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RESPIRATORY

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+ Review of ERS 2019

Madrid, Spain

Contents

"The peer-reviewed articles in this year's edition are as inspirational as ever. "

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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This Publication

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Front cover and contents photograph: Paris, France, home of the ERS 2018. © marina99 / 123rf.com

Welcome

I am proud to present to all our readers this year's edition of *EMJ Respiratory*, an eJournal fit to burst with the latest hotly discussed topics and research findings in the field of respiratory medicine. This year we journeyed to the elegant Spanish capital of Madrid for the European Respiratory Society (ERS) International Congress 2019 to bring to you all the latest cutting-edge research alongside a host of interviews with key opinion leaders and exciting abstract reviews.

Held at the IFEMA – Feria de Madrid, founded in 1980 and now crucial to the international circuit of the congress industry, ERS celebrated its 29th year. The gathering of >20,000 delegates over the 5 days featured no less than 420 scientific and educational sessions, with the main theme this year being prevention. Featured in our congress review, you will find some breaking news stories such as: lung disease being monitored with a 'smart shirt' named Hexoskin, which is able to measure the volume of inhaled and exhaled air; susceptibility to respiratory infections in babies being linked to having less well-connected bacterial networks across the nose, mouth, and gut; and truck drivers being found to be at high risk of a type of sleep apnoea that can cause them to crash whilst driving. EMJ Respiratory also showcases a taster of various abstract presentations that will really get you thinking about the future of this exciting field.

It is with great pleasure that I am also able to say that we have included fascinating interviews with some of the most influential experts in the field. Professor Barbara Hoffmann, Chair of the Environmental and Health Committee (EHC)-ERS, joined us for an interview about her interest in the area of air pollution on cardiopulmonary health and the influence of the EHC in regulating the upper limits of air pollutant emissions. We also had the pleasure of talking with the ERS Education Council Chair Professor Daiana Stolz, who spoke with us about her role in development, implementation, and refinement of a framework for respiratory healthcare professionals to follow. This journal also boasts a large selection of written contributions from respiratory specialists across the globe on topics such as adverse pregnancy outcomes in asthmatic women according to steps of treatment, and characterisation and molecular profiling of nonsmall cell lung cancer samples.

I would like to take this opportunity to personally thank all our contributors, peer-reviewers, Editorial Board members, and of course our staff behind the scenes at EMJ, who have all worked hard to ensure *EMJ Respiratory* is a success. So read on, enlighten yourself on the latest in respiratory research, and we hope you find this journal as much of a joy to read as it was to publish.

Spencer Gore

Spencer Gore

Chief Executive Officer, European Medical Group

Foreword

Dear colleagues,

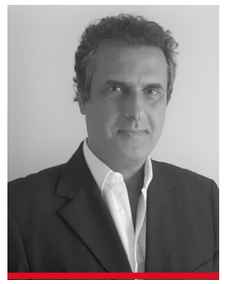
Allow me to welcome you to this year's edition of *EMJ Respiratory*, bringing you the latest cutting-edge developments in this ever-changing field.

I am delighted to introduce our review of the European Respiratory Society (ERS) International Congress annual meeting that was hosted in Madrid, Spain, from 28th September to 2nd October 2019. The three main topic areas that the event focussed on were smoking cessation, including e-cigarettes and heated tobacco products; air pollution; and vaccination. The programme presented trailblazing science in all fields of respiratory medicine, state-of-the-art educational programmes, specialised and practical courses, and a strong focus on daily practice. The ERS congress continues to be an opportunity to meet colleagues and experts and discuss projects directly, enabling the sharing of new ideas with fellow scientists, clinicians, and healthcare professionals from worldwide.

EMJ Respiratory includes a number of peer-reviewed articles covering a diverse range of pneumological topics, such as asthma. Asthma is the most common respiratory disease in children <5 years of age and is often underdiagnosed. The Semi-structured qualitative interviews with 22 rural primary care health professionals and 13 caregivers in Kyrgyzstan undertaken by Stubbe et al. explored and elucidated reasons for the underdiagnosis in under-5s. My Editor's pick is the cross-sectional study by David et al. evaluating the acute effects of noninvasive ventilation on autonomic modulation following exercise-induced bronchoprovocation in asthmatic children. The return of autonomic activity basal levels after the bronchial provocation test was reported both in the responding and nonresponding groups. Further included in this year's edition are two reviews that discuss the lung cancer histological subtypes, along with current and evolving approaches to diagnosis and staging to optimise the treatment in the era of precision medicine considering the growing field of targetable oncogenic driver mutations and of immuno-oncology.

On behalf of the *EMJ Respiratory* Editorial Board and the staff of the EMJ, I would like to thank all authors for their efforts in contributing to the publication of this new issue and I am sure you will enjoy reading all the stimulating articles in this new edition as much as I did.

Yours sincerely,



Dr Antonio Rossi

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Congress Review

Review of the 29th European Respiratory Society (ERS) International Congress

Location: IFEMA Exhibition Centre, Madrid, Spain
Date: 28th September - 2nd October 2019
Citation: EMJ Respir. 2019;7[1]:10-23. Congress Review.

The President of the European Respiratory Society (ERS) expressed his great pride in the "high-quality scientific and educational experience" of this year's Congress, held in sunny Madrid, in his Welcome to delegates. The event was certainly an endeavour to be proud of, hosting more than 20,000 delegates over five days and offering more than 420 scientific and educational sessions. Meet the Expert, Postgraduate Sessions, and much more was on offer to inspire delegates from across the field of respiratory. The central theme of the congress was prevention, and the coverage of this theme comprised three distinct branches: smoking cessation, air pollution, and vaccination. Delegates were treated to a scientific programme filled with exciting opportunities to learn, discuss, debate, and network; the key highlights of the event have been summarised in our Congress Review section.

Read our pick of some of the most pressing news updates announced at the Congress. This includes the news of a brand new treatment option for patients of rare genetic disease primary ciliary dyskinesia, the possible impact on offspring of pregnant women's exposure to bisphenol A (BPA) during pregnancy, and an exciting new smart shirt that could help physicians monitor lung function in chronic obstructive pulmonary disease patients. The advances announced at the congress will enable respiratory specialists and trainee physicians alike to take huge strides forward in patient care, diagnostics, and much more.

In addition to our roundup of respiratory news stories, we present a hand-picked selection of abstract summaries written by the presenters themselves. The ERS congress saw a wealth of abstract presentations representing the very best in respiratory research; our team was spoilt for choice when selecting high-quality presentations to include in the Abstract Reviews. Topics include coal mine dust lung disease in Australian men, the REVEAL 2.0 Risk Score from Australia and New Zealand, the development of an mHealth asthma app,

"The central theme of the congress was prevention, and the coverage of this theme comprised three distinct branches: smoking cessation, air pollution, and vaccination."

and sleep-disordered breathing in chronic kidney disease patients, amongst others. Keep an eye out for the authors, who are sure to be rising stars in the respiratory world!

Interviews with pre-eminent figures in the respiratory field add even more timely discussions to our Congress Review. Prof Barbara Hoffmann, Chair of the Environment and Health Committee (EHC), discusses the important work of this committee in shaping EU legislation and ERS Education Council Chair Prof Daiana Stolz enlightens us about the important collaborations happening between working groups, committees, and councils within ERS. Our interviews sections casts light on those more intricate topics within the field of respiratory, raising awareness of the work being done at all levels of the field to improve patient care and the infrastructure within which our colleagues and peers work, making them an invaluable addition to our Congress Review.

"The advances announced at the congress will enable respiratory specialists and trainee physicians alike to take huge strides forward in patient care, "

Next year, the ERS congress will be held in Vienna, Austria, and the EMJ team eagerly awaits the opportunity to witness even more progress in respiratory research and patient care. Until then, read all about our highlights of this year's congress.

Exposure to Different Pollutants and Areas in the UK Increases Risk of Infant Deaths

"We found that NO_2, PM10 and SO_2 are each linked in varying degrees to infant deaths from any cause, and to neonatal and post-neonatal deaths."

CHALLENGES to reduce the risk of air pollution exposure in infants are presented to researchers who have shown that certain air pollutants are associated with increased risk of death in the most polluted areas of the UK. This is according to findings presented at this year's ERS Congress in Barcelona, Spain and reported in a press release dated 27th September 2019.

Three pollutants, nitrogen dioxide (NO_2) and particulate matter (PM10), generated from traffic, and sulphur dioxide (SO_2), predominantly released from industrial activity, were found to be associated with increased risk of death in infants from highly polluted areas compared to those from areas with less pollution. The pollutants were shown to have this effect as separate components or in combination. One of the researchers, Dr Sarah Kotecha, Cardiff University School of Medicine, Cardiff, UK, commented on the findings: "We found that NO_2, PM10 and SO_2 are each linked in varying degrees to infant deaths from any cause, and to neonatal and post-neonatal deaths. This is an important finding as the pollutants are produced and derived from different sources."

Annual pollution exposure was calculated from data taken between 2001–2012 in England and Wales and used with data from 7,984,366 live births and deaths during these years to link death rates to the amount of pollution in each area of the country. The findings showed that there was an increased risk of up to 50% in death from any cause in infants from birth up to 1 year of age in the most polluted areas of the country. There was a 21% increased risk for SO_2, but not for NO_2 or PM10, in neonatal deaths, defined by death within the first 28 days of birth, which Dr Kotecha stated could be due to the individual mechanisms of the pollutants. The findings indicated that future research may include therapies depending on amounts of exposure to different types of pollutants posing a risk to the number of infant deaths.

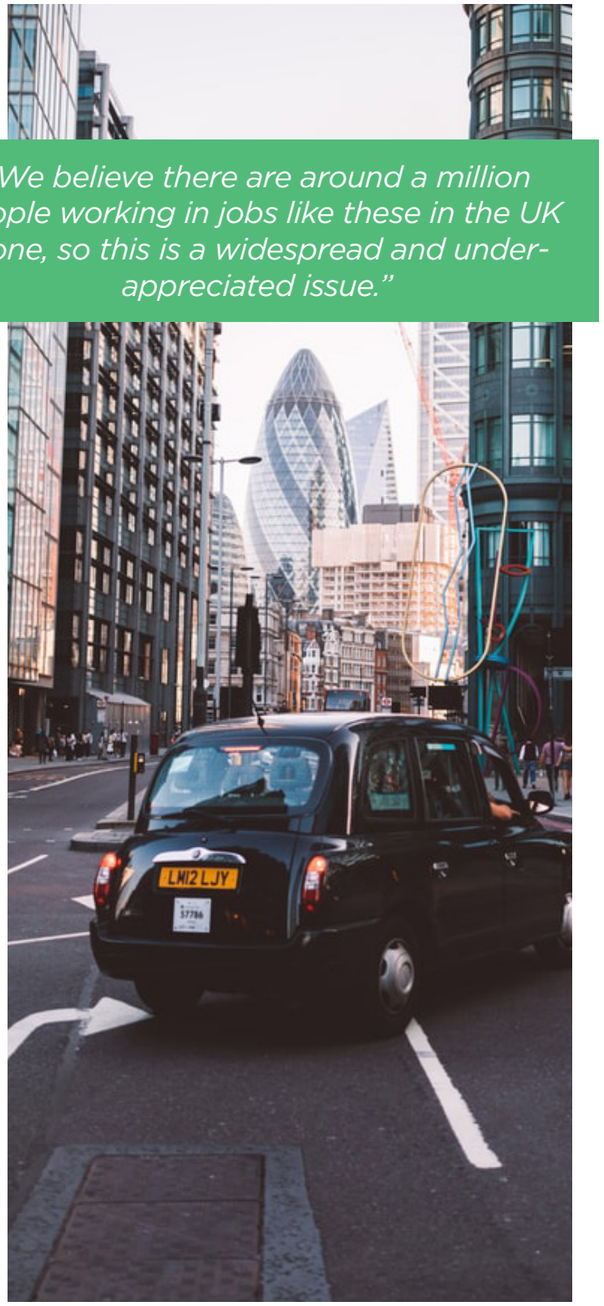
Professional Drivers Experience Different Levels of Black Carbon Exposure at Work

EXPOSURE to black carbon is, on average, highest in taxi drivers working in central London compared to other professional drivers in the city, or to those at a busy roadside. This is according to findings presented at this year's EASD Congress in Barcelona, Spain and reported in a press release dated 29th September 2019. The findings are a result of a collaboration between researchers from London, UK universities, King's College London and Queen Mary University of London.

A total of 140 individuals who worked as professional drivers in central London were required to drive for a total of 96 hours whilst carrying black carbon monitors in their vehicles. They provided details about the type of vehicle they drove, the hours they worked, and whether they had either their air vents or windows open when they drove. The researchers aimed to investigate the effect different levels of pollution exposure on the health of professional drivers in central London. Mr Shanon Lim, PhD candidate at King's College London, presented the research and commented: "We believe there are around a million people working in jobs like these in the UK alone, so this is a widespread and under-appreciated issue."

The monitors, linked with GPS trackers, measured exposure levels per minute. The research showed that professional drivers were subject to 4.1 micrograms of black carbon per cubic metre of air ($\mu g/m^3$) when they worked in central London, this is approximately four times as much the exposure received at the drivers' homes, or experienced by professionals who work at an office desk indoors. The drivers also encountered spikes of black carbon exposure which lasted up to 30 minutes and often exceeded 100 $\mu g/m^3$.

Emergency service drivers experienced the lowest levels of black carbon exposure, 2.8 $\mu g/m^3$, the researchers speculated whether this may be because of emergency vehicles' ability to escape congestion. Taxi drivers endured the highest levels of black carbon exposure at an average of 6.5 $\mu g/m^3$. The researchers suggested that air pollution may be highest in areas that taxi drivers typically work in and can become trapped inside the vehicle. The authors advise that it is possible for drivers to protect themselves from the effects of pollution by driving with the windows closed, taking alternative routes, and using air filters.



"We believe there are around a million people working in jobs like these in the UK alone, so this is a widespread and under-appreciated issue."

Truck Drivers at High Risk for Crash-Causing Sleep Apnoea

SLEEP-RELATED breathing problems, which can cause drivers to fall asleep while driving, are present in up to 50% of truck drivers, suggests a research study that was presented at ERS this year and reported in a press release dated 30th September.

In the study, 905 Italian truck drivers were interviewed to determine the prevalence of sleep-related breathing problems in the population, and the lifestyle factors that may increase the risk of such issues. Of the participants, 887 were men, average age was 46 (range: 19–78), and 77% were overweight (BMI ≥25). The structure of the study comprised a health survey that took place on 44 days between March and December in 2018. The interviews were conducted by volunteer expert patients, doctors, and nurses at truck dealerships, driver training days, and at a truck driver show. The questions in the health survey included:

• Do you sometimes stop breathing and have sleep apnoea at night?

• Do you snore?

• Do you wake up needing to urinate urgently?

• Are you dissatisfied with how you have slept?

• Do you frequently feel the desire or need to sleep during the day (except after lunch)?

• Do you take drugs for high blood pressure?

Strikingly, nearly 10% of drivers said that their partners noticed that they stopped breathing when they were sleeping sometimes. Furthermore, the answer 'yes' was given by 43% of participants to two of the survey questions, and therefore were at risk of obstructive sleep-apnoea.

Luca Roberti, President of Apnoici Italiani (the Italian Sleep Apnoea Patient Association), said: "This observational study has underlined the high prevalence of obstructive sleep apnoea among truck drivers, which is greater than the prevalence in the general population. This is due to a lifestyle that forces the drivers to sit for several hours a day, with little physical activity and a poor diet, leading to a greater risk of excessive daytime sleepiness and of dozing off unexpectedly while driving."

"This observational study has underlined the high prevalence of obstructive sleep apnoea among truck drivers, which is greater than the prevalence in the general population"

Lung Disease can be Monitored with a 'Smart Shirt'

'SMART SHIRTS', in conjunction with mobile phone apps, can accurately measure lung function for patients with lung disease, according to the results of a study presented at this year's ERS Congress held in Madrid, Spain, and reported in a press release dated 30th September.

Chronic obstructive pulmonary disease is a chronic, progressive disease that requires long-term lung-function monitoring to assess disease progression. Traditional monitoring is normally completed in a clinical setting and is not practical for everyday activity, unlike the smart shirts that can be worn underneath normal clothing. As the wearer's chest expands and contracts, the smart shirt, named Hexoskin, measures the volume of inhaled and exhaled air by sensing the stretch of the fabric, in addition to heart rate and movement.

Denise Mannée, a technical physician, PhD candidate, at Radboud University Medical Centre, Nijmegen, the Netherlands, presented the results of the study. The breathing of the healthy volunteers (N=15) was monitored whilst doing activities such as lying down, sitting, standing, climbing stairs, and vacuuming. This was completed whilst the volunteers wore the smart shirt alone, then repeated whilst also wearing traditional equipment to assess the accuracy of the smart shirt.

A marginal difference (0.2%) between the equipment whilst lying was observed, a slightly greater difference (3.2%) was observed in the more strenuous activities, such as vacuuming.

"These results are important because they indicate that the smart shirt can be worn by patients while they go about their daily lives to accurately measure their lung function"

"These results are important because they indicate that the smart shirt can be worn by patients while they go about their daily lives to accurately measure their lung function," Mrs Mannée explained. Thinking towards the future, the researchers now plan to investigate the use of the smart shirt for the monitoring of other respiratory disease such as asthma, cystic fibrosis, or post lung transplantation.

Susceptibility to Respiratory Infections in Babies Linked to Well-Connected Bacterial Networks

MICROBIAL communities, consisting of microscopic bacteria present in all humans that group together in various parts of the body such as the gut, lungs, nose, and mouth, have been shown to be linked to one another across the body. According to findings presented at this years ERS congress in Madrid, Spain, and reported in a press release dated 1st October 2019, for the first time the extent of which these microbial communities (microbiota) are linked to each other and their relevance to respiratory infections susceptibility in babies has been shown.

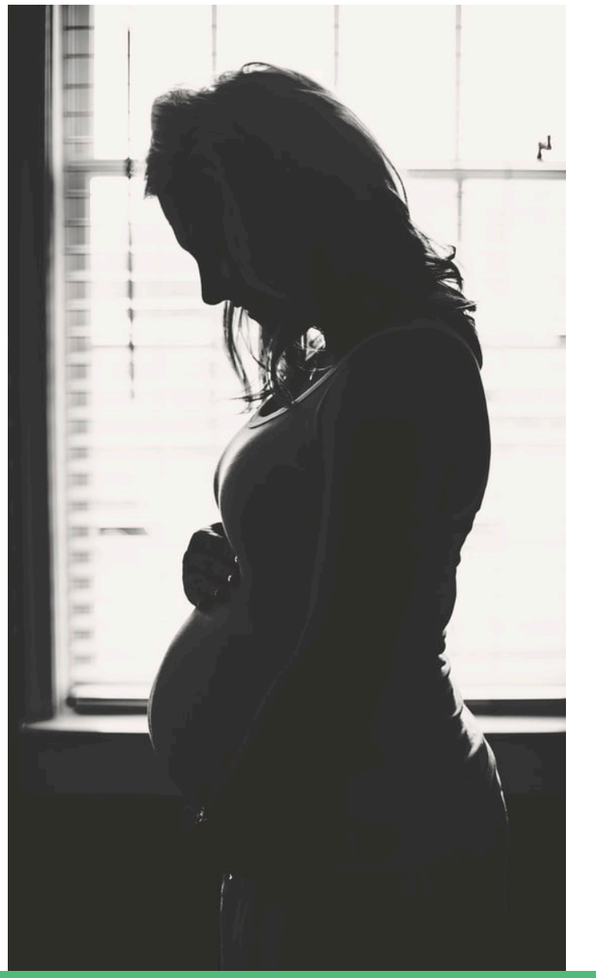
Dr Melanie Clerc, Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK, stated that infants with better connected and organised microbiota had fewer respiratory diseases compared to those with fragmented networks. For the study, samples from the nose, mouth, and gut were collected from 120 babies 1 week after birth and then at 2,4, and 6 months for the large prospective Microbiome Utrecht Study in Utrecht, Netherlands. Furthermore, data on lifestyle and environmental factors affecting the babies, and the amount of respiratory diseases they developed in their first year of life were gathered.

The bacteria from the collected samples were analysed at multiple timepoints and using a mathematical algorithm the researchers were able to create networks that elucidate the interactions between all of the microbes at each timepoint and over time. The study revealed that 1-week postpartum microbial networks had already been well-defined in babies who proceeded to experience 0–2 infections in their first year of life. Findings also uncovered that these networks were composed of four large clusters of bacteria, three clusters specific to either the nose, mouth, or gut; and a fourth, composed of species of mixed origin, that linked the other three groups.

Dr Clerc also noted that the children who developed more respiratory tract infections showed, small, less-well connected clusters from early on in life. She believes "our findings may lead to new insights into ways of using these cross-site microbial connections to prevent respiratory infections in childhood and to understand how susceptibility to disease is linked to the way these microbial communities mature." The researchers plan to investigate the specific mechanism by which bacteria communicate across different sites, and how the communication networks are affected by medical intervention around the time of birth.

"our findings may lead to new insights into ways of using these cross-site microbial connections to prevent respiratory infections in childhood and to understand how susceptibility to disease is linked to the way these microbial communities mature"

Phenol Exposure's Impact on Respiratory Function



PREGNANT women subjected to higher levels of bisphenol A (BPA), a group of chemicals used in the manufacture of food containers, plastic bottles, toys, and some paper, have a higher risk of having children who wheeze and poorer lung function. According to research revealed on the 1st October 2019 during a press release at this years ERS congress, these commonly used chemicals might affect the baby's development, and lung function in later stages of life.

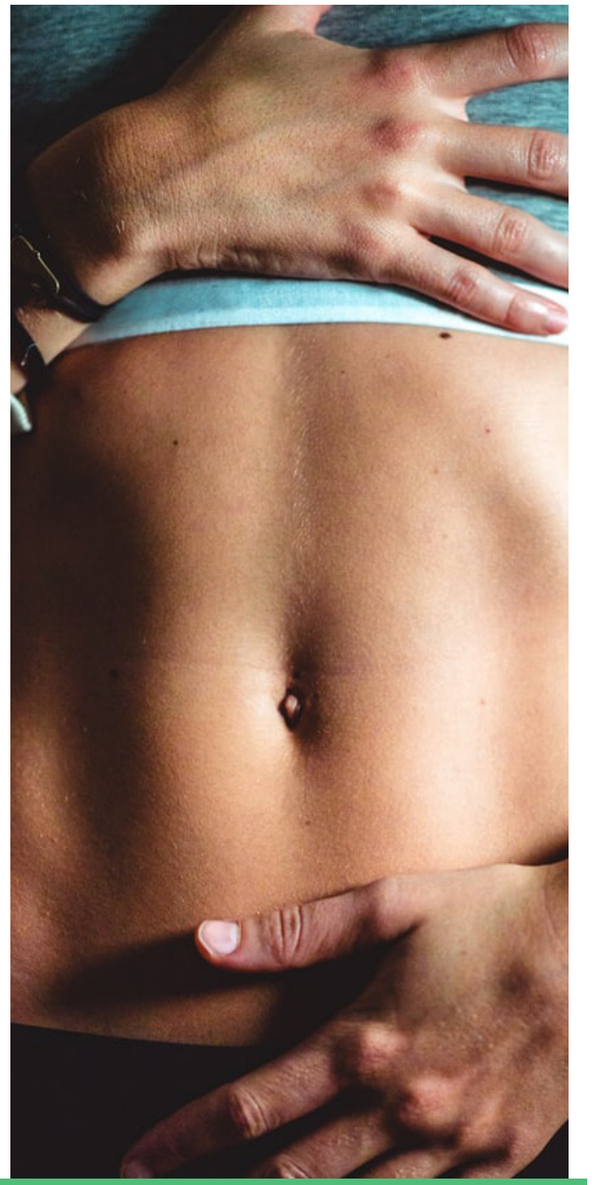
Research has shown that phenols such as BPA can interfere with hormone signals in the body. The recent research by predoctoral Alicia Abellan, Barcelona Institute for Global Health (ISGlobal), examined pregnant women's exposure to different phenols and discovered that the majority of them had detectable levels of BPA in their urine. According to Ms Abellan "when babies are still in the womb, they are especially vulnerable to these substances because they have not yet established the ability to remove toxic substances, and their respiratory and immune systems are still developing."

"when babies are still in the womb, they are especially vulnerable to these substances because they have not yet established the ability to remove toxic substances, and their respiratory and immune systems are still developing."

In the study 2,685 pairs of mothers and their children already enrolled in one of eight large European research projects were examined. Urine samples were used to examine the mothers' exposure to BPA and other phenols during pregnancy. Children's lung functions were measured when they were aged 6–10 years, and questionnaires were used to determine whether children wheeze. Results revealed that 79% of the women had detectable quantities of BPA in their urine; furthermore, higher levels of BPA in women corresponded to a 13% likelihood of having children who wheeze. Additionally, doubling of BPA in a mother's urine sample was associated with an estimated 5 mL decrease in a child's lung capacity.

Moving forward, the study group plans to continue investigating the effects of phenol exposure and the link to respiratory effects. Ms Abellan believes that "policy makers and clinicians should be aware of the role that these commonly used chemicals might play in the very earliest stages of a baby's development and the impact that could have on our population's health at later stages of life, as we know that having lower lung function in early life makes people more prone to developing chronic lung diseases like chronic obstructive pulmonary disease."

Breathing Difficulty Risk Linked to Polycystic Ovary Syndrome Prevalence



POOR respiratory health, determined by lung function tests and defined as lower lung capacity, appears to exhibit a positive association with polycystic ovary syndrome (PCOS), revealing a potential link between these two seemingly distal conditions. This message was delivered as part of a press release on Wednesday 2nd October at the ERS Congress in Madrid, Spain.

Using lung function data contributed by the UK Biobank project consisting of 182,619 women's records, as well as previously published genetic data related to PCOS, the group of researchers from Imperial College London, London, UK, aimed to determine why such a high prevalence of chronic obstructive pulmonary disease can be seen in patients who are neither male or smokers, the most-associated predictors of disease manifestation. Mendelian randomisation was incorporated into a strategy involving the testing of lung function using a spirometer, a device used to quantitate the volume of air a person can exhale in one second and the total exhaled in a singular, forced breath. Genetic variance linked to PCOS was also included within the investigative model, which due to its origin in birth and persistence throughout one's life, could be causatively linked to breathing difficulty in adulthood.

PCOS was seen to account for an approximately 10% increased likelihood of reduced lung function, conferring an increased risk for comorbidities such as cardiovascular disease. Dr Diana van der Plaat, a fellow from the institute involved with the RESPIRE 3 study, noted that "this research highlights the fact that PCOS can affect different parts of a woman's body, not only her reproductive organs." The researchers concede that their work does not fully explain the mechanisms of this connection, however insulin levels and diabetes were proposed to be implicated; these factors are both symptomatic in PCOS patients. The researchers next plan to investigate the effects of hormonal regulation on lung function.

"this research highlights the fact that PCOS can affect different parts of a woman's body, not only her reproductive organs."

Prof Daiana Stolz, Chair of the ERS Education Council, concluded that "Doctors need to be aware that women with PCOS may be at a higher risk of having poor lung function, which might require follow-up and treatment."

MicroRNA Linked to Respiratory Failure or Sepsis in Pneumonia Patients

A TEAM of Spanish researchers from Consorci Hospital Universitari de Valencia and the University of Valencia have produced findings identifying specific genetic fragments as predictors of respiratory failure or sepsis in pneumonia patients. This could allow for doctors to screen for these markers in pneumonia patients upon hospital admission, allowing a more efficient and informed service of care. This exciting discovery was presented as part of a press release on the 2nd October 2019 as part of the ERS annual congress in Madrid, Spain.

In the study, clinical data and blood samples from 169 patients with community-acquired pneumonia was analysed using quantitative PCR techniques. In this manner, microRNA seen to be enriched or depleted in the disease background upon hospital admission could be determined, and their abundancy could be correlated to respiratory complication risk throughout the course of the disease.

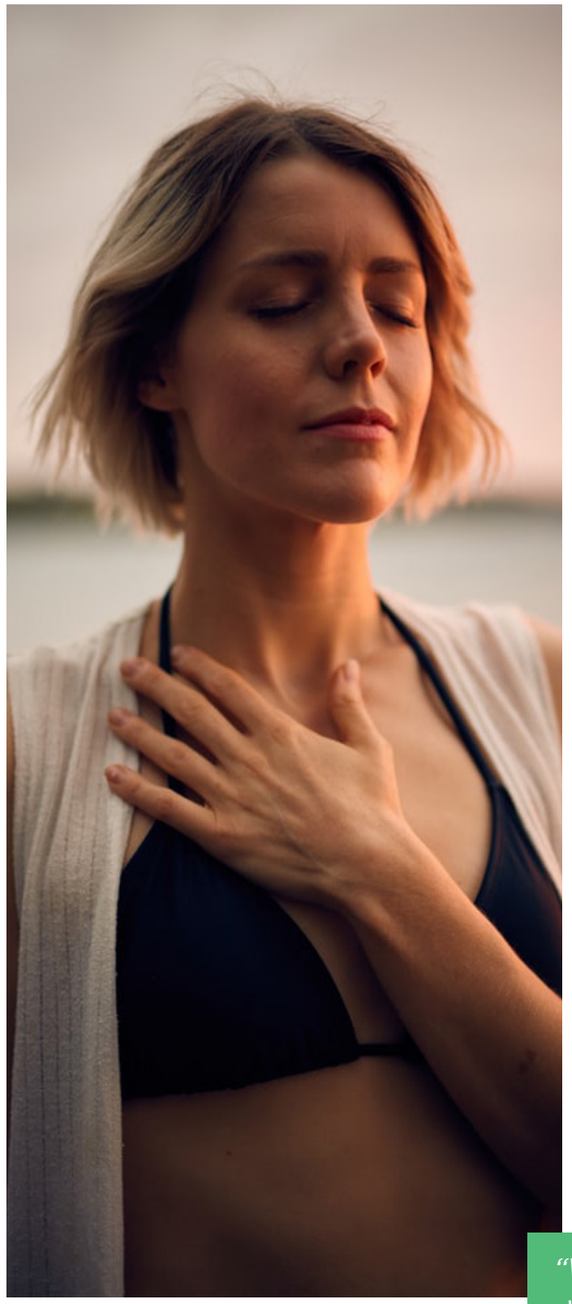
Three microRNA (mir-182, mir-223, and mir-574) known prior to be implicated in lung and systemic inflammatory processes were good predictors of sepsis or respiratory failure. Of the patient cohort, 64.5% developed complications, including respiratory failure (25.45) and sepsis (13.6%). Mir-223 effectively predicted sepsis onset (78% accuracy), whereas mir-574 was a good predictor of respiratory failure (77% accurate). Mir-182 was capable of providing prognostic warning for both conditions (sepsis: 83%; respiratory failure: 76%).

"our study has improved our understanding of the changes and processes that occur in the body in response to pneumonia by identifying the microRNA that specifically determine complications."

The researchers hope that establishing specific microRNA profiles in pneumonia patients may support the initiation of more intensive monitoring or support mechanisms. Importantly, such assessment is fast (1–3 hours) and very cost-effective, as well as being a routine enough procedure to administer at most hospitals.

Dr Francisco Sanz, associate professor at the University, concluded that "our study has improved our understanding of the changes and processes that occur in the body in response to pneumonia by identifying the microRNA that specifically determine complications."

Severe Asthma Patients Found to Take Harmful Amounts of Oral Steroids



HARMFUL doses of oral steroids could be taken by one third of patients who have severe asthma, as found in research presented at this year's ERS Congress in Madrid, Spain, and reported in a press release dated 2nd October 2019. The study also found that the majority of participants could decrease the need for oral steroids with stronger adherence to other asthma medication.

Dr Katrien Eger, Amsterdam University Medical Centre, Amsterdam, The Netherlands, discussed the study: "Our findings show that many patients with severe asthma are taking harmfully high doses of oral steroids. Every prescription for oral steroids should alert doctors to assess adherence to inhaled therapies and inhalation techniques in these patients. Furthermore, now that there is an increasing number of biologic asthma drugs available that avoid the need for oral steroids, doctors should initiate biologic treatment in suitable patients to reduce exposure to harmful oral steroids."

The research group identified Dutch patients taking ≥500mg of inhaled corticosteroids a day, along with long-acting beta agonists, while having severe asthma, as defined by the Global Initiative for Asthma (GINA). Questionnaires on medical history were sent to 5,002 patients, 2,312 of whom responded. Oral steroid use and medication adherence was also collected. Adherence to medication was measured by prescriptions being collected >80% of the time.

"We found that 29% of asthma patients who were using high doses of inhaled steroids were also taking harmfully high doses of oral steroids of 420 mg a year or more," explained Dr Eger. Some patients may be eligible for new biologic drugs to treat asthma, but it must be identified whether they could first attempt improving asthma medication adherence, as 78% of these patients were found to have poor adherence or incorrect technique for inhalation.

"We found that 29% of asthma patients who were using high doses of inhaled steroids were also taking harmfully high doses of oral steroids of 420 mg a year or more"

Good News for Primary Ciliary Dyskinesia Patients

EXCITING new results suggest that a 6-month course of low-dose antibiotic azithromycin could alleviate the symptoms of chronic lung condition primary ciliary dyskinesia (PCD), reports a ERS press release. The study is the first of its kind to find such positive results for this rare disease, which causes recurrent chest and ear infections in patients due to a build-up of mucus in the lungs.

Dr Helene Kobbernagel, Paediatric Pulmonary Service, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark presented the study, a 'gold-standard' randomised controlled clinical trial, at this year's ERS Congress, explaining: "We know that azithromycin is effective in treating a number of infections that occur in people with PCD, as well as having anti-inflammatory effects. It is also simple to administer and has mild side-effects." She added: "We wanted to see whether taking azithromycin over a period of time could also work to prevent infections and reduce symptoms."

To this aim, the team enrolled 90 PCD patients between the ages of 7 and 50 years from six hospitals across Europe. The group was split into two, the first group (n=49) was randomly assigned to azithromycin treatment for 6 months, the second (n=41) were given a placebo. All patients were assessed for lung function, hearing, the presence of infection-causing bacteria in their sputum, and quality of life.

During 6-month follow-up, the team noted a 50% reduction in episodes of symptoms in the azithromycin group (mean: 0.63) compared to the placebo group (mean: 1.37). The azithromycin group also had fewer infection-causing bacteria in their sputum samples, but were more likely to experience mild diarrhoea. Commenting on the results, Dr Kobbernagel said: "Our results show that azithromycin is safe for patients with PCD and that it could offer an effective maintenance therapy, reducing ill-health and helping children and adults get on with their daily lives."

In terms of future directions, the next step is to ascertain whether the antibiotic is safe for longer-term administration and whether it could help to prevent long-term damage to the lungs which PCD patients often experience as a result of recurrent infections. Although the researchers in this study did not record any significant differences in long-term lung function and hearing in this study, they cautioned that a longer study might be needed to assess this more accurately.

"Our results show that azithromycin is safe for patients with PCD and that it could offer an effective maintenance therapy"

Congress Interviews

The knowledge surrounding respiratory health is growing every year, and with it does the European Respiratory Society (ERS). We spoke to Prof Barbara Hoffmann and Prof Daiana Stolz to discuss their ERS-affiliated roles and their expertises in respiratory health

Prof Barbara Hoffmann

Chair of the Environment and Health Committee (EHC)-European Respiratory Society (ERS). Professor of Environmental Epidemiology, University of Düsseldorf, Düsseldorf, Germany; longstanding expertise in the conduction and analysis of epidemiological studies.

Q1 As the Chair of the ERS EHC, what does your work involve and how does it contribute to the overall goals of ERS?

Our main aim is to advocate for healthy environment and clean air policies in Europe and beyond; thereby, directly contributing to the overarching aim of ERS to improve lung health. We do so by communicating with policy makers and regulators; multipliers such as clinical physicians, patient organisations, and non-governmental organisations; and by collaborating with the World Health Organization (WHO) on a number of issues.

Q2 The ERS EHC are involved in many projects, what have been some of the most noteworthy developments in recent years in the projects that the committee support or have contributed to?

Some of our most important recent activities include the continuous participation in the European Commission (EC) process for the evaluation of the air quality guidelines as active stakeholders (the so-called 'fitness check'), and a joint statement together with the American Thoracic Society (ATS) on health effects of air pollution, of which was published in 2017.[1] Furthermore, we participated in the first global WHO conference on air pollution and health in 2018 and in the 'Healthy Lungs for Life' campaign of the ERS and the European Lung Foundation (ELF), as well as numerous statements together with other clinical and scientific societies on current air pollution and climate change-related issues across Europe. Currently, we are intensifying our collaboration with the WHO and other scientific societies to organise a joint workshop on the most up-to-date science in air pollution and health science to be held in Brussels, Belgium, early next year.

The EHC also supports strategies and projects to reduce the global burden of respiratory diseases associated with occupational risk factors, such

as our contribution to the ELF project that developed a public occupational respiratory disease interactive website or our active participation in the European Agency for Safety and Health at Work (EU-OSHA) Healthy Workplaces Campaign 2018 that focussed on raising awareness of the risks posed by dangerous substances in the workplace and to promote a culture of risk prevention.

With these activities, we aim to bring the most current science to policy makers and health care professionals and provide them with the facts necessary to design more effective protective regulation.

Q3 As an active partner in forming European policy, how does the ERS EHC influence current European Union (EU) legislation? Furthermore, which policies have the committee been able to influence?

The EHC has been very active in influencing the National Emission Ceiling Directive (NEC-Directive) that regulates upper limits of air pollutant emissions. For the first time, this directive also includes emissions from the agricultural sector, which is an often underappreciated source of air pollution. Moreover, currently we are highly engaged in the evaluation of the current air quality directive (the fitness check mentioned above) and in communicating the most recent results from large, continent-wide studies on air pollution at levels below current limit values to the EC. We have also conducted information campaigns in the EU parliament on climate change and interactions of air pollution and climate change mitigation policies, to show how closely these two environmental issues are related.

Q4 The committee has produced many resources including an "Air Quality & Health Booklet," how have these aided the promotion of better air quality, and are there any more resources currently being produced?

With these publications we aim to reach different target groups, among them are patients, who need to know how to protect themselves; doctors, who need to know how air pollution acts in the body, how they can advise their patients; and of course politicians and regulators. Depending on the target group, we produce different publications. One important new resource the ERS has produced is the booklet "10 Principles for Lung Health" geared towards the public, policy makers, and national authorities. Another important publication is the joint position paper on "The Health Impact of Air Pollution - An expert report of the International Society for Environmental Epidemiology (ISEE) and the European Respiratory Society (ERS)," which directly addresses the current level of evidence, the air quality guideline process of the WHO, current EU regulations, and the need for tighter air quality control.

Q5 What are the biggest challenges associated with the ERS EHC's work and the attempt to improve the impact of the environment on respiratory health?

The biggest challenge is to get the attention of policy makers and communicate the scientific facts in an understandable way.

Q6 You chaired the session entitled "Is your patient dying from air pollution?" at this year's ERS Congress. What were the take-home messages from this session?

One of our goals of this session was to improve physicians´ knowledge on how air pollution acts in the body and why it is important to reduce exposure as much as possible. We also wanted to provide some very concrete advise on how to counsel patients with lung disease, who are very sensitive to changes in air pollutant concentrations.

Q7 You are particularly interested in the effects of air pollution on cardiopulmonary health. How did you first begin your career in this area and when did you focus your interest into this research topic?

"With these activities, we aim to bring the most current science to policy makers and health care professionals and provide them with the facts necessary to design more effective protective regulation. "

"But overall, the associations of air pollution with very different diseases have been remarkably consistent across the globe, which provides a lot of credibility to these findings."

My very personal path into this area was through a study, in which we observed higher levels of atherosclerosis, thickening and obstruction of arteries, in people who lived close to busy streets. This led to the question, how air pollution and noise act together on influencing such a basic pathologic mechanism that is responsible for a multitude of downstream diseases such as myocardial infarction, stroke, and heart failure.

Q8 Particulate matter, ozone, and nitrogen oxides have all been attributed to damaging respiratory health. Is there a specific pollutant that is the greatest concern to respiratory health?

In terms of numbers of affected people, particulate matter is the most important air pollutant with the most extensive known health effects down to very low levels, well below current legislative limits. However, to those who are susceptible, high levels of nitrogen dioxide and ozone can be just as bad and lead to severe respiratory illness. We need to protect everybody; therefore, all of these pollutants need to be addressed.

Q9 Air pollutants and respiratory diseases are prevalent worldwide. Are there differences across Europe and the globe that can be attributed to air quality?

Certainly. Across the globe, across individual countries, and even across a region or a city, levels of individual air pollutants can differ substantially and can cause different diseases. But one mechanism is more or less common to all air pollutants, which is the elicitation of local pulmonary oxidative stress and inflammation, which can be propagated to the entire organism. Depending on the interactions with other risk factors such as other pollutants, lifestyle, demographic factors, and occupational factors, slightly different patterns of disease can result. But overall, the associations of air pollution with very different diseases have been remarkably consistent across the globe, which provides a lot of credibility to these findings.

Q10 The EU has set an objective to reach carbon neutrality by 2050. Do you think this is achievable and what impact do you believe this will have on the respiratory health of EU citizens?

Decarbonisation will in most cases also lead to less air pollution, since one of the major sources of air pollution is traffic and burning of fossil fuels. Other climate change mitigation activities such as changes in agriculture will also lead to less air pollution. We therefore have a win-win situation, which needs to be communicated more strongly to policy makers!

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Prof Daiana Stolz

ERS Education Council Chair

Associate Professor for Respiratory Medicine, Clinic for Respiratory Medicine and Pulmonary Cell Research, University Hospital Basel, Basel, Switzerland.

Q1 As the ERS Education Council Chair, could you start by briefly providing an overview of the duties and responsibilities of your role and the council?

As the Education Council Chair, I am one of the eight members of the managing board of the society. I overview a team of highly qualified and motivated professionals working in the development, implementation, and refinement of a continuous professional development framework for respiratory healthcare professionals within the ERS. Together with my team, I am responsible for all educational events of the ERS, including our annual conference counting on 25,000 international attendees, the ERS summer school, educational courses, as well as on-line educational materials such as continuing medical education online and respiratory digest. We also work on skill-workshops and certification of certain competencies such as endobronchial ultrasound, spirometry, sleep, and thoracic ultrasound. I overview the HERMES diploma and self-assessment exams, which are currently taking place in several continents next to Europe, such as South-America and Asia. In this position, I am also responsible for the educational publications of the ERS, such as Breath and the monograph. Aiming at fulfilling the needs of our membership, I support strategic decisions to further develop disease areas, or approaches, for instance our new Respiratory Failure and Mechanical Ventilation Conference launched this year or working group on cystic fibrosis. The educational council also have the possibility to support members and faculty through educational fellowships, dedicated to learning new techniques or competencies such as epidemiology and the Officer Excellence Program. I take responsibility for the general society strategy on key issues, such as diversity, inclusion and patient participation. The Education Council Chair is certainly a challenging role with fascinating potential to foster innovation in our society.

Q2 Collaboration is prevalent throughout ERS, who are some of the alliances or societies that the Education Council have collaborated with in the past and what are some of the projects or developments that are a product of these?

Indeed, the ERS is a society of societies and we are proud of our continuous bilateral collaboration with national and speciality societies. We have agreements with almost all respiratory societies world-wide counting on over 40,000 members and work together with thoracic surgeons, infectious disease specialists, paediatricians, cystic fibrosis specialists, allergologist, and ear, nose, and throat physicians to cite a few. We also have excellent collaboration with the American Thoracic Society (ATS) and American College of Clinical Pharmacy (ACCP). The collaboration with the ATS results for instance in guidelines endorsed by both societies, uniting practices and strengthening the expertise to a broader level. The vision of a world free of the suffering associated with respiratory disease is an audacious one and require us to join forces with all our allies with a similar goal.

Q3 The main goal of ERS is "promoting lung health in order to alleviate suffering from disease and drive standards for respiratory medicine globally," how does the Education Council contribute to this?

There is a tremendous heterogeneity in respiratory training both regarding knowledge and skills across the world. The ERS managed to get established, international experts together to frame the scope of what has to be known by respiratory healthcare providers world-wide for them to be considered up to date in each of the eight respiratory disease areas. Advice is provided for different tiers, starting at the training levels, over the general pneumologist levels, and extends to the super-specialist areas. These syllabi, encompassed as the continuing professional development programme, can be found online and provide guidance to all interested stake holders. In addition, live and online educational events, educational publications, skills workshops, competency training, and dedicated diploma level training assure access to high-level efficiency proved educational designs. The Education Council is constantly refining, revising, and refreshing its formats. Indeed, we have received two international awards for our innovations in education: one for the lungs of fire format, an interacting discussion of difficult cases involving a discussant, panel of experts, and the public and for the Game zone, an interactive, hands-on dedicated area which allows congress participants to experiment hands-on training and assess own knowledge in an uncomplicated, spontaneous way.

"It belongs to our duty to sensitise the general public to the needs and demands of our patients."

Q4 The ERS brings together patients and the public with respiratory professionals to positively influence lung disease. What relationship does the Education Council have with patients and the general public?

The main goal of everything we do is the patient. All basic and translational research, all training, all understating of disease mechanisms: the focus should always remain the fact that we need to advance to alleviate symptoms in those with respiratory disease. And patients are a crucial part of the chain for development, they are our allies in identifying needs and informing our priorities. Respiratory disease remains under-recognised, under-funded, and under-represented in priority political agendas; however, it is one of the major killers around the world. Respiratory disease has to become a focus of attention to the public because it is indeed a public health problem. And for many issues, regulation and legislation are powerful means for achievement. It is our duty to sensitise the general public to the needs and demands of our patients.

Q5 Continuing professional development (CPD) is considered the educational means to ensure that healthcare professionals have the required medical and nonmedical skills in their ever-changing field. How has the council contributed to CPD in the field of respiratory?

After having developed at in-training levels for both adult and paediatric respiratory medicine, and numerous other sub-specialty groups, the Educational Council recognised the need to provide practical advice on the topics needed to be covered by a general respiratory physician to assure that their knowledge, skills, and attitudes are up to date with current scientific developments. For this aim, ERS Assembly officers worked together to develop the "ERS CPD framework." The CPD focusses both on important scientific topics but also on soft topics, such as leadership and ethics. Importantly, the CPD has a modular format, adapting to the individual needs as well as time and resources availabilities.

Q6 Education of professionals is a vital aspect of the betterment of disease knowledge. Are there any noteworthy differences in education policies or guidelines across Europe?

Indeed, regulations and requirements are immensely diverse and scarily confusing. The ERS has taken this issue seriously and recognised the need for assessing this challenging landscape by competent means. Herein, we have appointed and supported a PhD student in charge of evaluating how the CPD is structured

internationally and which are the local differences. Only by understanding its diversity it was possible for us to consistently develop and structure the format of our current programme. Currently, the ERS has a further PhD student dedicated to understand preferences in CPD across our member societies. We have recently concluded the Phase one of the ENGAGE study, which is a qualitative study encompassing one-to-one interviews in national language. The second phase of the study will expand initial findings to a broader population. That is a good example of how evidence-based results should shape direction of our education strategy. I am personally convinced that the use of artificial intelligence could also be a great allied to advance our efforts in personalising our programmes in terms of complexity, format, and intensity to our target populations.

"I also believe it is important to evaluate how to translate study results to the clinical practice and how to communicate with patients. "

Q7

Knowledge of a disease is essential to development treatments and better the diagnostic process. Are there any diseases that the Education Council believe require increased funding and research?

Taken its major impact on morbidity and mortality, respiratory disease is generally underfunded. Major diseases, such as chronic obstructive pulmonary disease (COPD) and respiratory infection, are still poorly characterised and account for billions of deaths each year. The effect of early diagnosis and intervention should be widely explored, however, large, epidemiological studies allowing for the characterisation of the effect of early intervention in COPD, for instance, are time consuming and expensive. I am particularly concerned about the complete stagnation in the COPD research field. Other entities, such as chronic cough for instance, are really demanding to study, attributable to a lack of gold standards. At the ERS, we believe it is essential to support independent, investigator initiated and driven studies and facilitate collaborations. In this sense, the ERS catalyses and galvanises interested investigators and allow for international collaborations within the "Clinical-research Collaborations" framework. I also believe it is important to evaluate how to translate study results to the clinical practice and how to communicate with patients. Lastly, despite its costs and complexity, we should never stop looking for pathophysiologic mechanisms of disease in all its facets. The development of new medication and approach depends on our understanding of disease processes and on our ability to connect basic and clinical research.

Q8

In 2018 you were elected as a fellow of ERS, could you tell us a little more about this and how you came to be nominated for this award?

According to its original description, the Fellow of ERS award recognises excellence in contributions to research, education, and clinical leadership in respiratory medicine from amongst the ERS membership. The award brings together members who have excelled in their field to form an elite advisory board that will be called upon by the society on various matters in future years. It also provides recognition to those leaders in the field by entitling all selected Fellows to use the designation 'FERS' after their name. For many years, my research group has been dedicated to COPD and its mechanisms with a particular focus on exacerbation. I have designed and conducted several investigator-initiated studies in this field, and I believe our contributions have been acknowledged. Needless to say, that I was very pleased to receive this honour.

Q9

Your research interest is in the area of the mechanisms involved in COPD development, what sparked your interest to pursue a career in this field and particular research topic?

I have experienced my grandmother's symptoms in living with severe COPD already during my childhood and at the beginning of medical school, at the age of 16, I knew I wanted to become a respiratory physician. I was blessed with a fantastic mentor and the opportunity to engage in clinical research at the (at that time) leading hospital in pulmonary medicine in Brazil. A few years before the lung transplantation in Latin America took place at the same hospital and I envisioned that we would be able to cure COPD. And I have not given up so far.

Q10

Considering that there is currently no curative treatment for COPD, what do you believe are the most beneficial therapies to patients, and are there any new treatments that have great potential for COPD patients?

The most important measure in a patient with COPD is to stop smoking. Unfortunately, in many cases the disease is still causing constrain and deserves further medical therapy. We do have effective therapies for COPD: both long acting bronchodilators and inhaled steroids have an established role in the control of symptoms, improvement of health-related quality of life, and decrease of exacerbation rate, particularly in advanced disease. Furthermore, bronchoscopic volume reducing procedures are to be recommended in selected patients with too much air trapped in the lung. To be more effective, though, I am convinced that we would need to diagnose the disease earlier, which would require a change in disease definition, and start treating it at an earlier stage with disease modifying drugs, which still have to be identified. I am also positive about the fact that we will have to expand our diagnostic armamentarium and embrace the idea that spirometry alone is not enough and more complex diagnostic is required. The only way ahead is a personalisation of the therapy and approaches.

"The only way ahead is a personalisation of the therapy and approaches. "

Q11

You are due to deliver a clinical updates session at the ERS Respiratory Updates in Amsterdam, Netherlands. What do you believe are the main take-home messages from this session?

Indeed, we are all excited about the ERS Respiratory updates, a live and online event that will summarise major advances presented during our conference in Madrid, Spain. I am sure that several trials revealing advances in COPD, asthma, interstitial lung disease, and infections discussed during the ALERT (Abstracts leading to evolution in respiratory medicine trials) sessions will come up during the updates and I am also looking forward to the implications of these trials to our disease understanding and clinical routine. I would say: Stay tuned and do not miss it!

Building Hope by Restoring Breathing in Airways Diseases

This symposium took place on 1st October 2019, as part of the European Respiratory Society (ERS) International Congress held in Madrid, Spain

Chairpeople: Àlvar Agustí[1,2]

Speakers: Àlvar Agustí,[1,2] Salman Siddiqui,[3,4] Alberto Papi,[5] Bartolome R Celli,[6] Dave Singh[7]

1. University Hospital Clínic de Barcelona, Barcelona, Spain
2. University of Barcelona, Barcelona, Spain
3. University of Leicester, Leicester, UK
4. NIHR Leicester Respiratory Biomedical Research Unit, Glenfield Hospital BRU, Leicester, UK
5. University of Ferrara at Sant' Anna University Hospital, Ferrara, Italy
6. Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA
7. University of Manchester, Manchester, UK

Disclosure: Prof Agustí has received research grants for sponsored and principal investigator-initiated studies from AstraZeneca, GSK, and Menarini; advisory boards fees for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, and Menarini; and speaker fees from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, and Menarini. He is also the chairperson of the board of directors of GOLD. Prof Siddiqui has received speaker fees and honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, ERT, GSK, Mundipharma, Novartis, Owlstone Medical, Roche, and Thorasys. Prof Papi has received consultant or advisory board fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GSK, Mundipharma, Novartis IT, TEVA, and Zambon; speaker fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Gentili, GSK, MSD, Mundipharma, Novartis, Pfizer, and TEVA; and sponsored grants from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Fondazione Maugeri, Fondazione, GSK, Menarini, and MSD. Prof Celli has received advisory boards fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Menarini Novartis, and Pulmonx; and scientific board fees from GOLD. Prof Singh has received speaker fees, advisory boards, and research grants from Apellis, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GSK, Glenmark, Johnson & Johnson, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Skyepharma, Teva, Theravance, and Verona.

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Meeting Summary

Prof Agustí opened the session by explaining the new challenges in airway diseases including the changing paradigm of our understanding of chronic obstructive pulmonary disease (COPD) that considers the entire lung function trajectory from birth to death, the complexity and heterogeneity of the disease, and the need to diagnose and treat COPD earlier in life. Prof Siddiqui then explained that all of the airways, including small airways, are critically important in the pathophysiology of asthma and COPD. The world's largest multi-centre ATLANTIS study focussed on small airways dysfunction (SAD) confirmed that a simple combination of different assessments like oscillometry and spirometry could identify patients with the SAD phenotype. The prevalence of airway dysfunction in the full asthma cohort was 91%. Prof Papi discussed that exacerbations are a crucial event in the natural history of COPD and that they drive several health-related outcomes. He reviewed the clinical evidence to demonstrate the benefits of triple therapy in general and specifically of the extrafine fixed triple combination (beclometasone dipropionate, formoterol fumarate, glycopyrronium bromide) to consistently reduce the risk of exacerbations, and improve lung function and quality of life (QoL) with a favourable benefit-to-harm ratio. Furthermore, triple therapy showed promising signals in terms of improved survival. Prof Celli debated that inhaled corticosteroid (ICS) should be given to many patients because scientific trials have shown that: 1) ICS combined with bronchodilator (BD) are effective in improving health status and reducing exacerbations; 2) they also impact lung function decline and mortality; 3) ICS increase pneumonia risk (depending on type, dose, airflow limitation, BMI, and age) but have no untoward effect on mortality or hospitalisations for pneumonia; 4) blood eosinophil count (BEC) (<100 cell/µL) helps select patients unlikely to respond to ICS; and 5) 'many' COPD patients benefit from ICS combined with BD. Prof Singh focused on the fact that the magnitude of clinical benefit in preventing COPD exacerbations varies between individual patients, underlining the importance for clinicians of making the right decision for each patient when prescribing ICS, by balancing the potential risk/benefit. He concluded the debate by outlining that ICS have benefits in patients at increased exacerbation risk, and that the size of the benefits varies with BEC and the number/type of exacerbation.

New Challenges in Airway Diseases

Professor Àlvar Agustí

According to Prof Agustí, there are currently three key challenges to overcome to build hope in airway diseases. The first challenge is that the COPD paradigm is changing. Airway diseases (as many other chronic conditions of the adult individual) can start early in life (during pregnancy, infancy, and adolescence), albeit it is often not diagnosed until the sixth of seventh decade of age. Several lung function trajectories (Figure 1) exist throughout the life course, including a growth phase, a plateau phase, and a declining phase. This novel perspective provides a dynamic way to study how lifetime influences health and disease, including COPD. Therefore, time considerations in the understanding of airways disease are becoming increasingly important. Recent research has shown that 4–13% of the general population do not achieve normal peak lung function in early adulthood, albeit approximately two-thirds of children with reduced lung function at birth can catch up to a normal trajectory. At the other end of the spectrum, there are supranormal trajectories. These supranormal individuals may lose significant amounts of lung function through life and, nonetheless, present to the clinic in their sixties with evidence of lung damage (e.g., CT emphysema) and 'pseudonormal' spirometry.[2,3] Furthermore, low peak lung function in early adulthood is significantly associated with early development of comorbidities and premature mortality.[3] In total, there are two key biological phenomena (organ development and ageing) that need to be considered to better understand the pathogenesis of COPD.[2,3] In this context, COPD and asthma may be considered as a continuum of chronic airway diseases.[1,4-9]

The second challenge is that COPD in particular, and airway diseases in general, are complex and heterogeneous; therefore, one therapeutic strategy does not fit all patients. Disease complexity is defined by the presence or severity several components such as emphysema, exacerbations, rate of lung function decline, early life events, and inflammation, among others, and that these components are not linearly related (so one cannot be predicted from others). Furthermore, heterogeneous means that not all these components are always present in all patients or, in a single patient, they may change

with time, either because of disease progression and/or the effect of therapy. To address these complexities and heterogeneity, it has been recently proposed that a strategy based on the presence of specific treatable traits may be the way forward for personalised and precise treatment of these patients.[10-13] This is supported by the recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendation to individualise treatment based on two key treatable traits, namely emphysema and dyspnoea.

The third and final challenge, following directly the realisation of different lung function trajectories leading to COPD (Figure 1), is to diagnose and treat the disease much earlier. Generally, COPD is diagnosed later in life,[8,14] when a cure of the disease or the possibility to make a significant impact is unlikely.[14,15] Recent research (unpublished)[16] in the general population found that: 1) many factors relate to lung function throughout life; 2) these factors vary according to age; and 3) these factors interrelate. Older patients had an extremely complex interrelating network of influencing factors on lung function, which translates into an increasing complexity for treatment decision making. The current treatment strategy in COPD has been to follow the disease (e.g., the best predictor of future exacerbations is past exacerbations); Prof Agustí emphasised how it is time to start leading it.

Targeting the Sm(all) Airways in Asthma and Chronic Obstructive Pulmonary Disease

Professor Salman Siddiqui

Multiple evidence now exists supporting the role of the small airways in both asthma and COPD, yet, a deployable definition has remained elusive.[17] The reason is that the small airway compartment is a difficult anatomic area to study due to its relative inaccessibility. They include the small, conducting bronchioles; the bronchiolar airways; and the acinar airways.[18] Different tests measure different parts of this compartment and what we need is to move beyond individual tests to define SAD. Pathology evidence indicates small airways are strategically important in COPD. Micro-CT imaging of lung-resected tissue in patients with COPD, showed that even patients with early disease have loss of small airways (before the development of emphysema and extensive lung damage). The progression in patients across the spectrum of COPD severity was strongly associated with airway wall thickening, increasing lumen mucous exudates, and the number of airways containing acute inflammatory cells.[19,20] There is a growing body of evidence to show that extrafine therapies can reach the small airways. Several studies have shown that extrafine drugs can reach and are retained in the small airways and can treat them producing improved forced vital capacity, 6-minute walk distance test, and reduced exacerbations of COPD.[17,21]

The same concepts apply to asthma; however, a key challenge is that no gold standard test exists to detect SAD. There are several tests that have been used to study SAD, including spirometry, impulse oscillometry (IOS), mid expiratory flows, forced vital capacity, and multiple breath nitrogen washout to measure conductive and acinar ventilation heterogeneity. IOS is particularly useful because it can be deployed across the life course, takes only a few minutes to perform, and is highly reproducible. It uses sound waves to provide a measure of airway resistance at different frequencies.[22] This is supported by studies, which found that IOS R5-R20 parameters correlated with the degree of morphologic abnormalities of small airways in COPD and asthma patients.[23,24] These findings needed confirmation from large-scale clinical trials.[25] ATLANTIS, a 1-year, prospective, observational, multicentre, multinational study in 800 patients with asthma across a range of severity (including smokers) and 100 healthy controls, was initiated to address this need. This is the largest study to date on SAD and the objectives were to determine the role of small airway abnormalities in the clinical manifestations of asthma, and to evaluate which clinical methods best assesses the abnormalities of small airways and large airways disease in asthma and best relates to asthma severity, control, QoL, and future risk of exacerbations; thereby, potentially establishing a method of defining SAD.[26] The prevalence of SAD in asthma using all techniques was 90.7%. Gas exchange tests such as Sacin (index of diffusive ventilation heterogeneity in most peripheral pre-acinar/acinar airways) showed <20.0% prevalence of SAD (showing specificity but not sensitivity). Whilst, spirometry test (73.1% prevalence) appeared to be oversensitive, but not specific. Every patient was assigned a clinical SAD score from the model and this was used to identify SAD phenotypes using clustering. This identified two groups: patients with milder SAD and patients with severe SAD. Patients with severe SAD showed massive enrichment of abnormal oscillometry (up to 6-fold higher in some patients) when compared to those with mild SAD. When reviewing the CT scans to undertake a similar modelling, the two (physiological versus CT) did not closely correlate (potentially because of gravitational forces on lung function affecting the different way those are measured) (Figure 2).[27]

Prof Siddiqui concluded that there is clear evidence to show that all of the airways, including small airways, are critically important in the pathophysiology of asthma and COPD (including early COPD) and a high prevalence of SAD in asthma and COPD. The world's largest ATLANTIS study of SAD across asthma severities confirmed that a simple combination of oscillometry and spirometry can be used to identify SAD phenotype.

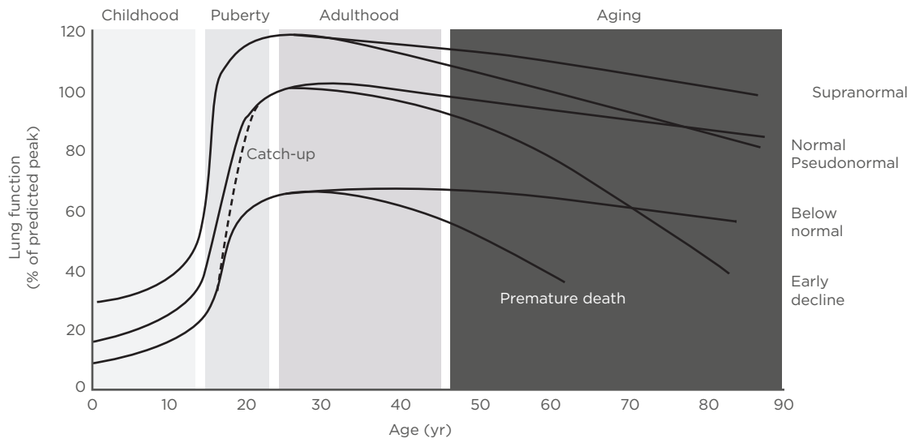
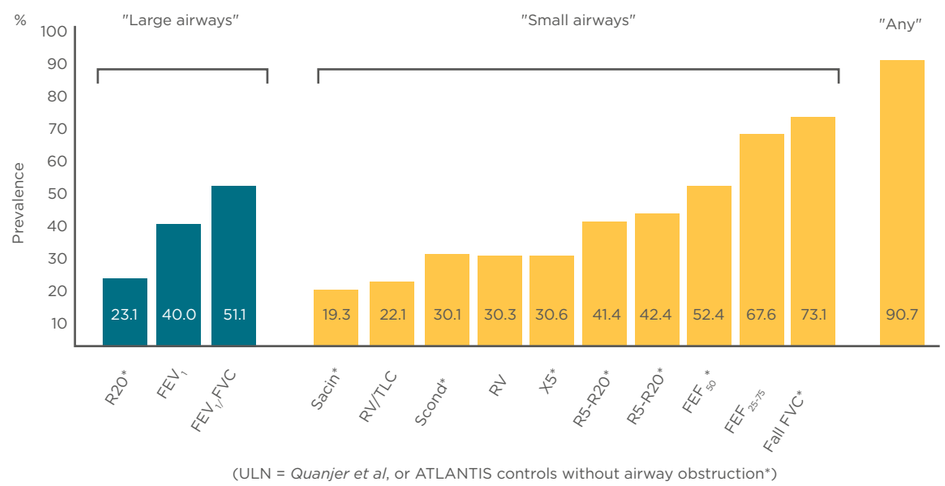


Figure 1: Lung function trajectories from birth to death.

Adapted from Agustí and Hogg.[1]



(ULN = *Quanjer et al*, or ATLANTIS controls without airway obstruction*)

Figure 2. Prevalence of abnormal physiological variables of SAD[28]

Furthermore, the SAD phenotype was associated with more severe disease and adverse outcomes such as worse asthma control and a higher risk of exacerbations.

Triple Therapies: Opening Spaces for Hope in Chronic Obstructive Pulmonary Disease Patients

Professor Alberto Papi

The GOLD define COPD as "a common, preventable, and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation [...] (which) is caused by a mixture of small airway disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person."[13] Hogg et al.[20] confirmed the relationship between airflow limitation and severity of inflammatory infiltrates (innate and adaptive inflammatory immune cells) in peripheral airways. The airway inflammatory process is amplified during acute exacerbation events. GOLD defines exacerbations of COPD as an acute worsening of respiratory symptoms that requires additional medication and/or hospitalisation.[13] COPD exacerbations are heterogeneous and the pathophysiology is not yet fully understood. The acute events and increased airway inflammation lead to structural changes, such as increased thickening of the airway wall, functional changes with bronchoconstriction, and increased mucus production and pathophysiology modifications (e.g., increased airflow limitation and hyperinflation) related to worsening of symptoms. The goal is to interfere with this cascade of events, at whatever level, to avoid the evolution of increased symptoms that characterise exacerbations.[28,29] Treatment or prevention of exacerbations are critical (and may require targeting of different pathways), due to the significant negative impact on pulmonary function, health status, QoL, risk of hospitalisation, outcomes, and healthcare costs.[13] In fact, the increased risk of mortality has not only been found during the acute episode but also up to 5 years after hospitalisation.[30] COPD exacerbations also increase the risk of cardiovascular events during and after an acute episode.[31] One mechanism for preventing exacerbations is the use of BD, via the effect on airway patency, but also the pathophysiological mechanisms they induce.[32] Treatment can be further improved with the addition of ICS as shown by a Cochrane review, which demonstrated that combination ICS therapy led to fewer exacerbations, improved QoL, lung function, and symptom scores when compared to the use of LABA monotherapy.[33] GOLD has recently updated their recommendations for initial treatment in patients with GOLD D stage.[13]

The previous 2017 version was supported by evidence of two bronchodilators (LABA and LAMA) in combination being more effective than a single long-acting BD in preventing exacerbations.[34] Since new evidence has become available showing that a combination of LABA/LAMA over LAMA monotherapy for exacerbation prevention has not been consistently demonstrated, the 3 options are recommended in this group of patients as initial treatment (LAMA, ICS/LABA, preferentially in patients with BEC ≥300 cells/µL, LABA/LAMA preferentially in symptomatic patients with a COPD Assessment Test score >20.[35] The new GOLD concept in the follow-up treatment is a personalised approach, considering the key needs and the current treatment, to orientate decisions. The recent changes are because of new clinical evidence.[13] The previous 2017 GOLD recommendation came after the publication of the results of the FLAME study, which showed that at 52 weeks, LABA/LAMA was associated with a significant reduction (11%) in the annual rate of exacerbation when compared to ICS/LABA in all levels of severity.[36] In 2018, data from the IMPACT study demonstrated that ICS/LABA resulted in a lower rate of COPD exacerbations than LAMA/LABA (1.07 per year with ICS/LABA versus 1.21 with LABA/LAMA).[37] Patients enrolled in the IMPACT study had a higher frequency of exacerbations when compared to the FLAME study population and thus are the population in greater need for effective exacerbation prevention.[38,39] If exacerbations occur in patients treated with dual (ICS/LABA or LABA/LAMA) therapy, the next step in the GOLD exacerbation algorithm is moving to triple therapy with ICS/LABA/LAMA (with BEC ≥100 cells/µL for those on LABA/LAMA).[13] The evidence for this recommendation comes from the TRILOGY study, which found an adjusted annual exacerbation frequency of 0.41 for triple therapy (ICS/LABA/LAMA) and 0.53 for ICS/LABA, corresponding to a 23% reduction in exacerbations with triple therapy. The TRILOGY study, for the first time, provides 1-year evidence showing that triple therapy is superior to ICS/LABA in terms of forced expiratory volume in one second (FEV_1), reduced exacerbation rate, and other symptoms-based and lung function parameters.[38] The subsequent TRINITY study found that exacerbation rates were 0.46 for fixed triple, 0.57 for LAMA monotherapy, and 0.45 for open triple; fixed triple was superior to LAMA (p=0.0025).[39] This is the first evidence to support triple therapy (either fixed or open) over LAMA monotherapy in preventing COPD exacerbations as primary outcome, which somehow raises questions of why you would escalate to dual therapy from LAMA treatment, given that the benefit of LABA/LAMA over LAMA is questionable in terms of exacerbation prevention. The TRIBUTE study further demonstrated the superior efficacy of extrafine triple therapy in reducing the rate of exacerbations as compared to LABA/LAMA (0.50 for triple and 0.59 for LABA/LAMA). This translates into a 15.2% reduction of moderate/severe COPD exacerbation risk for triple versus dual therapy. Triple therapy was also superior to LABA/LAMA in pre-dose FEV1 and improvement in QoL.[40] In addition, the IMPACT study showed that the annual rate of severe exacerbations resulting in hospitalisation in the triple-therapy group was 0.13 compared to 0.19 in the LAMA/LABA group (p<0.001).[37] Adverse events were similar across treatment groups.[40] Pneumonia was reported in a small number of patients across all three clinical trials (TRINITY, TRILOGY, and TRIBUTE), with similar incidences. This data show that the balance between the benefits of the reduction in COPD exacerbation versus the risk of development of pneumonia is 7–10-fold in favour of the benefits.[38-41] This is aligned with the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) review that the benefits of ICS continue to outweigh their risks.[42] Triple therapy, therefore, provides new treatment options and potentially new hopes for patients with moderate-to-severe COPD exacerbations. Triple therapy may provide the opportunity to lead this disease. Prof Papi questioned the need to wait for 2 exacerbations to escalate treatment when there is evidence showing that exacerbation risk is more than doubled in patients experiencing only 1 exacerbation in the past 12 months,[43]

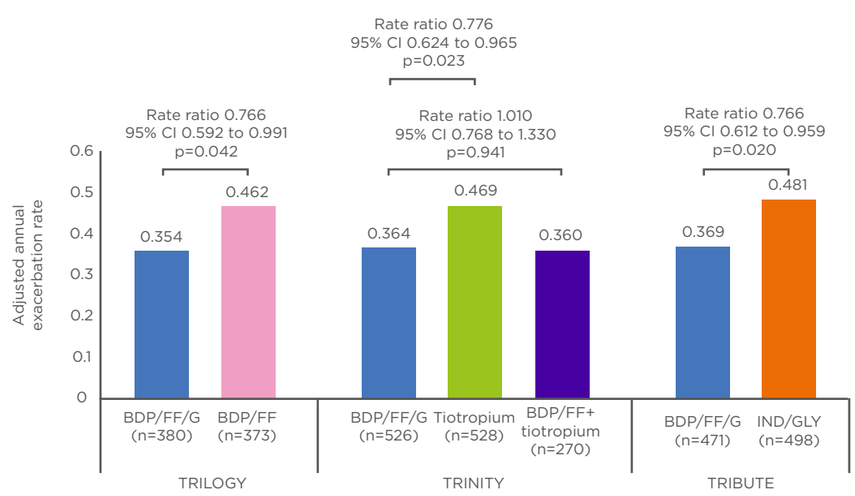


Figure 3: Adjusted annual rate of moderate-to-severe chronic obstructive pulmonary disease exacerbations (intention-to-treat population).

Triple therapy shows superior efficacy in reducing moderate to severe chronic obstructive pulmonary disease exacerbations.

BDP: beclometasone dipropionate; CI: confidence interval; FF: formoterol fumarate; G: glycopyrronium bromide; GLY: Glycopyrronium; IND: Indacaterol.

Adapted from Singh et al.[45]

considering that in the last years consistent evidence has become available showing the efficacy of ICS/LABA over LABA and of triple over dual combinations in preventing exacerbations episodes in COPD patients that have exacerbated once in the previous year (Figure 3).[37,44,45] A reduction in mortality rates using triple therapy has also been reported in the IMPACT study.[37,46] Moreover, pooled data from TRILOGY, TRINITY, and TRIBUTE studies on fatal events showed a clear trend towards the reduction of mortality risk with triple therapy.[46]

Inhaled Corticosteroid for many or Inhaled Corticosteroid for Some. Inspiration comes from Adaptation

Professor Bartolome R Celli and Professor Dave Singh

Prof Celli opened the debate by outlining that guidelines do not recommend the use of ICS alone in COPD.[13] The reason for this is that well-conducted studies have shown that ICS, when used as a monotherapy, is not very effective in COPD. The TORCH study in which ≥6,000 patients over 3 years compared combination therapy (ICS/LABA) versus placebo, LABA, and ICS monotherapy. The primary outcome was death from any cause, and the all-cause mortality rates for salmeterol or fluticasone propionate alone did not differ significantly from placebo. However, there was a statistically significant higher mortality rate in the fluticasone arm alone compared with the LABA/ICS arm.[47] Several studies have shown that when ICS is added to BD (either LABA or LABA+LAMA), the efficacy in different COPD outcomes is proven.[38-41] The goals for treatment outlined by the GOLD initiative are to reduce symptoms (improve symptoms, exercise tolerance, and health status) and risks (disease progression, exacerbations, and mortality).[13] This should be implemented in combination with the Hippocratic oath to "abstain from doing harm". The TORCH study showed that the ICS-combination regimen significantly improved QoL and spirometric values.[47,48] Furthermore, the SUMMIT trial including >16,500 patients showed ICS-containing regimens (ICS/LABA) had significantly lower adjusted rates of FEV1 decline versus placebo (p<0.03).[49] In TORCH, the ICS-combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85.[47] GOLD advocates that you need to have an exacerbation to be treated with ICS therapy.[13] However, SUMMIT demonstrated that patients with moderate, chronic airflow obstruction, experienced a reduction in moderate and severe exacerbations with ICS/LABA combination compared with placebo, irrespective of a history of exacerbations or baseline FEV1. In fact, >60% of the patients had no exacerbations in the year prior to study inclusion.[49,50] In addition, the TRIBUTE study showed that treatment with the extrafine single inhaler triple combination significantly reduced the rate of moderate-to-severe exacerbations compared with LABA/LAMA in severe and very severe COPD patients with a history of at least one or more moderate and severe exacerbation the year prior to enrolment.[40] Furthermore, as shown from Singh et al.,[51] treatment with extrafine triple delayed disease deterioration compared to LABA/LAMA in the TRIBUTE study. An understated argument for the use of ICS is its potential impact on mortality. Indeed, the reduction in the risk of death was found to be 17.5% in TORCH (p=0.052),[47] 12% in SUMMIT (p=0.137),[52] 42% in IMPACT (p=0.01),[37] and the pooled TRINITY, TRILOGY, TRIBUTE data showed a 28% reduction in the risk of death (p=0.066) with ICS/LABA/LAMA.[46] There is no question that the use of ICS increases the risk of pneumonia, however, this depends on the type of ICS used, the dose, the severity of airflow limitation, and the age and nutritional status of the patients. Interestingly, the incidence of severe pneumonia was similar amongst therapies in the TRIBUTE study.[40] Moreover, Festic et al.[53] found that despite the association of ICS with increased risk of pneumonia, their use has not been associated with increased risk of pneumonia-related or overall mortality, suggesting a possible double effect of ICS (i.e., an adverse effect plus an unexplained mitigating effect). Bafadhel et al.[54] postulated that BEC (≥100 cells/µL) might identify COPD patients taking ICS who will experience fewer exacerbations, with a continuous relationship between levels of eosinophils in the blood and ICS response in clinical trials.[54] This is supported by other studies.[55-57] This threshold of 100 cells/µL could potentially identify which patients are not suitable for ICS therapy and guide personalised medicine. These studies highlight that ICS-combination therapy can improve health status,[47] prevent disease progression,[48-49] prevent and treat exacerbations,[47,50] and reduce mortality.[37,46,47]

Prof Singh then countered by stating that using only group mean data from clinical trials to determine treatment approach is not precision medicine, and that there is more complexity to the art of medicine for individual patients. There is a huge variation in ICS response in asthma patients as shown by Martin et al.[58] in the distribution of the percent change in FEV1. Clinicians know that the benefit of ICS treatment also varies between COPD patients and that the challenge is to identify individuals in whom the benefits outweigh the risks. There is an interaction between the exacerbation risk and BEC for the individual patient. BEC clearly predict the responders versus nonresponders for ICS. Siddiqui et al.[59] showed that with lowering BEC, the adjusted reduction rate in COPD exacerbation decreased. Bafadhel et al.[54] showed this using binomial regression, that at around BEC=300 cells/µL, the reduction in ICS effect is approximately 50% and below BEC=100 cells/µL, appears to be no ICS effect.[54] However, this is a continuous relationship without definitive threshold values for response or nonresponse; instead, BEC but probabilities of response, i.e., with increasing BEC, the probability of an ICS response increases. GOLD therefore recommends using this biomarker as part of clinical decision making to provide an estimate of the probability of response to ICS.[13] Modelling BEC and response to triple and double combinations provide similar results regarding ICS treatment.[60] Kolsum et al.[61] conducted a bronchoscopy study to evaluate differences in airway biology associated with BEC and found that higher BEC had parallel increases in lung eosinophil counts, and other various inflammatory proteins. Furthermore, another study showed that patients with sputum eosinophil counts had less colonising bacteria.[62] Overall these findings show differences in inflammation and microbiome that could explain different responses to ICS. Furthermore, patients with more frequent exacerbations, have the highest potential for ICS benefits.[63] Those patients with less frequent exacerbations, but higher BEC will also benefit from ICS. So, in the age of personalised medicine, the point at which you would use an ICS inhaler depends on the complexity of clinical and biological information. This complexity of information includes the risk of adverse events.[64-66] The risk of pneumonia is personalised, with well-known risk factors, including increasing age, lower BMI, and history of pneumonia.[67] The regulators agree that the benefits of ICS outweigh the risks.[42] Prof Singh stressed that ICS effects are related to dose, there is no reason to use high dose ICS in COPD. Real-world data comparing extrafine formulation and fine-particle ICS found that extrafine formulation ICS/LABA (which deliver a lower dose due to efficient drug delivery) had significantly lower pneumonia risk.[68] Therefore, GOLD recommends a personalised treatment algorithm based on exacerbation risk and BEC, to treat some patients with ICS.[13] In conclusion, precision medicine is using all of the clinical and biological information available to make the right decision for the right patient.

Conclusion

Clinicians are facing the new challenges in airway diseases, particularly the changing paradigm toward precision medicine, addressing the complexity of this disease specifically in the ageing population and the critical need to treat COPD early to prevent future events and delay disease deterioration. Fixed triple therapy may help address these challenges with proven reductions in exacerbations, improvement in lung function, symptoms, and QoL, and reduction in the risk of mortality. These benefits far outweigh the risks of adverse events, including pneumonia. Extrafine fixed triple therapy moreover is able to reach both large and small airways, that are critically important in the pathophysiology of asthma and COPD.

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Optimising Clinical Outcomes in Asthma and Chronic Obstructive Pulmonary Disease: Focus on Inhaler Satisfaction and Patient Adherence

This symposium took place on 30th September 2019 as part of the European Respiratory Society (ERS) International Congress 2019 in Madrid, Spain

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Meeting Summary

The vast array of inhaler devices can be overwhelming for patients with chronic obstructive pulmonary disease (COPD) or asthma. Matching the right inhaler features to patients' needs is key to maximising adherence and achieving the best outcomes. During this symposium, leading global asthma and COPD experts took an in-depth look at the latest clinical data relating to inhaler satisfaction and clinical outcomes.

What Really Matters to Patients with Asthma and Chronic Obstructive Pulmonary Disease

Professor José Luis Izquierdo

The efficacy and safety of treatments for asthma and COPD are often the focus for healthcare professionals (HCP); however, there are other factors that should be considered to maximise patient adherence, such as the technical characteristics of inhaled therapy.[1]

Two systematic reviews of inhaler device use have shown, rather surprisingly, that a substantial proportion of HCP do not use inhalation devices correctly, and faulty inhaler technique by patients has not improved over a 40-year period (1975–2014).[2,3] Poor inhalation technique can significantly reduce the amount of drug deposited in the lung and thus reduce the effectiveness of treatment; therefore, correct inhalation technique is equally as important as the efficacy and safety of the pharmacological agent.

Importance of the Patient–Healthcare Professional Relationship

HCP require reliable information from patients in order to treat according to their needs.[4] In the COPD MIRROR study, most patients stated that they were not completely honest with their HCP, and a substantial proportion of pulmonologists and general practitioners did not recognise the insufficient frankness in their relationship with patients.[5] Improving the relationship between patients and HCP is important to allow open and honest discussion in order to make optimal decisions about relevant treatment options.

The main objective of COPD treatment from a patient's perspective is to minimise symptoms, maintain daily activity, and avoid exacerbations;[6,7] however, HCP and patients do not always agree on the impact of disease on daily life or satisfaction with treatment. Discordance between patients and HCP has ultimately been shown to be higher in patients with poor asthma control compared with patients with controlled asthma.[8]

Patient Factors that Affect Adherence to Inhaled Therapy

Poor adherence to inhaled therapy and incorrect inhalation technique have an adverse effect on outcomes in asthma and COPD, even with the availability of effective treatment. For example, improper use of a pressurised metered-dose inhaler (pMDI) is associated with decreased asthma stability, and poor adherence to inhaled therapy is associated with increased mortality in COPD.[9,10] With this in mind, it is essential to improve patient treatment satisfaction, because patients with high levels of overall inhaler satisfaction are more likely to be compliant.[11]

Several studies have evaluated patients' inhaler preferences. For example, the ASCONA real-life study of 778 patients with moderate or severe asthma across 59 hospitals in Spain found that a higher proportion of patients reported satisfaction with dry-powder inhalers (DPI) compared with pMDI (52% versus 28%; p<0.001).[12] Furthermore, a higher proportion of patients were satisfied with Easyhaler® (Orion Corporation, Orion Pharma [Fin], Espoo, Finland) compared with Turbuhaler® (AstraZeneca UK Limited, Cambridge, UK), or Diskus® (GlaxoSmithKline, Brentford, UK) in a sub-analysis of 328 patients from the same study (62% versus 43%; p=0.01).[13] Ultimately, understanding patients' inhaler preferences results in better adherence and asthma control.[14]

While HCP often focus on asthma and COPD treatments being effective and safe, patient preference for inhaler devices are also important as they affect adherence and outcomes.

Harnessing Inhaler Technology

Professor Federico Lavorini

The evolution of inhaled therapy for respiratory diseases dates back thousands of years. Important milestones in the development of modern-day inhaler devices for respiratory medicine include the introduction of pMDI and DPI in the 20th century.[15]

Technical Characteristics of Inhaler Devices

In pMDI, the drug and the propellant mixture are expelled from the metering chamber once the device is actuated. Although the appearance of modern-day pMDI has not changed significantly since the original device was introduced in 1956, there have been substantial improvements in the technical characteristics of the device, resulting in improved efficiency.[16] For example, innovations in aerosol formulations have led to smaller particle size, which increase lung deposition and decrease oropharyngeal deposition.[17]

In contrast to pMDI, DPI rely on patient's inspiratory effort to generate the pressure drop which drives the airflow through the inhaler. The energy associated with the airflow is used to deagglomerate the small drug particles from larger carrier particles. As it is the patient's inhalation which releases the powder, there is no requirement for hand-breath co-ordination. The turbulent airflow is produced by the patient's inspiratory effort and the resistance of the inhaler.[18] The resistance to airflow through a DPI is a fixed property unique to each inhaler, while the inspiratory power is a property of the patient. Together these determine the airflow rate through the inhaler.[19]

Optimal Drug Delivery with Inhaler Devices

There is a common misconception that patients with asthma or COPD may have difficulty achieving sufficient flow through a high-resistance DPI. Peak inspiratory flow has historically been the key consideration for DPI; however, peak inspiratory flow alone cannot be used to compare flows between devices, and it should only be the focus when considering the flows through an individual DPI, as seen in Figure 1.[18,20-22]

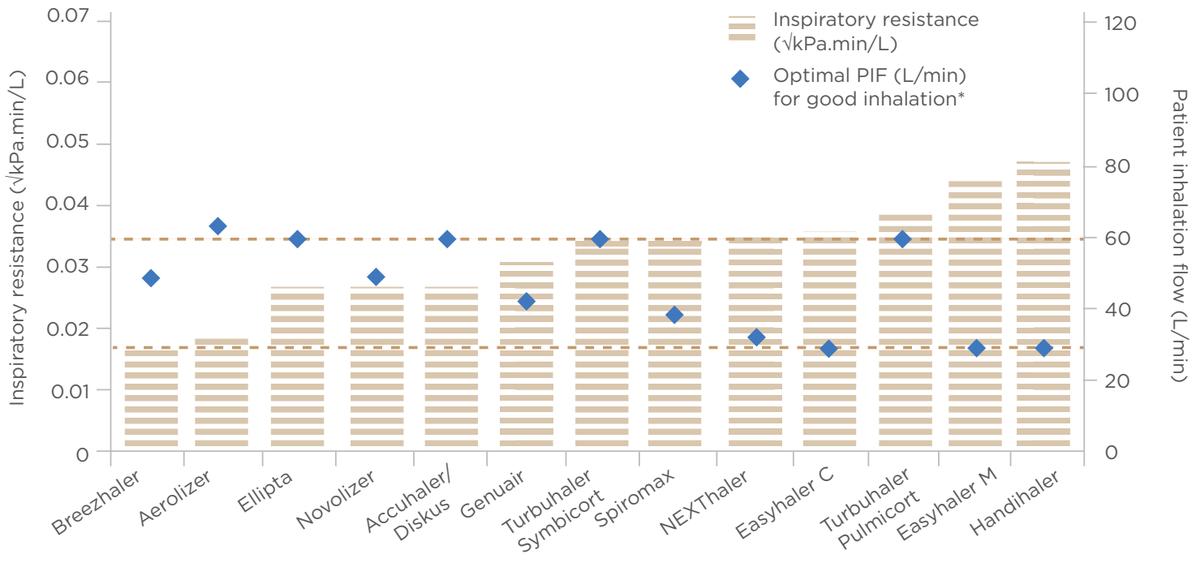

Figure 1: Inspiratory resistance and optimal peak inspiratory flow of marketed dry powder inhalers.

Accuhaler® (GlaxoSmithKline, Brentford, UK); Aerolizer® (Novartis, Basel, Switzerland); Breezhaler® (Novartis); Diskus® (GlaxoSmithKline); Easyhaler® (Orion Corporation, Orion Pharma [Fin] Espoo, Finland); Ellipta® (GlaxoSmithKline); Genuair® (AstraZeneca UK Limited, Cambridge, UK); Handihaler® (Boehringer Ingelheim Limited, Ingelheim am Rhein, Germany); NEXThaler® (Chiesi Limited, Parma, Italy); Novolizer® (Mylan N.V., Canonsburg, Pennsylvania, USA); Spiromax® (Teva Pharma B.V., Petah Tikva, Israel); Turbuhaler® (AstraZeneca UK Limited).

*Optimal PIF refers to the lower limit of desired inspiratory flow.

C: combination therapy; M: monotherapy; PIF: peak inspiratory flow.

Adapted from Levy ML et al.[22]

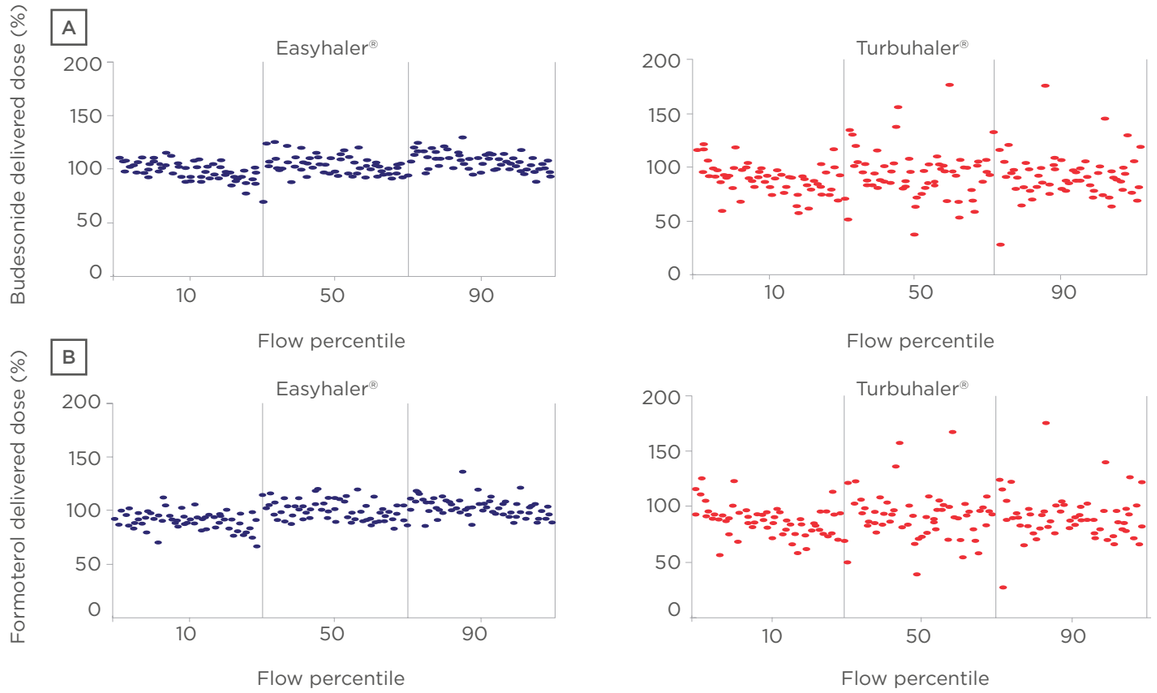

Figure 2: Dose delivery of (a) budesonide and (b) formoterol with the Easyhaler® and Turbuhaler® at different flow percentiles.

Easyhaler® (Orion Corporation, Orion Pharma [Fin] Espoo, Finland); Turbuhaler® (AstraZeneca UK Limited, Cambridge, UK).

Adapted from Haikarainen J et al.[24]

The inspiratory power of the patient determines the amount of energy available for the powder deagglomeration. The same energy output can be achieved either with a low inhalation flow through a high-resistance inhaler, or a high inhalation flow through a low-resistance inhaler. For example, with the medium-to-high resistance device Easyhaler, it has been shown that patient inspiratory flow of 30 L/min is sufficient for powder deagglomeration and consistent dose delivery. Almost all patients with asthma and COPD have been shown to achieve this flow rate.[21,23-26]

Dose delivery, consistency, and robustness for daily use are important characteristics of inhaler devices. An *in vitro* study comparing dose delivery of budesonide and formoterol with the Easyhaler and Turbuhaler at different patient airflow rates, showed that Easyhaler has superior dose delivery and consistency at all inhalation flows compared with the Turbuhaler (Figure 2). Environmental variations in moisture, dropping the device, vibration, and freeze-thawing similarly does not affect consistency of dosing with the Easyhaler.[24]

Modern inhaler devices are the result of decades of research and innovative engineering. The inspiratory effort of the patient and resulting energy associated with the airflow are the key factors for deagglomeration and drug delivery, irrespective of the device resistance.

Patient Factors in Successful Asthma and Chronic Obstructive Pulmonary Disease Therapy

Doctor Mark L. Levy

Patient satisfaction and correct use of inhaler devices are integral factors in the management

of asthma and COPD; however, inhaler technique errors are common and tend to increase with patient age and device complexity.[27-29] An association between inhaler technique errors and poor outcomes for patients with asthma or COPD has been published widely.[30-33]

Encouragingly, a study of >1,600 patients with asthma or COPD found that those who had more than one inhaler check had a lower risk of making critical errors, emphasising the positive impact of regularly checking inhaler technique.[33] Switching perspective to the use of inhaler devices by HCP, a study has shown that a large proportion of newly qualified clinicians were unable to correctly demonstrate inhaler devices.[34] Similarly, another study showed that only 5% of newly qualified medical interns used a pMDI perfectly; however, this increased to 73% after an intensive one-on-one training session.[35]

Appropriate Inhaler Selection

Six requirements for an ideal inhaler from a patient perspective have been summarised to help guide inhaler selection: effective, efficient, engaging, error-tolerant, easy-to-teach, and easy-to-switch to.[22] While inhaler satisfaction has been shown to increase adherence and asthma control,[12] patients will not always choose the inhaler that they are able to use correctly. A randomised, crossover comparison study of 50 patients with asthma or COPD found that while a higher proportion of patients were able to use Diskus with no critical errors compared with Turbuhaler (92% versus 74%; p=0.023), more patients expressed a preference for Turbuhaler than Diskus (25 versus 17 patients).[36]

The ASCONA real-life study confirmed that high patient satisfaction with an inhaler correlated with better adherence and asthma control (Figure 3).[12] Switching inhaler device is also a strategy that can improve outcomes, as demonstrated by a Swedish study of 117 adult patients with asthma who were using budesonide–formoterol Turbuhaler and switched to treatment with budesonide–formoterol Easyhaler. After switching from Turbuhaler to Easyhaler, patients had equivalent or improved disease control and improved quality of life.[37]

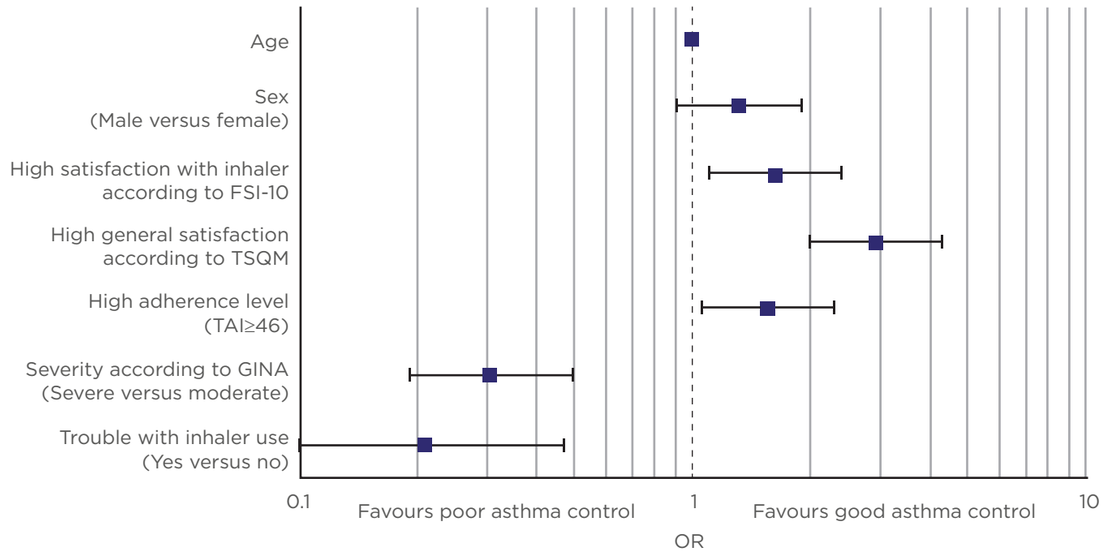

Figure 3: Asthma control according to the Asthma Control Test (ACT) score as the dependent variable.

ACT: Asthma Control Test; FSI-10: Feeling of Satisfaction with Inhaler questionnaire; GINA: Global Initiative for Asthma; OR: odds ratio; TAI: Test of Adherence to Inhalers; TSQM: Treatment Satisfaction Questionnaire for Medication.

Adapted from Plaza V et al.[12]

Education of Inhaler Technique

There are various methods to improve patients' inhaler technique, including training devices, videos of inhaler technique, websites, pharmacist-led individual and small group education, and specialist paediatric technique clinics.[38-41] Repeated assessment and correction of inhaler technique is vital to sustain optimal delivery of medication to the lungs and improve health outcomes. For example, a randomised controlled trial showed that repeated instruction by trained pharmacists at 0, 1, 2, 3, and 6 months significantly improved inhaler technique and lung function. Correct inhaler technique notably decreased after 3 months, emphasising the need to check inhaler technique regularly.[42]

Correct training on inhaler device technique is not only important for patients, but for prescribers and pharmacists. It is important to ensure patients are satisfied with their inhaler and repeated inhaler technique education is provided, to ensure better adherence and outcomes.

Empowering Patients with Maintenance and Reliever Therapy

Professor Eric Bateman

There are several evidence-based methods that can improve treatment adherence in asthma. For example, clinical approaches such as home visits by trained asthma educators, and eHealth solutions, such as inhaler reminders sent to mobile phones;[43,44] however, the challenge with these strategies is sustaining enthusiasm to achieve long-term adherence and clinical benefit. Empowering patients with asthma to self-manage their disease using a therapeutic approach that harnesses their typical human behaviour has the potential to increase adherence and improve outcomes.

Two therapeutic strategies have been shown to improve adherence: use of once-daily rather than twice-daily therapy, and the maintenance and reliever therapy (MART) approach.[45-48] In MART, the combination inhaler containing a reliever (such as formoterol, a long-acting β2-agonist with rapid onset of bronchodilator action) and a low-dose inhaled corticosteroid (ICS) is used both as maintenance treatment and for relief of symptoms. MART is highly effective in reducing the frequency of worsening and severe exacerbations of asthma. This is attributable to the fact that the treatment is given early during asthma worsening, and effectively 'titrated' against symptoms, resulting in increasing administration of the ICS component when an exacerbation threatens. Patients on MART no longer require a short-acting β2-agonist (SABA).

A number of studies have confirmed that budesonide–formoterol MART reduces severe exacerbations by 30–70% compared with a high-dose ICS plus as-needed SABA and a long-acting β2-agonist/ICS combinations plus as-needed SABA at both the same dose of the former, and given at a higher dose.[49-54] A post hoc analysis of data from the AHEAD study demonstrated that the greater the need for reliever use (>6 or >8 inhalations/day versus >2 or >4 inhalations/day of reliever), the greater the benefit of budesonide–formoterol MART in terms of the risk of an exacerbation after the first high-use reliever day.[54] In a study evaluating the efficacy and safety of a maintenance and reliever budesonide–formoterol combination inhaler in patients with asthma at risk of severe exacerbations, not only did MART reduce exacerbations compared with a standard fixed-dose regimen of budesonide–formoterol with as-needed salbutamol, but it reduced nonadherence to therapy.[55]

Over-Reliance on Reliever Therapy

With the aid of electronic monitoring of inhaler use, an exploratory post hoc analysis assessed inhaled β2-agonist use 14 days before patients presented to hospital with severe asthma. A large proportion of patients took very high doses of inhaled β2-agonists for prolonged periods, above the threshold that ought to have prompted medical review.[56] Therefore, it is important for patients to seek medical attention instead of overusing a SABA to attempt to prevent potentially life-threatening events. A written action plan for patients to self-manage exacerbations can act as an 'asthma safety net.'[57] Three evidence-based medication strategies include quadrupling maintenance dose of ICS, self-administration of high-dose oral corticosteroid, and MART or anti-inflammatory reliever approach.

Use of Maintenance and Reliever Therapy in Mild Asthma

The use of MART in mild asthma has also been investigated.[58-60] In the SYGMA-1 randomised, double-blind trial, the rate of severe and moderate exacerbations decreased by 60% and the rate of severe exacerbations by 64% with as-needed budesonide–formoterol compared with as-needed terbutaline in patients with mild asthma.[58] In the NOVEL START real-life study of anti-inflammatory reliever use in mild asthma, the risk of asthma exacerbations was lower with as-needed budesonide–formoterol than with as-needed albuterol. This study also defined asthma worsening as a high-use episode, an urgent medical care consultation, or a prescription of systemic glucocorticosteroids. The number of times the criteria were met for urgent medical care was 36 in the albuterol group, 24 in the regular budesonide maintenance plus SABA group, and 13 in the budesonide–formoterol as-needed group, with a similar trend for a course of systemic glucocorticoids. Thus, budesonide–formoterol as-needed was shown to be superior to the current standard of care at Step 2 of the Global Initiative for Asthma (GINA) treatment steps.[61]

Taking these data into consideration, the 2019 Global Initiative for Asthma Global Strategy for Asthma Management and Prevention no longer supports SABA-only treatment for Step 1, recommending that a bronchodilator given for relief of symptoms should always be accompanied by low-dose ICS, preferably in one inhaler. As-needed formoterol combined with an ICS is presented as the preferred reliever across all steps of asthma treatment. This therapeutic strategy empowers patients to self-manage their asthma with one single inhaler and offers a continuity of care across treatment steps.

Summary

Professor Piotr Kuna

Patient inhaler satisfaction, preference, and correct technique are key to achieving better asthma control and improved COPD outcomes. With high resistance devices, the flow rate required to achieve same power output for powder deagglomeration is lower than for low resistance devices; thus, the inspiratory effort is rarely a limiting factor when choosing the inhaler. The simple one-inhaler MART approach matches typical human behaviour to empower patients to take control of their disease.

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Living with Alpha-1 Antitrypsin Deficiency: Empowering Patients and Healthcare Professionals

This mini symposium, focussed on the rare genetic lung disease alpha-1 antitrypsin deficiency (AATD), took place on the 30th September 2019, as part of the 29th European Respiratory Society (ERS) International Congress in Madrid, Spain. Presented by leading experts in the field, the meeting highlighted key issues relevant to the day-to-day management of patients with AATD and discussed important approaches for optimising their clinical care moving forward.

Chairpeople: Robert A. Sandhaus,[1] Charlie Strange[2]

Speakers: Robert A. Stockley,[3] Andrea Zanichelli,[4] Karen Skålvoll,[5] Robert A. Sandhaus,[1] A. Rembert Koczulla[6,7]

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Disclosure: Prof Stockley has been an advisory board member for CSL Behring, Kamada, Mereobiopharma, Vertex, Inhibrx, Polypharma, Z Factor, Novartis, Shire, GlaxoSmithKline, Akari, AstraZeneca and Covasin. Dr Zanichelli has been a consultant and/or speaker for CSL Behring and Shire. Prof Sandhaus is Medical Director and Executive Vice-President of AlphaNet, and investigator on the CSL Behring RAPID trial. Prof Koczulla reports conflicts of interest with CSL Behring, Novartis, Roche, Sanofi, Schön Klinik, AstraZeneca, Berlin-Chemie Menarini, Teva, Chiesi, Mundipharma, GlaxoSmithKline, Novotec Medical, and Grifols.

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Meeting Summary

Exacerbations in chronic obstructive pulmonary disease (COPD) impose a substantial healthcare burden and are key drivers of negative clinical outcomes and reduced patient quality of life. Prof Stockley highlighted the main differences in exacerbations between alpha-1 antitrypsin deficiency (AATD) and non-AATD-related COPD and considered potential implications for patient management. Early treatment of exacerbations with purulent sputum is known to be associated with improved patient outcomes. Emerging evidence from clinical studies also suggests that alpha-1 antitrypsin (AAT) therapy can have a positive impact on the nature and course of exacerbations in AATD.

Dr Zanichelli outlined how self-administration of intravenous drugs, which is a routine procedure that patients safely implement in other indications, has the potential to be successfully used by carefully selected AATD patients. Reflecting the current trend towards a more personalised approach to AATD therapy, self-administration can empower patients to assume an increasingly active role in their own disease management, thereby bringing improvements in treatment satisfaction, disease control, clinical outcomes, and quality of life.

A unique patient's perspective on AAT self-administration was provided by Karen Skålvoll, who highlighted the key benefits offered by self-infusion, such as reduced localised trauma and increased freedom to travel and enjoy life. Photographs from Karen's many global travels illustrate the unparalleled freedom that self-administration has afforded her as an AATD patient.

From the physician's standpoint, Prof Sandhaus summarised his experience of how patients can be empowered to self-administer AAT therapy independently with minimal training. Among motivated individuals, self-administration can provide a successful long-term treatment solution for their AATD. The drive towards self-treatment also delivers the dual benefits of reduced healthcare burden and enhanced convenience and flexibility for patients.

Prof Koczulla reported that, overall, the available evidence indicates pulmonary rehabilitation as a successful strategy in AATD, which can significantly enhance a patients' physical performance. Although the most effective training algorithm still needs to be prospectively validated, this approach may prove particularly advantageous in patients with anxiety, dyspnoea, and fear of physical activity. In order to achieve maximum benefit, therapy and goals of pulmonary rehabilitation must always be tailored to the individual patient in a personalised approach to care.

The meeting concluded with the compelling 'AATD Strongman Contest,' which pitted Prof Koczulla against AATD patient Karen Skålvoll in a physical test of endurance (the so called 'farmer's walk' involving carrying a heavy obstacle) and strength (dumbbell raises). Notwithstanding the expected impairment in aerobic ability, the domination of Karen in the strength test clearly demonstrates the physical gains that patients with AATD can achieve with physical training.

Acute Exacerbations in Chronic Obstructive Pulmonary Disease: Are They Different in Alpha-1 Antitrypsin Deficiency?

Professor Robert A. Stockley

COPD is an umbrella term used to describe a number of progressive lung diseases, including emphysema and chronic bronchitis. AATD is a rare inherited condition caused by a deficiency in the enzyme inhibitor AAT, which predisposes individuals to both lung and liver diseases.[1] Therefore, patients with AATD lack the protective effect of AAT in the lung, rendering them more vulnerable to the damaging effects of smoking and/or infection.[1]

Both COPD and AATD are associated with acute events known as exacerbations where lung symptoms worsen suddenly, contributing to substantially poorer outcomes and reduced quality of life.[2] An exacerbation is characterised by worsening of the patient's respiratory symptoms beyond normal day-to-day variation and leads to a change in medication.[3]

Table 1: Anthonisen criteria.

Anthonisen criteria	
1.	Increased breathlessness.
2.	Increased sputum volume.
3.	New or increased sputum purulence.
Definition of exacerbations	
Type 1: Presence of all three above symptoms.	
Type 2: Presence of two symptoms.	
Type 3: Presence of one symptom plus at least one additional symptom: – Upper respiratory infection within the past 5 days. – Fever without other cause. – Increased wheezing. – Increased cough. – Increase in respiratory or heart rate by 20% compared with baseline.	

Different types of exacerbations are defined according to the Anthonisen criteria (Table 1).[4]

Evidence suggests that acute exacerbations in AATD are different to those experienced with usual (nondeficient) COPD in terms of both pathogenesis and severity. One study, examining the nature and effect of exacerbations in 265 patients with AATD, discovered that exacerbations occur commonly and are associated with declining health status.[2] During the first year of study, exacerbations occurred in 142 subjects (54%), with 47 (18%) experiencing frequent (≥3) exacerbations. A clear relationship was seen between the number of exacerbations and the St George's Respiratory Questionnaire total score, indicating worse health status with more frequent episodes. The median length of each exacerbation in the AATD study was 14 days. This compares to a shorter average exacerbation length of 7 days documented in patients with typical COPD.[5] In addition, exacerbations associated with purulent sputum were associated with significantly worse symptoms at presentation than those with mucoid sputum.[6]

Differences have also been noted between AATD and usual COPD exacerbations in sputum colour, and the concentration of neutrophil elastase and cytokines, even though the degree of bacterial colonisation/infection provides a similar initiating drive. Studying these differences provides important insights into the underlying disease processes in COPD versus AATD and how these contribute to the manifestation and severity of exacerbations and their consequences. AAT is a member of the serine protease inhibitor superfamily of proteins and its main function is to inhibit neutrophil elastase in the lung.[1] Deficiency of AAT results in increased levels of uninhibited neutrophil elastase leading to breakdown of lung tissue and emphysema-like changes.[1] Bacterial load is directly correlated with the same initiating IL-8 levels in both AATD and usual COPD. However, AATD has been shown to be associated with a greater neutrophil load, and higher elastase activity which drives leukotriene B_4 production, and epithelial damage leading to greater serum protein leak than in matched patients without the deficiency.[7] However, after treatment with antibiotics there was a reduction in sputum myeloperoxidase levels activity indicating a reduction in neutrophil recruitment and the other cytokines. Despite this, elastase activity persisted, as did the sputum chemoattractant leukotriene-B_4, remaining higher than baseline data in the COPD cohort.[8]

The impact of these worse exacerbation manifestations in AATD may have important

implications for clinical management and treatment decisions. Protease inhibitor Z is the most common deficiency allele in AATD, with a large majority of individuals with severe disease being homozygous for the deleterious allele (*PI*ZZ*).[9] A prospective study looking at the natural history of AATD in 43 patients with the protease inhibitor Z phenotype over 2 years showed that annual decline in forced expiratory volume (FVC) was directly related to exacerbation frequency (r=0.50; p<0.001).[10] These results show that progression of lung function decline in AATD is exacerbations, underscoring the importance of prompt treatment for these episodes. Despite this, evidence suggests that delays or failure to treat exacerbations in AATD are common. In one study, delay was shown to be influenced by a number of factors including symptom score, severity at onset, airflow obstruction, and lung density.[11] Treatment delay was shorter in patients with higher symptom scores at onset and in those with lower baseline FEV1, FEV1/ forced vital capacity, and 15th percentile lung density. The key independent predictor of delay in starting treatment was lung density (which is a direct measure of the amount of emphysema), as demonstrated by multivariate analysis.[11] There also appeared to be a significant association between Anthonisen criteria and length of a treated exacerbation, with Type 1 events lasting longer than Type 2, which were in turn longer than Type 3. Resolution of exacerbation after treatment initiation was found to be unaffected by the delay in therapy, but was correlated negatively with gas transfer, a physiological measure of the emphysema.[11]

Overall, the substantially higher protease activity appears to be the main differentiator in the disease process between AATD and typical COPD and may be attributable to the worse exacerbations seen in the former group. This is of great importance because proteases such as neutrophil elastase drive proteolytic degradation of lung tissue in patients with AATD, which is allowed to continue unopposed due to already reduced levels of protective AAT.[12] Prof Stockley stressed that new or a worsening of sputum purulence is mandatory for antibiotic therapy, as it indicates the presence of new or increasing bacterial growth. In addition, early initiation of treatment is an important step towards reducing total exacerbation length.

Self-Administration: Taking Patient Empowerment Seriously

Doctor Andrea Zanichelli

AAT replacement therapy is currently the only available treatment that targets the underlying cause of lung disease in AATD. Treatment requires lifelong weekly intravenous infusions of AAT therapy with the approved dose of 60 mg/kg, typically administered by a healthcare professional (HCP) in the clinic or physician's office. The associated travel and waiting times impose a significant burden on the patients' everyday lives and contribute to treatment dissatisfaction. As a result, there is an increasing interest in intravenous self-administration of AAT therapy as a means of optimising the treatment experience and potentially enhancing the patients' quality of life. Self-administration has the scope to deliver a raft of benefits for individuals with AATD, including greater independence and autonomy, fewer healthcare visits and hospitalisations, and active involvement in their own care.

Self-treatment with intravenous drugs outside of the clinic is already commonplace in other rare inherited conditions such as hereditary angioedema (HAE) and haemophilia, and important lessons can be learnt from this experience to support the paradigm of self-administration in AATD.[13-15] Central to the successful implementation of this approach are educational programmes designed to support the self-administration of therapy and overcome key issues, such as fear of injections and lack of skills or confidence.[16-18] Furthermore, patients and their families must learn the technical skills needed for self-infusion and the associated practical issues.

Similar initiatives in HAE have proven successful, with studies demonstrating the feasibility and positive impact of self-administration training.[16,19] SABHA was an observational, single-centre, prospective study that assessed the self-administration of plasma-derived nanofiltered C1 inhibitor (pnf C1-INH) in 15 patients with HAE.[16] It should be noted that the low patient number included in this study was due to the rarity of HAE as a disease. Patients, sometimes accompanied by caregivers, underwent a self-infusion training course prior to the study. This consisted of a theoretical session taught by a physician, followed by a nurse-led practice session on an artificial arm. Administration courses were then performed in small groups, consolidated by a second HCP-supervised practical session (if required) for those still lacking confidence. Overall, results from this study showed a trend towards improved quality of life in patients self-administering, together with significant growth in global satisfaction scores (p=0.0072) between the first and second quarter of drug use. Notably, the percentage of patients reporting high levels of stress decreased over time, demonstrating improved confidence with treatment and a greater ability in self-infusing.

Second-generation products are now available for AATD and offer the advantages of higher specific activity, easier reconstitution, and shorter infusion times, which increases their amenability for use in the home environment. Self-administration of the AAT therapy Respreeza® is currently approved in the European Union (EU) but is rarely used because access to treatment imposes a major limiting factor.[20] Although no guideline recommendations for self-administration in AATD currently exist, some patients are already successfully self-infusing. Dr Zanichelli concluded that moving forward, and with appropriate education and training, self-administration has the potential to be more widely implemented in carefully selected patients with AATD. This is an important step on the road to personalised therapy, freeing patients from their current treatment burden and empowering them to seize greater control of their own disease and its management.

A Patient's Perspective on Alpha-1 Antitrypsin Self-Administration

Karen Skålvoll

Ms Skålvoll, a patient with AATD and lung disease, described her own personal experiences of intravenous self-infusion, highlighting the increased independence and greater control that patients can gain by adopting a central role in their own treatment. Although patients may be unaware or nervous about self-administration, it is important to communicate the potential benefits that can be attained, such as reduced localised trauma at the infusion site, and explain how readily and safely the technique can be learned and performed. Access to home treatment offers patients greater freedom from the shackles of hospitalisation, providing practical advantages

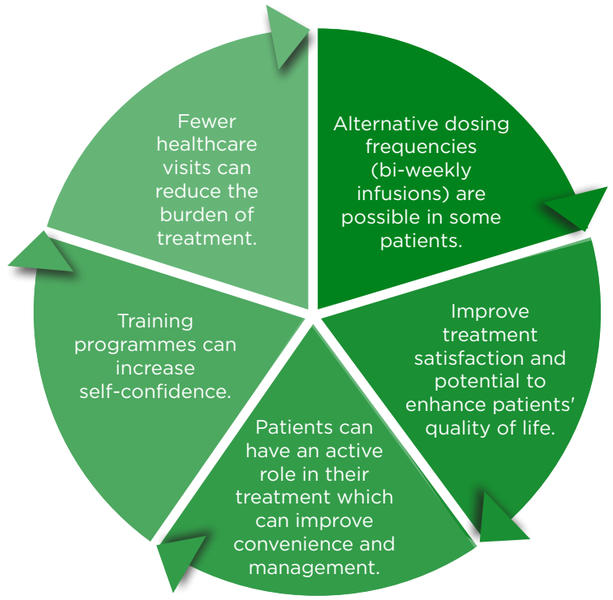

Figure 2: A holistic approach to treatment.

like flexibility and convenience together with wider benefits such as an increasing sense of autonomy and dignity in the AATD treatment process.

In an insightful video set in her own home, Karen demonstrated how easily the practicalities of reconstitution and intravenous infusion of AAT therapy can be carried out. Photographs from Karen's many global travels highlight the unparalleled freedom and enhanced enjoyment of life that self-administration has afforded her.

A Physician's Perspective on Alpha-1 Antitrypsin Self-Administration

Professor Robert A Sandhaus

Prof Sandhaus explained that selecting the right patients for self-administration of AAT therapy is pivotal, as the patient's own capacity to self-administer effectively is likely to be the critical factor in success. Key considerations for the implementation of self-administration include the patient's age, dexterity, motivation, disease status, and cognition.

A questionnaire sent to AATD experts indicated that they see an impaired ability to monitor patient adherence and potential safety issues surrounding intravenous infusion as the main concerns to self-administration.[18] However, data from a recent AlphaNet[21] survey of patients included in the Alpha-1 Disease Management and Prevention Program (ADMPP) showed that a number of patients are already successfully and safely self-administering their AAT therapy.[17] This cross-sectional, observational, telephone survey included patients aged ≥18 years diagnosed with AATD and receiving AAT therapy with Respreeza®. The overarching aim of the survey was to assess the occurrence, practicalities, satisfaction, and challenges of AAT self-administration. Of the 555 patients surveyed, only a minority (7.9%; 44 patients) were found to be actively self-administering their AAT therapy. However, all patients self-administering described being either 'very satisfied' (95.4%) or 'satisfied' (4.6%) with their treatment. The survey also revealed that patients who were self-administering required minimal training and infusions did not appear to differ from those conducted by HCP. A slight majority of patients (56.4%) required only 2–3 training sessions to learn how to successfully self-administer, with this training largely provided by a home nursing agency. Infusion duration was generally aligned with licensing recommendations and administration in the hospital-setting, with most patients requiring <1 hour to carry out the infusion. Encouragingly, patients experienced few problems with self-administration, with the majority (83.7%) reporting no difficulties whatsoever; only five respondents described infusion-related issues at some point in time. Almost all patients (~98.0%) also confirmed that easy access to help or advice was available if required.

In conclusion, Prof Sandhaus noted that the overall results of the AlphaNet survey should help to address and assuage physician concerns by demonstrating that self-administration can, and is, being safely performed in patients with AATD. Among motivated individuals, self-administration can prove a viable long-term treatment approach, with nearly 20% of the surveyed patients successfully self-infusing their AAT therapy for over a decade. Careful selection of patients is essential to optimise the benefits of AAT self-administration, and appropriate physician-led follow-up is also important, providing help and advice with infusion-related issues where required.

What Pulmonary Rehab Can Do for Alpha-1 Antitrypsin Deficiency Patients

Professor Andreas Rembert Koczulla

Pulmonary rehabilitation is a comprehensive intervention in lung disease that is based on thorough patient assessment followed by patient-tailored therapies, including, but not limited to, exercise training, education, and behavioural change. These are designed to improve the physical and psychological condition of people with chronic respiratory diseases and promote the long-term adherence to health-enhancing behaviours.[22] Although rehabilitation is currently recommended for AATD-related COPD, there is no reference to AATD-specific studies in the guidelines and there is scarce evidence on the impact of training in this particular patient cohort.[22]

Prof Koczulla cautioned that patients with ATTD have very individualised problems that may affect their pulmonary rehabilitation, most notably physical and psychological comorbidities. These treatable traits, which include anxiety or depression, cognitive impairment, low muscle mass and muscle weakness, osteoporosis, and abnormal weight may require a targeted approach to rehabilitation. Interestingly, anxiety, dyspnoea, and fear of physical activity have all been associated with underlying structural changes within the grey matter of the brain.[23,24] Encouragingly, however, studies have shown that patients with these psychological comorbidities respond better to pulmonary rehabilitation than those free from these conditions or with more physical complications. When tested, patients with the psychological cluster of symptoms demonstrated greater improvements in lung capacity and a higher likelihood of achieving meaningful improvements in the 6-minute walking distance than their counterparts without, or with more physical, comorbidities.[25,26]

Evidence confirms that pulmonary rehabilitation is as successful a strategy in AATD as it is in COPD. In a study of patients awaiting lung transplantation, pulmonary rehabilitation increased the 6-minute walking distance by 48 m in the AATD cohort, with 18% also experiencing an improvement in their mental quality of life measured by the SF-36 questionnaire.[27] Medication is another important player in pulmonary rehabilitation. For example, aclidinium bromide-induced bronchodilation significantly improved symptom-mediated activity limitation in a Phase III trial in COPD.[28] Data from the large COPD Biomarker Qualification Consortium database of 1,200 patients investigated the average improvement in constant work rate cycle ergometer endurance in patients with COPD with different degrees of lung function impairment (Global Initiative for Chronic Obstructive Lung Disease [GOLD] category 1–4). While comparable increases in exercise tolerance in response to rehabilitative exercise training were achieved across the full range of lung function impairment, bronchodilator therapy became an important means to achieve a higher training capacity the higher the GOLD class.[29] However, average increases in exercise tolerance in response to rehabilitative exercise training showed equivalence across the full range of lung function impairment.[29]

A recent comparative study specifically evaluated the impact of training in nine patients with AATD versus ten with 'usual' COPD.[30] Participants performed an incremental cycling test and underwent musculus vastus lateralis biopsies before and after a 3-week pulmonary rehabilitation programme including exercise training. Physical training and pulmonary rehabilitation were shown

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Association Between Leukocyte Telomere Length and Functional Decline in Patients with Idiopathic Pulmonary Fibrosis on Antifibrotic Treatment

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BACKGROUND

Patients with idiopathic pulmonary fibrosis (IPF) display an unpredictable and heterogeneous disease behaviour with a progressive functional decline towards respiratory failure.[1] In the last few years, score systems have been developed to assess the disease progression; however, they have shown limited value in predicting disease outcome at the time of diagnosis.[2,3] Among molecular biomarkers, short leukocyte telomere length (LTL) is considered a risk factor for the development of IPF and it has been linked to worse transplant-free survival in untreated patients.[4] Antifibrotics have proven effective in slowing down the rate of functional decline and disease progression of IPF.[5] However, a significant variability in treatment response still exists,[6] and it remains unclear whether TL contributes to such variable response to treatment in patients with IPF.

AIM

The study investigated whether TL correlates with functional decline and survival in a phenotypically well-defined population of IPF patients treated with antifibrotic drugs (nintedanib or pirfenidone).

METHODS

Telomere length was measured by real-time PCR in genomic DNA extracted from peripheral blood leukocytes in 105 consecutive patients with a diagnosis of IPF who started therapy (either with pirfenidone or nintedanib equally distributed). Data were expressed as number of telomere repeats (T) normalised to single copy reference gene β-globin (S) and results were expressed as T/S ratio. Twenty-three healthy well-matched individuals served as controls. A subsequent analysis was conducted after the first year of therapy in 28 subjects and after 3 years in 17 subjects. The authors categorised patients as stable or decliners based on the forced vital capacity decline in the first year of therapy (<5% or >5%, respectively).

RESULTS

Demographic characteristics of the whole population, at baseline, reflect a typical patient with IPF (male and former smoker) and the functional profile reflects a mild disease. The study revealed that IPF patients had shorter TL compared to healthy matched controls (1.26±0.34 versus 1.64±0.53; p=0.002). The probability of survival according to TL was explored, and when the data analyses was limited to TL at baseline <10%, 25%, and 50%, no significant differences in terms of survival were observed. In summary, LTL at T0 did not predict a survival difference in treated patients. Additionally, IPF patients were separated as stable (n=19) and decliners (n=9), who displayed similar demographics and functional characteristics but different forced vital capacity decline after 1 year of treatment. TL at baseline in stable patients and decliners was then compared; however, no significant difference was observed (1.19±0.25 versus 1.24±0.29, respectively; p=0.46) suggesting that the different treatment response occur regardless if TL is at baseline. Analysis of TL dynamics and functional trajectory in treated patient with IPF-1 year (n=28) displayed no significant change (p=nonsignificant) suggesting the potential influence of treatment on the attrition rate of telomere shortening. Similarly, in the subgroup of 17 patients out of 105 who were treated up to 3 years, TL did not change significantly. A strong correlation was found between TL at baseline and telomere attrition rate from baseline up to the third year (r=-0.7; p=0.001); therefore, individuals with longer telomeres at baseline experience the largest telomere attrition rates over time.

CONCLUSION

TL at baseline is associated neither with the rate of functional decline over time nor with survival in IPF patients on antifibrotic therapy. The rate of LTL shortening over time correlates strongly with LTL at baseline. Further studies are needed to clarify whether antifibrotic therapy slows down disease progression by reducing telomere shortening.

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What Do Patients Want in an Asthma App?

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Keywords: Asthma, asthma application (app), mobile health (mHealth), patient perspective, patient reported outcome, respiratory medicine, self-management, telemedicine.

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BACKGROUND

Asthma is estimated to affect 300 million people worldwide,[1] and the literature advocates the beneficial effect of self-management programmes on asthma control.[1-3] The use of smartphones and tablet applications (app) for self-management of asthma is progressing, showing promising results in patient self-management.[4] Understanding patients' perspectives is a fundamental step in the development of user-centered mobile health (mHealth) systems.[5]

AIM AND OBJECTIVES

The authors wanted to develop and implement a mobile health (mHealth) app to aid the treatment of asthma patients diagnosed and treated at an outpatient asthma clinic, and to aid the patient in preventing deterioration of their disease. Also, the authors wanted to examine the patients' experience and demands for this app.

Building Hope by Restoring Breathing in Airways Diseases

This symposium took place on 1st October 2019, as part of the European Respiratory Society (ERS) International Congress held in Madrid, Spain

Chairpeople: Àlvar Agustí[1,2]

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Meeting Summary

Prof Agustí opened the session by explaining the new challenges in airway diseases including the changing paradigm of our understanding of chronic obstructive pulmonary disease (COPD) that considers the entire lung function trajectory from birth to death, the complexity and heterogeneity

of the disease, and the need to diagnose and treat COPD earlier in life. Prof Siddiqui then explained that all of the airways, including small airways, are critically important in the pathophysiology of asthma and COPD. The world's largest multi-centre ATLANTIS study focussed on small airways dysfunction (SAD) confirmed that a simple combination of different assessments like oscillometry and spirometry could identify patients with the SAD phenotype. The prevalence of airway dysfunction in the full asthma cohort was 91%. Prof Papi discussed that exacerbations are a crucial event in the natural history of COPD and that they drive several health-related outcomes. He reviewed the clinical evidence to demonstrate the benefits of triple therapy in general and specifically of the extrafine fixed triple combination (beclometasone dipropionate, formoterol fumarate, glycopyrronium bromide) to consistently reduce the risk of exacerbations, and improve lung function and quality of life (QoL) with a favourable benefit-to-harm ratio. Furthermore, triple therapy showed promising signals in terms of improved survival. Prof Celli debated that inhaled corticosteroid (ICS) should be given to many patients because scientific trials have shown that: 1) ICS combined with bronchodilator (BD) are effective in improving health status and reducing exacerbations; 2) they also impact lung function decline and mortality; 3) ICS increase pneumonia risk (depending on type, dose, airflow limitation, BMI, and age) but have no untoward effect on mortality or hospitalisations for pneumonia; 4) blood eosinophil count (BEC) (<100 cell/µL) helps select patients unlikely to respond to ICS; and 5) 'many' COPD patients benefit from ICS combined with BD. Prof Singh focused on the fact that the magnitude of clinical benefit in preventing COPD exacerbations varies between individual patients, underlining the importance for clinicians of making the right decision for each patient when prescribing ICS, by balancing the potential risk/benefit. He concluded the debate by outlining that ICS have benefits in patients at increased exacerbation risk, and that the size of the benefits varies with BEC and the number/type of exacerbation.

New Challenges in Airway Diseases

Professor Àlvar Agustí

According to Prof Agustí, there are currently three key challenges to overcome to build hope in airway diseases. The first challenge is that the COPD paradigm is changing. Airway diseases (as many other chronic conditions of the adult individual) can start early in life (during pregnancy, infancy, and adolescence), albeit it is often not diagnosed until the sixth of seventh decade of age. Several lung function trajectories (Figure 1) exist throughout the life course, including a growth phase, a plateau phase, and a declining phase. This novel perspective provides a dynamic way to study how lifetime influences health and disease, including COPD. Therefore, time considerations in the understanding of airways disease are becoming increasingly important. Recent research has shown that 4–13% of the general population do not achieve normal peak lung function in early adulthood, albeit approximately two-thirds of children with reduced lung function at birth can catch up to a normal trajectory. At the other end of the spectrum, there are supranormal trajectories. These supranormal individuals may lose significant amounts of lung function through life and, nonetheless, present to the clinic in their sixties with evidence of lung damage (e.g., CT emphysema) and 'pseudonormal' spirometry.[2,3] Furthermore, low peak lung function in early adulthood is significantly associated with early development of comorbidities and premature mortality.[3] In total, there are two key biological phenomena (organ development and ageing) that need to be considered to better understand the pathogenesis of COPD.[2,3] In this context, COPD and asthma may be considered as a continuum of chronic airway diseases.[1,4-9]

The second challenge is that COPD in particular, and airway diseases in general, are complex and heterogeneous; therefore, one therapeutic strategy does not fit all patients. Disease complexity is defined by the presence or severity several components such as emphysema, exacerbations, rate of lung function decline, early life events, and inflammation, among others, and that these components are not linearly related (so one cannot be predicted from others). Furthermore, heterogeneous means that not all these components are always present in all patients or, in a single patient, they may change

with time, either because of disease progression and/or the effect of therapy. To address these complexities and heterogeneity, it has been recently proposed that a strategy based on the presence of specific treatable traits may be the way forward for personalised and precise treatment of these patients.[10-13] This is supported by the recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendation to individualise treatment based on two key treatable traits, namely emphysema and dyspnoea.

The third and final challenge, following directly the realisation of different lung function trajectories leading to COPD (Figure 1), is to diagnose and treat the disease much earlier. Generally, COPD is diagnosed later in life,[8,14] when a cure of the disease or the possibility to make a significant impact is unlikely.[14,15] Recent research (unpublished)[16] in the general population found that: 1) many factors relate to lung function throughout life; 2) these factors vary according to age; and 3) these factors interrelate. Older patients had an extremely complex interrelating network of influencing factors on lung function, which translates into an increasing complexity for treatment decision making. The current treatment strategy in COPD has been to follow the disease (e.g., the best predictor of future exacerbations is past exacerbations); Prof Agustí emphasised how it is time to start leading it.

Targeting the Sm(all) Airways in Asthma and Chronic Obstructive Pulmonary Disease

Professor Salman Siddiqui

Multiple evidence now exists supporting the role of the small airways in both asthma and COPD, yet, a deployable definition has remained elusive.[17] The reason is that the small airway compartment is a difficult anatomic area to study due to its relative inaccessibility. They include the small, conducting bronchioles; the bronchiolar airways; and the acinar airways.[18] Different tests measure different parts of this compartment and what we need is to move beyond individual tests to define SAD. Pathology evidence indicates small airways are strategically important in COPD. Micro-CT imaging of lung-resected tissue in patients with COPD, showed that even patients with early disease have loss of small airways (before the development of emphysema and extensive lung damage). The progression in patients across the spectrum of COPD severity was strongly associated with airway wall thickening, increasing lumen mucous exudates, and the number of airways containing acute inflammatory cells.[19,20] There is a growing body of evidence to show that extrafine therapies can reach the small airways. Several studies have shown that extrafine drugs can reach and are retained in the small airways and can treat them producing improved forced

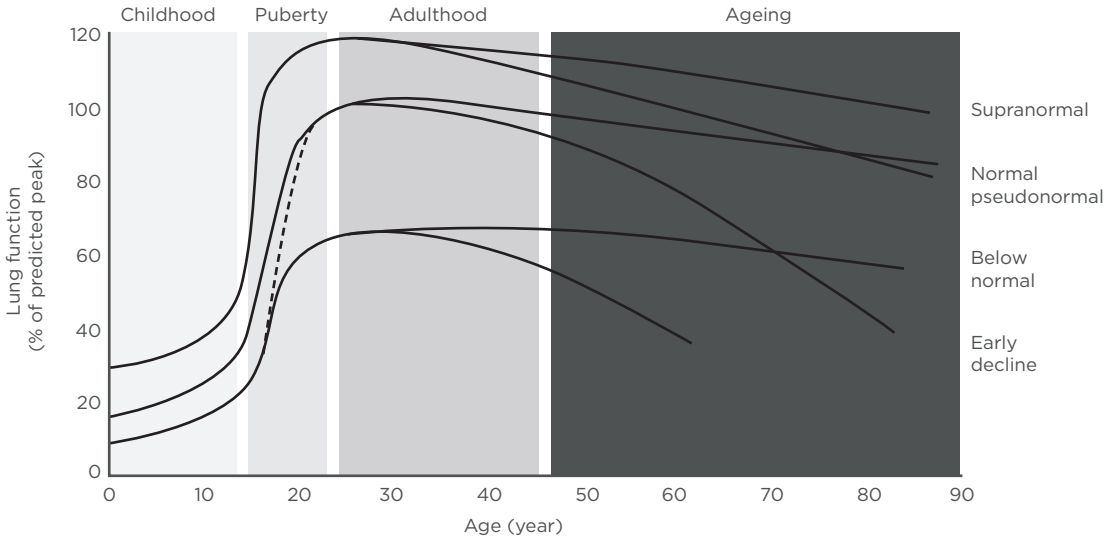

Figure 1: Lung function trajectories from birth to death.

Adapted from Agustí and Hogg.[1]

vital capacity, 6-minute walk distance test, and reduced exacerbations of COPD.[17,21]

The same concepts apply to asthma; however, a key challenge is that no gold standard test exists to detect SAD. There are several tests that have been used to study SAD, including spirometry, impulse oscillometry (IOS), mid expiratory flows, forced vital capacity, and multiple breath nitrogen washout to measure conductive and acinar ventilation heterogeneity. IOS is particularly useful because it can be deployed across the life course, takes only a few minutes to perform, and is highly reproducible. It uses sound waves to provide a measure of airway resistance at different frequencies.[22] This is supported by studies, which found that IOS R5-R20 parameters correlated with the degree of morphologic abnormalities of small airways in COPD and asthma patients.[23,24] These findings needed confirmation from large-scale clinical trials.[25] ATLANTIS, a 1-year, prospective, observational, multicentre, multinational study in 800 patients with asthma across a range of severity (including smokers) and 100 healthy controls, was initiated to address this need. This is the largest study to date on SAD and the objectives were to determine the role of small airway abnormalities in the clinical manifestations of asthma, and to evaluate which clinical methods best assesses the abnormalities of small airways and large airways disease in asthma and best relates to asthma severity, control, QoL, and future risk of exacerbations; thereby, potentially establishing a method of defining SAD.[26] The prevalence of SAD in asthma using all techniques was 90.7%. Gas exchange tests such as Sacin (index of diffusive ventilation heterogeneity in most peripheral pre-acinar/acinar airways) showed <20.0% prevalence of SAD (showing specificity but not sensitivity). Whilst, spirometry test (73.1% prevalence) appeared to be oversensitive, but not specific. Every patient was assigned a clinical SAD score from the model and this was used to identify SAD phenotypes using clustering. This identified two groups: patients with milder SAD and patients with severe SAD. Patients with severe SAD showed massive enrichment of abnormal oscillometry (up to 6-fold higher in some patients) when compared to those with mild SAD. When reviewing the CT scans to undertake a similar modelling, the two (physiological versus CT) did not closely correlate (potentially because of gravitational forces on lung function affecting the different way those are measured) (Figure 2).[27]

Prof Siddiqui concluded that there is clear evidence to show that all of the airways, including small airways, are critically important in the pathophysiology of asthma and COPD (including early COPD) and a high prevalence of SAD in asthma and COPD. The world's largest ATLANTIS study of SAD across asthma severities confirmed that a simple combination of oscillometry and spirometry can be used to identify SAD phenotype.

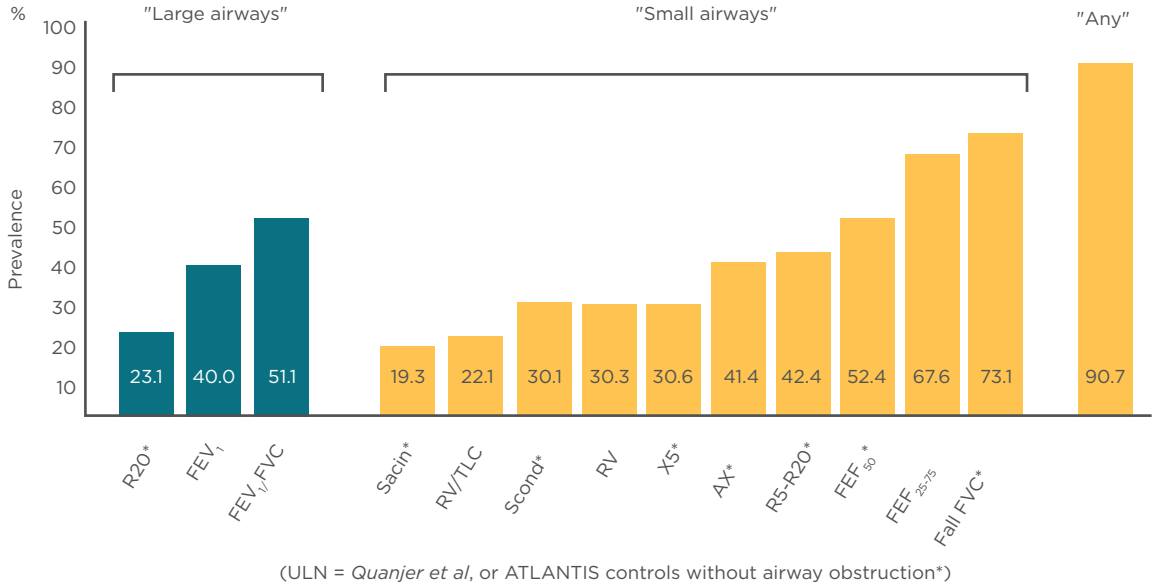

Figure 2: Prevalence of abnormal physiological variables of SAD[28]

Furthermore, the SAD phenotype was associated with more severe disease and adverse outcomes such as worse asthma control and a higher risk of exacerbations.

Triple Therapies: Opening Spaces for Hope in Chronic Obstructive Pulmonary Disease Patients

Professor Alberto Papi

The GOLD define COPD as "a common, preventable, and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation [...] (which) is caused by a mixture of small airway disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person."[13] Hogg et al.[20] confirmed the relationship between airflow limitation and severity of inflammatory infiltrates (innate and adaptive inflammatory immune cells) in peripheral airways. The airway inflammatory process is amplified during acute exacerbation events. GOLD defines exacerbations of COPD as an acute worsening of respiratory symptoms that requires additional medication and/or hospitalisation.[13] COPD exacerbations are heterogeneous and the pathophysiology is not yet fully understood. The acute events and increased airway inflammation lead to structural changes, such as increased thickening of the airway wall, functional changes with bronchoconstriction, and increased mucus production and pathophysiology modifications (e.g., increased airflow limitation and hyperinflation) related to worsening of symptoms. The goal is to interfere with this cascade of events, at whatever level, to avoid the evolution of increased symptoms that characterise exacerbations.[28,29] Treatment or prevention of exacerbations are critical (and may require targeting of different pathways), due to the significant negative impact on pulmonary function, health status, QoL, risk of hospitalisation, outcomes, and healthcare costs.[13] In fact, the increased risk of mortality has not only been found during the acute episode but also up to 5 years after hospitalisation.[30] COPD exacerbations also increase the risk of cardiovascular events during and after an acute episode.[31] One mechanism for preventing exacerbations is the use of BD, via the effect on airway patency, but also the pathophysiological mechanisms they induce.[32] Treatment can be further improved with the addition of ICS as shown by a Cochrane review, which demonstrated that combination ICS therapy led to fewer exacerbations, improved QoL, lung function, and symptom scores when compared to the use of LABA monotherapy.[33] GOLD has recently updated their recommendations for initial treatment in patients with GOLD D stage.[13]

The previous 2017 version was supported by evidence of two bronchodilators (LABA and LAMA) in combination being more effective than a single long-acting BD in preventing exacerbations.[34] Since new evidence has become available showing that a combination of LABA/LAMA over LAMA monotherapy for exacerbation prevention has not been consistently demonstrated, the 3 options are recommended in this group of patients as initial treatment (LAMA, ICS/LABA, preferentially in patients with BEC ≥300 cells/µL, LABA/LAMA preferentially in symptomatic patients with a COPD Assessment Test score >20.[35] The new GOLD concept in the follow-up treatment is a personalised approach, considering the key needs and the current treatment, to orientate decisions. The recent changes are because of new clinical evidence.[13] The previous 2017 GOLD recommendation came after the publication of the results of the FLAME study, which showed that at 52 weeks, LABA/LAMA was associated with a significant reduction (11%) in the annual rate of exacerbation when compared to ICS/LABA in all levels of severity.[36] In 2018, data from the IMPACT study demonstrated that ICS/LABA resulted in a lower rate of COPD exacerbations than LAMA/LABA (1.07 per year with ICS/LABA versus 1.21 with LABA/LAMA).[37] Patients enrolled in the IMPACT study had a higher frequency of exacerbations when compared to the FLAME study population and thus are the population in greater need for effective exacerbation prevention.[38,39] If exacerbations occur in patients treated with dual (ICS/LABA or LABA/LAMA) therapy, the next step in the GOLD exacerbation algorithm is moving to triple therapy with ICS/LABA/LAMA (with BEC ≥100 cells/µL for those on LABA/LAMA).[13] The evidence for this recommendation comes from the TRILOGY study, which found an adjusted annual exacerbation frequency of 0.41 for triple therapy (ICS/LABA/LAMA) and 0.53 for

ICS/LABA, corresponding to a 23% reduction in exacerbations with triple therapy. The TRILOGY study, for the first time, provides 1-year evidence showing that triple therapy is superior to ICS/LABA in terms of forced expiratory volume in one second (FEV_1), reduced exacerbation rate, and other symptoms-based and lung function parameters.[38] The subsequent TRINITY study found that exacerbation rates were 0.46 for fixed triple, 0.57 for LAMA monotherapy, and 0.45 for open triple; fixed triple was superior to LAMA (p=0.0025).[39] This is the first evidence to support triple therapy (either fixed or open) over LAMA monotherapy in preventing COPD exacerbations as primary outcome, which somehow raises questions of why you would escalate to dual therapy from LAMA treatment, given that the benefit of LABA/LAMA over LAMA is questionable in terms of exacerbation prevention. The TRIBUTE study further demonstrated the superior efficacy of extrafine triple therapy in reducing the rate of exacerbations as compared to LABA/LAMA (0.50 for triple and 0.59 for LABA/LAMA). This translates into a 15.2% reduction of moderate/severe COPD exacerbation risk for triple versus dual therapy. Triple therapy was also superior to LABA/LAMA in pre-dose FEV1 and improvement in QoL.[40] In addition, the IMPACT study showed that the annual rate of severe exacerbations resulting in hospitalisation in the triple-therapy group was 0.13 compared to 0.19 in the LAMA/LABA group (p<0.001).[37] Adverse events were similar across treatment groups.[40] Pneumonia was reported in a small number of patients across all three clinical trials (TRINITY, TRILOGY, and TRIBUTE), with similar incidences. This data show that the balance between the benefits of the reduction in COPD exacerbation versus the risk of development of pneumonia is 7–10-fold in favour of the benefits.[38-41] This is aligned with the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) review that the benefits of ICS continue to outweigh their risks.[42] Triple therapy, therefore, provides new treatment options and potentially new hopes for patients with moderate-to-severe COPD exacerbations. Triple therapy may provide the opportunity to lead this disease. Prof Papi questioned the need to wait for 2 exacerbations to escalate treatment when there is evidence showing that exacerbation risk is more than doubled in patients experiencing only 1 exacerbation in the past 12 months,[43]

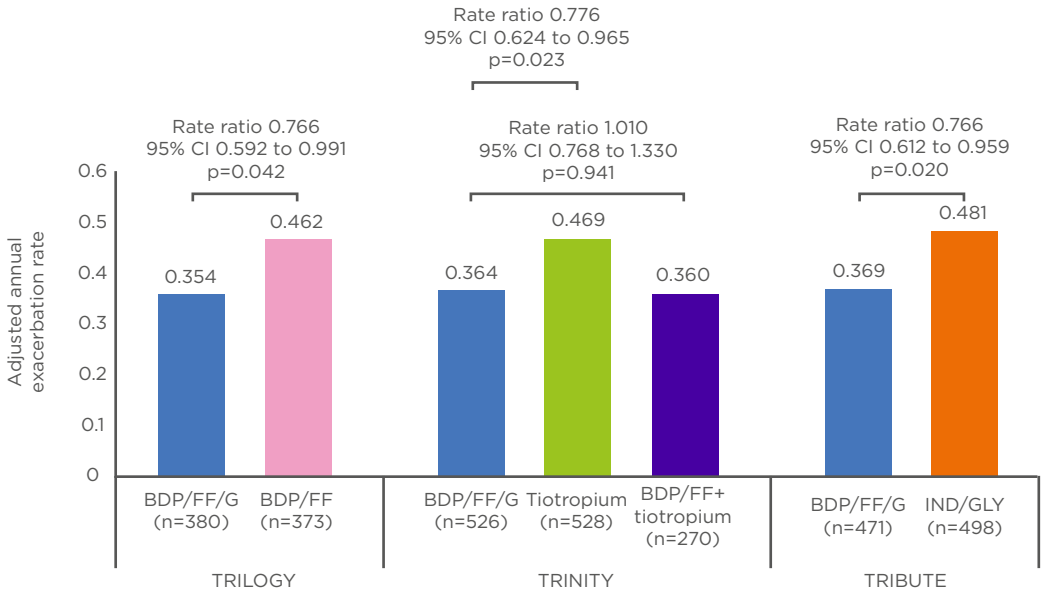

Figure 3: Adjusted annual rate of moderate-to-severe chronic obstructive pulmonary disease exacerbations (intention-to-treat population).

Triple therapy shows superior efficacy in reducing moderate to severe chronic obstructive pulmonary disease exacerbations.

BDP: beclometasone dipropionate; CI: confidence interval; FF: formoterol fumarate; G: glycopyrronium bromide; GLY: Glycopyrronium; IND: Indacaterol.

Adapted from Singh et al.[45]

considering that in the last years consistent evidence has become available showing the efficacy of ICS/LABA over LABA and of triple over dual combinations in preventing exacerbations episodes in COPD patients that have exacerbated once in the previous year (Figure 3).[37,44,45] A reduction in mortality rates using triple therapy has also been reported in the IMPACT study.[37,46] Moreover, pooled data from TRILOGY, TRINITY, and TRIBUTE studies on fatal events showed a clear trend towards the reduction of mortality risk with triple therapy.[46]

Inhaled Corticosteroid for many or Inhaled Corticosteroid for Some. Inspiration comes from Adaptation

Professor Bartolome R Celli and Professor Dave Singh

Prof Celli opened the debate by outlining that guidelines do not recommend the use of ICS alone in COPD.[13] The reason for this is that well-conducted studies have shown that ICS, when used as a monotherapy, is not very effective in COPD. The TORCH study in which ≥6,000 patients over 3 years compared combination therapy (ICS/LABA) versus placebo, LABA, and ICS monotherapy. The primary outcome was death from any cause, and the all-cause mortality rates for salmeterol or fluticasone propionate alone did not differ significantly from placebo. However, there was a statistically significant higher mortality rate in the fluticasone arm alone compared with the LABA/ICS arm.[47] Several studies have shown that when ICS is added to BD (either LABA or LABA+LAMA), the efficacy in different COPD outcomes is proven.[38-41] The goals for treatment outlined by the GOLD initiative are to reduce symptoms (improve symptoms, exercise tolerance, and health status) and risks (disease progression, exacerbations, and mortality).[13] This should be implemented in combination with the Hippocratic oath to "abstain from doing harm". The TORCH study showed that the ICS-combination regimen significantly improved QoL and spirometric values.[47,48] Furthermore, the SUMMIT trial including >16,500 patients showed ICS-containing regimens (ICS/LABA) had significantly lower adjusted rates of FEV1 decline versus placebo (p<0.03).[49] In TORCH, the ICS-combination regimen reduced the annual rate of exacerbations from 1.13 to 0.85.[47] GOLD advocates that you need to have an exacerbation to be treated with ICS therapy.[13] However, SUMMIT demonstrated that patients with moderate, chronic airflow obstruction, experienced a reduction in moderate and severe exacerbations with ICS/LABA combination compared with placebo, irrespective of a history of exacerbations or baseline FEV1. In fact, >60% of the patients had no exacerbations in the year prior to study inclusion.[49,50] In addition, the TRIBUTE study showed that treatment with the extrafine single inhaler triple combination significantly reduced the rate of moderate-to-severe exacerbations compared with LABA/LAMA in severe and very severe COPD patients with a history of at least one or more moderate and severe exacerbation the year prior to enrolment.[40] Furthermore, as shown from Singh et al.,[51] treatment with extrafine triple delayed disease deterioration compared to LABA/LAMA in the TRIBUTE study. An understated argument for the use of ICS is its potential impact on mortality. Indeed, the reduction in the risk of death was found to be 17.5% in TORCH (p=0.052),[47] 12% in SUMMIT (p=0.137),[52] 42% in IMPACT (p=0.01),[37] and the pooled TRINITY, TRILOGY, TRIBUTE data showed a 28% reduction in the risk of death (p=0.066) with ICS/LABA/LAMA.[46] There is no question that the use of ICS increases the risk of pneumonia, however, this depends on the type of ICS used, the dose, the severity of airflow limitation, and the age and nutritional status of the patients. Interestingly, the incidence of severe pneumonia was similar amongst therapies in the TRIBUTE study.[40] Moreover, Festic et al.[53] found that despite the association of ICS with increased risk of pneumonia, their use has not been associated with increased risk of pneumonia-related or overall mortality, suggesting a possible double effect of ICS (i.e., an adverse effect plus an unexplained mitigating effect). Bafadhel et al.[54] postulated that BEC (≥100 cells/µL) might identify COPD patients taking ICS who will experience fewer exacerbations, with a continuous relationship between levels of eosinophils in the blood and ICS response in clinical trials.[54] This is supported by other studies.[55-57] This threshold of 100 cells/µL could potentially identify which patients are not suitable for ICS therapy and guide personalised

medicine. These studies highlight that ICS-combination therapy can improve health status,[47] prevent disease progression,[48-49] prevent and treat exacerbations,[47,50] and reduce mortality.[37,46,47]

Prof Singh then countered by stating that using only group mean data from clinical trials to determine treatment approach is not precision medicine, and that there is more complexity to the art of medicine for individual patients. There is a huge variation in ICS response in asthma patients as shown by Martin et al.[58] in the distribution of the percent change in FEV1. Clinicians know that the benefit of ICS treatment also varies between COPD patients and that the challenge is to identify individuals in whom the benefits outweigh the risks. There is an interaction between the exacerbation risk and BEC for the individual patient. BEC clearly predict the responders versus nonresponders for ICS. Siddiqui et al.[59] showed that with lowering BEC, the adjusted reduction rate in COPD exacerbation decreased. Bafadhel et al.[54] showed this using binomial regression, that at around BEC=300 cells/µL, the reduction in ICS effect is approximately 50% and below BEC=100 cells/µL, appears to be no ICS effect.[54] However, this is a continuous relationship without definitive threshold values for response or nonresponse; instead, BEC but probabilities of response, i.e., with increasing BEC, the probability of an ICS response increases. GOLD therefore recommends using this biomarker as part of clinical decision making to provide an estimate of the probability of response to ICS.[13] Modelling BEC and response to triple and double combinations provide similar results regarding ICS treatment.[60] Kolsum et al.[61] conducted a bronchoscopy study to evaluate differences in airway biology associated with BEC and found that higher BEC had parallel increases in lung eosinophil counts, and other various inflammatory proteins. Furthermore, another study showed that patients with sputum eosinophil counts had less colonising bacteria.[62] Overall these findings show differences in inflammation and microbiome that could explain different responses to ICS. Furthermore, patients with more frequent exacerbations, have the highest potential for ICS benefits.[63] Those patients with less frequent exacerbations, but higher BEC will also benefit from ICS. So, in the age of personalised medicine, the point at which you would use an ICS inhaler depends on the complexity of clinical and biological information. This complexity of information includes the risk of adverse events.[64-66] The risk of pneumonia is personalised, with well-known risk factors, including increasing age, lower BMI, and history of pneumonia.[67] The regulators agree that the benefits of ICS outweigh the risks.[42] Prof Singh stressed that ICS effects are related to dose, there is no reason to use high dose ICS in COPD. Real-world data comparing extrafine formulation and fine-particle ICS found that extrafine formulation ICS/LABA (which deliver a lower dose due to efficient drug delivery) had significantly lower pneumonia risk.[68] Therefore, GOLD recommends a personalised treatment algorithm based on exacerbation risk and BEC, to treat some patients with ICS.[13] In conclusion, precision medicine is using all of the clinical and biological information available to make the right decision for the right patient.

Conclusion

Clinicians are facing the new challenges in airway diseases, particularly the changing paradigm toward precision medicine, addressing the complexity of this disease specifically in the ageing population and the critical need to treat COPD early to prevent future events and delay disease deterioration. Fixed triple therapy may help address these challenges with proven reductions in exacerbations, improvement in lung function, symptoms, and QoL, and reduction in the risk of mortality. These benefits far outweigh the risks of adverse events, including pneumonia. Extrafine fixed triple therapy moreover is able to reach both large and small airways, that are critically important in the pathophysiology of asthma and COPD.

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A chest X-ray was performed and showed a right sided pleural effusion (Figure 1a). A chest CT scan (Figure 1b) confirmed the right effusion with mild pleural thickening and small nodules in the inferior aspect of the right parietal pleura.

INVESTIGATIONS

The patient's white cell count was normal, and C-reactive protein was 97 g/L, where a normal range is <5.

A pleural tap was performed, and 50 mL of straw-coloured fluid was removed. Analysis showed a protein count of 46 g/L (serum total protein count of 76 g/L), lactate dehydrogenase (LDH) of 247 units/L (serum LDH count of 150 units/L), and a pH of 7.55. Cytological and microbiological analyses were negative.

The patient was treated with a 10-day course of co-amoxiclav and clarithromycin for a presumed lower respiratory tract infection and a reactive effusion.

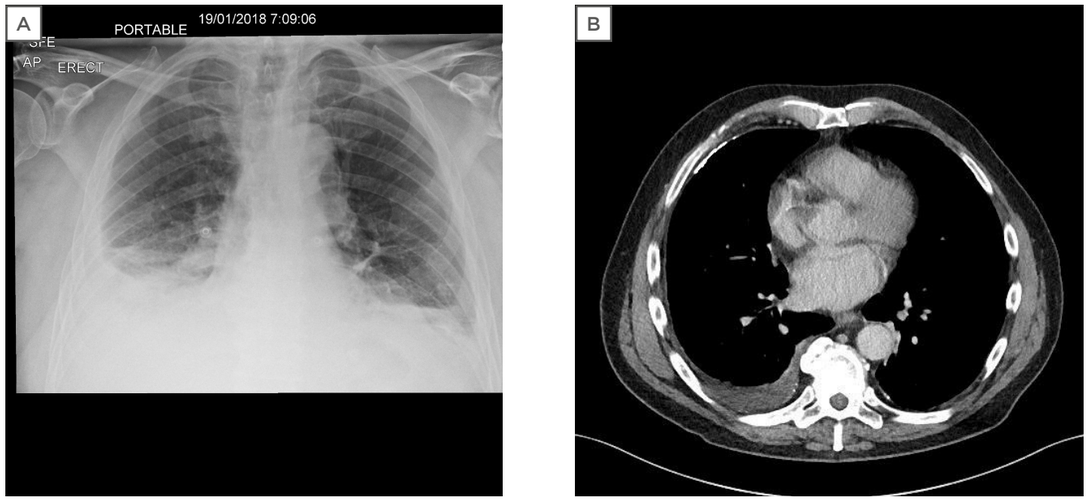

Figure 1: A) chest X-ray showing right pleural effusion; B) CT scan showing right pleural effusion with mild pleural thickening and small nodules and a right pleural plaque.

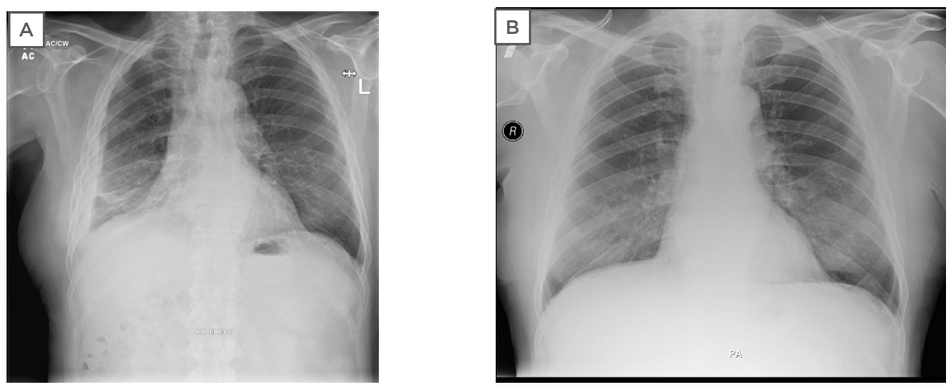

Figure 2: A) chest X-ray showing right sided pleural thickening with very small effusion; B) chest X-ray showing resolution of right pleural effusion.

After 2 months, his symptoms had completely resolved. A chest radiograph showed resolution of his effusion (Figure 2b). His C-reactive protein had normalised, and he was consequently discharged from the respiratory service.

When another 3 months had passed, at 5 months after initial presentation, the patient was referred to the pleural clinic with progressive exertional dyspnoea and 2 kg of weight loss. A repeat chest radiograph showed extensive right sided pleural thickening and a small effusion (Figure 2a). A targeted history revealed that he had never been a smoker. His asbestos exposure started when he was 21 years old and began work as a joiner. He cut asbestos boards and fitted them for roofs, as well as fitting pipes that were lagged with asbestos.

A repeat CT (Figure 3) revealed extensive pleural thickening extending onto the mediastinum with nodular growths which was suspicious for a primary pleural malignancy. An ultrasound-guided pleural biopsy was performed. Histopathological analysis confirmed a sarcomatoid mesothelioma.

DISCUSSION

A pleural effusion is an exudate if the ratio of pleural fluid protein to serum protein is >0.5, ratio of pleural fluid LDH to serum LDH is >0.6, or if pleural fluid LDH is greater than two-thirds of the upper limit of normal serum LDH. This is known as Light's criteria. The fluid protein count classifies this effusion as an exudate.[1] A pH of 7.55 is unusual for an exudate. The author suspects there might have been a few air bubbles in the pleural fluid sample, resulting in the reading being impaired.

Cytology of pleural fluid has variable sensitivity; it can be as low as 10% for MM but increases to approximately 60% in breast or gynaecological cancers.[1,2]

The patient's symptoms were infective, and the effusion had a negative cytology. There was a sense of false reassurance with the chest radiograph having normalised as seen in Figure 2b. Consequently, the effusion was ascribed to a noncancerous, benign aetiology.[3] The patient was discharged from the respiratory service. A CT scan was not performed at that time, although a thoracic ultrasound confirmed there was no fluid.

There was no bacterial growth from the pleural fluid and there was no fever, with the caveats that the patient is immunosuppressed, and pleural fluid only yields positive culture in about 40% of samples.[1]

Relapsing remitting effusions occur with asbestos exposure, and form part of the spectrum of asbestos related pleural disease and benign asbestos pleuritis, although mesothelioma presents with an effusion in roughly 90% of cases.[2]

The author presumes that the patient had benign asbestos pleural effusion (BAPE) and a lower respiratory tract infection when he first presented. BAPE are usually unilateral and associated with evidence of asbestos exposure, with asbestos plaques in >90% of cases.[4] This is shown in Figure 1b. A typical course of BAPE was followed by the patient. BAPE resolve over an average of 4.5 months and can lead to pleural thickening. A review of the literature suggests that BAPE do not predict an increased risk of mesothelioma beyond that of individuals with similar asbestos exposure without BAPE.[4,5]

However, it is well described in the literature that patients with inflammation of the pleura due to asbestos, or fibrinous pleuritis, have a 15% risk of developing a pleural malignancy over a mean follow-up time of 16 months.[6] Two cases of malignant mesothelioma after seemingly benign effusions have been described.[7] Presence of an asbestos plaque does not prove the absence of a developing malignancy; the mild pleural thickening and nodules seen on the initial CT scan could have meant a tumour was already growing. As such, this case helps to suggest that patients with BAPE require regular follow-up rather than discharge. Chest radiographs can be misleading, even if reported as normal, and a repeat CT scan might have shown more pleural thickening that would have been amenable to a biopsy.

Prognosis with MM is poor and median survival ranges from 8–14 months from diagnosis. There are four main histological sub-types: epithelioid, sarcomatoid, biphasic or mixed, and desmoplastic. The sarcomatoid variant is associated with the most aggressive course, with a median survival of just 4 months.[2-4]

Whilst the diagnosis was delayed here, it is unlikely that an earlier diagnosis would have made a difference as the treatment for MM is chemotherapy only and the patient retained his fitness for treatment.

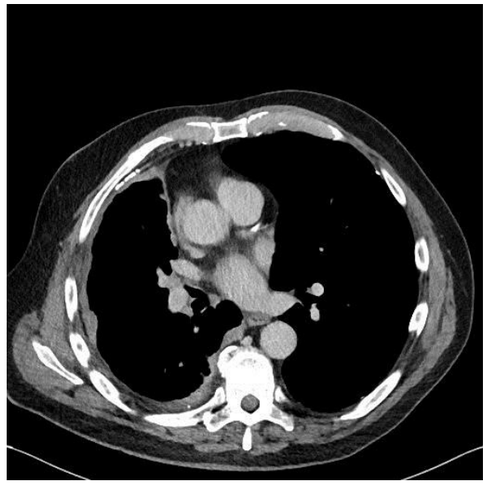

Figure 3: CT scan showing small right effusion with pleural and mediastinal nodularity. A right anterior pleural plaque can be seen also.

OUTCOME AND FOLLOW UP

The patient has been referred for chemotherapy with palliative intent. The doses of his immunosuppressants have been reduced and he is currently under active follow up.

PATIENT'S PERSPECTIVE

I had initially felt better on antibiotics and thought that the presentation was of another infection and I was very anxious as I waited on the results of the biopsy. My current concerns are of difficulty sleeping, constant fatigue, and worries about remaining lifespan. I have no interest in usual hobbies, probably due to lack of physical strength, breathlessness, and cough, especially at night

From my wife's perspective, it has been a rollercoaster of emotions from the shock of the diagnosis. We have received excellent care from the medical team, and we hope that the forthcoming chemotherapy treatment will give us some quality of life without many side effects.

TAKE-HOME MESSAGES

The authors conclude with three take-home messages from this case-study:

- Benign asbestos pleural effusions usually resolve over 4.5 months and are associated with pleural plaques.
- Pleural malignancies, such as malignant mesothelioma, can develop after apparently benign asbestos pleural effusions and in the vicinity of pleural plaques.
- Physicians should have a low threshold for ongoing follow up in patients with seemingly benign pleural effusions and asbestos exposure.

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Unilateral Right Exophthalmia Revealing Systemic Sarcoidosis: A Case Report and a Review of the Literature

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Abstract

Background: Sarcoidosis is only revealed in 3% of the cases among Caucasians by ophthalmic damage and, when it does, it presupposes that the visceral impairment has remained silent so far. In this article, the exceptional case of a patient with systemic sarcoidosis revealed by unilateral exophthalmia is reported.

Case presentation: The patient is a female with no history of substantial pathology. She had a unilateral right exophthalmia and ptosis evolving over 3 years. A dyspnea and dry cough were also reported with a duration of 1 year. The chest X-ray and CT scan revealed bilateral hilar opacities and mediastinal lymphadenopathy that lead to the suspicion of sarcoidosis. The cerebro-orbital CT scan led to the classification of the patient's exophthalmia as Grade I and eliminated the possibility of other aetiologies. The mediastinoscopy indicated a granulomatous adenitis with no caseous necrosis, which allowed the diagnosis of a mediastinopulmonary sarcoidosis.

Discussion and conclusion: The diagnostic approach to exophthalmia should involve a systematic search for sarcoidosis, although this aetiology remains exceptional.

INTRODUCTION

Sarcoidosis is a granulomatous systemic condition that can affect any organ with a predilection for the lungs and lymphatic system. Ophthalmic disorders, mostly bilateral, are reported in 25–50% of the patients with sarcoidosis and may at times reveal this systemic disease. In exceptional cases, mainly anterior uveitis, and ocular sarcoidosis in other instances, can take the form of exophthalmia. In the following case, an unusual unilateral exophthalmia revealing systemic sarcoidosis in a female patient is reported.

CASE PRESENTATION

A 65-year-old Caucasian female patient with no history of substantial pathology presented to the authors with a unilateral right exophthalmia and ptosis evolving for 3 years in an afebrile context and conservation of her general condition. The onset of exertional dyspnea and dry cough was reported for 1 year. The pleuropulmonary physical examination was without abnormalities, and the rest of the examination is not specific except for this right exophthalmia (Figure 1).

While chest X-ray showed bilateral hilar opacities, the chest CT scan revealed numerous calcified mediastinal lymphadenopathy in various locations: pre-tracheal (and bilateral), retro and precranial, left para-aortic, and intrabronchial (Figure 2).

In the framework of an aetiological evaluation, fiberoptic bronchoscopy was performed and revealed a diffuse and bilateral inflammatory aspect. Tiered bronchial biopsies and bronchoalveolar lavage (BAL) were inconclusive. BAL revealed a cell formula which comprised 79% macrophages, 17% lymphocytes, 4% neutrophils, no eosinophils, and no mast-cells. It showed that Golde score was 0. No pathogens, ferruginous bodies, or tumour cells could cytologically be identified; however, minor salivary gland biopsy showed a nonspecific chronic sialadenitis.

Biologically, the immunological assessment was negative and the phosphocalcic assay had no particularities. Angiotensin-converting enzyme activity was positive and IL-2 receptor was not investigated. The phthisiological analysis was negative. The plethysmography showed a total lung capacity of 79% and the diffusion capacity of the lung for carbon monoxide was 75%.

The conducted mediastinoscopy has exposed a granulomatous adenitis with no caseous necrosis (Figure 3). The ophthalmic examination was without abnormalities. Thus, the cerebro-orbital CT scan led to the classification of the patient's exophthalmia as Grade I and a calcified aspect of the left eyeball's wall.

Based on this data, the diagnosis of mediastinopulmonary sarcoidosis with exophthalmia was strongly referred and the subject was placed under systemic corticotherapy, initially at the dose of 1 mg/Kg/day then at progressively reduced doses. After approximately 2 months of treatment, substantial clinical benefits were seen through a reduction in the coughing and a slight progressive decrease of the exophthalmia. The latter could have been measured by orbital-cerebral CT scan, but there was a concern for the consequences of successive and closely spaced irradiation; this was eventually reconsidered afterwards.

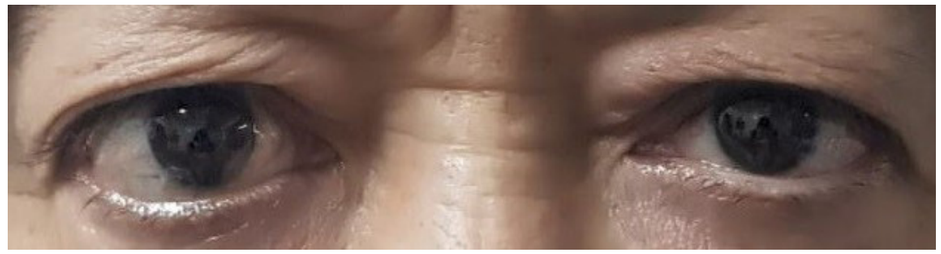

Figure 1: Patient with right exophthalmia.

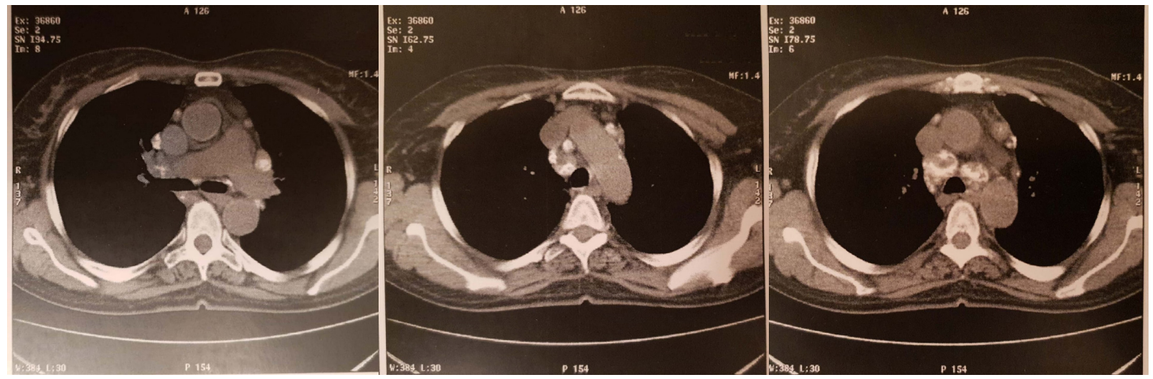

Figure 2: Chest CT scan revealing numerous calcified mediastinal adenopathy.

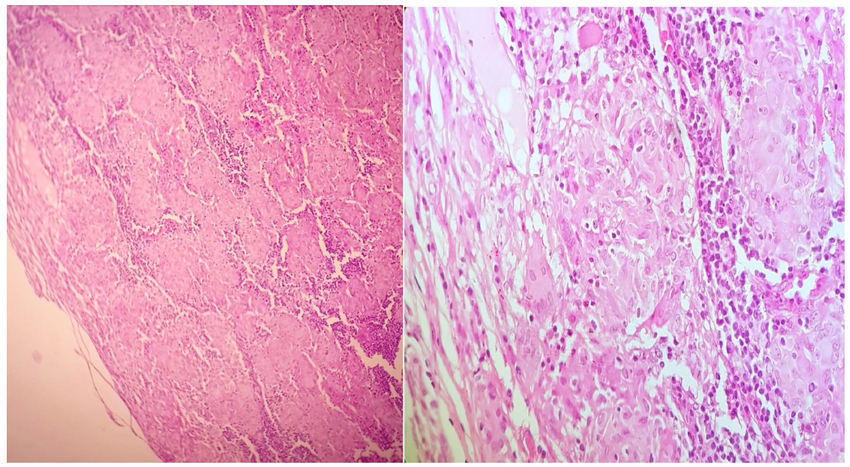

Figure 3: Medium and high magnification, haematoxylin, and eosin staining.

DISCUSSION

Sarcoidosis, also known as Besnier–Boeck–Schaumann disease, is a multisystemic granulomatosis of unknown aetiology. In the study by Bezo et al.,[4] the average age of consultation was 48 years old (from 36–87); for others, it has been documented as 42 or 43 years old, the patient in this present study was 65 years old. Currently, there is no accurate test for sarcoidosis. Diagnosis is based upon a conjunction of three stringent criteria as defined by the American Thoracic Society (ATS), European Respiratory Society (ERS), and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) Consensus Conference:

- A consistent medical and radiological record.
- Demonstration of noncaseating granuloma.
- Exclusion of other causes of granulomatosis.

In the literature, the median free interval between diagnosis and the first ophthalmic symptoms is 8 years (3–14 years).[4] In this present case, the symptoms started 3 years before the disease had been diagnosed. Ophthalmic manifestations may be revealing of systemic sarcoidosis, as seen in 80% of the cases in the study of Beso et al.,[4] along with the case of the present authors' patient, who presented exophthalmia before the respiratory symptoms, leading to the accurate diagnosis.

Regarding the clinical presentation, Benouhoud et al.[5] reported a case of pulmonary mediastinal sarcoidosis disclosed by a unilateral right exophthalmia, further complicated by sight loss and combined with dyspnea. Another study reported two cases: a bilateral exophthalmia combined with a bilateral maxillary sinusitis and dry cough; the second was afflicted by exertional dyspnea in conjunction with his right exophthalmia resulting in a complication of blindness.[6] This study is staging a right unilateral exophthalmia with exertional dyspnea and dry cough.

Eye diseases at the origin of exophthalmia are exceptional, whether accompanied or not by systemic damage. They have only been reported a few times in literature, and granulomatous orbital infiltration leading into exophthalmia and dysmotility disorders has exceptionally been encountered. Obenauf et al.[8] conducted a study involving 532 patients with sarcoidosis; only 2% presented with trouble of ocular dysmotility. This was not observed in the present authors' female patient either, which aligned with the findings of other studies.[5,6] If Benouhoud[5] could identify granulomatous inflammation in his patient, this was not observed in the case reported by Sabir,[6] nor in this present study. Obanauf only identified it in 1% of the subjects.

The treatment of ocular sarcoidosis is mostly based on local or systemic corticotherapy at a dose of 1 mg/kg/day for 1 years, but may be needed for up to 2 years. The treatment is so effective that exeresis or reduction surgery is rarely needed. Immunosuppressants are only used as a second-line therapy when steroid-sparing treatment is required in the event of corticodependency or corticoresistance. At all times, it would be necessary to prevent the potential side effects of corticoids.

The patient in this current report benefitted from systemic corticosteroids at doses of 1 mg/kg/day and thereafter at progressively reduced doses. Her clinical course was positive with a slight decrease of the exophthalmia. This therapeutic approach and the clinical evolution are thus in line with the ones reported in the literature.[5,6,]

During the active phase of the disease, close supervision is required, and subsequently adapted to the disease progression. Multidisciplinary surveillance remains the best policy, given that the risk of disability in the ocular affection of sarcoidosis imposes optimum care.

CONCLUSION

Sarcoidosis is a multisystemic granulomatosis of unknown aetiology, of which the diagnosis is difficult to establish because it is based on a series of clinical, paraclinical, and histological arguments. The presence of epithelioid granulomas is very suggestive, although not pathognomonic. The diagnostic approach to exophthalmia should involve a systematic search for sarcoidosis, taking into consideration the therapeutic implications that arise from it, although this aetiology remains exceptional.

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A Case of Empyema and a Review of Practice in a District General Hospital

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Abstract

The authors describe an empyema in an immunosuppressed patient. Thoracentesis was attempted and only 60 mL of pus was obtained from her pleural space. She was treated as an outpatient with antibiotic therapy. The authors have recently performed a review of all cases of pleural infection between December 2016 and December 2017 in their trust, of which there were 36. Here, they describe failings that have now been addressed and which helped in managing this particular case. As a result of this review, the authors have developed a pleural procedure form that encompasses all of the recommendations from their case review.

BACKGROUND

The Northumbria Healthcare NHS Foundation Trust serves just over half a million people across four different sites. There is a well-established pleural service.[1] Approximately 57% of patients with pneumonia develop a pleural effusion, which normally resolves with antibiotics. Due to a number of factors, including bacterial translocation and activation of inflammation via cytokine production, fibrin strands and locules can develop. Empyema, i.e., pus in the pleural space, can result and is a progressive process from a simple exudate to fibrinopurulent stage, before commencing towards an organising stage with pleural peel formation.[2] Clinical outcomes remain poor, with up to 20% requiring surgery and up to 30% of frail, elderly, or immune-compromised patients dying in the first year. Length of stay in hospital varies between 12 and 21 days, and the overall incidence is about 1.98 per 1,000 in the UK.[2]

CASE PRESENTATION

A 75-year-old female patient presented to her general practitioner with a 2-week history of cough, fevers, decreased appetite, and purulent green phlegm. Her past medical history included psoriatic arthritis controlled by azathioprine and hydroxychloroquine; Type 2 diabetes mellitus on insulin, metformin, and gliclazide; and hypertension controlled by atenolol, irbesartan, and furosemide. She had never been a smoker. She had a temperature of 39.7 °C but was normotensive. Heart rate and oxygen saturations on room air were normal. She was referred to the medical ambulatory care department.

INVESTIGATIONS

A chest radiograph showed a large right sided pleural effusion (Figure 1A). A CT showed typical features of empyema with pleural enhancement,

lenticular effusion, and internal loculations (Figure 2A). A thoracic ultrasound showed a hyper-echoic effusion with significant loculations (Figure 2B). Thoracentesis under aspesis was attempted. Only 60 mL of frank pus was aspirated. Two further attempts in different intercostal spaces were unsuccessful.

The pus was sent for analysis in both a white topped bottle and a blood culture bottle. A repeat chest radiograph post aspiration showed a smaller effusion with a central air containing space. The patient's oxygen saturations remained normal. Her white cell count was 12.4 x10^9 cells/L (4.0–11.0), urea concentration was 7.9 mmol/L (2.5–7.8), creatinine concentration was 85 µmol/L (49–90), albumin concentration was 25 g/L (35–50) and C-reactive protein (CRP) concentration was 363 mg/L (normal <5). Her HIV status was negative. Her RAPID (R: renal factors [blood urea nitrogen]; A: age in years; P: purulence of pleural fluid; I: infection source [community or hospital-acquired]; D: dietary factors [serum albumin]) score was 4.

TREATMENT

The patient's azathioprine and hydroxychloroquine treatments were withheld and co-amoxiclav was prescribed, pending the analysis of the pus. A fortnightly review was planned. Her blood cultures were negative. The pleural fluid grew *Streptococcus intermedius* which was sensitive to amoxicillin and clindamycin. She did not have any further attempts at instrumentation of her chest and was treated for 6 weeks with oral amoxicillin and co-amoxiclav.

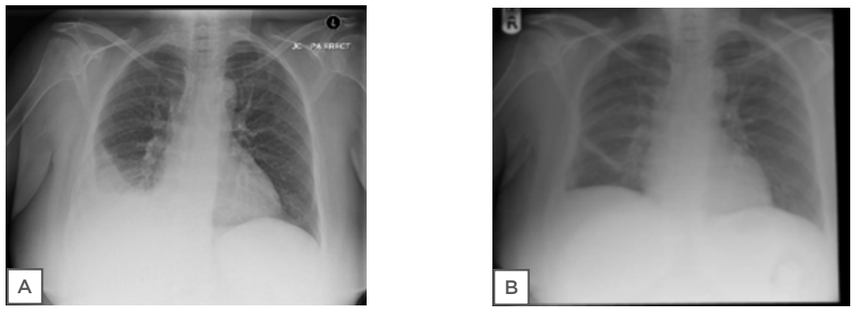

Figure 1: A) Chest radiograph showing large right sided pleural effusion. B) Chest radiography showing good resolution of the patient's effusion with minimal pleural reaction remaining.

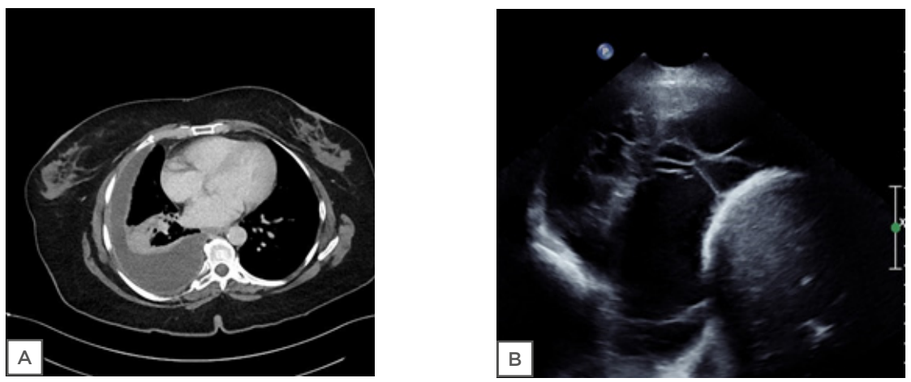

Figure 2: A) CT scan showing typical features of empyema with pleural enhancement and a lenticular effusion. B) Thoracic ultrasound showing loculations and hyperechoic effusion.

OUTCOME AND FOLLOW-UP

Her white cell count and CRP improved upon antibiotic treatment, and she thus finished the course with no issues. Her final chest radiograph (Figure 1B) showed good resolution of her effusion with minimal pleural reaction remaining. Her white cell count and CRP normalised. Her immunosuppressants have been restarted and she continues under regular follow up.

DISCUSSION

Pleural infection or empyema is associated with significant morbidity and mortality and accrues long inpatient hospital stays. The 2010 British Thoracic Society (BTS) guidelines have provided a concise review of the literature available at the time.[2]

Management is dependent on drainage of any infected collection and provision of antibiotics, which should be tailored to any microbiological growth or towards the pathogens most likely to have caused the infection. As such, local microbiological and epidemiological data is important.[2,3]

The authors audited local empyema cases to optimise local practice. Between December 2016 and December 2017, 36 patients were identified in the coding registry, with an average age of 64.5 years. A total of 19 patients were >65 years old. The most common past medical history included malignancy (n=7) and alcohol excess (n=5). Of the patients, 9 were current smokers and 16 were ex-smokers. No data was recorded for 5 of the patients. Recreational drug use was recorded for 1 patient. A total of 8 of the patients had an HIV test, all of whom were negative. HIV testing is strongly recommended in conditions associated with an undiagnosed HIV prevalence of greater than 0.1%. Community acquired pneumonia and invasive pneumococcal disease form part of those conditions.[4]

No sampling of pleural fluid was done in six cases as the effusions were felt to be too small, and two attempts failed. Of the 28 samples available, fluid was frank pus or turbid in 13 cases, haemoserous in 5, serous in 6, and not commented on in 4. pH results were available for 17 cases, and the pH was below 7.2 in 8. Lactate dehydrogenase (LDH) levels were recorded in 14 samples.

BTS guidance recommends sampling of pleural fluid in all cases of pleural infection and that all samples should be sent for pH, LDH, protein, glucose, and microbiology assessment. Pleural fluid analysis is crucial to the diagnosis, along with clinical and radiological features. Increased lactic acid formation, glucose, and anaerobic metabolism leads to a decrease in pH, decrease in glucose, and an increase in LDH levels.[2]

Of the samples, 11 (39%) were culture positive: 2 grew fully sensitive *Streptococcus pneumonia*, 1 grew *S. intermedius*, 1 previous intravenous drug user grew *Actinomycosis turicensis* and *Haemophilus parainfluenzae*, 1 grew *Stenotrophomonas maltophilia* as well as *Klebsiella oxytoca*, and 2 patients with indwelling pleural catheters tested positive for *Staphylococcus aureus*. Other organisms included *S. intermedius*, *Streptococcus dysgalactiae*, *Streptococcus anginosus*, and mixed anaerobes. All samples were sent in white topped bottles. Radiographic consolidation was noted in 23 patients. Two patients had indwelling pleural catheters.

It is important to know if any preceding parenchymal lung infection is community or hospital-acquired as the pathogens differ significantly. In a previous review, 1,523 patients with pleural infection and streptococcal infections were most commonly associated with community-acquired pneumonia, whereas *S. aureus* and *Staphylococcus enterococcus* were implicated in the hospital-acquired group. The median age of the patients was 64.0 years and the median percentage positivity of pleural fluid culture was 69% (48–77%).[2,3]

The authors' case agrees with this evidence, although our microbiological sensitivity is much lower than the quoted culture positivity. This is probably because samples were not concurrently sent in blood culture bottles. The addition of bottled blood culture to standard culture increases the proportion of patients with identifiable pathogens by 20.8%. The authors have now incorporated this into their practice.[5] Nine patients received antibiotics only. All patients received piperacillin/tazobactam or co-amoxiclav initially, except one who received tigecycline due to a penicillin allergy. All patients received >2 weeks of antibiotics, up to a maximum of 8 weeks. Clindamycin (combination

or monotherapy) was prescribed in over half of all cases, but many organisms were gram negative and some of the *Streptococcus* strains were resistant. Clindamycin was also given for 6 weeks for fully sensitive *Streptococcus* strains. There is thus significant scope to tailor antibiotic prescriptions and adhere to local stewardship programmes.[6] Local microbiological guidance suggests that, for sensitive strains, an addition of 500 mg amoxicillin thrice daily to 625 mg co-amoxiclav (amoxicillin/clavulanic acid) thrice daily achieves the oral equivalent dosage of 1.2 g intravenous co-amoxiclav. To provide excellent pleural penetration and be suitable for treatment of sensitive strains, 1.2 g is optimal.[7]

Drainage of any pleural effusion is recommended if the pH is less than 7.2 or if pus is present. This is based on expert opinion rather than objective, supportive evidence.[2] In real-life clinical studies, up to 30% of such effusions are not drained due to technical difficulty or patient and physician choice. This is reflected in our practice. BTS guidance recommends the use of thoracic ultrasound for any intervention for pleural fluid.[2] It is important to properly document any radiological findings. However, robust governance systems for thoracic ultrasound reporting do not exist; there is much intra- and inter-observer variation. Pleural fluid septation from pleural infection does not have an independent impact on mortality, although it may have an influence on other relevant clinical outcomes such as clearance of the pleural space and use of intra-pleural fibrinolytics.[8] In the cohort, ultrasound findings were documented in only 15 notes. The most common comment was of multi-loculated fluid (n=11). Other comments were 'small or moderate size' and 'echogenic.'

The mean length of stay was 9 weeks (range: 1–56 weeks). All survived to discharge after the first admission, 3 (9%) had died within 30 days, and 3 more within 6 months. Eight patients were readmitted within 38 days: 75% due to ongoing pleural infection, with 50% of those staying for an average of 4 weeks. The total 6-month mortality of the cohort was 17%. This is in line with known evidence.[9,10]

A score for mortality prediction in pleural infection has recently been developed called the RAPID score.[11] Patients with a RAPID score of 0–2 are considered low-risk, a score of 3–4 indicates a medium-risk, and a score of 5–7 indicates high-risk mortality at 3 months. Eight patients had a low-risk rapid score (≤2), but no patients were managed as an outpatient. The score can be potentially used for risk stratification for outpatient management. As mentioned above, pus is thought to be an indication for immediate drainage, but recent reviews have argued that not all infected pleural spaces need to be drained and respond well to high dose antibiotics.[10-12]

CONCLUSIONS

To ensure compliance with various guidance available, we have produced a pleural procedure form (Figure 3) that encompasses all the recommendations from the above case review.[12] Providing a safe and effective pleural service is a topical issue. Evison et al.[13] have provided a number of documents to ensure a pre-procedure checklist and adequate reporting of a pleural procedure. The authors believe this form is merely an adaptation of those and is better suited for local governance.[14]

The authors found significant room for improvement in their practice and believe that these findings can be applicable to any service dealing with pleural infection:

- Checking HIV status.
- Having a system for ultrasound reporting.
- Performing the required biochemical tests (pH, LDH protein, glucose) on pleural fluid.
- Improving culture rates by sending fluid in blood bottles.
- Determing specific local mircrobiological epidemiology and applying correct antibiotic stewardship.

Pleural ultrasound or procedure
Northumbria Healthcare NHS Foundation Trust

AFFIX PATIENT STICKER FIRST NAME ..... SURNAME ..... DATE OF BIRTH / / MRN	**CONSENT**: Written ☐ Verbal ☐ If verbal, risks and benefits explained:
Pleural ultrasound findings Side: Left ☐ Right ☐ Include size, depth, appearance, loculations etc	
Procedure report *tick if done* Procedure performed: Diagnostic tap ☐ Aspiration ☐ Chest drain ☐ Drain size (*if appropriate*) ..... Aseptic technique ☐ Local anaesthetic infused subcut ☐ Drug..... Dose..... Document any difficulties or complications:	
Pleural fluid report *volume, appearance etc* **Drainage plan** (*if applicable*) **Performed by**:..... **Signed**: .....**GMC**..... **Grade**..... **Supervisor/Assistant**: ..... **Date**:...../...../..... **Time**:.....	**Sent for**: pH ☐ Glucose Protein ☐ Albumin ☐ LDH ☐ Cytology ☐ C&S ☐ AFB/TB ☐ Lipids ☐ Amylase ☐
	CXR required? Yes ☐ No ☐

Figure 3: Northumbria Healthcare NHS Foundation Trust pleural procedure form.

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Asthma in Children Under 5 Years in Rural Kyrgyzstan: A Diagnostic Vacuum? a Qualitative FRESH AIR Study

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Abstract

Background: Worldwide, asthma is the most frequent non-communicable disease in childhood, often starting in infancy. However, asthma is underdiagnosed in children <5 years of age (Under-5s) in low and middle-income countries.

Aims: This study explored perceptions of, and reasons for, underdiagnosis of asthma in Under-5s in rural Kyrgyzstan.

Methods: Semi-structured qualitative interviews with 22 rural primary care health professionals and 13 caregivers to Under-5s with recurrent lower respiratory tract illnesses.

Results: Most health professionals and caregivers perceived asthma as a severe, debilitating, and potentially fatal disease in young children. None of the health professionals had diagnosed any Under-5s with asthma. In the health professionals' biomedical understanding, asthma occurs predominantly in adolescents and adults, and consists of attacks of respiratory distress, with mandatory heredity and allergy. The health professionals veered away from the asthma diagnosis to avoid scaring parents, and they replaced the diagnostic vacuum with infectious diagnoses. Surprisingly, stigma regarding the population with asthma appeared to be uncommon. Most caregivers were receptive to the idea of treatment with inhaled medication and to the statement that asthma could also be a mild disease.

Conclusion: The apparent systemic underdiagnosis of asthma in rural Kyrgyzstan seemed self-perpetuating. The misconceptions and dated diagnostic criteria and tradition had no provision for asthma in Under-5s; therefore, few children were diagnosed with asthma. This reinforced the inappropriate fear and belief in society that asthma is a rare, severe, and debilitating disease. Training of health professionals and providing information to the public should address the current perception of asthma and raise awareness that asthma is often a mild and treatable disease.

INTRODUCTION

Asthma is the most common non-communicable disease in children worldwide,[1] affecting about 14% of children globally,[1,2] often occurring in infancy.[3,4] Infants and young children are particularly vulnerable to respiratory disease.[5] Children living in low and middle income countries (LMIC) have more severe asthma symptoms than those in high-income settings.[2] The burden of wheezing and asthma is greatest in children <5 years (Under-5s),[6] who display significantly higher proportions of emergency department visits.[7] Furthermore, asthma hospitalisation rates among preschool children remain high.[8-11] Wheezing in early infancy due to viral infections is a strong predictor of school-age asthma.[12]

The few epidemiological studies on Under-5s in LMIC found a high prevalence of asthma or wheezing: 14% of 4-year-old children in Tanzania,[13] 18% of 4-year-old children in Southern Brazil,[14] 12% of 2–59 month old children in Sao Paulo, Brazil,[15] and 18% of 2–4 year old children in Jamaica had >3 wheezing attacks in the last year.[6]

Historically, asthma in young children was severely underdiagnosed in high-income countries.[16-19] Therefore, a drive to reduce underdiagnosis and undertreatment followed in the 1990s. However, unawareness of asthma in young children still prevails in LMIC,[2,20] and poor knowledge and misconceptions of asthma signs, symptoms, and triggers are prevalent.[21-24] Nearly 30% of children in LMIC with severe asthma symptoms have never been diagnosed with asthma.[2]

Children with asthma symptoms who are not diagnosed with asthma are not treated appropriately, and the health consequences are substantial.[16,25] Undiagnosed asthma leads to inappropriate infection diagnoses and an excessive use of antibiotics in both primary care[26,27] and secondary care.[8-11] In many LMIC, underdiagnosis of asthma is a problem due, in part, to health systems that are overwhelmed by communicable respiratory diseases.[28]

The symptoms of asthma in Under-5s are defined as recurrent or chronic/long term cough, wheeze and/or breathing difficulties, particularly at night and early morning. The diagnosis is reaffirmed by the efficacy of asthma drugs.[1,29] The Lancet Commission emphasises that asthma is an umbrella term describing a clinical syndrome.[30]

Diagnosing asthma in young children is still challenging, as no gold standard diagnostic tests with high validity exist, including the lung function test, which is not possible in clinical practice in Under-5s. Therefore, the diagnosis depends on health professionals' awareness of the symptom pattern, the communications between health professionals and caregivers, and a positive treatment trial.[1]

Globally, most children with respiratory illness are managed in primary care clinics. Strategies to prevent asthma morbidity in this youngest age group are still needed.[7] The authors hypothesised that understanding of asthma in young children is poor among primary care health professionals and caregivers in Central Asia, and that underdiagnosis of asthma in Under-5s is substantial. Therefore, the authors sought to evaluate perceptions of asthma in these groups and explore reasons for the potential underdiagnosis of asthma in Under-5s in primary care. The study was conducted as part of the FRESH AIR programme.[31] Kyrgyzstan is a 200,000 km^2 mountainous LMIC, situated in Central Asia, with 6 million inhabitants.

AIMS

The study explored perceptions of asthma and potential reasons for underdiagnosis of asthma in Under-5s in rural Kyrgyzstan.

METHODS

The study was conducted as a qualitative study, using the principles of qualitative data collection and analysis under the COREQ consensus statement.[32] Semi-structured qualitative interviews were conducted with 22 rural primary care health professionals and 13 caregivers to Under-5s with recurrent lower respiratory tract illness.

Settings

Data collection for the study was conducted in primary care health clinics in two different Kyrgyz provinces, one in the lowlands (Chui province) close to the capital Bishkek and one in the highlands (Naryn province), far from the capital. In rural districts, primary care operates with health professionals in medical centres, staffed with family doctors, nurses, paramedics, or paediatricians.

Interviews and Topic Guide

The semi-structured interviews were carried out on a face-to-face basis with primary care consulting health professionals and caregivers to gain insight into knowledge based, theoretical, and sociocultural perceptions of asthma in young children. The interview guide was inspired by explanatory models of illness formulated by Arthur Kleinman[33] and by theoretical perspectives on healthcare availability by Paul Farmer,[34] as well as by papers investigating parents´ perceptions towards asthma in children.[21-24] The main themes and the topic guide from the standardised interviews with the caregivers and health professionals are depicted in Table 1.

Inclusion and Recruitment Criteria

The health professionals were purposely sampled from different health centres in different villages in the two provinces. They all had independent consultations, although different educational levels. The inclusion criteria for the participant caregivers were to have a child aged between 12–59 months with long-term and/or recurrent cough and respiratory distress visiting a local health clinic for lower respiratory tract illness, without a diagnosis of tuberculosis.

Reflexivity

Prior to the study, the researchers thoroughly discussed their preconceptions and professional experiences with the field and on this basis, the interview guide was developed by two clinicians (MSØ, JK) and a clinician and anthropologist (SR). The interviews were carried out by two Kyrgyz clinicians (EI, AA), while data analysis was conducted by the Danish study team consisting of one clinician (MSØ) and one anthropologist (MMK), with ongoing discussions with all the research team. The various professional backgrounds of the study team resulted in extensive discussions about theoretical and analytical approach.

Data Collection

Pilot interviews took place during May 2016 in Naryn with two caregivers and one health professional, and in Chui with one health

Living with Alpha-1 Antitrypsin Deficiency: Empowering Patients and Healthcare Professionals

This mini symposium, focussed on the rare genetic lung disease alpha-1 antitrypsin deficiency (AATD), took place on the 30th September 2019, as part of the 29th European Respiratory Society (ERS) International Congress in Madrid, Spain. Presented by leading experts in the field, the meeting highlighted key issues relevant to the day-to-day management of patients with AATD and discussed important approaches for optimising their clinical care moving forward.

Chairpeople: Robert A. Sandhaus,[1] Charlie Strange[2]

Speakers: Robert A. Stockley,[3] Andrea Zanichelli,[4] Karen Skålvoll,[5] Robert A. Sandhaus,[1] A. Rembert Koczulla[6,7]

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Meeting Summary

Exacerbations in chronic obstructive pulmonary disease (COPD) impose a substantial healthcare burden and are key drivers of negative clinical outcomes and reduced patient quality of life. Prof Stockley highlighted the main differences in exacerbations between alpha-1 antitrypsin deficiency (AATD) and non-AATD-related COPD and considered potential implications for patient management. Early treatment of exacerbations with purulent sputum is known to be associated with improved patient outcomes. Emerging evidence from clinical studies also suggests that alpha-1 antitrypsin (AAT) therapy can have a positive impact on the nature and course of exacerbations in AATD.

Dr Zanichelli outlined how self-administration of intravenous drugs, which is a routine procedure that patients safely implement in other indications, has the potential to be successfully used by carefully selected AATD patients. Reflecting the current trend towards a more personalised approach to AATD therapy, self-administration can empower patients to assume an increasingly active role in their own disease management, thereby bringing improvements in treatment satisfaction, disease control, clinical outcomes, and quality of life.

A unique patient's perspective on AAT self-administration was provided by Karen Skålvoll, who highlighted the key benefits offered by self-infusion, such as reduced localised trauma and increased freedom to travel and enjoy life. Photographs from Karen's many global travels illustrate the unparalleled freedom that self-administration has afforded her as an AATD patient.

From the physician's standpoint, Prof Sandhaus summarised his experience of how patients can be empowered to self-administer AAT therapy independently with minimal training. Among motivated individuals, self-administration can provide a successful long-term treatment solution for their AATD. The drive towards self-treatment also delivers the dual benefits of reduced healthcare burden and enhanced convenience and flexibility for patients.

Prof Koczulla reported that, overall, the available evidence indicates pulmonary rehabilitation as a successful strategy in AATD, which can significantly enhance a patients' physical performance. Although the most effective training algorithm still needs to be prospectively validated, this approach may prove particularly advantageous in patients with anxiety, dyspnoea, and fear of physical activity. In order to achieve maximum benefit, therapy and goals of pulmonary rehabilitation must always be tailored to the individual patient in a personalised approach to care.

The meeting concluded with the compelling 'AATD Strongman Contest,' which pitted Prof Koczulla against AATD patient Karen Skålvoll in a physical test of endurance (the so called 'farmer's walk' involving carrying a heavy obstacle) and strength (dumbbell raises). Notwithstanding the expected impairment in aerobic ability, the domination of Karen in the strength test clearly demonstrates the physical gains that patients with AATD can achieve with physical training.

Acute Exacerbations in Chronic Obstructive Pulmonary Disease: Are They Different in Alpha-1 Antitrypsin Deficiency?

Professor Robert A. Stockley

COPD is an umbrella term used to describe a number of progressive lung diseases, including emphysema and chronic bronchitis. AATD is a rare inherited condition caused by a deficiency in the enzyme inhibitor AAT, which predisposes individuals to both lung and liver diseases.[1] Therefore, patients with AATD lack the protective effect of AAT in the lung, rendering them more vulnerable to the damaging effects of smoking and/or infection.[1]

Both COPD and AATD are associated with acute events known as exacerbations where lung symptoms worsen suddenly, contributing to substantially poorer outcomes and reduced quality of life.[2] An exacerbation is characterised by worsening of the patient's respiratory symptoms beyond normal day-to-day variation and leads to a change in medication.[3]

Table 1: Anthonisen criteria.

Anthonisen criteria	
1.	Increased breathlessness.
2.	Increased sputum volume.
3.	New or increased sputum purulence.
Definition of exacerbations	
Type 1: Presence of all three above symptoms.	
Type 2: Presence of two symptoms.	
Type 3: Presence of one symptom plus at least one additional symptom: – Upper respiratory infection within the past 5 days. – Fever without other cause. – Increased wheezing. – Increased cough. – Increase in respiratory or heart rate by 20% compared with baseline.	

Different types of exacerbations are defined according to the Anthonisen criteria (Table 1).[4]

Evidence suggests that acute exacerbations in AATD are different to those experienced with usual (nondeficient) COPD in terms of both pathogenesis and severity. One study, examining the nature and effect of exacerbations in 265 patients with AATD, discovered that exacerbations occur commonly and are associated with declining health status.[2] During the first year of study, exacerbations occurred in 142 subjects (54%), with 47 (18%) experiencing frequent (≥3) exacerbations. A clear relationship was seen between the number of exacerbations and the St George's Respiratory Questionnaire total score, indicating worse health status with more frequent episodes. The median length of each exacerbation in the AATD study was 14 days. This compares to a shorter average exacerbation length of 7 days documented in patients with typical COPD.[5] In addition, exacerbations associated with purulent sputum were associated with significantly worse symptoms at presentation than those with mucoid sputum.[6]

Differences have also been noted between AATD and usual COPD exacerbations in sputum colour, and the concentration of neutrophil elastase and cytokines, even though the degree of bacterial colonisation/infection provides a similar initiating drive. Studying these differences provides important insights into the underlying disease processes in COPD versus AATD and how these contribute to the manifestation and severity of exacerbations and their consequences. AAT is a member of the serine protease inhibitor superfamily of proteins and its main function is to inhibit neutrophil elastase in the lung.[1] Deficiency of AAT results in increased levels of uninhibited neutrophil elastase leading to breakdown of lung tissue and emphysema-like changes.[1] Bacterial load is directly correlated with the same initiating IL-8 levels in both AATD and usual COPD. However, AATD has been shown to be associated with a greater neutrophil load, and higher elastase activity which drives leukotriene B_4 production, and epithelial damage leading to greater serum protein leak than in matched patients without the deficiency.[7] However, after treatment with antibiotics there was a reduction in sputum myeloperoxidase levels activity indicating a reduction in neutrophil recruitment and the other cytokines. Despite this, elastase activity persisted, as did the sputum chemoattractant leukotriene-B_4, remaining higher than baseline data in the COPD cohort.[8]

The impact of these worse exacerbation manifestations in AATD may have important

implications for clinical management and treatment decisions. Protease inhibitor Z is the most common deficiency allele in AATD, with a large majority of individuals with severe disease being homozygous for the deleterious allele (*PI*ZZ*).[9] A prospective study looking at the natural history of AATD in 43 patients with the protease inhibitor Z phenotype over 2 years showed that annual decline in forced expiratory volume (FVC) was directly related to exacerbation frequency ($r=0.50$; $p<0.001$).[10] These results show that progression of lung function decline in AATD is exacerbations, underscoring the importance of prompt treatment for these episodes. Despite this, evidence suggests that delays or failure to treat exacerbations in AATD are common. In one study, delay was shown to be influenced by a number of factors including symptom score, severity at onset, airflow obstruction, and lung density.[11] Treatment delay was shorter in patients with higher symptom scores at onset and in those with lower baseline FEV1, FEV1/ forced vital capacity, and 15th percentile lung density. The key independent predictor of delay in starting treatment was lung density (which is a direct measure of the amount of emphysema), as demonstrated by multivariate analysis.[11] There also appeared to be a significant association between Anthonisen criteria and length of a treated exacerbation, with Type 1 events lasting longer than Type 2, which were in turn longer than Type 3. Resolution of exacerbation after treatment initiation was found to be unaffected by the delay in therapy, but was correlated negatively with gas transfer, a physiological measure of the emphysema.[11]

Overall, the substantially higher protease activity appears to be the main differentiator in the disease process between AATD and typical COPD and may be attributable to the worse exacerbations seen in the former group. This is of great importance because proteases such as neutrophil elastase drive proteolytic degradation of lung tissue in patients with AATD, which is allowed to continue unopposed due to already reduced levels of protective AAT.[12] Prof Stockley stressed that new or a worsening of sputum purulence is mandatory for antibiotic therapy, as it indicates the presence of new or increasing bacterial growth. In addition, early initiation of treatment is an important step towards reducing total exacerbation length.

Self-Administration: Taking Patient Empowerment Seriously

Doctor Andrea Zanichelli

AAT replacement therapy is currently the only available treatment that targets the underlying cause of lung disease in AATD. Treatment requires lifelong weekly intravenous infusions of AAT therapy with the approved dose of 60 mg/kg, typically administered by a healthcare professional (HCP) in the clinic or physician's office. The associated travel and waiting times impose a significant burden on the patients' everyday lives and contribute to treatment dissatisfaction. As a result, there is an increasing interest in intravenous self-administration of AAT therapy as a means of optimising the treatment experience and potentially enhancing the patients' quality of life. Self-administration has the scope to deliver a raft of benefits for individuals with AATD, including greater independence and autonomy, fewer healthcare visits and hospitalisations, and active involvement in their own care.

Self-treatment with intravenous drugs outside of the clinic is already commonplace in other rare inherited conditions such as hereditary angioedema (HAE) and haemophilia, and important lessons can be learnt from this experience to support the paradigm of self-administration in AATD.[13-15] Central to the successful implementation of this approach are educational programmes designed to support the self-administration of therapy and overcome key issues, such as fear of injections and lack of skills or confidence.[16-18] Furthermore, patients and their families must learn the technical skills needed for self-infusion and the associated practical issues.

Similar initiatives in HAE have proven successful, with studies demonstrating the feasibility and positive impact of self-administration training.[16,19] SABHA was an observational, single-centre, prospective study that assessed the self-administration of plasma-derived nanofiltered C1 inhibitor (pnf C1-INH) in 15 patients with HAE.[16] It should be noted that the low patient number included in this study was due to the rarity of HAE as a disease. Patients, sometimes accompanied by caregivers, underwent a self-infusion training course prior to the study. This consisted of a theoretical session taught by a physician, followed

by a nurse-led practice session on an artificial arm. Administration courses were then performed in small groups, consolidated by a second HCP-supervised practical session (if required) for those still lacking confidence. Overall, results from this study showed a trend towards improved quality of life in patients self-administering, together with significant growth in global satisfaction scores (p=0.0072) between the first and second quarter of drug use. Notably, the percentage of patients reporting high levels of stress decreased over time, demonstrating improved confidence with treatment and a greater ability in self-infusing.

Second-generation products are now available for AATD and offer the advantages of higher specific activity, easier reconstitution, and shorter infusion times, which increases their amenability for use in the home environment. Self-administration of the AAT therapy Respreeza® is currently approved in the European Union (EU) but is rarely used because access to treatment imposes a major limiting factor.[20] Although no guideline recommendations for self-administration in AATD currently exist, some patients are already successfully self-infusing. Dr Zanichelli concluded that moving forward, and with appropriate education and training, self-administration has the potential to be more widely implemented in carefully selected patients with AATD. This is an important step on the road to personalised therapy, freeing patients from their current treatment burden and empowering them to seize greater control of their own disease and its management.

A Patient's Perspective on Alpha-1 Antitrypsin Self-Administration

Karen Skålvoll

Ms Skålvoll, a patient with AATD and lung disease, described her own personal experiences of intravenous self-infusion, highlighting the increased independence and greater control that patients can gain by adopting a central role in their own treatment. Although patients may be unaware or nervous about self-administration, it is important to communicate the potential benefits that can be attained, such as reduced localised trauma at the infusion site, and explain how readily and safely the technique can be learned and performed. Access to home treatment offers patients greater freedom from the shackles of hospitalisation, providing practical advantages

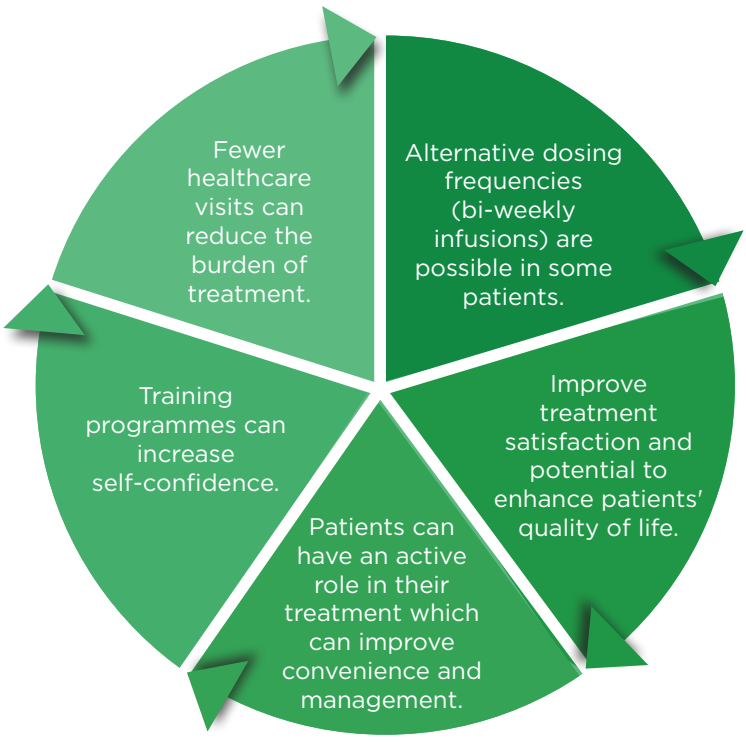

Figure 2: A holistic approach to treatment.

like flexibility and convenience together with wider benefits such as an increasing sense of autonomy and dignity in the AATD treatment process.

In an insightful video set in her own home, Karen demonstrated how easily the practicalities of reconstitution and intravenous infusion of AAT therapy can be carried out. Photographs from Karen's many global travels highlight the unparalleled freedom and enhanced enjoyment of life that self-administration has afforded her.

A Physician's Perspective on Alpha-1 Antitrypsin Self-Administration

Professor Robert A Sandhaus

Prof Sandhaus explained that selecting the right patients for self-administration of AAT therapy is pivotal, as the patient's own capacity to self-administer effectively is likely to be the critical factor in success. Key considerations for the implementation of self-administration include the patient's age, dexterity, motivation, disease status, and cognition.

A questionnaire sent to AATD experts indicated that they see an impaired ability to monitor patient adherence and potential safety issues surrounding intravenous infusion as the main concerns to self-administration.[18] However, data from a recent AlphaNet[21] survey of patients included in the Alpha-1 Disease Management and Prevention Program (ADMPP) showed that a number of patients are already successfully and safely self-administering their AAT therapy.[17] This cross-sectional, observational, telephone survey included patients aged ≥18 years diagnosed with AATD and receiving AAT therapy with Respreeza®. The overarching aim of the survey was to assess the occurrence, practicalities, satisfaction, and challenges of AAT self-administration. Of the 555 patients surveyed, only a minority (7.9%; 44 patients) were found to be actively self-administering their AAT therapy. However, all patients self-administering described being either 'very satisfied' (95.4%) or 'satisfied' (4.6%) with their treatment. The survey also revealed that patients who were self-administering required minimal training and infusions did not appear to differ from those conducted by HCP. A slight majority of patients (56.4%) required only 2–3 training sessions to learn how to successfully self-administer, with this training largely provided by a home nursing agency. Infusion duration was generally aligned with licensing recommendations and administration in the hospital-setting, with most patients requiring <1 hour to carry out the infusion. Encouragingly, patients experienced few problems with self-administration, with the majority (83.7%) reporting no difficulties whatsoever; only five respondents described infusion-related issues at some point in time. Almost all patients (~98.0%) also confirmed that easy access to help or advice was available if required.

In conclusion, Prof Sandhaus noted that the overall results of the AlphaNet survey should help to address and assuage physician concerns by demonstrating that self-administration can, and is, being safely performed in patients with AATD. Among motivated individuals, self-administration can prove a viable long-term treatment approach, with nearly 20% of the surveyed patients successfully self-infusing their AAT therapy for over a decade. Careful selection of patients is essential to optimise the benefits of AAT self-administration, and appropriate physician-led follow-up is also important, providing help and advice with infusion-related issues where required.

What Pulmonary Rehab Can Do for Alpha-1 Antitrypsin Deficiency Patients

Professor Andreas Rembert Koczulla

Pulmonary rehabilitation is a comprehensive intervention in lung disease that is based on thorough patient assessment followed by patient-tailored therapies, including, but not limited to, exercise training, education, and behavioural change. These are designed to improve the physical and psychological condition of people with chronic respiratory diseases and promote the long-term adherence to health-enhancing behaviours.[22] Although rehabilitation is currently recommended for AATD-related COPD, there is no reference to AATD-specific studies in

the guidelines and there is scarce evidence on the impact of training in this particular patient cohort.[22]

Prof Koczulla cautioned that patients with ATTD have very individualised problems that may affect their pulmonary rehabilitation, most notably physical and psychological comorbidities. These treatable traits, which include anxiety or depression, cognitive impairment, low muscle mass and muscle weakness, osteoporosis, and abnormal weight may require a targeted approach to rehabilitation. Interestingly, anxiety, dyspnoea, and fear of physical activity have all been associated with underlying structural changes within the grey matter of the brain.[23,24] Encouragingly, however, studies have shown that patients with these psychological comorbidities respond better to pulmonary rehabilitation than those free from these conditions or with more physical complications. When tested, patients with the psychological cluster of symptoms demonstrated greater improvements in lung capacity and a higher likelihood of achieving meaningful improvements in the 6-minute walking distance than their counterparts without, or with more physical, comorbidities.[25,26]

Evidence confirms that pulmonary rehabilitation is as successful a strategy in AATD as it is in COPD. In a study of patients awaiting lung transplantation, pulmonary rehabilitation increased the 6-minute walking distance by 48 m in the AATD cohort, with 18% also experiencing an improvement in their mental quality of life measured by the SF-36 questionnaire.[27] Medication is another important player in pulmonary rehabilitation. For example, aclidinium bromide-induced bronchodilation significantly improved symptom-mediated activity limitation in a Phase III trial in COPD.[28] Data from the large COPD Biomarker Qualification Consortium database of 1,200 patients investigated the average improvement in constant work rate cycle ergometer endurance in patients with COPD with different degrees of lung function impairment (Global Initiative for Chronic Obstructive Lung Disease [GOLD] category 1–4). While comparable increases in exercise tolerance in response to rehabilitative exercise training were achieved across the full range of lung function impairment, bronchodilator therapy became an important means to achieve a higher training capacity the higher the GOLD class.[29] However, average increases in exercise tolerance in response to rehabilitative exercise training showed equivalence across the full range of lung function impairment.[29]

A recent comparative study specifically evaluated the impact of training in nine patients with AATD versus ten with 'usual' COPD.[30] Participants performed an incremental cycling test and underwent musculus vastus lateralis biopsies before and after a 3-week pulmonary rehabilitation programme including exercise training. Physical training and pulmonary rehabilitation were shown to improve physical performance in patients with COPD both with and without AATD; however, the maximum exercise capacity on the bike was found to be lower in patients with AATD, and adjustments in skeletal muscle were also different between the two groups. Overall, these findings suggest that disease-specific training may be required to optimise pulmonary rehabilitation in AATD. To address this question, a trial is currently ongoing evaluating a high-intensity approach in AATD that combines heavier weight loads with increased endurance goals.

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