The authors concluded that cardiorespiratory features came out as much more relevant than movement, which indicates that the latter may be omitted without risking a meaningful decrease in scoring accuracy. However, further validation is still needed to secure a safer diagnosis, especially in the elderly and in patients with heart failure or severe OSA.

An important study was presented by Ingrid Jullian-Desayes (Grenoble, France) on the association of chronic intermittent hypoxia in OSA with non-alcoholic fatty liver disease (NAFLD), which aimed to further elucidate severity indices. The study population was examined with polysomnography and noninvasive tests to evaluate liver steatosis. The main risk factors for fibrosis were apnoea–hypopnoea index (AHI) >30 events·h^{-1}, male sex, hypertension and type 2 diabetes. Another similar work was presented by Wojciech Trzepizur (Angers, France), which investigated the association between OSA and NAFLD by using magnetic resonance imaging (MRI). Liver steatosis evaluation was performed by measuring the proton density fat fraction, which is the fraction of MRI-visible protons bound to fat divided by all protons in the liver. Analysis of the results showed that severe OSA is associated with increased liver steatosis, but this association is not maintained after adjustment for confounders, including body mass index (BMI).

The Swedish team of Eva Lindberg (Uppsala, Sweden) investigated the connection between snoring and nocturnal gastro-oesophageal reflux (nGOR) with daytime sleepiness. Sending a questionnaire to randomly selected women, a total of 4882 subjects was screened for daytime sleepiness and involuntary sleep during the day. The main finding of this study was that women with nGOR were at increased risk of developing daytime sleepiness, and snoring augmented this association.

An assessment of cardiometabolic burden in OSA was performed by the means of proteomic-based technologies, allowing the measurements of cardiac and inflammatory proteins. This was presented by Mirjam Ljunggren (Uppsala, Sweden). A total of 400 women participating in the "Sleep and Health in Women" cohort study in Sweden underwent polysomnography, anthropometric measurements and blood sampling. Two proteomic assays, each measuring 92 proteins, were analysed in a subsample of 253 women. The study concluded that OSA severity was not strongly correlated to certain cardiac and inflammatory proteins, and that BMI and age were the most important contributing factors. However, it is important to note that this study included only women, in whom the alterations in hormones may also play crucial cardioprotective role.

In summary, it is now well established that cardiovascular disease should be carefully investigated in OSA patients. Furthermore, it is increasingly becoming evident that liver diseases should be included in the list of comorbidities of OSA.

Obstructive sleep apnoea

In the OSA poster discussion session, several important studies focusing on the impact of OSA on general health and its correlation with chronic

heart disease were presented. The session featured a couple of large European population studies.

An outstanding multinational European study, presented by Izolde Bouloukaki (Heraklion, Greece), aimed to investigate the association between mild OSA and hypertension in the European Sleep Apnoea Database (ESADA). A total of 7995 adults with simple snoring or mild OSA in an overnight sleep study was studied. It was shown that arterial hypertension was prevalent in 37% of mild OSA patients, with a statistically significant difference from non-apnoeic snorers. Moreover, higher waist/hip ratio, type 2 diabetes mellitus and hyperlipidaemia were more prevalent in the OSA group. In conclusion, this study demonstrated that mild OSA (AHI 11–15 events·h^{-1}) is an independent risk factor for hypertension.

Another study was presented by Izolde Bouloukaki on the cardiovascular risk in OSA, which investigated potential sex differences. A large population of 6716 patients underwent polysomnography, Epworth sleepiness scale evaluation and Beck Depression Inventory measurement. Female sex independently predicted prevalent cardiovascular risk and depressive symptoms, whereas men independently were more likely to report driving problems and daytime sleepiness.

A large population-based study (EpiHealth) from Sweden aimed to correlate dietary habits with OSA. This was presented by Jenny Theorell-Haglöw (Uppsala, Sweden). With a total of 24944 subjects, this is one of the biggest studies of this type to date. Participants answered questionnaires on sleep and diet (adherence to a Mediterranean diet (mMED score)). The main finding was that having short sleep time and disturbed sleep has a negative impact on adherence to diet. The relationship seems to be sex specific, mainly affecting women.

The elderly population is an important population that most of the sleep studies usually omit from investigation. A study population of 283 subjects, with a mean age of 72 years, underwent a single home polygraphic recording, as reported by Annachiara Sarno (Rome, Italy). Metabolic syndrome was more frequent in OSA patients, males were prone to OSA and females prone to insomnia.

Felipe Uriza (Bogota, Colombia) presented a study attempting to correlate OSA with cognitive impairment and small vessel disease. MRI of the brain was used to identify lesions in white matter. The frequency of cardiovascular disease was higher in patients with OSA, and mild cognitive impairment in patients with OSA was shown to be associated with cardiovascular disease.

An innovative study, presented by Jean-Benoit Martinot (Namur, Belgium), examined the relationship between head and body positions with apnoeas and hypopnoeas in OSA. Using additional sensors for head movements, the study team attempted to correlate both the head and body positions to events during sleep. It was finally shown that prone pitching and right yawing were the most important positions contributing to most apnoea events.

In summary, the three large-scale population-based studies that were presented in this session further illustrated the existence of cardiovascular disease and hypertension even in "mild" OSA patients. Moreover, the adherence to a healthy diet is crucial for reducing disease burden in OSA.

Finally, the Sleep and Breathing Conference 2019 offered important new insights from many large European cohorts and it is definitely worthwhile to attend for Early Career Members in the field.

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Conflict of interest

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