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RESPIRATORY

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INSIDE

Review of

ERS 2015

Amsterdam, Netherlands

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Respiratory

EMJ GORELY NEW MEDIA

European Medical Journal
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The MedBIC,
Anglia Ruskin University,
Chelmsford, CM1 1SQ

Welcome

Hello and a very warm welcome to this edition of *European Medical Journal Respiratory*, your comprehensive source for insights and developments in the field of respiratory medicine.

In this edition, we have the great pleasure of reporting the exciting events of the European Respiratory Society (ERS) International Congress 2015, which took place from 26th–30th September in the historic city of Amsterdam; an authentic hub of culture, steeped in scientific history and artistic heritage. Complementing the numerous captivating pieces of research that we have endeavoured to bring to you, we also present a series of pioneering abstract reviews written by a host of brilliant academics, as well as interesting interviews with our editorial board members.

An amalgamation of modern urban flair and rich history, Amsterdam, a world-leader in discovery, economics, and architecture, provided the picture-perfect background to the presentation of medical developments at ERS 2015. It seemed that inspiration was rife in the world's cycling capital, as researchers presented on a range of topics including: new characterisations for severe asthma that could ultimately improve optimisation of individual care; the differences in aetiology and prognosis of non-smokers and smokers with non-small-cell lung cancer; and the relationship between lung transplant rejection and proximity to high-pollution areas.

This eJournal features various calls to arms, as the global research community aim to: incite improvements to clinical trials seeking to stem the wave of drug-resistant tuberculosis; change our approach to comorbidities with asthma; and revolutionise methods of diagnosing chronic obstructive pulmonary disease. Other exciting content includes an abstract review on the future of computer-driven weaning protocols in paediatric mechanical ventilation and a report on obstructive sleep-disordered breathing in children.

As the end of the year speeds towards us, we would like to thank both our readership for their vital ongoing support and our editorial board for their time and assistance. We are honoured to be a part of the scientific community – entrusted with reporting advances as they happen and contributing to a global wealth of knowledge. We hope that this edition not only invigorates your practice, but also provides inspiration for your future endeavours and, finally, we wish you all the best for the coming year and look forward to seeing you in 2016!

Spencer Gore

Director, European Medical Journal

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Front cover and contents photograph: Zoë Webster/EMJ

Proof changes everything

Respreeza®
alpha$_1$-proteinase inhibitor (Human)

In the treatment of alpha-1 antitrypsin deficiency (AATD)…

Newly approved in Europe in August 2015

GUIDE THEM TO THE FUTURE

with Respreeza®—the only alpha-1 proteinase inhibitor proven to slow the progression of emphysema in a prospective, placebo-controlled trial[1,2]

References:
1. Respreeza® EU SmPC August 2015
2. Chapman KR, Burdon JGW, Piitulainen E, et al; for the RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;386(9991):360-368.

1. Name: Respreeza® 1000 mg powder and solvent for solution for infusion. **2. Composition:** Respreeza is a highly purified, pasteurized, nanofiltered, lyophilized, stable human plasma alpha1-proteinase inhibitor (A1-PI) concentrate. One vial contains approximately 1000 mg of A1-PI, as determined by its capacity to neutralize human neutrophil elastase. The specific activity of Respreeza is > 0.7 mg of functional A1-PI per milligram of total protein. The total protein content is approximately 1100 mg per vial. After reconstitution with 20 ml solvent, the solution contains approximately 50 mg/ml of A1-PI. Excipients: Respreeza contains approximately 1,7 to 2,0 mg sodium, 1,2 to 1,5 mg chloride, 1,5 to 1,9 mg phosphate and 22 to 31 mg mannitol per ml of reconstituted solution. **3. Indications:** Respreeza is indicated for maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha1-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency. **4. Contraindications:** Hypersensitivity to the active substance or to any of the excipients. IgA deficient patients with known antibodies against IgA, due to the risk of severe hypersensitivity and anaphylactic reactions. **5. Special warnings and precautions for use:** ***Hypersensitivity/Anaphylaxis:*** Caution should be used when administering Respreeza to patients with known allergies to an A1-PI product. In the case of known allergies to Respreeza, with observed symptoms like rash, urticaria, dyspnoea, decrease of blood pressure, tachycardia, and where administration of the product is essential, corticosteroids and antihistamines should be administered for prophylaxis. Respreeza may contain trace amounts of IgA. Patients with selective or severe IgA deficiency can develop antibodies to IgA and, therefore, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. If anaphylactic or severe anaphylactoid reactions occur, the infusion should immediately be discontinued. Epinephrine and appropriate supportive therapy including shock treatment has to be available for the treatment. Hypersensitivity reactions may occur in patients who have well tolerated previous treatment with A1-PI. ***Home-treatment/Self-administration:*** There are limited data regarding the use of Respreeza in home-treatment/self-administration. Potential risks associated with home-treatment/self-administration are related to the handling and administration of the medicinal product as well as to the handling of adverse reactions, particularly hypersensitivity. Patients should be informed of signs of hypersensitivity reactions. The decision of whether a patient is suitable for home-treatment/self-administration is made by the treating doctor, who should ensure appropriate training is provided (e.g. regarding reconstitution, use of transfer device or filter, assembly of intravenous tubing, infusion techniques, maintenance of a treatment diary, identification of adverse reactions and measures to be taken in case such reactions occur), and the use is reviewed at regular intervals. ***Transmissible agents:*** Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A (HAV) and parvovirus B19 virus. Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived proteinase inhibitors. It is strongly recommended that every time Respreeza is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. ***Smoking:*** Tobacco smoke is an important risk factor for the development and progression of emphysema. Therefore cessation of smoking (> 6 months) and the avoidance of environmental tobacco smoke and air pollution are strongly recommended. ***Sodium content:*** Respreeza contains approximately 1.9 mg (<1 mmol) sodium per ml of reconstituted solution. This would be a dose of 142 – 168 mg sodium for an adult with a bw of 70 kg if the recommended dose (60 mg/kg bw) is administered. That should be taken into consideration for patients on a controlled sodium diet. ***Pregnancy:*** The safety and effectiveness of Respreeza for use in human pregnancy has not been established in controlled clinical trials. Animal reproduction studies have not been conducted with Respreeza. Respreeza should be given to a pregnant woman only if clearly needed. ***Lactation:*** It is not known whether Respreeza and its metabolites are excreted in human milk. Therefore, Respreeza should be given to nursing mothers only if clearly needed. ***Fertility:*** No animal fertility studies have been conducted with Respreeza and its effect on human fertility has not been established in controlled clinical trials. Clinical experience with Respreeza does not suggest a harmful effect on fertility. ***Effects on ability to drive and use machines:*** Respreeza may have a minor influence on the ability to drive and use machines. Adverse reactions such as dizziness may occur following administration of Respreeza. **6. Interactions with other medicinal products and other forms of interactions:** ***Incompatibilities:*** No interactions of Respreeza with other medicinal products are known so far. **7. Undesirable effects:** ***Summary of the safety profile:*** Hypersensitivity or allergic reactions have been observed during treatment with Respreeza. In the most serious cases, allergic reactions may progress to severe anaphylactic reactions even when the patient has shown no hypersensitivity to previous administrations. ***Tabulated list of adverse reactions:*** The adverse reactions (ARs) collected from six clinical studies in 221 patients and post-marketing experience are presented in the table below according to the MedDRA System organ classification (SOC and Preferred Term (PT) Level). Frequency per patient (based on six months of exposure during clinical trials) has been evaluated according to the following convention: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and very rare (<1/10,000). The frequency of ARs during post marketing only is considered as "not known (cannot be estimated from the available data)". Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequency of Adverse Reactions (ARs) in clinical studies and post-marketing experience with Respreeza

System Organ Class (SOC)	Frequency of ARs			
	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Very rare (<1/10,000)	Not known
Blood and lymphatic system disorders				Lymph node pain
Immune system disorders		Hypersensitivity reactions (including tachycardia, hypotension, confusion, syncope, oxygen consumption decreased and pharyngeal oedema)	Anaphylactic reactions	
Nervous system disorders	Dizziness, headache	Paraesthesia	Hypoaesthesia	
Eye disorders				Eye swelling
Vascular disorders		Flushing		
Respiratory, thoracic and mediastinal disorders		Dyspnoea		
Gastrointestinal disorders		Nausea		Lip swelling
Skin and subcutaneous tissue disorders		Urticaria, rash (including exfoliative and generalized)	Hyperhidrosis, pruritus	Face swelling
General disorders and administration site conditions		Asthenia, infusion- site reactions (including infusion site hematoma)	Chest pain, chills, pyrexia	

Paediatric population: Safety and effectiveness in the pediatric population have not been established. ***Geriatric population:*** The safety and efficacy of Respreeza in elderly patients (65 years of age or older) have not been established in clinical trials but the post-marketing experience suggests that they should not be different than in adults. No dosage adjustment is therefore recommended. ***Reporting of suspected adverse reactions:*** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions. **8. Prescription status:** Prescription-only drug. **9. Manufacturer:** CSL Behring GmbH, Emil-von-Behring-Str. 76, 35041 Marburg, Germany. **10. Date of information:** 08.2015

Foreword

Prof David Price

Professor of Primary Care Respiratory Medicine, University of Aberdeen, Aberdeen, UK

Dear Colleagues,

It is a great honour to welcome you to the latest edition of *European Medical Journal Respiratory*, which will round off what has been a glorious year of discoveries and innovative treatment strategies in our field. Particular highlights have included the development of a new, better-tolerated method of oxygen delivery, which should help patients at risk of respiratory failure after surgery, and the outstanding results from 3D printing of flexible growth implants, which have saved the lives of three infants with tracheobronchomalacia.

This issue of *EMJ Respiratory* summarises the main events of the 2015 European Respiratory Society (ERS) congress, which was held in late September in Amsterdam, Netherlands. The 25th anniversary of this world-renowned event proved to be a momentous occasion during which esteemed professionals gathered and both presented and analysed the significant advances that have occurred in recent times. I believe that our efforts there have significantly contributed towards the society's main goal of promoting lung health and combatting lung diseases.

This year, ERS provided their scientific and educational programme in digital form for the first time, allowing delegates to build their own personal itinerary and to download and print abstracts of interest at their leisure. This progressive innovation was matched by what was on show during the enthralling 5 days of the congress. From the research methodology perspective, a much greater focus on real-life research clearly became part of the mainstream, with many presentations focussing on real-life outcomes beyond classical clinical trials. In addition to the presentations and lectures delivered by highly esteemed members of the respiratory community, a range of educational sessions were available for attendees, such as 'meet the expert' in which an ERS faculty member was on hand to stimulate discussion, answer questions, and offer advice; and a patient forum during which healthcare professionals were able to better understand the experiences of patients who had completed a programme of pulmonary rehabilitation. This congress will mark the start of the second 'Healthy Lungs for Life' campaign, which further emphasises the awareness of lung disease on a global scale.

On behalf of EMJ, I would like to thank everyone involved in this publication for their efforts, including my fellow editorial board members, and indeed all who attended and contributed to ERS 2015.

Yours sincerely,

David Price

Professor of Primary Care Respiratory Medicine, Academic Primary Care, University of Aberdeen, Aberdeen, UK; Co-founder of the Respiratory Effectiveness Group; Member of Allergic Rhinitis and its Impact on Asthma, and the European Position Paper on Rhinosinusitis and Nasal Polyps.

ERS ANNUAL CONGRESS 2015

AMSTERDAM RAI EXHIBITION AND CONVENTION CENTRE,
AMSTERDAM, NETHERLANDS
26TH-30TH SEPTEMBER 2015

Welcome to the *European Medical Journal* review of the European Respiratory Society International Congress 2015

Hello and a very warm welcome to the *European Medical Journal* review of the European Respiratory Society International Congress 2015.

The location of this year's congress was Amsterdam, a city whose historically quaint buildings and charming atmosphere juxtapose its reputation as the commercial and cultural capital of Netherlands. Amsterdam is also widely regarded as a healthy city, where it is more popular to own a bicycle than a car, making it the perfect destination for the ERS International Congress, as the theme for the global Healthy Lungs for Life campaign was 'Take the Active Option', which was launched during ERS in light of the growing evidence that supports the importance of regular physical activity for healthy lungs.

The meeting was a momentous affair that brought together the most influential minds in the field of respiratory research. From fascinating live endoscopy sessions and presentations on cutting-edge research to a variety of educational sessions, the attendees certainly had a wealth of knowledge and inspiration to take away from the event. The ERS President, Prof Elisabeth Bel, commented at the opening ceremony: "It was really a privilege for me to work together with so many talented and dedicated professionals, and their tremendous efforts are reflected in the achievements of our society over

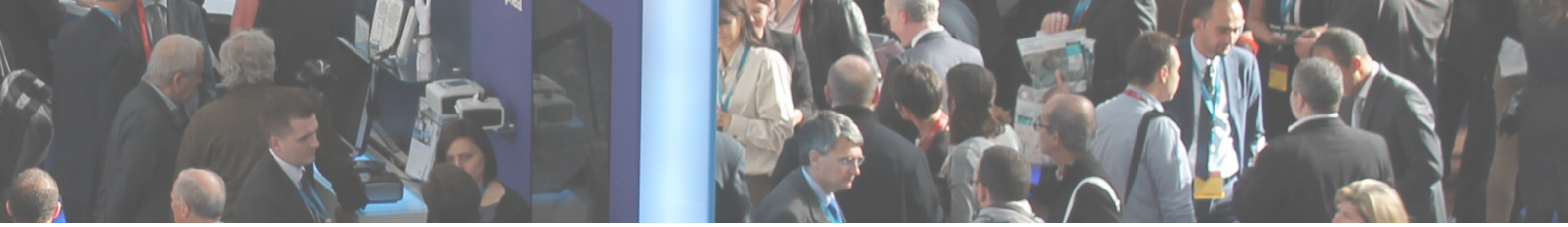
"the last year," showing her pride in the society and its annual congress.

As usual, there were a number of awards presented for excellent achievements in respiratory research throughout the congress. Notably, the ERS Presidential Award was given to Prof Jeffrey M. Drazen (USA) for his outstanding contribution to the strengthening of respiratory medicine worldwide, such as in defining the role of novel endogenous chemical agents in asthma, which consequently meant that four new pharmaceuticals were licensed. Prof Antonio Artigas (Spain) received the ERS Educational Award, which is bestowed upon a European clinician, scientist, allied respiratory professional, or individual in any other profession who has made a contribution of extraordinary magnitude to education in respiratory medicine at a European or international level. Of his many contributions to the field of respiratory education, he has created a Catalan network of teaching committees for coordinating medical training programmes in the region. Finally, for inspiring many through his athletic achievements following his double lung transplant, including becoming the Dutch national champion of the 200 m sprint in a race against men who had never had a transplant in 2008, and in honour of the Healthy Lungs for Life theme, 'Take the Active Option', Mr André Lassooij (Netherlands) was honoured with the ELF Award.

"It was really a privilege for me to work together with so many talented and dedicated professionals, and their tremendous efforts are reflected in the achievements of our society over the last year."

Keeping its doors open until the very last minute, the congress was buzzing with new and potentially influential information from an abundance of presentations. Among these was the discovery that severe asthma may have a number of distinct categories, each with their own sputum 'handprint', which is hoped will lead to the tailoring of drug development and the personalisation of treatment. Furthermore, it has been found that the chances of death or chronic organ rejection in lung transplant patients are higher for those who live on or close to busy roads with elevated air pollution levels. Another study suggested that disease development may be predicted by the interaction between infant lung infections such as rhinovirus and respiratory microbiota, which in turn could help with disease prevention, as well as with the development of new therapeutic procedures.

The inspiring congress certainly provided food for thought and fuel for action. Taking the active option, as the congress proposed, can also be applied to research and development in the field, which will undoubtedly progress exponentially before the return of next year's congress in the metropolitan city of London, UK.



HIGHLIGHTS

Novel Method May Identify COPD

A NOVEL questionnaire that uses only five questions could be used to diagnose chronic obstructive pulmonary disease (COPD), according to study findings presented at ERS 2015. The tool may speed up current diagnosis times for the condition and detect COPD before significant exacerbations and further loss of function have occurred.

The study aimed to create a questionnaire to aid clinicians in identifying patients with moderate or severe COPD, or patients at risk of exacerbations of COPD prior to loss of lung function. A total of 186 patients with clinically significant COPD were included and compared with a control group of 160 patients with mild or no COPD. Both groups completed questionnaires and had their lung function evaluated using peak flow and spirometry.

The researchers used a method of analysis called random forests to analyse the data and identify the optimum and smallest set of questions that differentiated patients with clinically significant COPD from the control group. The results yielded a set of five 'yes or no' questions that together could accurately identify patients with moderate or severe COPD or patients at risk of exacerbations of COPD. The questions discussed breathing, how easily a person tires, and acute respiratory illness; they did not discuss smoking, cough, or sputum.

In an ERS press release dated 29th September, Prof David Mannino, University of Kentucky College of Public Health, Lexington, Kentucky, USA, noted: "The results of our study indicate that a five-item questionnaire of carefully selected questions can help identify people before they have serious complications of COPD. This is also the first time a questionnaire has included assessment of exacerbation risk. Previous screening methods focussed on smoking histories and sputum production. Our study also found that when clinicians include peak flow measurements in addition to the questionnaire, the identification of people with COPD is even more accurate.

"We hope these findings will improve how physicians find COPD and benefit patients by identifying those with more severe disease and at risk of exacerbations so they can be treated."

New Combination for First-Line Maintenance in COPD

COMBINATION therapy with tiotropium and olodaterol (TIO/OLO) may represent a promising new first-line maintenance therapy option for chronic obstructive pulmonary disease (COPD), according to new clinical trial data presented at ERS 2015.

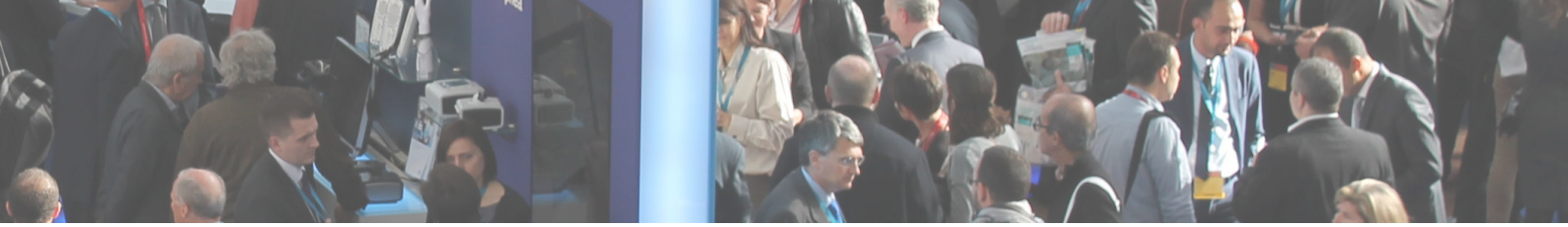
An ongoing Phase III clinical trial programme (TOvITO®) investigating the efficacy of TIO/OLO in >15,000 patients has so far built on the results of the TONADO® trials, which demonstrated that the new combination leads to improvements in lung function and breathlessness, with a reduction in rescue medicine use, compared with TIO alone.

"When many patients are first diagnosed their condition is already declining rapidly. Doing as much as possible early on can give patients the best opportunity to maintain a good quality of life for longer."

A *post hoc* analysis of results from the OTEMTO I and II trials indicates that TIO/OLO leads to a clinically significant 4-point improvement in quality of life (QoL) compared with placebo in COPD patients with GOLD 2 disease. When compared with treatment with TIO alone, 13% more patients achieved a significant improvement in QoL when given the combination therapy (52.8% versus 39.2%). The TIO/OLO combination demonstrated a safety profile comparable to TIO or OLO alone.

Results from the ENERGITO® trial, which compared the efficacy of TIO/OLO with the use of inhaled corticosteroid (ICS) therapy, were also presented. Despite being associated with severe side effects, ICS therapy is used in patients with severe COPD and frequent exacerbations (>2 per year). The new analysis showed that, in patients with moderate-to-severe COPD, TIO/OLOmet all lung function endpoints and led to a 42% improvement in trough FEV_1 compared with a twice daily combination of long-acting beta agonist and ICS (salmeterol/fluticasone propionate).

In a press release dated 28th September, Prof Dave Singh, Professor of Clinical



Pharmacology and Respiratory Medicine, University of Manchester, Manchester, UK, concluded: "When many patients are first diagnosed their condition is already declining rapidly. Doing as much as possible early on can give patients the best opportunity to maintain a good quality of life for longer. This sub-analysis shows that Spiolto® Respimat® could give patients this opportunity."

COPD is a growing world health priority and has been predicted to become the third leading cause of death by 2030. COPD is characterised by progressive airflow limitation that results in decreasing lung function and breathlessness early on in its clinical course. Exacerbations can significantly impair QoL and increase risk of disability and death.

SUMMIT: COPD in Patients at Cardiovascular Risk

CHRONIC obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) each represent a leading cause of death globally, and often coexist in the same patient. The SUMMIT study investigated the relationship between these two diseases and survival in patients treated with 100/25 µg fluticasone furoate/vilanterol (FF/VI).

The study included 16,485 patients diagnosed with COPD and displaying both moderate airflow limitation (FEV_1 50–70% of predicted) and either a history or increased risk of CVD. The results, reported by GlaxoSmithKline PLC and Theravance Inc. in a press release dated 8th September and presented at ERS 2015, showed a 12.2% reduction in the risk of dying in those receiving FF/VI compared with placebo, although this was not statistically significant (p=0.137). The researchers also demonstrated a significant reduction in lung function decline of 8 mL per annum (p=0.019), as well as a decreased risk of on-treatment CV events (CV death, myocardial infarction, stroke, unstable angina, and transient ischaemic attack) of 7.4% in those receiving FF/VI, although statistical significance was not established (p=0.475). Further COPD endpoints assessing the efficacy of FF/VI relative to placebo were also analysed, including FEV_1 (post-bronchodilator), rate of moderate/severe exacerbations, time to first moderate/severe exacerbation, rate of severe (hospitalised) exacerbations, time to first severe (hospitalised) exacerbation, health-related quality of life, and health status. An improvement was observed in all COPD endpoints, with nominal p values for each endpoint being ≤0.002.

"The SUMMIT study is the first prospective study to investigate the interaction between these two diseases and set out to achieve the ambitious goal of demonstrating a reduction in death from any cause in patients with both COPD and CVD."

The lead investigator of the study, Prof Jørgen Vestbo, Centre for Respiratory Medicine and Allergy, University Hospital South Manchester NHS Foundation Trust and University of Manchester, Manchester, UK, summarised the study: "The SUMMIT study is the first prospective study to investigate the interaction between these two diseases and set out to achieve the ambitious goal of demonstrating a reduction in death

from any cause in patients with both COPD and CVD. While the study was unable to demonstrate a statistically significant improvement on this endpoint, it provides us with a wealth of data to help us as clinicians understand the interplay between these two conditions and insights on how to improve the management of these patients."

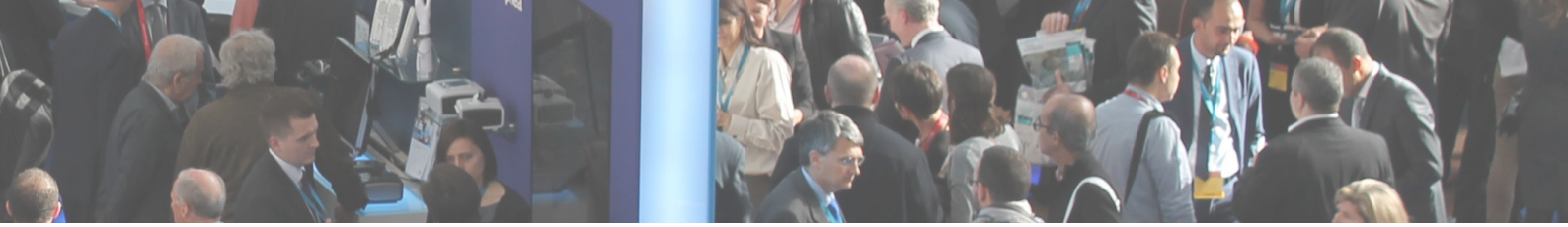
First Classification of Severe Asthma Types May Strengthen Treatment Options

THREE distinct types of severe asthma have been defined through analysis of sputum samples from a patient group, according to study data presented at ERS 2015. Severe asthma can have a substantial impact on sufferers' quality of life, and is difficult to treat since it does not exist as a single disease entity.

"We believe that our work, dividing severe asthmatics into meaningful categories, is the first step towards being able to provide each sufferer with optimal individualised treatment, the ultimate goal of personalised medicine."

Ms Diane Lefaudeux, Research Engineer, European Institute of Systems Biology and Medicine, Lyon, France, claimed that her team's results represent the first step towards understanding how the various categories of patients differ in terms of what is causing their severe asthma, indicating that this would allow the development of drugs tailored to each category in the long term, as well as helping to identify existing drugs that may be used to aid a particular group of patients. "We knew that each new treatment does not work in all people with the disease, which is why we decided to undertake sputum 'handprinting' in 72 people across the severity of asthma, including smokers," said Ms Lefaudeux.

The research was conducted by U-BIOPRED (Unbiased BIOmarkers in PREDiction of respiratory disease outcomes), a public/private partnership, using information and samples from European adults and children, and aimed to learn more about the different types of asthma. The researchers analysed patient sputum samples using gene expression (transcriptomics), abundance of proteins (focussed and non-focussed proteomics), and measurements of abundance of certain lipids (focussed lipidomics). "Each 'omic' type brings a



different and complementary piece of information concerning the biology of asthma and severe asthma, leading to the combination of fingerprints which make up the handprint of disease," said Ms Lefaudeux.

The team aims to link these findings to the substantial amount of clinical data and additional 'omics' data types that have been gathered by U-BIOPRED. "We believe that our work, dividing severe asthmatics into meaningful categories, is the first step towards being able to provide each sufferer with optimal individualised treatment, the ultimate goal of personalised medicine," concluded Ms Lefaudeux in an ERS press release dated 29th September.

Increased Incidence of Asthma Linked to Smoking Grandmothers

CHILDREN with grandmothers who smoked have an increased risk of asthma, even when the mothers did not smoke, according to the results of a study presented at ERS 2015.

"We found that smoking in previous generations can influence the risk of asthma in subsequent generations. This may also be important in the transmission of other exposures and diseases."

There has been a rapid increase in asthma incidence over the last 50 years, which has been attributed to changing environmental factors. It is known that tobacco use may affect the activity of genes, and the study researchers hypothesised that these changes could then be passed to subsequent generations. The team investigated whether smoking in women, while they were pregnant with daughters, was associated with an increased risk of asthma in their subsequent grandchildren. Data was extracted from the Swedish Registry and included 44,853 grandmothers from 1982–1986. Smoking exposure was recorded during pregnancy and the use of asthma medication was noted in 66,271 grandchildren.

The findings showed that if grandmothers smoked whilst they were pregnant, the risk of asthma in grandchildren increased from 10% to 22%, even if their mothers had not smoked during pregnancy. In an ERS press release dated 30th September, Dr Caroline Lodge, Research Fellow, Allergy and Lung Health Unit, University of Melbourne, Melbourne, Australia, said: "We found that smoking in previous generations can influence the risk of asthma in subsequent generations. This may also be important in the transmission of other exposures and diseases."

"Researchers in this area need to be aware, when interpreting the asthma risk from current exposures and genetic predisposition, that individuals may carry an inherited, non-genetic risk from exposures in previous generation[s]. This knowledge will help to clarify the findings concerning current risk factors in asthma research," she added.

Prof Bertil Forsberg, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, said: "The next stage for the research team is to investigate the potential inheritance of asthma risk through the male line, by assessing the risk of asthma in grandchildren whose grandmothers

smoked whilst pregnant with their fathers. The findings also encourage research into inherited disease risks for other environmental exposures."

Nintedanib Shows Positive Long-Term Results in IPF

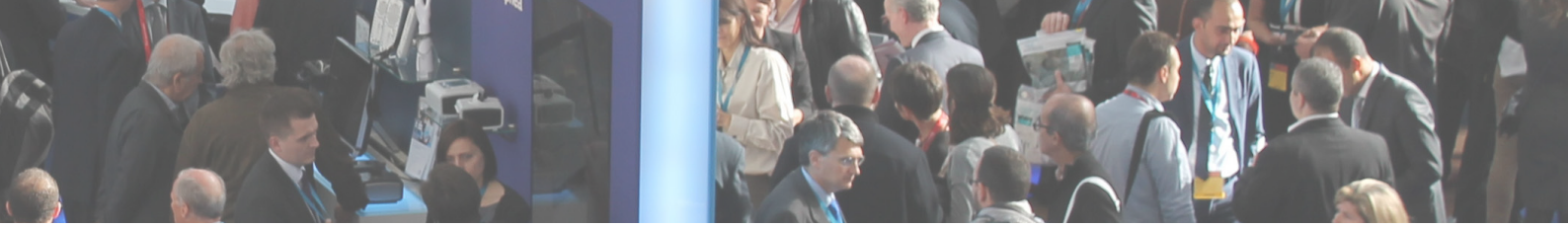
INTERIM analysis of the INPULSIS®-ON extension trial has shown that nintedanib (marketed in the EU as OFEV®) has a positive long-term effect on slowing disease progression and a manageable side-effect profile in patients with idiopathic pulmonary fibrosis (IPF), according to study data presented at ERS 2015.

IPF is a life-threatening and progressive disease that affects approximately 14–43 people per 100,000 globally. Those afflicted require long-term treatment and acute IPF exacerbations (rapid deteriorations of symptoms within days or weeks), to which all patients are susceptible, can occur at any point in the course of the disease.

The previous INPULSIS trials evaluated the effect of oral nintedanib on a broad range of IPF types in 1,066 patients over a period of 52 weeks and showed a slowing of disease progression, with an approximately 50% reduction in the decline of forced vital capacity (FVC). Furthermore, less than 5% of patients discontinued the treatment due to adverse events. The INPULSIS-ON interim analysis builds on these results by following-up 734 of the patients who completed the initial trials, and showed that the change in FVC from baseline to 48 weeks was comparable to that observed during the 52 weeks of the previous trials. No new safety signals were identified during long-term follow-up in INPULSIS-ON. The most frequent adverse events were gastrointestinal in nature, with diarrhoea affecting 64% of patients but only leading to discontinuation in 5%.

"The safety and efficacy data presented for OFEV is very reassuring with regards to the long-term outcomes of treatment with OFEV and its effect on slowing disease progression. They add further weight to the growing body of evidence in support of OFEV as an effective and manageable treatment for IPF," reported Prof Luca Richeldi, Professor of Respiratory Medicine, University of Southampton, Southampton, UK, in a press release dated 29th September.

Over 20,000 respiratory professionals



Successful Use of Pirfenidone in Idiopathic Pulmonary Fibrosis

PIRFENIDONE is a viable treatment option for idiopathic pulmonary fibrosis (IPF), a condition that causes fatal and irreversible fibrosis, and affects 100,000 people in the USA and 110,000 in Europe, according to a new analysis of three Phase III clinical trials presented at ERS 2015.

Typically affecting those over 45 years of age, IPF is a progressive disease which has previously had worse survival rates than most cancers. The 5-year survival rate for IPF is currently estimated at between 20–40%. Previously, the only viable treatment was a lung transplant; this is however a limited option. According to a press release dated 29th September, the results of the ASCEND and CAPACITY I and II trials have been pooled and show that the risk of death after ≤2 years is reduced by 38% when using oral perfenidone.

The trials had a combined 1,247 patients who were followed-up for 2 years. In the first year the loss of lung function was slowed by 48%, and 2.3-times more patients lost no function at all compared with the placebo group. Results also showed that if the patients were hospitalised within the first 6 months of treatment, there was a reduction in disease progression (less decline in lung function) or death by more than two-thirds compared with the placebo group. These data demonstrate the efficacy of continuous treatment. A subsequent analysis observed the same patients following their second year of treatment.

Continued observation showed that the patients had a 38% reduced risk of death after 2 years, and that pirfenidone has a good safety profile. The drug is now approved in Europe and the USA for patients with mild-to-moderate IPF, and is also available in 36 other countries.

While it is not yet clear exactly how pirfenidone works, it has been suggested that it disrupts the production of transforming growth factor beta, a protein which is involved in cell growth and fibrosis formation. Another theory is that it may interfere with tumour necrosis factor alpha, which is involved in inflammation.

The results of the ASCEND and CAPACITY I and II trials have been pooled and show that the risk of death after ≤2 years is reduced by 38% when using oral perfenidone.

This drug could revolutionise treatment of IPF and help hundreds of thousands of people worldwide. There are currently 20,000 patients who have been using pirfenidone since its approval last year and its clinical use may soon become established practice.

Differences Detected in Symptoms and Prognoses Between Smokers and Non-Smokers with NSCLC

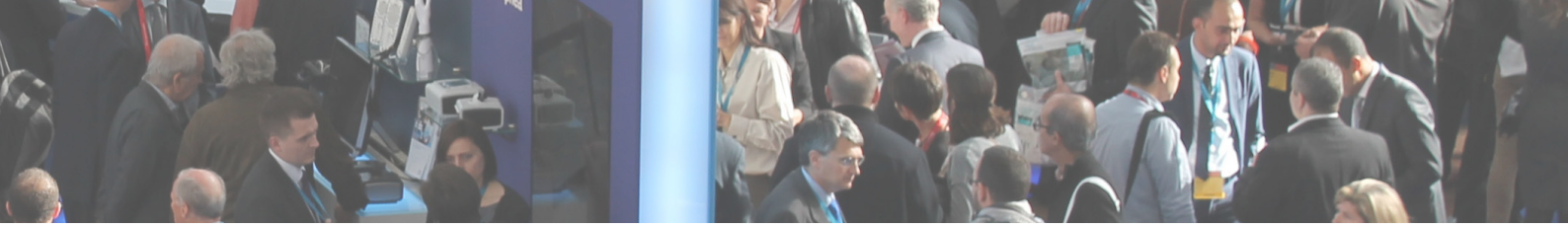
SIGNIFICANT differences have been observed in clinical features and survival between smokers and non-smokers who develop non-small-cell lung cancer (NSCLC), according to the results of a study presented at ERS 2015. Tobacco smoking is known to be the main risk factor for NSCLC, although non-smokers are also susceptible.

Dr Cátia Saraiva, Department of Pulmonology, Portuguese Institute of Oncology, Lisbon, Portugal, and colleagues studied 504 Portuguese non-smokers and 904 smokers who all had NSCLC. They discovered that non-smoking patients were more likely to be women; however, adenocarcinoma, chronic obstructive pulmonary disease, heart disease, previous cancer of the larynx, and weight loss were all greater in the smoking group. Additionally, non-smokers had a significantly longer survival post-diagnosis: 51 months versus 25 months for smokers.

"This is the first study to look at the differences in symptoms and prognoses in non-smokers and smokers with NSCLC in Europe," said Dr Saravia in an ERS press release dated 27th September. "We believe we have made a major contribution towards improving diagnosis and treatment for these patients."

The researchers suggest further prospective studies to find additional prognostic factors in areas such as ageing, human predisposition, and lifestyle between the two groups. "In the non-smoking group, we found professional exposure to carcinogens in 9%, a family history of lung cancer in 5%, and a previous cancer diagnosis in 6%. Additionally, 18% had high blood pressure," Dr Saravia added.

"This is the first study to look at the differences in symptoms and prognoses in non-smokers and smokers with NSCLC in Europe. We believe we have made a major contribution towards improving diagnosis..."



The non-smoking group were often diagnosed at an advanced stage of disease, including 59% of patients at Stage IV. By this time the cancer had spread to other areas of the body, including different parts of the same lung, the opposite lung, bones, and brain. "It seems plausible that the non-smoking Portuguese population is not aware of lung cancer risks. But we need to confirm our results through population based studies, before public education issues can be addressed," said Dr Saravia.

CT Scan Follow-Up Improves Lung Cancer Survival Rates

RECURRENT lung cancer patients have superior post-surgery survival rates if their management includes a follow-up programme based on computed tomography (CT) of the chest, according to study data presented at ERS 2015 by Dr Niels-Christian Hansen, Department of Respiratory Medicine, Odense University Hospital, Odense, Denmark.

Previous research has shown that after the introduction of the CT-based follow-up, most cases of recurrent lung cancer can be detected prior to symptom onset, allowing for earlier diagnosis and an improved chance of having a radical treatment for the relapse. This study aimed to assess whether this follow-up also improved survival rates.

The study recruited 391 patients who had surgery following a diagnosis of lung cancer between 2008 and 2013. After the introduction of a CT-based follow-up in July 2010, all patients received a scan every 3 months for 2 years, then every 6 months for 3 years. In May 2015 the team recorded whether the patients were alive and free from lung cancer.

Data showed that the number of patients alive 4 years post-surgery increased from 54% to an estimated 68%. In addition, for patients experiencing a relapse during the first 24 months post-surgery, the probability of being alive 4 years after the initial treatment increased from 2% to an estimated 27%.

Dr Hansen said in an ERS press release dated 27th September: "Our results show a significant improvement for survival rates for patients post-surgery in a CT follow-up programme currently running in Denmark. A key strength of our study is the real-life setting we used, where we were able to demonstrate successful results in a representative sample of lung cancerpatients from Denmark. This is very encouraging news and we believe that our results could contribute to the planning of similar treatment programmes in other centres and countries."

The team plans to perform a similar experiment looking at the follow-up of those undergoing radiation therapy for their lung cancer, to see if this may also prove successful.

Live endoscopy

Early Clinical Trials of Anti-TB Drugs Should Include HIV Patients

EXCLUSION of HIV-infected patients with tuberculosis (TB) from clinical trials may be hindering drug development for drug-resistant TB, according to study data presented at ERS 2015.

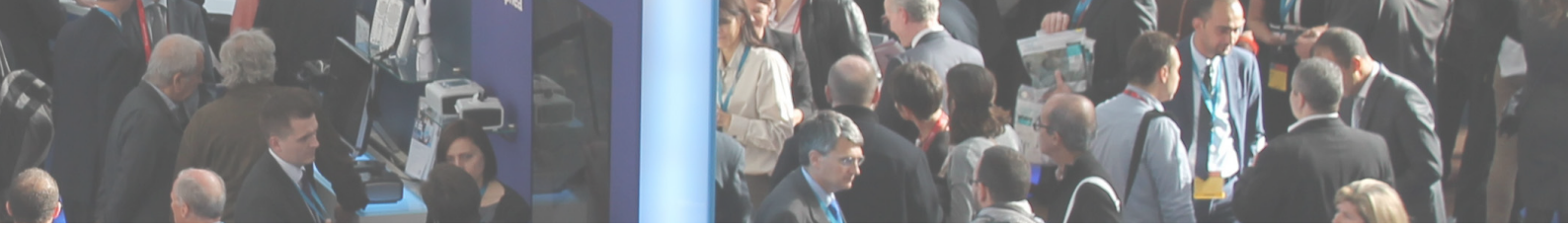
Dr Florian von Groote-Bidlingmaier, Director of TASK Applied Science, Cape Town, South Africa, and colleagues studied the records of 421 patients with multi-drug-resistant (MDR) TB who had been referred to Brooklyn Chest Hospital, Cape Town, for consideration for participation in clinical drug trials investigating a new anti-TB drug. They discovered that 24.9% were excluded for having a low $CD4^+$ cell count, 6.9% had died, and 17.1% did not have true MDR TB. Of the 55 remaining patients (13.1%) who did qualify for the trials, only 12 (2.9%) were eventually formally evaluated.

"It is very, very difficult to recruit suitable patients with MDR TB for trials of new drugs. Inclusion of HIV patients early on would increase the number of participants and the relevance of the results."

"We need new anti-TB drugs and we need to develop them fast. Drug development is a lengthy and expensive process and should be accelerated as much as possible. It is very, very difficult to recruit suitable patients with MDR TB for trials of new drugs. Inclusion of HIV patients early on would increase the number of participants and the relevance of the results," said Dr von Groote-Bidlingmaier in an ERS press release dated 29th September.

Currently, HIV patients are often excluded from early phase clinical trials in order to remove any confounding factors. However, Dr von Groote-Bidlingmaier noted that >60% of TB patients in South Africa are HIV positive, and that the compatibility of concomitant anti-retroviral treatment with new TB treatments is yet to be verified. He said that HIV patients should make up at least a subset of participants in any clinical trial for TB, in order for their safety to be guaranteed.

Dr von Groote-Bidlingmaier concluded: "South Africa is one of the few countries where bedaquiline (one of the new TB drugs) is available without cost to the patient. This is a great



success and a major breakthrough 10 years after the first clinical trial with bedaquiline was done in Cape Town."

Digital Health Agenda for Action Aims to Help End TB

DIGITAL health could play a significant role in efforts to eradicate tuberculosis (TB). On 29th September 2015, the WHO Global TB Programme and the European Respiratory Society (ERS) launched a new Agenda for Action focussed on integrating information and communication technology into the prevention and treatment of TB. The organisations hope that using powerful and ever-growing digital tools will accelerate efforts to combat the infection.

It is estimated that around one-third of the world's population is infected with latent TB, and that up to 10% of this population will become 'active' at some point in their lives. Although TB can usually be cured with treatment, 1.5 million people died from the disease in 2013 and another 9 million fell ill; these numbers highlight the importance of TB as a global health threat.

"It is vital that we tackle TB, in particular the growing threat of drug-resistant TB, and digital technologies present a valuable resource to facilitate this goal."

The digital health Agenda for Action from WHO/ERS aims to oppose TB by:

- Advocating that TB programmes, other national authorities, and all stakeholders integrate digital health solutions into their implementation of the End TB Strategy. Patient care, surveillance, programme management, staff development, and the engagement of communities can be advanced through information and communication technology
- Guiding programmes on promising options for first focus of efforts, building on currently limited evidence about the effectiveness of digital health interventions for ending TB
- Promoting continued monitoring and investment in research on implementation of digital health interventions in order to increase the evidence base on effectiveness and impact

"This Agenda for Action can spur the acceleration and scale-up of TB efforts needed in the next few years. It is vital that we tackle TB, in particular the growing threat of drug-resistant TB, and digital technologies present a valuable resource to facilitate this goal," commented Prof Giovanni Migliori, ERS Secretary General, in an ERS press release dated 29th September.

WHO/ERS hope to implement their agenda by means of target product profiles, which aim to create solutions that are applicable in multiple settings by facilitating engagement between system developers and national programmes, policy makers, TB specialists, etc. They expect this plan to have an extensive positive impact on the global problem of TB.

Benefits of Personalised Treatments for Sleep-Disordered Breathing

PERSONALISED treatments for sleep-disordered breathing (SDB) are both beneficial and becoming more widely available. Data presented at ERS 2015 demonstrated new treatments that provide options to suit patients' lifestyles and individual needs. From a device tailored to treat women's symptoms, to a tool designed to help patients manage their own therapy, it is hoped that these innovative products will contribute to improving the quality of life for millions of SDB patients all over the world.

SDB is a condition that describes abnormal breathing during sleep. It normally refers to a patient whose breathing rate increases or decreases in an unusual manner, resulting in pauses in breathing and reduced blood oxygen saturation levels. SDB has been associated with cardiovascular complications such as heart failure, stroke, and chronic obstructive pulmonary disease. Treatments are continuously improving to minimise the risk of these health issues, and those introduced at ERS 2015 highlight the progress that is continuously being made for SDB patients, according to a press release dated 26th September.

Treatments are continuously improving to minimise the risk of these health issues, and those introduced at ERS 2015 highlight the progress that is continuously being made for SDB patients.

Addressing the problem that men and women present with different symptoms of SDB, the aforementioned female-specific device responds to women's symptoms of obstructive sleep apnoea by delivering two auto-adjusting algorithms to manage the condition. It is complemented by masks that are also tailored to fit women and has shown high efficacy in trials. Another personalised therapy is the custom-made mandibular repositioning device (MRD); this was designed to avoid the problem of dental and temporomandibular joint side effects that often result from traditional respiratory devices. This MRD optimises patient acceptance and treatment efficacy with physiological articulation and comfortable splints.

Furthermore, a therapy management application has been released for patients with SDB to help them start and stay on therapy. Providing patients with support, education, and troubleshooting tools, the application aims to empower patients to take an active role in their health and to give them more confidence and motivation to manage their treatment themselves.

These treatments are a small selection of a larger number of therapies presented at ERS 2015, all of which endeavour to improve the personalisation and the quality of care received by patients with SDB, often by maximising the connection between patients and healthcare providers. The ongoing development of such tools is encouraging for those fighting against SDB and other related conditions.

Rhinovirus Infection Can Reduce Diversity of Respiratory Microbiota in Infants

MICROBIOTA of the respiratory system are known to change during chronic lung diseases, and viral infections, such as rhinovirus (RV), early in life are thought to be key in the development of respiratory conditions later in life. A new study suggests that the interaction between viral infections and respiratory microbiota during infancy could provide clues to disease development later in life.

The study, presented at ERS 2015 by Dr Insa Korten, University Children's Hospitals, Bern and Basel, Switzerland, examined the link between nasal viral infections and microbiota in 32 healthy infants from the BILD cohort study. Nasal swabs were taken from the children every 2 weeks from the age of 5 weeks until the age of 1 year; the microbiota and 12 different viruses were analysed in each sample.

> "Our findings indicate an interaction between RV infections and nasal microbiota in early life that persists over time."

The results show a relative decrease in bacterial diversity within the respiratory microbiota of infants with symptomatic RV infections compared with those with no infection or asymptomatic RV colonisation. This suggests that a reduction in nasal microbial composition only occurred following the respiratory symptoms caused by the reaction of an infant's immune system. Researchers also found that overall bacterial diversity was reduced at the end of the study period in infants who experienced frequent infection, indicating that recurrent infections reduce the normal variety of the microbiota.

Dr Korten remarked in an ERS press release dated 27th September: "Our findings indicate an interaction between RV infections and nasal

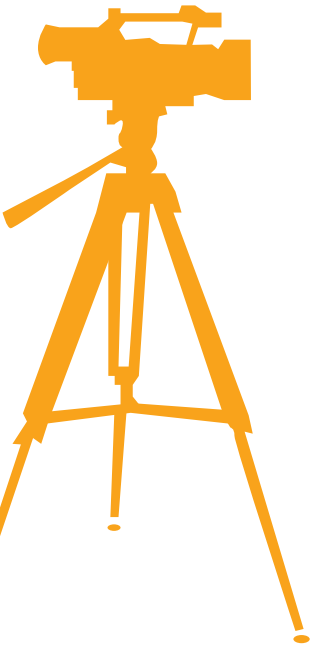
microbiota in early life that persists over time. Although our findings need to be confirmed in other cohorts, the interaction of the virus and the microbiota could be of importance in future preventative or therapeutic procedures."

The research team plans to build on this study by investigating the same children at the age of 6 years in order to determine how many develop asthma, and whether early changes in the respiratory microbiota persist. Investigating the significance of the effect of viruses relative to other influencing factors will also be of interest.

Metalworking Fluid May Cause Irreversible Lung Condition

OCCUPATIONAL exposure to fluid commonly used in metal machining operations may be related to a rare, irreversible lung disease, according to research presented at ERS 2015.

Many factories worldwide use metalworking fluid as a lubricant and coolant, especially during cutting and grinding operations. After four workers developed lymphocytic bronchiolitis (LB) in one factory, the National Institute for Occupational Safety and Health undertook this research. This was especially important as LB can be debilitating. The researchers found that exposure correlated with reported symptoms but not with lung function.



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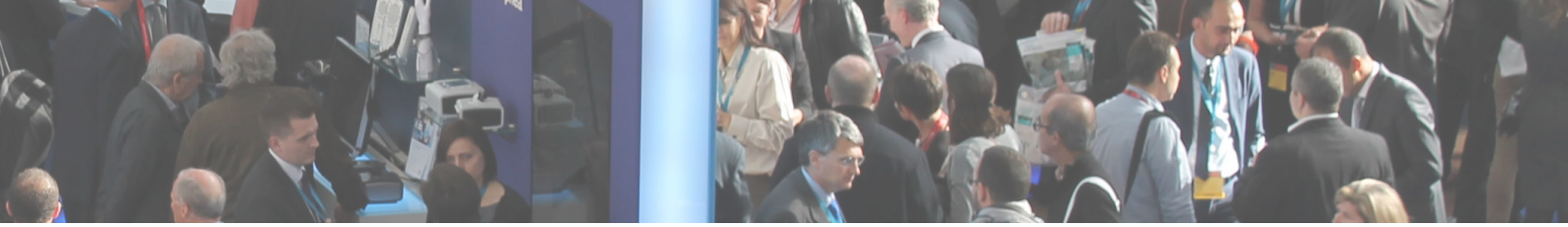
LB, which is caused by an overgrowth of immune cells, damages the bronchioles, which suggests that LB is caused by an immune response to exposure. In metalworking fluid many bacteria and fungi can grow; these micro-organisms could be the cause rather than the fluid itself. Work-related lung diseases are hard to diagnose as they often resemble common conditions and may only develop and present symptoms after a long exposure. It is therefore essential that any clustering of diseases around a workplace are investigated, so that any similar workplace environments worldwide can also reduce risk factors.

"We recommend that microbial growth in metalworking fluid be maintained at the lowest level possible and that airborne exposures be kept as low as possible through the use of mist collectors and other types of exhaust systems."

The researchers recruited and interviewed 388 workers at the factory and measured lung function. "Although workplace exposures were generally low, we found that workers with higher workplace exposure to the fluid reported more symptoms than those with less exposure," said Dr Kristen Cummings, Respiratory Health Specialist, National Institute for Occupational Safety and Health, US Centers for Disease Control and



Prevention, Morgantown, West Virginia, USA, in an ERS press release dated 28th September. "However, their lung function was about the same, regardless of exposure levels. The finding of symptoms with normal lung function could mean that some workers are at risk of developing the disease as well."

"We recommend that microbial growth in metalworking fluid be maintained at the lowest level possible and that airborne exposures be kept as low as possible through the use of mist collectors and other types of exhaust systems," Dr Cummings concluded.

Using Less Busy Routes Decreases Exposure to Air Pollution

EXPOSURE to peaks in the ambient level of black carbon, a pollutant adversely associated with respiratory and cardiovascular health, can be decreased by walking quieter routes, according to a study presented at ERS 2015.

As the general population becomes increasingly aware of the effect of air pollution on their health, many wish to mitigate personal risk as much as possible. "We know that short-term exposure to black carbon is associated with increased hospital admissions due to respiratory symptoms, and that long-term exposure is associated with exacerbations and increased prevalence of asthma," stated Mrs Lee Koh, a researcher at the Blizard Institute, Queen Mary University of London, London, UK, when describing the motivation for the study in a press release dated 27th September.

The study measured levels of black carbon present in the air whilst walking from one area of London to another using either main roads or a quieter route. Both routes were walked six times between February and May, and the average level of black carbon was calculated for every 5-minute period.

On the busy route, the average levels of black carbon per 5 minutes ranged from 3,339–6,995 ng/m^3, while averages on the quieter route ranged from 2,555–5,854 ng/m^3. Compared with the peaks observed on the busy route, in which levels of the particulate exceeded 10,000 ng/m^3 per 5 minutes, the levels of black carbon particulate remained consistent and relatively low on the quieter route. These findings are concerning given the recommendations from the UK's Daily Air Quality Index, which suggest that exposure to fine particles of air pollution ≤2.5 μm (which includes black carbon) should be <35,000 ng/m^3 per day.

"Our study suggests that, in London, it is possible to reduce exposure to peaks of black carbon particles, mainly from diesel soot, by choosing to walk a less polluted route. Government action will be required to further improve the general air quality around us," concluded Mrs Koh.

Air Pollution Linked to Death and Organ Rejection in Lung Transplant Patients

LUNG transplant patients in Europe who live on or near to busy roads with high levels of air pollution are more likely to die or experience chronic organ rejection compared with those living in less polluted areas.

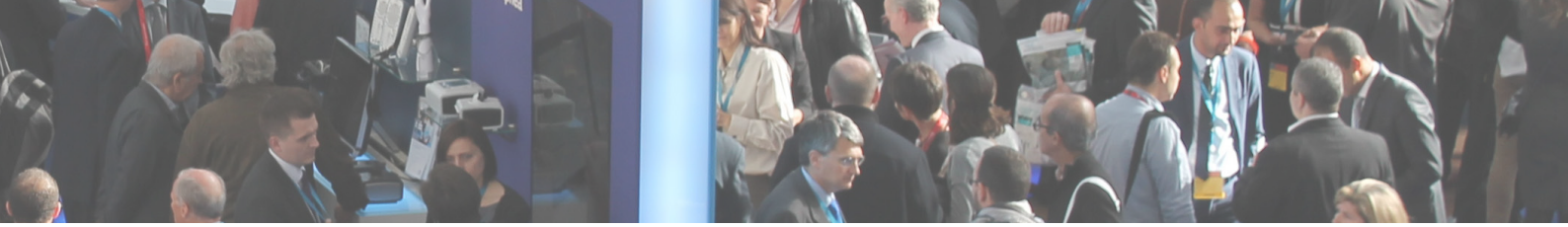
Dr David Ruttens, University of Leuven, Leuven, Belgium, told ERS 2015 that the risk of dying increased by 10% for patients living in an area where air pollution was above World Health Organization recommended maximum levels compared with patients living in areas with reduced pollution levels. However, this enhanced risk was not observed in lung transplant patients who were taking a class of antibiotics called macrolides, including azithromycin and clarithromycin.

The researchers gathered data from 5,707 lung transplant patients from 13 major lung transplant centres across Europe. They estimated the patients' exposure to PM_{10} particles in their homes, and gathered information including the density of roads around their home addresses, and matched this with outcomes, including chronic rejection and death. Throughout an average of 5.6 years of follow-up, 2,577 patients (45.2%) died and 2,688 (47.1%) developed chronic organ rejection. A total of 3,511 patients (62.2%) took macrolides at some point during treatment, and 2,149 patients (37.7%) did not.

"Our results show that both deaths and chronic rejection in lung transplant patients are associated with air pollution and exposure to traffic. Lowering the levels of air pollution in Europe would significantly improve the chances of these patients' survival and lower their risk of organ rejection."

Chronic organ rejection occurred in 61.5% versus 38.5% of patients in the macrolide and non-macrolide groups, respectively, while 29.8% of macrolide-taking patients died compared with 54.5% of macrolide-free patients. The team found an association between road length in the area around patients' homes and chronic rejection in the macrolide-free patients; in the 200, 500, and 1,000 m buffer zones the risk of organ rejection increased by 11–13% per 100 m increase in road length.

"Our results show that both deaths and chronic rejection in lung transplant patients are associated with air pollution and exposure to traffic," said Dr Ruttens in an ERS press release dated 29th September. "Lowering the levels of air pollution in Europe would significantly improve the chances of



these patients' survival and lower their risk of organ rejection."

Danger of Talcosis in the Food Industry

RISK of developing talcosis is often underestimated in the food manufacturing industry, in which talc is used as a minerally inert substance, and greater awareness is required to prevent its onset according to a study presented at ERS 2015. Talc (hydrated magnesium silicate) is often used in food manufacturing and passes undigested through the body. Talc is considered a harmless food additive and has not previously been considered a danger in the industry. Following the diagnosis of talcosis in an employee of a chocolate production company, research was undertaken to assess the risk and causes of the condition.

The study observed the individual exposure of all workers who came into contact with talcum dust. Those who had the highest exposure (n=111) were asked to complete a questionnaire regarding their occupational history and respiratory symptoms. After analysing their level of exposure, 18 workers were selected based on having a high cumulative exposure and were referred for a high-resolution thoracic computed tomography scan. At least 1 worker, and possibly 2 workers out of the 18, were diagnosed with talcosis.

In an ERS press release dated 28th September, Dr Jos Rooijackers, Pulmonologist, Netherlands Expertise Centre for Occupational Respiratory Diseases (NECORD), Utrecht, Netherlands, said: "Our research shows that comprehensive surveillance programmes including exposure assessment and structured medical evaluation are the keystone of prevention and contribute to a safe and healthy workplace. The health effects of occupational exposure to dust, gasses, and vapours are not well recognised by health professionals and neglected by public authorities and employers, reinforced by a conflict of interest, and leading to missed diagnoses and a high burden of disease, thus putting employees in danger."

Following the study, the company implemented control measures to ensure a limited amount of exposure in workers. The researchers said that inhalation of other manufacturing products, such as flavourings and enzymes, may pose an as yet unidentified respiratory hazard and should therefore be the focus of further study.

Nicholas Hill

Professor of Medicine, Tufts University; Chief of the Pulmonary, Critical Care, and Sleep Division, Tufts Medical Center, Boston, Massachusetts, USA.

Q: Who or what was your inspiration for pursuing a medical career in the field of respiratory medicine?

A: I attended Dartmouth Medical School in Hanover, New Hampshire, USA, and the respiratory physiology group there, headed by Dr Marsh Tenney, had excellent teachers who were enthusiastic researchers. The experience of working with them stimulated me to pursue graduate work with them within respiratory physiology; this got me 'hooked' on the field.

Q: Are there any differences in the types of cases you tend to see now compared with when you first started in the clinic?

A: I receive more referrals for pulmonary hypertension (PH) now, partly because I have a greater reputation in the field, but the more important reason is the progress in therapeutics. We now have multiple medical therapies available, as well as lung transplantation, that were not available when I finished my fellowship.

Q: What kind of impact has greater public awareness of the risk factors for respiratory disease, such as exposure to cigarette smoke, air pollution, and allergens, had on the incidence and prevalence of respiratory disease?

A: An enormous impact, especially with regard to cigarette smoking, which is highlighted by the fact that smoking rates continue to fall steadily. When I finished my fellowship, over a third of US residents were smokers – now it is less than half that. This has led to reductions in the rates of both lung cancer and chronic obstructive pulmonary disease (COPD).

Q: Is there any more that governments and healthcare providers could be doing to reduce the prevalence of respiratory disease?

A: In the US there are still too many people who smoke cigarettes and who are being exposed to poor air quality. We must continue to try to snuff out the use of cigarettes and other forms of tobacco, not only in the US but in other parts of the world. In Europe, smoking rates are considerably higher than in the US (even among physicians in some countries). In the developing world, smoking rates have climbed in recent decades and indoor air pollution continues to be a big problem. This is a disaster and there have been international efforts to try to address these problems, including those by the UN, international respiratory societies, and many governmental agencies. Despite this, the tobacco industry remains very powerful. More legislation is needed to curb smoking in public places and limit the sale and free distribution of cigarettes to young people throughout the world.

Q: How has the use of non-invasive positive pressure ventilation evolved during your time in the clinic, and what effect(s) has this had on lung disease outcomes?

A: The proliferation of non-invasive ventilation for both acute and chronic forms of respiratory failure is one of the most, if not *the* most, important developments in the field of pulmonary and critical care medicine in the past couple of decades. It has proved effective in patients with respiratory failure due to neuromuscular disease, obesity hypoventilation, and COPD. Uses also extend to acute respiratory failure (ARF) in patients with acute hypercapnic respiratory failure (mainly due to COPD exacerbations), as well as cardiogenic pulmonary oedema.

Non-invasive ventilation represents a 'less is more' approach, and has enabled many patients with chronic respiratory failure to remain at home. It has been shown to both extend and improve the quality of their lives, and has saved many lives in patients with ARF by averting intubation and its attendant complications. The technology has been steadily improving, with more comfortable masks and ventilators that are better at synchronising with and monitoring

patients are being developed. We continue to see new innovations, such as the recent advent of high-flow nasal oxygen.

Q: Your research also focusses on the management of pulmonary hypertension – to what degree are modern therapies able to ameliorate this rare but serious condition?

A: When I finished my fellowship in pulmonary medicine in 1982, we had no approved therapies for PH and the diagnosis was pretty much a death sentence. Today, we have nine (almost ten) pharmacotherapies approved in the US. Lung transplantation is also an option if medical therapy fails, and we know much better how to manage the disease. Average survival has probably more than doubled since the 1980s and patients have an improved quality of life and function while on therapy. We are still seeking better therapies and a cure because the average life span of those with the disease is still much less than 'normal' individuals.

Q: Could you speculate on what is likely to be the 'next big thing' in the field of respiratory medicine?

A: We are making progress with idiopathic pulmonary fibrosis, with two new therapies introduced within the past year. Although these therapies slow the progression of the disease, they do not reverse it and so we are testing multiple additional agents and will be looking at combinations to see if we can achieve that goal. In the critical care field, there has been a rise in the use of extracorporeal membrane oxygenation. Soon we will see the use of extracorporeal CO_2 removal devices to treat patients with hypercapnic respiratory failure for whom non-invasive ventilation fails.

Q: In your opinion, what is the greatest challenge facing respiratory medicine today?

A: Lack of research support, especially from the National Institutes of Health in the US. The agency has essentially kept funding the same for more than 10 years and has not kept up with the rate of inflation. Our research infrastructure is eroding and many young investigators have shied away. This is not unique to respiratory medicine, of course, but will have a negative effect on research advancement for many years to come. Within the respiratory field, we continue to have major problems with exposure to environmental pollution via cigarette smoking and indoor air pollution, as alluded to above. These are, ultimately, problems of political will.

Q: What advice would you give to young medical students thinking about specialising in respiratory medicine?

A: Do it! Respiratory medicine offers a great diversity of clinical and research opportunities and very interesting physiology and pathophysiology. I have found it very exciting to experience and, in small ways, to participate in the advances we have seen since I entered the field. The improvements we have been able to bring to many patients' lives have been very rewarding.

Jim Reid

Deputy Dean, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand.

Q: What inspired you to pursue a career in respiratory medicine having been previously trained as a pharmacist?

A: I felt that the activities of a pharmacist were not fulfilling my career hopes. I had previously wondered if I was intelligent enough to become a doctor, but experiences with doctors while I was a pharmacist soon dispelled that doubt!

Q: How much of an influence did your studies at the University of Miami have on your career?

A: My time in Miami had a major influence on the remainder of my career. There was no real difference in the content of the medical training, but as a teaching fellow I was able to advance that aspect of my professional life, and it cemented my activities in academia.

"As long as people smoke, COPD will continue."

Q: What are the main differences that you have noticed between the way healthcare is administered in the USA and New Zealand?

A: New Zealand has a two-tier system of healthcare: both a private system (supported by insurance) and a public one. While there is a fee for service for primary care, public hospitals are free, as are medications and investigations. The system in the USA was (and essentially still is) 'user pays', and I must admit that I was stunned by the amount that patients paid for healthcare.

Q: How would you describe the state of healthcare in New Zealand? Are there any changes/improvements that you would like to see?

A: New Zealand, by international standards, has an excellent healthcare system. As mentioned above, it is a two-tier system. As with other healthcare systems all over the world, it is struggling with an ageing population and the associated problems that come with age (degenerative disease, diabetes, joint replacement, etc.).

Q: How far has our understanding of asthma improved since you first began your research into this area? To what extent has this translated into effective treatments?

A: There has been a major shift from treating the symptoms of asthma, as was the case in the 1970s, to the current treatment of the cause of the symptoms. There has been recognition that asthma has an inflammatory cause and treatment is now directed at that. One may now debate the cause of the inflammation, but that is for another day. At one time, my country had the highest mortality rate from asthma in the world, and over the past 30 years it has progressed to being among the lowest. Status asthmaticus is now rare.

Q: How significant is the overall impact of chronic obstructive pulmonary disease (COPD), and are there effective treatments available?

A: New Zealand has its share of COPD, and it has a similar impact here as compared with comparable countries. There is a major project in progress to eliminate cigarette smoking by 2025. While the number of smokers has dropped, it is still a big ask to achieve complete elimination within 10 years. As long as people smoke, COPD will continue. Smoking cessation is still the only 'treatment' that will improve disease outcome in COPD. We use both short and long-acting bronchodilators, and, when indicated, inhaled steroids.

Q: Have you noticed any emerging trends in terms of the types and extent of respiratory conditions that you see in day-to-day practice?

A: I believe that there has been a decline in acute asthma and a rise in COPD. Tuberculosis is rare here (I have not seen a case in 10 years). In addition, I think we are seeing more interstitial lung disease, but it is still uncommon.

Q: What more can be done by healthcare providers and governing bodies to raise public awareness of the risk factors for respiratory diseases?

A: Publicity is essential and respiratory disease is often seen as the poor cousin of other types of disease, e.g. cardiology, infections, etc.

Q: In your opinion, what are the biggest challenges facing pulmonologists today?

A: Smoking cessation, smoking cessation, and smoking cessation!

Q: What advice would you give to young medical students about to begin a career in respiratory medicine?

A: I find respiratory medicine fascinating. What advice would I give? Go for it!

Q: What is the most fulfilling aspect of your work?

A: Successfully getting a patient to stop smoking cigarettes – as you can see from my answers, I have somewhat of a fixation!

"New Zealand has its share of COPD, and it has a similar impact here as compared with comparable countries."

Antonio Rossi

Medical Oncologist, Division of Medical Oncology, S.G. Moscati Hospital, Avellino, Italy.

Q: Please give us a brief overview of your career to date. What were your first experiences in the clinic and what led you to your current position at the S.G. Moscati Hospital?

A: As a student at the Faculty of Medicine of the University of Naples, I was attracted to the possibility of integrating the clinical aspect of medicine with clinical research in oncology. At that time (1989), clinical research into lung cancer (LC) was just beginning and, due to poor results, most clinicians were not interested in managing this disease. These aspects and my determination to fight against LC led me to start my career in the treatment and clinical research of this 'big killer'. When I moved to the S.G. Moscati Hospital (2002), the head of the department assigned me to LC research in order to organise a local multidisciplinary team to manage the disease and to be involved in national and international clinical trials, investigating new approaches and drugs, in the hope of contributing to the improvement of LC prognosis.

Q: Your clinical research concerns the development of drugs for treating non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). How much have our knowledge and the overall standard of treatment improved in these indications since your career began?

A: When I began my career, the median survival of metastatic NSCLC was around 4 months. Later, third and fourth-generation drugs were developed, leading to a median survival of 10–12 months. Advances in the knowledge of tumour biology and the mechanisms of oncogenesis have led to the identification of several molecular targets for NSCLC treatment. These molecular targets, for which specific inhibitors have been investigated and are now available in clinical practice, define a subgroup of patients, about 15–20% of cases, who can benefit a lot from these treatments, reaching median survival of around 3 years. Considering that only 65–70% of radically resected NSCLC patients survive 5 years even at Stage I, these approaches are also being investigated in the early stages of NSCLC, with the final results of ongoing trials still pending. Unfortunately, despite intensive research, the prognosis of SCLC remains poor, with no substantial improvement upon the preceding decades.

Q: Tell us a little about your current research. What are the overall aims and what do you hope to achieve in the next year?

A: We are currently involved in international clinical trials investigating immunotherapeutics, including CTLA-4 and PD-1/PD-L1 checkpoint inhibitors. We hope to stimulate the immune system to fight against LC cells. Preliminary clinical results are very promising, making immunotherapy the new frontier to be investigated in the battle against LC in the coming years.

Q: Do you know the incidence of LC in Italy relative to other European nations, and are there any specific cultural, behavioural, or dietary risk factors that may account for any difference?

A: In 2014, new LC diagnoses were approximately 40,000 in Italy, with an incidence of 92/100,000 in men and 35/100,000 in women. This incidence was similar to that reported from other European nations close to Italy. For both sexes combined, the highest rates were observed in Hungary and the lowest in Cyprus. Smoking is the main risk factor for the onset of LC, and it is believed to be responsible for 85% of cases observed. European variations in LC rates and trends largely reflect differences in the stage and degree of the tobacco epidemic. In countries where the tobacco epidemic had peaked by the middle of the past century, such as the United Kingdom and Finland, LC rates have been decreasing in men and plateauing in women.

"This year, the ERS congress included a day focussed on LC."

By contrast, in countries where the epidemic onset was more recent and smoking has just peaked or continues to increase, such as Eastern European countries, LC rates are increasing and are likely to continue to increase for the next few decades at least. Other reported risk factors are exposure to second-hand smoke, radon gas, asbestos, or other chemicals, and family history of LC. No direct correlation between dietary risk and LC has been proven to date, although total fat, butter, and retinol supplements (in smokers only) are considered as possible causes of LC.

Q: What is the greatest hurdle in the fight against LC, and how can it be overcome?

A: Different genetic abnormalities observed in different metastatic sites of the tumour represent the greatest problem in the fight against LC. This intratumoural heterogeneity is particularly evident in advanced disease, making this stage of LC untreatable with curative intent. The increasing knowledge of all the mechanisms responsible for the alteration, proliferation, and continuous transformation of LC cells may help in overcoming this obstacle.

Q: As a medical practitioner whose primary focus is oncology, how closely do you work with pulmonologists and other respiratory specialists when treating LC patients?

A: The management of LC is becoming increasingly complex, therefore several professionals are needed to offer the best approach to these patients. In this modern era, cooperation with other professionals is very important to the diagnosis of LC at the earlier stages, with a higher probability of treating the patient with curative intent. Nonetheless, this cooperation is also very important in the presence of advanced disease as it is important to take enough tumour samples to define the histotype and genetic characteristics of a specific LC in order to implement the best 'personalised' treatment. Thus, a local multidisciplinary team, which includes several experts, as well as national and international networks, are of paramount importance to optimise the management of LC patients.

Q: What more can healthcare providers, governments, and other influencers do to better raise awareness of LC?

A: Primary prevention of LC mainly involves deterring smoking. Several public service campaigns promoted by general physicians, schools, and mass media have been performed to reach this goal in most European countries. This effort should be constantly reiterated by healthcare providers and supported by governments. Secondary prevention of LC is based on screening through tests to detect the disease before the appearance of signs or symptoms. Prevalence and mortality justify the absolute necessity of adequate screening programs for LC at an early stage in the asymptomatic population considered at high risk (i.e. individuals aged >50 years and smoking one pack of cigarettes per day, individuals occupationally exposed to carcinogens). Several screening studies, using different testing methods, in particular thoracic spiral computed tomography and miRNA, have shown interesting results. Ongoing larger studies, enrolling populations at high risk, may provide further information to apply routine LC screening through the support of governments and professionals involved in the battle against LC.

Q: How important are events such as the ERS congress for the development of better practice? How do the larger international events compare with the smaller, more specialised national events, and how much focus is there on oncology?

A: The ERS congress is a well-known European meeting on respiratory diseases. The most important news on these topics is presented at this international meeting, and then the new achievements should be presented and discussed in specialised national events to colleagues who could not attend the congress. This year, the ERS congress included a day focussed on LC. This opportunity is of paramount importance because, at this international and crowded meeting, there is the possibility to share the latest developments in LC with different professionals from all over the world and who are involved in the clinical management of this disease.

"I am proud of every step I have made in my career..."

Q: Which aspect of your medical career are you most proud of?

A: I am proud of every step I have made in my career that has led me to where I am now, and I am sure I will be extremely proud of the next steps I hope to make in clinical LC research to help our patients.

"No direct correlation between dietary risk and LC has been proven to date..."

Jacques Bouchard

Associate Professor of Clinical Medicine, Laval University; Head of the Medicine Department, La Malbaie Hospital, Quebec City, Quebec, Canada.

Q: Who or what inspired you to specialise in the field of respiratory medicine?

A: During my medical training I was very interested in respiratory physiology. When I graduated from university and started to practise I was working in a small community hospital, which is where I am still based, and I decided to undertake postgraduate training in respiratory diseases including allergy testing when the allergist in residence left. It was during this period that the role of allergy in asthma was becoming better defined.

Q: What have been the most important developments in the field that you have witnessed since you first began your career?

A: The introduction of inhaled corticosteroids (ICS) for the treatment of asthma was important, but I believe the most important development has been the advent of combination therapy (long-acting ß2-agonist [LABA] and ICS combined in the same device). It was a highly effective new therapy and it was important to educate family physicians about its appropriate use and administration; I would say that this remains true today.

Q: Have you noticed any trends in the types and prevalences of conditions that you have treated in recent years? If so, could you speculate on the reason(s) for this?

A: When I started my career, we often had to hospitalise asthmatic patients or keep them in the emergency room for 24–48 hours in order to stabilise them. Despite some recent data suggesting that the rate of hospitalisation has stalled in the UK, we have noticed in our small community that this situation has progressively disappeared following the introduction of combination therapy (LABA/ICS) and now we only need to hospitalise very severe asthmatics, with the disease seeming to be better controlled in the other patients (as long as they continue to take their medicine on a regular basis). I believe that many people who were working in an emergency room many years ago and who still work within emergency medicine today would agree that asthmatics are, in general, less sick compared with those in the past. Do not forget that over 80% of all asthmatics are in the mild-to-moderate category and, in Canada, are followed by family physicians.

Q: How would you describe the status quo of the Canadian healthcare system? Are there any new initiatives that have proven especially successful or any areas that you believe could be improved?

A: I think that we have a very good healthcare system here in Canada and in the province of Quebec where I practise. However, there is naturally a lot of discussion about government reimbursement for new drugs because their price continues to get higher and higher. Patient education in collaboration with prescribers (doctors) is the cornerstone of ensuring appropriate use of these drugs. The Canadian guidelines, developed by the Canadian Thoracic Society, were highly innovative when first published. We are also proud to have many internationally renowned respirologists and family physicians involved in numerous important international scientific committees and research projects.

Q: How well integrated are the medical services of French-speaking Quebec and the other Canadian provinces that have English as their main language? Does this language difference ever complicate cooperation or communication with patients or other physicians?

A: Being bilingual is important in some areas, mainly the western part of the province, but less important in most of the cities. English is the international language for medical science, and everybody involved in clinical trials or any other respiratory specialty should be able to read and speak English. Occasionally it can be difficult to translate the science for French-speaking doctors, but overall there are no major problems in doing so.

Q: How and why did you decide to become involved in developing continuing medical education (CME) programmes for family physicians and specialists? What impact do these programmes have on patient care?

A: Before I started my medical studies I was involved in education in many ways; I was a ski instructor and teaching felt very natural to me. During my clinical training I was in charge of a group of students in the anatomy laboratory and this was the start of my career in medical education for colleagues and other healthcare professionals.

Many years ago, a few colleagues and I were involved in a project to create an education network for patients called the 'Quebec Asthma Education Network'. At that time we had more than 110 educational centres with well-trained educators. The network still exists and I am still involved with it. It has now been merged with the chronic obstructive pulmonary disease (COPD) programme and it will be expanded to include some other respiratory diseases in the near future.

I am very close with my colleagues who are family physicians, which helps me as an educator because it makes it easier to know what the challenges are, including the gaps and the needs. I am also close to my colleagues in respiratory medicine and am frequently invited to national advisory board meetings to participate in discussions about new drugs and new data from published studies. Naturally, these discussions are always related to the interests and roles of a family physician.

Q: How rewarding is your postgraduate medical education work at the university? Are there any changes that you would like to see in how such education is provided/administrated in the future?

A: I contributed to the development of several specific CME programmes organised by the university. It was very challenging at the time and now they are not being developed any longer because budgets have been cut and the rules on ethics have become stricter (e.g. research could previously be funded by a pharmaceutical sponsor but this is no longer allowed due to potential influence). However, I am still involved in the development and accreditation of CME programmes for industry or accredited organisations, fully respecting of the new ethics rules. These new challenges and rules are very exciting and have helped guide us to create some fantastic programmes without any bias; this is the future of CME.

Q: What advice would you give to young physicians about to begin their career in respiratory medicine?

A: Respiratory medicine is very exciting. There are very challenging and interesting issues with regard to diagnosis and treatment. For example, look at all the new devices and upcoming drugs, including combination therapies. Respiratory diseases such as COPD are chronic conditions and we have to work in close collaboration with other healthcare professionals. The patient should be always be at the centre of care and all our efforts should be devoted to this specific aspect.

Q: How important are congresses such as ERS to physicians such as yourself? How does this event compare with congresses in North America?

A: I have followed international congresses such as ERS for many years. It has given me a new way of thinking because there are so many different aspects represented in Europe (e.g. respiratory kinesiologists). A lot of new drugs have been presented there, as well as recent abstracts, which made it possible to anticipate what the situation here may be like in 2 or 3 years. Unfortunately, the

large European congresses such as ERS are now not so different when compared with congresses in North America, such as ATS. I still attend, but they are definitely too big to facilitate easy debate and discussions with colleagues. I am very appreciative of the new primary care section in the ERS congress.

Q: What is likely to be the 'next big thing' in respiratory medicine in your view?

A: There are some new challenges on the horizon and also a lot of new drugs, devices, and combination therapies. This area of medicine will become more sophisticated and I believe it will be difficult for the average family physician to absorb this amount of information and apply it for the benefit of their patients. This is likely to be a very challenging issue for me as I continue to prepare educational programmes for my colleagues.

"I am very appreciative of the new primary care section in the ERS congress."

Giovanni Viegi

Acting Director, Institute of Biomedicine and Molecular Immunology, National Research Council, Palermo; Head of the Pulmonary Environmental Epidemiology Unit, Institute of Clinical Physiology, National Research Council; and Contract Professor, Faculty of Environmental Sciences, University of Pisa, Pisa, Italy.

Q: Who or what inspired you to specialise in respiratory medicine?

A: My familial history of respiratory diseases, my own personal interest, and a particular professor of respiratory medicine who taught me whilst I was an undergraduate student at the School of Medicine in the University of Pisa.

Q: Your work in occupational health concerns the relationships between respiratory diseases and air quality/pollution. Are respiratory conditions that are caused or exacerbated by low air quality more or less frequent compared with when you began your clinical work?

A: Symptoms of asthma and chronic obstructive pulmonary disease are more frequent. Chronic bronchitis may be less frequent now due to changes in the prevailing air pollutants: a shift from a reducing mixture of larger particles and sulphur dioxide to the oxidising type of smaller particles and ozone.

"Pulmonology is also very interesting with regard to emerging diseases..."

Q: Is the prevalence of asthma in Italy increasing or decreasing and, if so, is it known why this may be changing?

A: The prevalence of asthma in Italy seems to be levelling off in some age ranges (adolescents and young adults), but is still increasing in the general population. Asthma is a multi-factorial disease and there is an urban factor affecting the prevalence rate.

Q: Are there any preventive measures that citizens can take in order to minimise their risk of developing respiratory disease?

A: Advocate for more stringent clean-air rules for the outdoor environment and occupational settings; avoid smoking in all three known forms: active, second-hand, and third-hand; adhere to vaccination campaigns against flu and pneumonia; eat vegetables and fruit frequently.

Q: Is there any observable upward or downward trend in Italy with regard to tobacco smoking? Are there any differences between specific demographic groups?

A: Since the introduction of the public smoking ban in Italy (2005) there has been a downward

trend in the number of people smoking tobacco. This has plateaued in the last couple of years, with youngsters now being the age group of most concern.

Q: In addition to prevention, screening programmes have been proposed as a way of improving cancer survival rates. What are your views on the introduction of public screening programmes for lung cancer?

A: Although still a contentious issue, it seems that promising results may be obtained through a combination of imaging and biomolecular techniques. However, public screening programmes should not divert resources from the main activity of health services in this field, i.e. primary prevention.

Q: Europe has fairly stringent environmental protection laws – do your colleagues in other regions of the world have to deal with a very different case mix compared with European pulmonologists?

A: I do not agree with your judgement of European legislation, at least concerning outdoor air pollution. Europe has not yet introduced and reinforced the WHO Air Quality Guidelines, which recommend lower concentrations of air pollutants and which aim to reduce the proportion of the population affected by the adverse health effects of air pollution. In addition, I believe better air quality should be guaranteed for indoor environments such as schools and nursing homes.

Q: How important are international congresses to pulmonologists? Are there any specific congresses that you look forward to each year?

A: The international congresses are very important for continuous medical education and networking. I participate in the European Respiratory Congress every year and in the American Thoracic Society Congress every 2 or 3 years.

Q: What advice would you give to young researchers or medics thinking about specialising in pulmonology?

A: Pulmonology is a very important discipline for chronic respiratory diseases, which, according to WHO, are one of the four major categories of non-communicable diseases worldwide (along with cardiovascular diseases, diabetes, and cancers). Pulmonology is also very interesting with regard to emerging diseases, such as interstitial lung diseases, and rare diseases. This branch of medicine requires a deep knowledge of physiology, and it has both public and individual health aspects.

Dario Olivieri

Professor of Respiratory Medicine, University of Parma, Parma, Italy.

Q: When did you decide to pursue a career in respiratory medicine and what were the main reasons behind your decision?

A: In the 1960s, tuberculosis (TB) was no longer *the* respiratory disease. Asthma, chronic bronchitis, and emphysema became relevant and widely studied; I was particularly interested in the close relationship between bronchial hyperreactivity (BH) and asthma.

"Diagnosis and treatment of TB has improved tremendously..."

Q: How far has our understanding of BH and asthma developed since you first began research in this area?

A: I can remember, with a certain nostalgia, how many questions we discussed every day in our university department and how we tried to understand the mechanisms underlying BH through studies investigating bronchial stimulation with methacholine, allergens, and cold air or fog.

Q: How satisfactory are the main treatment options currently available for BH? Is there a need for new therapies?

A: Our understanding of the role of bronchial inflammation in BH now allows us to treat the

different forms of bronchoconstriction in a fairly satisfactory way. Of course, our understanding of bronchodilators, corticosteroids, and their associated effects are constantly improving and 'new therapies' can also be seen as finding the best way of combining several drugs together, preferably within the same inhalation device.

Q: How has the diagnosis and treatment of TB improved in recent years? How concerning is the emergence of drug resistance?

A: Diagnosis and treatment of TB has improved tremendously due to advances in imaging and the discovery and use of antibiotics. Unfortunately, TB has not yet been eradicated. The problem of drug resistance is *the* problem at the moment. The solution will certainly be connected with a better understanding of the basic mechanisms of infection and disease dissemination.

Q: Is TB a growing problem or a declining problem in Europe? Are there any demographic groups that are particularly at risk?

A: TB infection is a growing problem in Europe due to high rates of immigration from less-developed countries. The immune defences of some groups are less effective compared with Western people, and vaccination can have frustrating results.

Q: Are there any respiratory conditions that are particularly prevalent (or absent) in Italy compared with other European nations? If so, what are the main reasons for this difference?

A: No, respiratory diseases are fairly equally distributed across Europe. Of course, some national guidelines can slightly vary from one country to another, but this is only to help cope with local difficulties.

Q: Could healthcare providers do more to inform citizens about how to minimise the risk of respiratory conditions?

A: Yes, healthcare providers are of fundamental importance for the dissemination of correct information regarding prevention, therapy, and respiratory rehabilitation. In this regard, the publications, courses, and local initiatives of the ERS create special opportunities for European healthcare providers.

Q: Are there any other areas of research within respiratory medicine that you are interested in moving into?

A: From the clinical point of view, I have always been interested in asthma, chronic obstructive pulmonary disease, and pulmonary fibrosis. At the moment I am particularly fascinated by immune mechanisms in the lung, immune defences in the lungs, and the possibility of improving these. The new aspects of lung microbiomes, respiratory infections, and exacerbations of bronchial inflammation are of great clinical and speculative interest to me.

Q: In your opinion, what is likely to be the 'next big thing' in respiratory medicine?

A: I think we are ready to answer the question: "what really is idiopathic pulmonary fibrosis?". It would be a great step forward in our understanding of some mechanisms of lung ageing, alveolar damage, and the progression of pulmonary diseases.

Q: How important to pulmonologists are large meetings such as the annual ERS congress, and what do you believe their focus should be?

A: From the time of its foundation, ERS always had two main aims: firstly, to promote research in respiratory medicine, similar to other scientific societies in Europe; and secondly, to harmonise the professional development of respiratory physicians in Europe. The ERS annual meeting is an excellent opportunity for every chest physician to update their scientific knowledge and to validate their professional preparation.

"TB infection is a growing problem in Europe due to high rates of immigration from less-developed countries."

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[1]Slebos DJ et al. Bronchoscopic Coil Treatment for Patients with Severe Emphysema: A Meta-Analysis. Respiration 2015; DOI:10.1159/000431384

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TREATING INADEQUATELY CONTROLLED ASTHMA: EXPLORING THE POTENTIAL OF PHENOTYPE-TARGETED THERAPY

This symposium took place on 28th September 2015, as part of the European Respiratory Society International Congress 2015 in Amsterdam, Netherlands

Chairperson

Mario Castro[1]

Speakers

Ratko Djukanovic,[2] Michael Wechsler[3]

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MEETING SUMMARY

Asthma is inadequately treated with the current standard of care. This session aimed to explore the potential of a phenotype-targeted approach to asthma management, which would allow a more tailored approach to treatment and result in better clinical outcomes for difficult-to-treat patients. Evidence was presented indicating that eosinophils play an important role in the pathogenesis of asthma. The importance of anti-interleukin (IL)-5 therapies, with the focus on therapies currently in development and their potential clinical benefit for the eosinophilic asthma phenotype, was also explored.

Inadequately Controlled Asthma: The Unmet Needs and Impact on Asthma Management

Professor Ratko Djukanovic

Asthma is a heterogeneous disease with many phenotypes. The Global Initiative for Asthma (GINA) lists a number of asthma phenotypes, including allergic asthma, non-allergic asthma, late-onset asthma, asthma with fixed airflow limitation, and asthma with obesity,[1] although a clearly defined phenotype is not in use in routine clinical practice.

Over the past few years, significant progress has been made to define asthma phenotypes more clearly. Stimulation of airway epithelial cultures from healthy individuals and patients with mild-to-moderate asthma with IL-13 revealed overexpression of the biomarkers periostin, CLCA1, and SerpinB2 in only a proportion of asthmatics, leading to the definition of two groups of patients: T-helper type 2 (Th2)-high and Th2-low.[2] Patients

with Th2-high genotype expression had a higher number of eosinophils in their peripheral blood and in their bronchoalveolar lavage fluid.[2] Other features of Th2-high asthmatics include higher serum immunoglobulin E (IgE) concentrations, more positive skin prick tests, higher expression of the mucins MUC5AC and MUC5B, and a thicker basement membrane.[2] The clustering of genes induced by Th2 cytokines, coupled with the readily measurable features of asthma, in particular eosinophils, may help to define a clearer asthma phenotype and how this is related to a specific biological mechanism.

Using topological data analysis (TDA), which creates topological networks revealing statistically significant patterns of complex data, a recent study of asthmatics demonstrated that individuals with mild, predominantly steroid-naïve asthma had elevated Th2 cytokines (IL-13, IL-4, and IL-5).[3] Two clusters of patients were identified as having severe asthma: one cluster consisted of individuals who were older, obese, and atopic, with upregulated Th2 cytokines and mast cell mediators. The second cluster consisted of individuals who were obese, non-atopic, female, and also had raised mast cell mediators, a finding that was unexpected (Figure 1).[3]

Further characterisation of patients has been undertaken in the Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) study, a public/private partnership dedicated to applying systems biology to develop new preclinical models of asthma to advance drug development for severe disease.[4] Multiple sample types were analysed in the study using 'omics' methods, clustering the data by standard methods as well as TDA to identify 'fingerprint' biomarkers, with the aim of combining them to determine a few biomarkers identifying particular phenotypes.

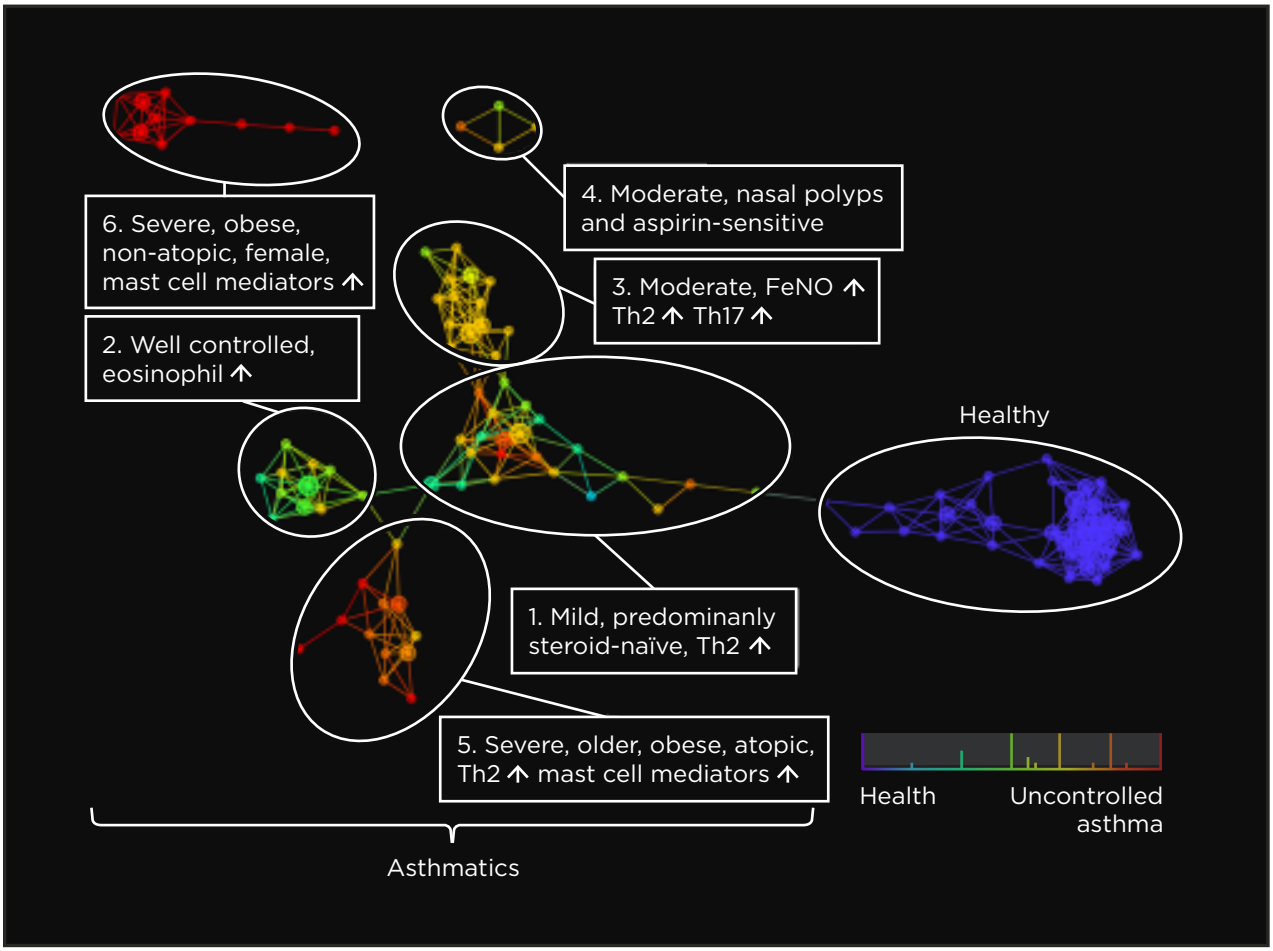

Figure 1: Multi-dimensional clinico-pathobiological clusters in asthmatic patients and healthy individuals.[3] The network is coloured according to disease severity (GINA classification), with patients with the most severe disease in red and patients with the milder forms in varying shades of orange, yellow, and green. FeNO: fractional exhaled nitric oxide; Th2: T-helper type 2; Th17: T-helper type 17.

Mass spectrometry was used to analyse proteins in sputum samples from asthmatic patients, and TDA was applied to these results, revealing 10 clusters of asthma. Three clusters representing more severe asthma were highly eosinophilic and could be identified as being three subtypes of eosinophilic asthma.[4] When blood biomarkers were investigated as indicators of biomarkers in sputum samples, periostin was found to be a good biomarker for inflammation in patients with eosinophilia in sputum.[4]

It is hoped that the findings from the U-BIOPRED study will help to provide a more granular definition of asthma, one that may allow determination of which phenotypes of the disease are responsive to specific biologics. The use of these sophisticated tools will potentially allow a more stratified approach to treatment, leading to the development of drugs that are safer and more effective, resulting in better and more economical healthcare.

Treating Inadequately Controlled Asthma: the Role of the Eosinophil

Professor Michael Wechsler

Currently available therapies for asthma include short and long-acting beta-agonists, inhaled corticosteroids (ICS), leukotriene modifiers, anti-IgE, systemic steroids, immunotherapy, anticholinergics, bronchial thermoplasty, and allergy immunotherapy. However, these treatments do not offer patients personalised therapy and, despite the widespread adoption of guideline-based approaches (including the National Asthma Education and Prevention Program[5] and the GINA guidelines),[1] in many patients asthma remains poorly controlled and associated with significant morbidity.

A more personalised approach to treatment would involve identification of different phenotypes, including gender, age, obesity, ethnicity/race, smoking history, and early versus late-onset asthma; however, this approach can sometimes be non-specific. Identification of endotypes, such as levels of blood and sputum eosinophils and immunoglobulins as well as neutrophils, may offer a more specific approach to treatment that allows the targeting of a mechanistic pathway.[6] Ideally, tailoring treatment using pharmacogenetics would allow for an even more individualised approach to asthma therapy.

Asthma is complex and heterogeneous. One paradigm of asthma pathogenesis involves allergens stimulating Th2 cells to release a variety of cytokines that act on different cells to mediate the inflammatory response. The development of asthma therapies is evolving to target specific aspects of the allergic cascade. One such cell is the eosinophil, which has recently been discovered to have an important role in the pathogenesis of asthma and releases a number of cytokines that contribute to the chronic inflammatory process, including IL-5.

Around 40–60% of asthma is classified as eosinophilic[7] and is often associated with symptom severity.[8] A study of non-invasive markers of inflammation in sputum, resulting from exacerbations induced by a reduction in ICS therapy, demonstrated that exacerbations developed in 7 patients (N=15) over 8 weeks and were associated with an increase in baseline sputum eosinophils.[9] The same study found a decrease in peak expiratory flow variability and forced expiratory volume in 1 second (FEV_1) in relation to eosinophilia.[9] Similarly, a study that measured the expression of two markers of eosinophil activity in mucosal eosinophils, eosinophil cationic protein and major basic protein, found that these increased when ICS therapy was withdrawn.[10]

Analysis of data from the National Health and Nutrition Examination Survey (NHANES), an annual cross-sectional survey of the US general population, provided a further link between eosinophilia and exacerbations. Results across 2001–2010 surveys found that 3,162 patients with asthma had blood eosinophil data. Of these, 56% of children and 53% of adults had a self-reported asthma attack in the previous year, with elevated blood eosinophil counts (≥300 cells/μL) being associated with more self-reported asthma attacks compared with lower eosinophil counts.[11] In the PREDictors of UNcontrolled Asthma (PREDUNA) study, adult patients with asthma and eosinophil levels ≥400 versus <400 cells/μL in 2010 had significantly increased asthma exacerbations, emergency department visits, and excessive short-acting β_2-agonist dispensing in 2011.[12]

Results from these studies demonstrate that there is an increased number of eosinophils in allergic symptomatic asthma, particularly when ICS therapy is withdrawn, ultimately leading to airway hyperresponsiveness.

In the last 10–15 years, evidence has emerged suggesting that asthma management can be guided by sputum eosinophil count.[13] When patients with moderate-to-severe asthma were given ICS therapy titrated according to the British Thoracic Society guidelines[13] or according to changes in their sputum eosinophil counts,[14] it was observed that, although ICS therapy was similar in the two groups, there was a 50% reduction in exacerbations in individuals who had their asthma managed based on sputum eosinophils.[13]

It is clear that eosinophils play an important role in the pathogenesis of asthma in a large proportion of patients, with the degree of eosinophilia being associated with a greater degree of exacerbations. Targeting eosinophils with inhaled and systemic corticosteroids and with anti-IL-5 therapy results in a reduction in exacerbations. The availability of newer, more specific biomarkers for asthma severity will facilitate better mechanism-focussed management of this disease in the future.

The Clinical Benefits of Reducing IL-5 Signalling Among Inadequately Controlled Asthma Patients: The Latest Evidence

Professor Mario Castro

There are a number of potential phenotype-targeted therapies in severe asthma, in particular treatments targeting eosinophilic asthma that include anti-IL-5, anti-IL-4, anti-IL-13, and IL-4α.[15] Recently, greater understanding of the role of the eosinophil in driving the pathobiology of asthma has emerged,[16] along with evidence that targeted treatment of this phenotype is beneficial, particularly in patients with difficult-to-treat asthma.

Eosinophils release several mediators that have effects on the epithelium, fibroblasts, smooth muscle, mast cells, and Th2 cells, and in combination lead to airway hyperresponsiveness and remodelling. Evidence implicating IL-5 in asthma includes the increased expression of IL-5 mRNA in bronchial biopsies taken from patients with asthma compared with non-asthmatic controls, and increased IL-5 mRNA following bronchial provocation with allergen in patients with asthma.[17] Furthermore, inhalation of recombinant human IL-5 leads to increased eosinophilia in induced sputum and in airway hyperresponsiveness.[18]

Several interdependent determinants of anti-IL-5 response in asthma include blood and airway eosinophils, exposure to drug therapies (e.g. ICS), disease severity, and other factors such as associated comorbidities and allergies. Understanding these key factors will allow targeted treatment currently active tissue eosinophilia, as well as prevention of the influx associated with future exacerbations.

Initial clinical results for the investigational anti-IL-5 therapy mepolizumab (750 mg or placebo) in 24 unselected patients with mild asthma revealed that, despite a clear reduction in blood eosinophil levels, there were no changes in clinical outcomes of asthma in these patients.[19] A larger study included 362 unselected patients with asthma on ICS therapy who received intravenous (IV) mepolizumab and, similarly, although there was a significant reduction in blood and sputum eosinophils in both groups, there were no statistically significant differences in any of the clinical endpoints measured.[20] However, when the same therapy was used in selected patients with severe asthma with persistent sputum eosinophilia (median sputum eosinophils in placebo group: 4.0%, range: 1.6–4.3%; in mepolizumab group: 16.6%, range: 0–35.3%) despite oral prednisone (5 monthly infusions of IV mepolizumab 750 mg), there was a reduction in exacerbations, with 10 exacerbations in the placebo group and 2 exacerbations in the mepolizumab group (p=0.008). A single infusion of mepolizumab was associated with a significant reduction in sputum (p=0.005) and blood (p=0.004) eosinophils versus placebo. Although there was no significant reduction in FEV_1, there was a significant improvement in the Asthma Control Questionnaire (ACQ) scores.[21] These results were confirmed in a trial of 61 patients with persistent eosinophilic asthma who had ≥2 exacerbations and who were treated with mepolizumab (750 mg, monthly) for 12 months. A decrease in cumulative exacerbations and a significant reduction in blood (p<0.001) and sputum (p<0.002) eosinophils occurred,[22] highlighting the importance of selecting the correct patients for anti-IL-5 therapy.

In the DREAM trial, carried out in a much larger cohort than the previous trials, 621 patients were randomised to receive placebo or mepolizumab (75, 250, or 750 mg) at 4-week intervals.[23] IV mepolizumab 750 mg significantly reduced the number of asthma exacerbations in patients with severe eosinophilic asthma compared with placebo (52% reduction, range: 36–64%; p<0.0001), and

lowered blood and sputum eosinophilic counts. There were small effects of mepolizumab on FEV_1 and Asthma Quality of Life Questionnaire (AQLQ) and ACQ scores, but these did not differ significantly from placebo and the overall frequency of serious adverse events was similar across treatment groups.[23]

A new anti-IL-5 therapy not currently licensed for the treatment of asthma, reslizumab, has been trialled in patients with elevated eosinophil counts (induced sputum eosinophils ≥3%). Although reslizumab (IV 3 mg/kg) in patients with poorly controlled eosinophilic asthma did not result in a statistically significant improvement in baseline ACQ score, FEV_1 did significantly improve from baseline after 4 weeks (p=0.0364); this rapid improvement was sustained after 16 weeks (p=0.0025).[24] When looking at a subgroup of patients who had a history of nasal polyps, there was a profound improvement in the ACQ score from these patients.

Two multi-centre, parallel, double-blind, randomised, placebo-controlled, Phase III trials assessed the efficacy and safety of reslizumab (IV 3 mg/kg) in patients with inadequately controlled, moderate-to-severe asthma over 52 weeks.[25] Both trials had similar demographics, with similar corticosteroid use and a mean blood eosinophil count of 610–696 cells/μL. In both studies, patients receiving reslizumab displayed a significant reduction in the frequency of asthma exacerbations compared with those receiving placebo (Study 1 rate ratio [RR]: 0.50, 95% confidence Interval [CI]: 0.37–0.67; Study 2 RR: 0.41, 95% CI: 0.28–0.59; p<0.0001 for both studies). An improvement in FEV_1 with reslizumab versus placebo was seen in both trials by the first on-treatment assessment at Week 4 and was sustained through to Week 52 (0.11 L, 95% CI: 0.067–0.15; p<0.0001). Pooled sub-analyses showed increasing mean FEV_1 improvements with increasing disease severity on the basis of background medication, which was most evident at 52 weeks (0.081 L, 95% CI: −0.02 to 0.18 for ICS; 0.113 L, 95% CI: 0.06 to 0.16 for ICS plus long-acting beta-agonists; and 0.151 L, 95% CI: 0.02 to 0.290 for oral corticosteroid-dependent patients).[25] Compared with placebo, reslizumab treatment also resulted in significant improvements in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index score, and was associated with a reduction in blood eosinophil counts. The overall safety profile of reslizumab was similar to that of placebo.[25] These early results in eosinophilic asthma show that reslizumab can be targeted to the patients with blood eosinophil counts of 400 cells/μL who have inadequately controlled severe asthma on current therapy. However, it must be noted that there are different definitions of eosinophilic asthma between mepolizumab and reslizumab trials, with blood eosinophil counts ranging between 150 cells/μL (mepolizumab) and 400 cells/μL (reslizumab).[25]

Another targeted anti-eosinophil therapy, benralizumab, is currently under investigation. Benralizumab is a humanised, afucosylated monoclonal antibody that binds to the α subunit of the IL-5 receptor and depletes eosinophils through antibody-dependent cell-mediated cytotoxicity.[26] In the initial open-label, single, dose-escalation study of benralizumab, IV doses (0.0003–3 mg/kg) were administered to 44 patients with mild atopic asthma over approximately 3–30 minutes. Results showed that mean peripheral blood eosinophil levels decreased in a dose-dependent manner and eosinophil cationic protein levels were reduced from 21.4±17.2 μg/L (baseline) to 10.3±7.0 μg/L (24 h post-dose).[27] When the effect of benralizumab on sputum eosinophils was investigated, it was found that, when administered intravenously (1 mg/kg) or subcutaneously (SC, 100 mg or 200 mg), benralizumab significantly reduced the percentage of sputum eosinophils in asthmatic patients.[28]

An additional study used a mathematical algorithm that predicts sputum eosinophils from complete blood count to select patients according to their phenotype. Non-eosinophilic patients were randomised to placebo or benralizumab (SC 100 mg) and eosinophilic patients were randomised to placebo or three doses of benralizumab (SC 2 mg, 20 mg, or 100 mg).[29] The primary results showed that, in the eosinophilic group, there was a significant rate reduction in the exacerbation rate with benralizumab 100 mg versus placebo (0.34 versus 0.57, 41% reduction, 80% CI: 11–60; p=0.096), but not in the 2 mg or the 20 mg group. In patients with a baseline blood eosinophil cut-off of at least 300 cells/μL, exacerbation rates in the benralizumab group were lower than in the placebo group (20 mg: 0.30 versus 0.68, 57% reduction, 80% CI: 33–72, p=0.015; 100 mg group: 0.38 versus 0.68, 43% reduction, 80% CI: 18–60, p=0.049). There was also a significant improvement in FEV_1 in the non-eosinophilic group and the eosinophilic group at all doses, as well as in patients with baseline blood eosinophils ≥300 cells/μL.[29] ACQ-6 scores significantly improved in eosinophilic and non-eosinophilic patients and in patients with baseline

blood eosinophils ≥300 cells/μL treated with benralizumab at all doses.[29] Treatment-emergent adverse events occurred in 277 (72%) of 385 participants receiving any benralizumab dose, compared with 143 (65%) of 221 receiving placebo. Most adverse events were mild-to-moderate in severity, indicating that benralizumab had an acceptable safety profile at all doses.[29]

These early Phase IIb findings show the potential of benralizumab in treating difficult-to-treat patients and support further clinical development of benralizumab as a potential novel anti-IL-5 therapy that may affect exacerbations, lung function, and be of clinical benefit to patients with uncontrolled eosinophilic asthma.

Q&A session

Do patients migrate from one endotype to another depending on the time of sampling?

Prof Djukanovic replied that they probably do not, although this may be dependent upon the intensity of the endotype. Some evidence has shown that levels of sputum eosinophils measured over 1 year were enormously variable. Prof Wechsler added that the endotype is probably fluid and is likely to change depending on the therapy. Blocking Th2 pathways resulted in the animal model switching to a non-Th2 phenotype of asthma, but blocking both of these pathways resulted in better outcomes.

How variable are eosinophil counts? Is variability the same with peripheral eosinophil counts and sputum eosinophil counts? Is more than one analysis required?

Prof Djukanovic replied that sputum eosinophil counts vary, but blood eosinophil counts have not been studied in as much detail. However, it is thought that these are relatively stable. Essentially, this is because the homeostatic mechanisms are less stable in the lungs than they are in the blood. It is important to consider that there is a limited amount of information that has determined that blood eosinophil counts are more stable than sputum eosinophil counts.

What would be the best choice between an anti-IL-5 and an anti-IgE therapy for asthma patients who are atopic and have high eosinophils?

Prof Wechsler stated that there have been no head-to-head studies comparing anti-IgE and anti-IL-5 therapy. Given the specificity for eosinophils, anti-IL-5 would be preferred in eosinophilic asthma. However, some evidence has shown that patients with higher eosinophil counts responded better to anti-IgE therapy. There is a need for a clinical trial that compares biologics head-to-head.

Are exacerbations and lung function improvement related and/or unrelated? And because of the underlying cause in the eosinophils, what type of mechanistic hypothesis do you propose to explain this difference amongst the anti-IL-5 therapies?

Prof Castro replied that it is clear that biologic inhibition of IL-5 has an anti-eosinophilic and anti-inflammatory mechanism, although the evidence is limited about whether this translates to an improvement in airflow. Prof Djukanovic added that there needs to be a head-to-head comparison of the various anti-IL-5 therapies. The higher the eosinophil count then the better the clinical effect. Prof Wechsler also added to the discussion by stating that there is currently an ongoing study in 135 patients with eosinophilic granulomatosis with polyangiitis treated with reslizumab or placebo. This will hopefully confirm results from previous studies that have shown that reslizumab significantly reduces exacerbations and reduces steroid dosing by 75%. The study should be completed next August and results will probably be available by the time of the ERS congress next year.

Is there a flaw in anti-IL-5 therapy?

Prof Djukanovic answered by stating that if the accumulation of eosinophils is not dependent on IL-5 then anti-IL-5 therapy will not work.

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INHALER DEVICES: THE PAST, THE PRESENT, AND THE FUTURE

This symposium took place on 27th September 2015, as part of the European Respiratory Society International Congress 2015 in Amsterdam, Netherlands

Chairperson

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MEETING SUMMARY

Inhaler handling errors negatively impact asthma control and represent one of the most common challenges in asthma management. Overcoming inhaler handling errors can be achieved by increased awareness of errors, more explicit and consistent training in inhaler use, and development of 'intuitive' devices. Clinical studies have shown that dry powder inhalers (DPIs) have better dose consistency and delivery to the lungs, but this is also dependent on device and inhalation technique. In addition, recent clinical studies have demonstrated that Spiromax® is a more intuitive device than Turbuhaler®. In studies analysing patient device mastery, intuitive devices are preferred by patients because they are easy/simple to use and have effective dose delivery.

Are Inhalers Failing Our Patients?

Professor Gary Wong

The inhaled route for the administration of steroids for asthmatics has been used for more than 60 years, and the majority of asthma treatments are directed against Th2-type inflammation. A variety of guidelines to treat asthma are established worldwide. The Global Initiative for Asthma (GINA) guidelines[1] provide stepwise management using pharmacotherapy. Despite the availability of a wide variety of medications, a significant portion of asthmatic patients have poorly controlled asthma. This was shown in the Asthma Insights and Reality in Asia-Pacific (AIRIAP 2) study, in which over 50% of children in this region were found to have poorly controlled asthma.[2] To address this issue, there is a need to understand whether patients with uncontrolled asthma need extra medication or whether they are using their inhalers incorrectly.

Patients who are 75–100% adherent to taking their medication are half as likely to have an asthma exacerbation.[3] In addition, patients who do not use their inhalers correctly are more likely to have poor adherence to their medication.[4] Therefore, the correct use of inhalers is heavily reliant on patient behaviour. Patient behaviour influences correct use of inhalers in three ways: 1) competence: the patient can use the device in the correct manner; 2) contrivance: the patient has the knowledge to use the device correctly, but does not use the inhaler as instructed once they have left the clinic; and 3) compliance: the patient takes the medication as recommended. It is therefore important to have simple devices that are easy both for the physician to demonstrate to patients and for patients to use.[5,6]

In summary, inhaled corticosteroids, delivered via inhaler devices to minimise possible systemic adverse effects, are the standard of treatment for asthma. Ineffective inhaler use resulting in poor asthma control is a major problem for patients with asthma. Factors influencing inhaler technique include the availability of training with the prescribed device(s), patient preference and satisfaction, and their physical ability to use the device.

Improving Patient Outcomes and Adherence in Asthma: All Devices Are Not Equal

Professor J. Christian Virchow

Due to the undesired long-term adverse effects of systemic administration of corticosteroids, inhalation therapy is the most effective targeted treatment for airway diseases. Inhalation therapy provides high local concentrations of medication with low systemic effects. Therefore, the inhaler device itself is crucial for drug delivery. Poor asthma control is often a result of underestimation of disease severity, ineffective treatment guidelines,[7] wrong/incomplete diagnosis,[8] or delay in diagnosis. In addition, further reasons for poor asthma control include poor treatment compliance, wrong inhaler choice, insufficient inhaler instructions, and poor inhaler technique.[7] While there are marginal differences in the efficacy of available medications, the choice of inhaler device and inhaler technique has a huge impact on asthma control and thus the healthcare system costs for asthma patients. Inhaler misuse is associated with decreased asthma stability and therefore good adherence to treatment is not helpful if a patient has poor technique.[9] In a study of children with severe asthma, improving inhalation technique from 65–95% resulted in improved asthma control and a reduction in required daily corticosteroid dose.[10]

Assessing adherence is difficult as several parameters need to be taken into consideration, including patient reports, dose counters, and weighing, all of which carry a degree of imprecision in data reporting. All of these are subject to manipulation: selection bias of the patient population and patients' temporary adherence for the sake of the trial. A recent study analysed patient adherence utilising electronic monitors versus a self-reported questionnaire. The self-reported questionnaire overestimated inhaler use by a mean of 2.2–8.4 inhalations over a 1-week period (limits of agreement: ±15.8–25.6 inhalations).[11] This was a result of over-users under-reporting, and under-users over-reporting, their medication use. These discrepancies may be due to patients forgetting, or trying to please the caregiver by confirming that they followed instructions.

New strategies are being studied to improve adherence. One such study analysed inhaler reminders versus behaviour intervention in which doctors have a personalised discussion with

patients about the necessity of treatment.[12] Electronic reminders were demonstrated to improve adherence at both time points used (6 months and >6 months). In addition, adherence is not the same thing as compliance: patients often do not take their medication once they feel better, which is acceptable provided that the patient achieves his/her personal goals without increasing healthcare resource utilisation. A recent study showed that mild-to-moderate asthmatics can effectively manage their medication themselves, while moderate-to-severe asthmatics have better symptom control while taking their medication regularly.[13]

It is important to utilise the 'most forgiving device' with which there are no crucial errors made during drug delivery. A minimally complicated process of 'exhale–open–inhale–close' is the least complicated, most forgiving technique. In order to improve adherence, the patient's choice of device and technique should also be taken into account. A safety and efficacy study compared Spiromax with Turbuhaler over 12 weeks in which the same medication was used in the two devices (the ASSET study).[14] In this study, patient satisfaction was greater with Spiromax and more patients were willing to continue treatment with Spiromax past the 12-week study period.

In summary, adherence to therapy is an important consideration in asthma management. Allowing patients to choose which inhaler technique they prefer is likely to influence treatment success and should be considered an integral part of asthma management.

Can an Intuitive Device Reduce Critical Errors?

Professor Richard Dekhuijzen

Slow inhalation and (almost) simultaneous activation of the canister is the correct way to use pressurised metered-dose inhalers (MDIs). However, almost 25% of patients with asthma or chronic obstructive pulmonary disease (COPD) use their inhaler incorrectly, which impacts drug delivery, lung deposition, and disease control. For MDIs, 92% of patients fail to use slow, deep inhalation,[15] 54% fail to coordinate inhalation with actuation, 24% have premature cessation of inhalation, and 12% inhale through the nose.[16] In addition, patients also fail to shake their inhaler before actuation or fail to hold the inhaler upright.[15-17] For DPIs, the correct usage is the generation of a forceful and deep inhalation. Failure to achieve this at the start of inhalation results in drug particles being deposited in the mouth and oropharynx.[18] DPI devices are also dependent on correct orientation of the device and inspiratory effort to achieve adequate inhalation volume.[18,19] Errors may lead to insufficient drug delivery, which adversely influences drug efficacy and may contribute to inadequate control of asthma and COPD. Overall, the design of an intuitive inhaler that is simple to understand and easy to open should reduce the number of critical errors.

GINA guidelines[1] recommend that healthcare professionals (HCPs) train and assess patients on device mastery at every visit, and recommend HCP training in device use. A second randomised, cross-over, observational trial (HCP-ELIOT) was performed to compare maintenance of device mastery with Spiromax versus Turbuhaler in HCPs naïve to both devices. HCPs were exposed to the same training levels as patients in the ELIOT study. Overall, significantly more participants achieved device mastery with Spiromax prior to training or after reading the manufacturer's instructions compared with Turbuhaler. In addition, participants using Spiromax required fewer device training steps in order to achieve device mastery compared with those using Turbuhaler. In conclusion, significantly more participants using Spiromax achieved device mastery in fewer steps with fewer errors, although it must be noted that this is an interim analysis of the data.

A Real-Life Inhaler that the Patient Can and Will Use: What Are We Still Missing?

Professor Henry Chrystyn

The key criteria to be considered for any 'real-life' inhaler include that it be effective and well tolerated, easy and simple to use, preferred by patients, cost-effective, and that it provides a consistent dose to the patient.[20,21] Most importantly, it should be a device that patients can and will use.[21] The problems with current inhalers include dose emission variation and common errors in dose preparation and inhalation manoeuvres (Table 1).

Table 1: Problems with inhaler use.

Aspect of inhaler use	Metered-dose inhaler devices	Dry powder inhaler devices
Metered-dose/dose emission	Consistent	Ranges from erratic to consistent
Dose preparation	Errors common	Errors dependent on device
Inhalation manoeuvre	Errors common	Errors common

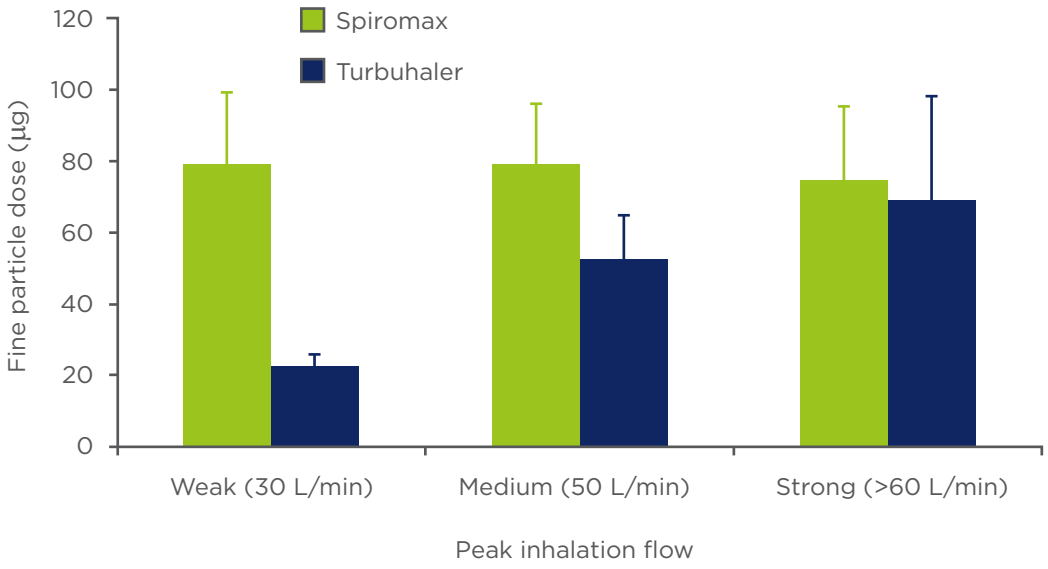

Figure 1: Mean (standard deviation) fine particle dose emission from 320/9 µg budesonide/formoterol dry powder inhaler using different inhalation profiles (weak, medium, and strong peak inhalation flow).

Currently, MDIs are the most commonly prescribed treatment worldwide, with a wide range of products that are cost-effective and have consistent dose emission, but inhalation errors are still common.[17,22-27] Electronic monitoring of training techniques in the use of MDIs revealed that, even after the third attempt, over 54% of patients fail the inspiratory flow criterion.[28] A recent study has shown that there is a significant improvement in asthma control when using an MDI with slow inhalation.[15] In addition, the increased deposition of the drug into the lung observed with slow inhalation can offset any lack of coordination of actuation.[29] However, most patients inhale too fast and the recommended instruction to use an inhalation that is "steady and deep" is subjective and interpreted differently by users and trainers. A recent study has shown that defining this instruction as an inhalation that takes an adult approximately 5 seconds to complete will ensure the required slow inhalation flow when using an MDI. When adult patients with asthma were given this instruction verbally, the result was a dramatic reduction in their peak inhalation flow when using their MDI. This slow flow was maintained when they demonstrated the use of their inhaler 4 weeks later without any further training.[30]

Studies of dose emission for DPIs have shown that dose delivery varies according to the DPI.[31,32] In contrast, analysis of DuoResp® (BF) Spiromax dose emission throughout the life of the inhaler (beginning, middle, and end of life) at three doses (low, medium, and high strength) revealed very consistent emitted doses.[33]

Patient technique for using DPIs can be divided into two categories: the inhalation manoeuvres and dose preparation.[24,26] The incidence of errors with respect to the inhalation manoeuvre is independent of the DPI used. However, DPIs differ in terms of dose preparation.[24,26] Inhalation errors include not exhaling, not inhaling fast, inhaling too short, and not holding the breath. As dose preparation for each device is different, they should not be classified as generic products. The Turbuhaler is associated with two critical errors: 15% of patients performed only a one-side twist, and 18% did not hold the device in the correct orientation when

preparing a dose, which results in the dose not being loaded.[26] Spiromax, on the other hand, can be used in any orientation to achieve dose loading and emission.[33] Dose preparation errors with this device should therefore be lower and its use should be more intuitive.

A recent study has analysed the variability in how patients use inhalation devices across age groups and disease states. Children and patients with COPD were observed to inhale more slowly, and faster inhalation was seen with Spiromax versus Turbuhaler.[34] *In vitro* analysis of fine particle dosing demonstrated that Turbuhaler has a steep flow-dependent dose emission,[31,32] but this study was performed using a vacuum pump, which does not produce physiologically relevant inhalation values. Using inhalation profiles from Spiromax and Turbuhaler studies[34] instead of a vacuum pump revealed that the Turbuhaler is subject to a traditional flow-dependent dose emission while Spiromax delivers a consistent dose regardless of the inhalation profile (Figure 1).[35]

In summary, MDI inhalation technique can be improved by training patients to perform a slow and deep inhalation, in which they actuate a dose and inhale while counting to 4–5 seconds (2–3 seconds with a child). DPIs are subject to dose preparation errors, which can be solved by a device that is intuitive/simple to use and minimally affected by device orientation. Inhalation manoeuvre errors can be minimised by choosing devices that have minimal flow-dependent dose emission.

Q&A session

How do we address the issue that the more devices there are for asthma and COPD, the more difficulties there are for paramedical personnel, primary care physicians, and patients?

Prof Virchow replied that it is not a negative thing to have more options to choose from in order to provide the patient with a device that is reliable and user-friendly to them. It is important to give patients devices requiring the same inhalation technique so as to not create confusion between devices. Research is getting closer to the development of an optimal inhaler and physicians need to try to match inhalers to what patients want. An important topic for the future is to make all drugs available in a single inhaler type instead of having to give different inhalers to one patient. Prof Chrystyn added that there is only one generic MDI. Most DPIs are branded products with different dose preparation steps, and new inhalers should include a range of therapies, including short-acting beta-agonists.

Some MDIs and DPIs resemble one another, so should extra care be taken to instruct patients in preparing a device and using it correctly?

Both Prof Chrystyn and Prof Virchow agreed that it is very important to train patients about the specific techniques and specificities for any inhaler, especially if devices look similar.

Is there any way to address the issue of patient compliance? What do physicians do when patients know how to use a device but choose not to?

Prof Wong replied that it is important to have a good rapport with the patient. You can rely on relatives a little to give an honest answer about inhaler use, but it is also important not to judge when asking about medication usage. He also recommended that physicians listen carefully to the feedback from their patients. It can be helpful to try different devices in order to find something that they are willing to use.

Why is the dose emission lower in the beginning of the inhaler's life and does this have any clinical importance?

Prof Chrystyn replied that it was only slightly lower and was within regulatory ranges. He stated that the reason for this minimal difference is not known, but speculated that it may be because the inhaler contains more in the reservoir at that point.

Is there any future for MDIs?

Prof Chrystyn emphasised that there is a future for MDIs. The main issue is to better train people to use the inhalers. Being able to define a slow and deep inhalation would make a huge difference. Prof Dekhuijzen added that the majority of asthma drugs prescribed worldwide are provided via MDIs.

What should be the current working diagnosis? Should physicians first select which molecule to prescribe or should they pick a device first?

Prof Dekhuijzen suggested that physicians should first think about the device before selecting the type of drug, because there are many drug classes available and minimal differences in efficacy among drugs.

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THERAPY FOR ALPHA-1 ANTITRYPSIN DEFICIENCY: THE EVIDENCE FOR EFFICACY

This symposium took place on 28th September 2015 as part of the European Respiratory Society International Congress 2015 in Amsterdam, Netherlands

Chairperson

Noel Gerard McElvaney[1]

Speakers

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MEETING SUMMARY

Prof McElvaney opened the symposium with a brief overview of the disease history and available treatments to date for alpha-1 antitrypsin deficiency (AATD). He then introduced Dr Reeves, who gave a description of the physiological function of alpha-1 proteinase inhibitor (α1-PI), specifically its effect on neutrophil function in AATD. Dr Parr then discussed the limitations of using forced expiratory volume (FEV_1) to observe lung disease progression, and the development and use of measurements of lung density as an alternative. Dr Seersholm followed with a comprehensive overview of recent clinical studies demonstrating the efficacy of α1-PI augmentation therapy. Dr Chapman gave the final presentation that expanded on this by describing the findings of the randomised, placebo-controlled trial of augmentation therapy in α1-PI deficiency (RAPID) study. The meeting objectives were to present the current treatment landscape for AATD-associated emphysema and the role of α1-PI therapy within this.

Welcome and Introduction

Professor Noel Gerard McElvaney

AATD was first described in 1963.[1] Subsequent studies linked AATD to both familial emphysema[2,3] and liver disease,[4] and also demonstrated a relationship between α1-PI and neutrophil elastase.[5] The first α1-PI therapy, Prolastin®, received FDA approval in the USA in 1987 and received approval in European countries in 1989. The efficacy

endpoint of lung density for α1-PI augmentation therapy was first suggested in 1999 by a Danish/Dutch trial[6] that showed a trend toward the slowing of lung density decline in AATD patients receiving α1-PI augmentation therapy versus placebo. In part as a result of this finding, a statement was published by the American Thoracic Society (ATS) and European Respiratory Society (ERS) in 2003 regarding the standards for diagnosis of AATD.[7] In 2003, Zemaira®, the first second-generation α1-PI product, was granted FDA approval in the USA. Second-generation α1-PI products are highly purified (≥90% α1-PI), with lower infusion volumes and shorter infusion times than their first-generation counterparts.

In 2009, the use of computed tomography (CT) densitometry was encouraged further by the publication of the EXAcerbations and Computed Tomography scan as Lung End-points (EXACTLE) trial, which demonstrated a trend toward slowing of emphysema progression.[8] The RAPID study has since demonstrated the clinical efficacy of the second-generation α1-PI therapy Respreeza® in patients with AATD-associated emphysema.[9] Respreeza has now received EU market authorisation.

Anti-Inflammatory Properties of α1-PI Augmentation Therapy

Doctor Emer Reeves

α1-PI is an acute phase protein predominantly synthesised by hepatocytes. As the main inhibitor of various neutrophil-derived serum proteases, such as proteinase 3, cathepsin G, and neutrophil elastase, its key role is to maintain a protease/antiprotease balance in the airways.[10]

AATD is the only clearly identified genetic risk factor for chronic obstructive pulmonary disease (COPD). The most common allele variant, Z, is produced by a single amino acid substitution in the *SERPINA1* gene that leads to polymer formation and protein retention in the liver, thus reducing concentrations of circulating Z-AAT to approximately 10%.[10]

As the main source of the proteolytic burden, neutrophils are of great importance in the pathogenesis of AATD. α1-PI also regulates neutrophil function and plays a vital role in neutrophil adherence, chemotaxis, degranulation, apoptosis, and associated changes in neutrophil properties in AATD individuals. In addition, neutrophil adherence is activated by leukotriene B4 (LTB4) signalling via BLT-1 receptors.

Confocal microscopy has shown α1-PI bound to the outer membrane of neutrophils,[11] with significantly higher levels associated with the outer membrane of MM (normal control) neutrophils versus ZZ neutrophils, and significantly increased levels associated with the outer membrane of neutrophils in an AATD patient who had received a liver transplant.[11]

The Effect of α1-PI on Neutrophil Adherence, Chemotaxis, and Degranulation

α1-PI has been shown to reduce neutrophil adherence and also exhibit an inhibitory effect on LTB4 response in MM and ZZ genotype neutrophils.[12] Furthermore, it was shown that levels of α1-PI associated with the outer membrane of ZZ neutrophils were lower, but significantly increased following therapy.[12,13]

Increased neutrophil elastase activity was also observed on neutrophils isolated from ZZ individuals with or without COPD. It is possible that neutrophil elastase could trigger the synthesis of LTB4, as these individuals also exhibited higher plasma LTB4 levels.[12] However, augmentation therapy significantly decreased neutrophil elastase activity and lowered plasma LTB4 concentrations.[12]

An increase in neutrophil chemotaxis was observed in patients with AATD who underwent bronchoalveolar lavage.[14] Tumour necrosis factor alpha (TNFα), a factor associated with COPD which causes degranulation of neutrophils,[15,16] has also been found in significantly higher levels on the membranes of ZZ neutrophils compared with those of MM neutrophils.[17] AATD patients receiving α1-PI augmentation therapy exhibited significantly lower levels of TNFα.[17]

Q&A session

Do you think the effects you are seeing are dose-related?

Dr Reeves: A dose effect was found using *in vitro* experiments, where doses of up to 27.5 µmol/L effectively inhibited neutrophil response to IL-8, TNFα, and LTB4. It is difficult to confirm if these effects were inhibited altogether. Certain concentrations of IL-8 will overcome 27.5 µmol/L α1-PI, which is important to allow the neutrophil to transmigrate and kill bacteria.

The Relevance of CT Lung Density for Assessing Emphysema in AATD

Doctor David Parr

FEV_1 has been the gold standard surrogate measure for emphysema, although there are various limitations to this method. A study conducted with several hundred patients over several years found very little FEV_1 decline in patients with both mild and severe disease.[18] Despite the large number of patients, the measure showed broad variability and was not a sensitive measure of disease progression. In order to achieve sufficient power, 494 subjects per arm would be required to detect a treatment effect over 3 years if FEV_1 was used as an outcome measure.[19]

So-called 'modern definitions' of emphysema have come to recognise dilatation of lung air spaces and destruction of the walls,[20] along with the importance of excluding conditions that have obvious fibrosis, although this can be difficult to distinguish from emphysema.[21] More recently, the principles of design-based stereology recognise the importance of measuring lung dimensions in inflation.[22] Panlobular and centrilobular emphysema, which present the same basic structure seen in histopathological images of the lungs, can be distinguished using CT scans. In CT imaging, each pixel in the images relates to a volume of lung tissue, hence the term voxel is used, and each voxel has a value which is a measure of the density of the corresponding volume of lung tissue. Voxel distribution histograms can therefore be used to generate densitometric indices, while the percentile point method for monitoring over time has been used more recently due to its superior sensitivity.[23] These methods are of great importance in quantifying emphysema and may also help to inform patients about the extent and progress of their disease. Emphysema distribution can also influence where treatment effects are seen. For example, Prolastin-treated patients showed the greatest reduction in loss of lung mass in the basal region of the lung when compared with the placebo group, although this was not statistically significant.[23]

The changes in lung size and dimensions that occur when breathing may affect precise measurements of lung volume. Assuming that lung mass is preserved whilst breathing, a linear volume–density relationship can be shown and the density measurements of CT scans can be adjusted according to changes in lung volume.[24] If volume is standardised (constant) then we can calculate the density change, which should indicate a change in lung mass.[24]

The Alpha-1 Detection and Programme for Treatment (ADAPT UK registry) programme measured changes in lung volume and compared this with changes in lung density over a 2-year period. A linear relationship was found between the two, the results of which indicated a loss of lung mass in the patients[25] – a relationship also demonstrated by the EXACTLE trial data, which show a reduction in lung mass when using Prolastin.[8]

As CT directly correlates with the histopathological gold standard for emphysema assessment when scanning at full inspiration, as well as with lung function, we now know that CT is a clinically relevant outcome measure. CT lung density reduction has proven to be linked to lung mass reduction and a deterioration in clinical measures, even though these studies are not powered to demonstrate a treatment effect using physiological outcomes.

Q&A session

One of the concerns with CT has been radiation dose. Would you like to comment on that?

Dr Parr: The protocols developed have reduced the radiation dose further while maintaining good reproducibility, even at low doses. However, errors in densitometric analysis may arise in patients with a large body mass index when very low dose protocols are used. With increasing use of CT in clinical practice, there has been concern regarding inappropriate use of imaging for diagnosis and the associated radiation risks, but the radiation dose of densitometric scans is significantly lower than that of diagnostic imaging.

Where do you see the advances in CT over the next number of years in this area?

It is likely that more studies will combine inspiratory and expiratory images, which will allow mapping and registering of different parts of the image together, even when there is movement. Further improvements in magnetic resonance imaging may well displace CT as the gold standard measure of emphysema.

Efficacy of α1-PI Augmentation Therapy – a Review of Evidence

Doctor Niels Seersholm

It was first shown in 1987 that weekly doses of α1-PI augmentation therapy can significantly increase α1-PI plasma levels.[26] Despite the inability to do large-scale, long-term studies based on lung function, the α1-PI treatment was approved in several countries following this study.[25-28]

A decade later, a Danish/German registry study followed up on these findings by observing FEV_1 decline over time in patients who were treated with α1-PI augmentation therapy.[29] German patients who were treated with augmentation therapy exhibited a significantly slower rate in FEV_1 decline compared with the non-treated Danish patients ($p<0.04$).[29]

These findings were subsequently echoed by a larger American registry study of 1,129 patients who had never, always, or partly received augmentation therapy.[18] THE ATS/ERS guidelines published as a result of the aforementioned studies advised that augmentation therapy should be used for patients with FEV_1 between 30% and 65% of that predicted.[7]

A year later, a placebo-controlled, parallel, double-blind Danish/Dutch study of α1-PI versus placebo[6] reported that pulmonary function tests showed a faster rate of FEV_1 decline in the active treatment group compared with placebo. However, CT scan results did show a slower change in lung density and a trend toward benefit in the active treatment group ($p<0.07$).[6] It was clear from this study that power calculations based on annual decline in FEV_1 are not feasible due to the large number of patients required for this method.[6] CT lung density scans may better facilitate future randomised controlled trials as lower numbers of patients are needed to power the analyses.[6]

The role of CT densitometry was further investigated a decade later in the EXACTLE trial.[8] Similarly to the Danish/Dutch study, the trial revealed a reduced rate of lung density loss in the treatment arm versus placebo ($p<0.07$). No effect on lung function, quality of life, or mortality was observed, indicating again that CT densitometry is a more sensitive outcome measure than physiology and health status.[8]

The RAPID Trial: Evidence for the Efficacy of α1-PI Augmentation Therapy

Doctor Kenneth R. Chapman

For the RAPID study, 180 patients were randomised in a double-blind fashion and treated with either 60 mg/kg per week of a highly purified α1-PI (Respreeza) or placebo over the course of 2 years. Patients were well-matched for baseline characteristics and CT scans were performed at baseline, 3, 12, 21, and 24 months. A higher withdrawal rate was seen in the placebo group due to slightly higher rates in death, adverse events, and withdrawn consent.[9]

The RAPID trial is the first adequately powered, randomised clinical trial that has been able to demonstrate statistically significant efficacy of α1-PI in slowing emphysema progression. The main outcome of the RAPID trial was that α1-PI therapy slowed the progression of emphysema as measured by CT lung density, which is a more sensitive measure of disease progression in AATD-associated emphysema than conventional lung function parameters. Over a 2-year period, the difference in annual rate of decline in adjusted CT scan lung density was 0.74 g/L in favour of α1-PI when measured at full inspiration (total lung capacity [TLC]; Figure 1). The change in lung density was significantly different between treated and placebo groups ($p=0.033$, two-sided test).[9]

The reduced decline in lung density, i.e. slower rate of lung tissue destruction, under treatment with Respreeza is expected to extend the time towards terminal respiratory function (i.e. death, lung transplantation, or severe respiratory dysfunction). Results from the RAPID trial were extrapolated over time to calculate the time until a terminal lung density of approximately 20 g/L would be achieved. This limit of 20 g/L was the average level of lung density of five RAPID trial patients who exited the study due to death, lung transplantation, or severe respiratory dysfunction.[9] Results from the RAPID trial suggest that the time to predicted terminal respiratory function is 12 years in placebo subjects, but is increased by approximately 6–18 years in Respreeza-treated patients (Figure 2).[9]

The RAPID trial was not large or long enough to assess differences in traditional lung function outcomes. Although no statistically significant differences between the augmented and non-augmented groups were observed in terms of FEV_1 or diffusing capacity of lung for carbon monoxide

(DLCO), statistically significant cross-sectional correlations were found between CT scan density and DLCO and FEV_1 as a percentage of predicted and St George's Respiratory Questionnaire activity scores both at the beginning and the end of the study, respectively.[9]

Patients who completed the 2-year treatment and observation period of the RAPID trial outside the USA were invited to participate in the RAPID Extension trial for an additional 2 years. All participants in the RAPID Extension trial received Respreeza at 60 mg/kg body weight per week, including those who were on placebo during the RAPID trial. The results presented below (Figure 3) are based upon the 97 patients who, as of December 2013, had completed both the RAPID and RAPID Extension trial. Patients in the Early-Start cohort maintained a therapeutic effect across 4 years of treatment, whereas patients in the Delayed-Start cohort showed a clear inflection in the slope of decline, i.e. a slower rate of lung density decline after switching to Respreeza. Initial lung density loss in the Delayed-Start cohort during placebo treatment from Months 0–24 was not regained. The results support the conclusion of a disease-modifying effect of Respreeza.

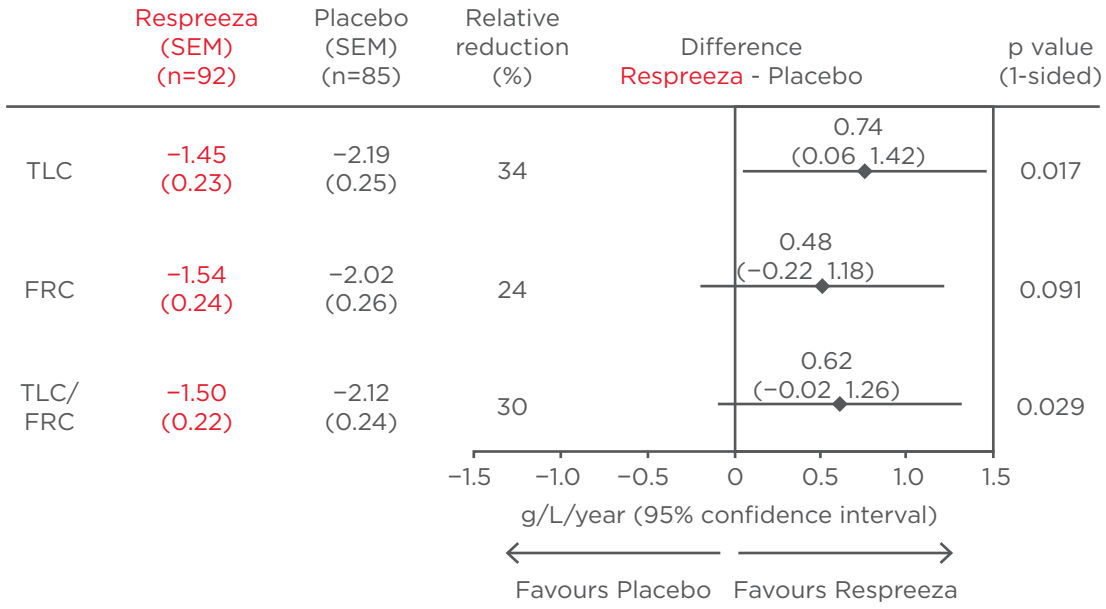

Figure 1: Primary outcome measure in the RAPID trial: difference in annual rate of decline of adjusted P15 (intention-to-treat population, physiologic adjustment).[9]

FRC: functional residual capacity; SEM: standard error of the mean; TLC: total lung capacity.

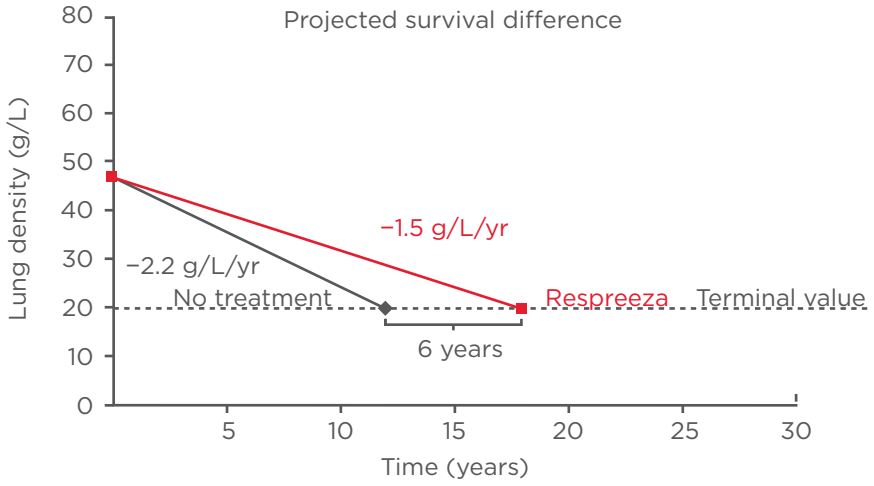

Figure 2: Potential life extension projected using RAPID study data.[9]

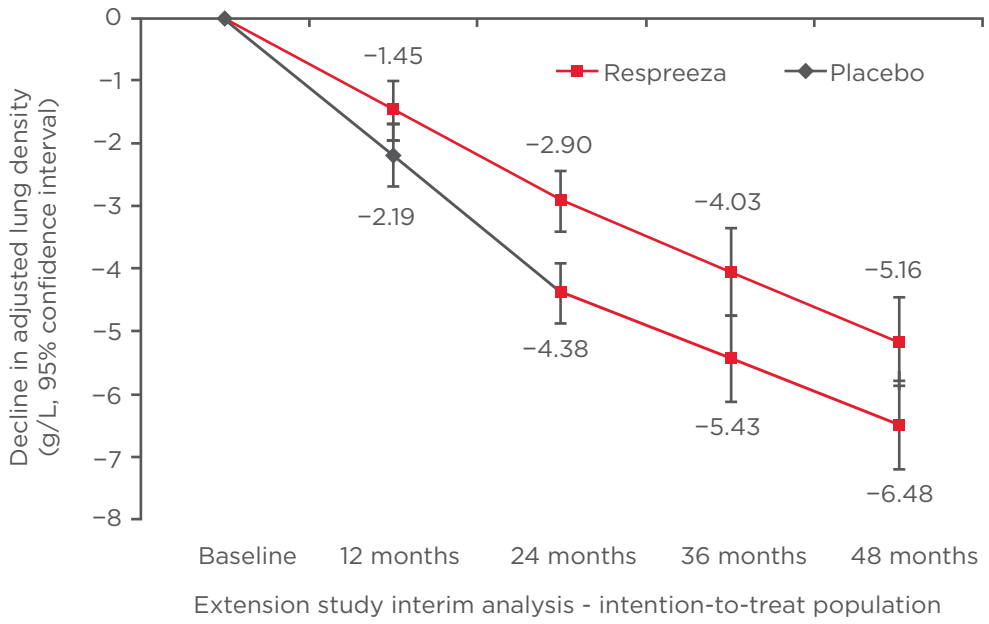

Figure 3: Decline in adjusted lung density over time (change from baseline).[9]

When considering whether further trials are required, it is not only important to consider the reproducibility of available data, but also the time required for patient recruitment and for the study to be carried out. For example, patient recruitment for the RAPID study took 7 years, along with the 2 years taken to conduct the trial. These results are very consistent with both the Danish/Dutch[8] and EXACTLE[6] trials in terms of decline in lung density (P15 decline TLC, g/L per year) as measured by CT scanning.[9]

Q&A session

When would you start augmentation therapy in a patient with AATD?

Dr Chapman stated that traditional measures of lung function are used as guides and that he would not wait for a further loss of FEV_1 to initiate therapy if the patient's FEV_1 at the time of diagnosis was below the predicted value. Dr Chapman then wondered whether a CT scan should also be performed, and if therapy might be initiated if emphysema were present radiologically while FEV_1 was relatively normal. Dr Chapman's viewpoint was that the presence of emphysema on a CT scan suggests that the patient has suffered from the loss of lung parenchyma, and that he would want to initiate therapy if coverage could be obtained.

Dr Seersholm then expressed his disapproval of the rule that the FEV_1 should be between 30% and 65% of that predicted, stating that augmentation therapy should be initiated when deterioration/holes in the lungs are shown by CT scan. He then stated the importance of defining the emphysema from the scan.

How do you think considerations of reimbursement influence the decision to initiate therapy?

Dr Chapman commented that the costs of augmentation therapy are similar to those of blood products for haemophilia treatment, but due to the immediate danger surrounding these bleeding events, the need for these products seems more apparent. The loss of lung function resulting in death or transplantation is so gradual that the need for therapy can be underestimated.

In the data shown by Dr Chapman, the higher values in the nadir level and α1-PI concentration seem to be matched with a better response. What are your thoughts on changing the current recommended dose of 60 mg/kg per week?

Dr Chapman recognised that an increase in dose will increase the cost, although this could be offset if a better result is seen. A dose of 120 mg/kg per week is currently under study. The investigation of other delivery schemes or schedules may be necessary, such as self-administration or more frequent and smaller doses to achieve the same serum level. However, Dr Chapman stated that more research is required before a decision is made on this.

How close did you get to a normal non-alpha rate of CT scan density decline in the RAPID trial?

Dr Parr stated that in future studies there will be a need to individualise and monitor the doses for patients. He mentioned that CT densitometry may not be the best method for this purpose, although using a biomarker may prove difficult in practice.

How do exacerbations and infections affect CT lung density measurements?

Dr Parr commented that most of the studies have a strict protocol with a window between any event and imaging, and as a consequence most of the exacerbations would not have been close to the timing of the CT scan. However, he stated that other factors have been known to affect CT lung density in observational studies, i.e. the development of pulmonary oedema brought on by a cardiac event or the development of pneumonia. Dr Parr then stressed the importance of contextualising any diagnostic test with the clinical situation and patient's medical history in order to avoid errors. This principle should be adopted when using CT as a tool to measure rather than diagnose.

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Click here to view the online CME activity on 'Clinical Evidence for Augmentation Therapy in Patients with Emphysema due to Alpha-1 Antitrypsin Deficiency (AATD)', available on Medscape.

ADVANCES IN AMBULATORY OXYGEN WORKSHOP AND LONG-TERM OXYGEN THERAPY IN REAL-LIFE PRACTICE

The practical workshop took place on Sunday 27th September 2015 and the symposium took place on Monday 28th September 2015, as part of the European Respiratory Society (ERS) International Congress 2015 in Amsterdam, Netherlands

PRACTICAL WORKSHOP

Chairperson

Enrico Clini[1]

Speakers

Enrico Clini,[1] Daniel Veale,[2] Joao Carlos Winck[3]

MINI SYMPOSIUM

Chairperson

Jean-François Muir[4]

Speakers

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MEETING SUMMARY

The practical workshop presented recent advances in the field of ambulatory oxygen (AO), with experts discussing identification of patients who would benefit from AO, as well as current trials to measure specific benefits of AO in chronic patients. In particular, AO prescription in clinical practice and developments in pulsed-dose delivery of AO as a more efficient method of oxygen delivery were extensively discussed. After audience questions, the attendees had the opportunity to handle the AO systems on display in order to gain greater insight into their functionality and wearability, which should assist them in providing the most appropriate device for each patient.

The symposium addressed considerations required when prescribing long-term oxygen therapy (LTOT). Dr Kampelmacher reviewed current indications for LTOT, emphasising the importance of accurate assessment of patients for LTOT, optimisation of oxygen dose, and patient education. Dr Vivodtzev discussed the evidence for LTOT in patients with exercise-induced desaturation, the role of portable oxygen concentrators, and the optimisation necessary to benefit from their use. The symposium concluded with a health economic study presented by Dr Little, demonstrating the cost benefits of a reform of the Scottish healthcare oxygen supply service.

Advances in Ambulatory Oxygen

Professor Enrico Clini

Prof Clini opened the workshop by reviewing which patients should be given AO. The most recent guidelines recommend that AO should not be routinely prescribed for all patients needing stationary oxygen supplementation, but should be offered to improve walking and exercise within a pulmonary rehabilitation course, with muscle training encouraged in patients with reduced lung function.[1]

Patient selection is an important unresolved issue. Lung function measurements have some predictive value for low (FEV_1 <50%) and high (FEV_1 ≥80%) scores,[2] but do not address those with intermediate scores, and there is variation in oxygen saturation between patients who have the same lung function. A scoring system for identifying patients at risk of walking-induced desaturation has recently been developed, which takes both resting oxygen saturation and lung function into account.[3] However, the type of exercise used to test for exertional desaturation is also a contributory factor.[4]

The efficacy of LTOT for chronic obstructive pulmonary disease (COPD) patients who are normoxic at rest but who desaturate during physical activity was identified as an important issue for future research.[5] In clinical practice, AO is often prescribed to patients outside of the guideline recommendations in order to enable them to carry out activities of daily living. While these patients report improved quality of life, such as reduced breathlessness and tiredness, AO does not appear to fully improve ability to exercise nor to increase survival.[6] The functional limitations of theoxygen delivery system (e.g. portability of oxygen cylinders) may contribute to this, but providing AO to patients who will not benefit has cost implications both for patients and for the healthcare system. Current research includes the Long-term Oxygen Treatment Trial (LOTT, NCT00692198) study of the survival and quality-of-life benefits of LTOT versus no LTOT in COPD patients who are normoxic at rest but who desaturate during exercise; results are yet to be reported. Results are also awaited from the OM-COPD trial (NCT01722370) investigating the physiological benefits of AO therapy in this COPD patient population.

Ambulatory Oxygen Prescription in Practice

Doctor Daniel Veale

As with any therapy, AO should be appropriately prescribed for each patient with precision, specifying the dose, frequency, and timing. There are many questions that need to be answered in order to define these parameters for AO. Reliability in the measurement of blood gas is needed, as well as a standard definition of the level of desaturation at which a patient should be given AO (currently there is variation between clinicians regarding which level should be considered significant).[7] The oxygen dose may also be important given the potential for oxygen toxicity.

The cost of AO to the healthcare system (in the USA, for example, one million Americans are on LTOT at a cost of over $2 billion per year)[8] necessitates that AO is only prescribed to patients who will benefit, and that oxygen is used efficiently. The key recommendations in prescribing effective and efficient oxygen therapy have been identified by the LTOT Consensus as: education of all stakeholders, technical optimisation of LTOT delivery systems, evaluation of optimal oxygen delivery in individual patients, and patient compliance with the therapy.

Patient compliance with LTOT can be influenced by disease severity, being prescribed oxygen for >15 hours, acceptance of treatment, availability of an ambulatory device, and patient education.[9] The prescriber can address these factors by ensuring that the indication for the therapy is correct, that the patient is educated, and that there is good medical and technical follow-up in the use of their device. Negotiation with the patient to modify their lifestyle is also part of good prescribing practice.

Ideally, portable oxygen devices would be small, silent, easy to handle, validated, and tested. Trials comparing the XPO_2 and $SOLO_2$ pulsed-delivery systems with continuous-flow oxygen in patients with COPD showed no significant difference in the overall improvement in exercise ability (6-minute walk test [6MWT]), but there was significant variability in effectiveness between individual patients (Figure 1).[10,11] Each prescription should thus be individualised and validated by an ambulatory walk test to determine the effective setting. While the XPO_2 and $SOLO_2$ portable concentrators were similar in clinical performance to continuous liquid oxygen, they gave patients more freedom of movement to continue physical and social activities.

Figure 1: Oxygen saturation during 6-minute walk test (6MWT) with XPO_2 pulsed-dose oxygen delivery (A) or $SOLO_2$ pulsed-dose oxygen delivery (B) versus C100 continuous-flow oxygen delivery.
Note the individual variation in results indicated by the error bars.
Reprint permission requested from Elsevier (Couillard A et al. Rev Mal Respir. 2010;27:1030-8).

The Use of Pulsed Dose in Ambulatory Oxygen

Professor Joao Carlos Winck

Pulsed-dose oxygen delivery is an 'on-demand' delivery system for low-concentration oxygen therapy[12] that can provide the same oxygen saturation to patients at a much lower volume per minute than continuous-flow oxygen. Pulsed-dose systems aim to increase the oxygen tank duration and battery life of the concentrator and allow adjustable oxygen delivery, as well as smaller, more wearable machines. Delivering the oxygen bolus early in inspiration provides patients with the same oxygen concentration as continuous-flow oxygen.[13] In models of lung function, the fraction of inspired oxygen (FiO_2) is affected by the interaction of the patient's inspiratory flow pattern and flow from the oxygen source.[13] With a constant flow of oxygen, it is estimated that the final third of inspired volume remains in 'dead space' and does not reach the alveolar region of the lungs to participate in gaseous exchange. With pulsed-dose delivery, triggered by the patient's inspiratory effort, no anatomical reservoir is established and the FiO_2 is not reduced.[13]

Pulsed-dose devices have varying characteristics, such as the minute volume delivered at different pulse frequencies or their oxygen delivery performance in normal and COPD-affected lung models,[14] and their performance in clinical practice should be evaluated. Previous studies have shown that pulsed-dose oxygen during exercise can provide similar oxygen saturation to continuous flow,[15] although a comparison of four different demand oxygen delivery systems found significant differences in performance, with better performance shown by the devices that delivered a bolus of oxygen at the onset of inspiration.[16]

Several trials comparing pulsed-dose oxygen with continuous-flow oxygen have found comparable clinical efficacy, although patients preferred the portable devices.[10,17,18] During exercise, a 3-fold increase in oxygen flow compared with resting levels is recommended.[17] Clinical evaluation of different oxygen concentrators for preventing desaturation during the 6MWT in patients with COPD found differences in performance,[19] which reinforces the recommendation for evaluating efficacy of the individual patient's prescription.

Fewer studies have been performed on the efficacy of nocturnal pulsed-dose oxygen delivery in patients with COPD and nocturnal hypoxaemia. An early comparison found on-demand oxygen delivery was comparable to continuous-flow oxygen in the majority of patients,[20] which was confirmed by a more recent study using a portable concentrator.[21] A Spanish study comparing the use of a single portable pulsed-dose device with combined use of stationary and portable oxygen delivery in patients with COPD found that patients preferred using the single pulsed-dose device, but also found that hypoxaemia was more frequent with a single device, especially at night.[22] Individual patient titration of settings, using an oximeter to evaluate oxygen saturation, would be recommended for nocturnal use, although there are not sufficient data at present to make recommendations for calibration of night-time oxygen delivery with pulsed-dose devices.

In a study simulating air travel, comparison of the performance of several pulsed-dose oxygen delivery devices found that patients needed to use the maximum settings in order to maintain oxygen saturation, which rapidly drained the batteries.[23] While the portability of pulsed-dose oxygen delivery can make travel easier for people with COPD, these findings are useful to take into account when considering air travel (Figure 2).

Q&A session

Could the panel comment on progress with oximeter-controlled pulsed-dose oxygen flow system devices?

Prof Winck answered that there is only one system commercially available at present, but that the technology would be developed more widely as oximeter control made good sense. For clinicians, it made evaluation of efficacy and trialling the device's performance in patients much easier.

Is it important for the patient to be in a stable state before starting LTOT? Or can it be started while the patient is still in an exacerbated state, before they leave hospital?

Prof Veale answered that the recommendation for patients to start LTOT when stable is due to the original trials of LTOT, which were carried out in patients who were stable. He felt that it was worth giving LTOT to patients during exacerbations and in hospital.

Figure 2: Following the audience questions, attendees were invited to a hands-on demonstration of ambulatory oxygen delivery devices.

Long-Term Oxygen Therapy in Real-Life Practice: Introduction

Professor Jean-François Muir

LTOT has entered a new era as a result of technological developments such as portable oxygen concentrators, concentrator-compressors, and, in the future, concentrator-liquefiers. The smaller size of these oxygen delivery systems can improve patients' mobility and quality of life. Recent recommendations by the French government specified the type of equipment that should be prescribed for a patient's particular oxygen needs,[24] which have resulted in increased use of portable oxygen concentrators and decreased use of liquid oxygen tanks, with reduced costs to the healthcare system.

Current Indications of Long-Term Oxygen Therapy

Doctor Mike Kampelmacher

Dr Kampelmacher discussed current guidelines for prescribing LTOT[1] to identify which patients will benefit from which type of oxygen therapy. Oxygen therapy is prescribed for hypoxaemia, defined as resting daytime PaO_2 ≤7.3 kPa,[1] and not for breathlessness alone, as there is no evidence that oxygen improves breathlessness. Hypoxaemia can be measured most easily by pulse oximeters, but more accurately by arterial blood gas (ABG) measurements; pulse oximetry alone should not be used to assess patients for LTOT prescription.[1]

When prescribing oxygen, clinicians should be aware of, and educate patients about, the risks of fire (especially among patients who smoke), explosion, and freezing with gaseous and liquid oxygen, as well as the possibility of toxicity, if FiO_2 is greater than 0.4, and hypercapnia.[25,26] However, hypercapnia should not prevent the treatment of hypoxaemia.

The prescription of LTOT is indicated to improve oxygenation in patients who have been given short-term oxygen therapy to treat hypoxaemia, or electively in patients with persistent low oxygenation.[1] The assessment for LTOT is by ABG measurement in the absence of supplemental oxygen in patients who have been clinically stable for around 8 weeks since their last exacerbation. Patients should be reassessed and informed that their LTOT may be discontinued if blood gas assessments show clinical improvement.[1] In some cases, LTOT is also indicated in patients with exercise-induced hypoxaemia or nocturnal hypoxaemia.

The Nocturnal Oxygen Therapy Trial (NOTT) and Medical Research Council trials in patients with COPD or chronic bronchitis and emphysema, respectively, showed significantly increased survival in the LTOT arms.[27,28] The hypoxaemia indications for prescribing LTOT are based on these trials, with subsequent studies confirming the survival benefit of LTOT given for at least 15 hours per day.[29] The evidence for other benefits, such as reduced pulmonary vascular resistance, reduced haematocrit, reduced hospital admissions, improved quality of life, improved exercise tolerance, and improved neurophysiological functioning, is not as robust due to being based on smaller studies.

When prescribing LTOT, clear instructions should be given to patients regarding the aims and effects of the treatment and the potential complications and dangers, and a follow-up visit by a specialist nurse should be carried out within 4 weeks of initiating therapy. The oxygen flow rate should aim to give patients PaO_2 levels of 8.0–9.3 kPa or SaO_2 levels >90%, achieved by pulse oximetry titration. Ambulatory and nocturnal oximetry may be performed to allow more accurate flow rates to be prescribed for exercise and sleep, respectively,[29] as some patients who are adequately oxygenated during the day may become desaturated during sleep.[30] Home oxygen therapy can be withdrawn from patients who smoke if the risks are considered to be too high.[27] Furthermore, there is evidence that patients who continue to smoke while on LTOT may have worse survival.[31]

Prescription of LTOT for moderate hypoxaemia is not indicated in the British Thoracic Society guidelines, as there is no evidence for a survival benefit. A recent study, the National Emphysema Treatment Trial, suggested that LTOT may be associated with worse survival in patients with moderate hypoxaemia.[32] The LOTT study aims to determine the effect on mortality and hospitalisation in patients with COPD and moderate resting hypoxaemia, or normoxia and exercise-induced desaturation, with results expected during 2015.[33]

Long-Term Oxygen Therapy During Exercise

Doctor Isabelle Vivodtzev

Providing AO to those with chronic respiratory failure allows patients to exercise without becoming hypoxaemic, and exercise is a key part of pulmonary rehabilitation in patients with COPD. Currently, there is some debate as to whether normoxic patients who only desaturate during exercise should be given LTOT.[1,34]

It has been shown that AO improves quality of life in patients with COPD.[35] Initial portable oxygen delivery devices (liquid or gaseous oxygen) had drawbacks to their use, in particular the dependence on a delivery service.[36] Pulsed-dose delivery devices were developed in order to reduce oxygen requirements and improve portability, and demonstrated similar performance to continuous-flow in patients at rest.[37] However, the clinical efficiency of pulsed-dose oxygen delivery devices versus continuous-flow oxygen during exercise is controversial.[38] The portable oxygen concentrator is an alternative technological development, which has potential advantages for AO in that it is free of the constraints of a delivered oxygen supply, has fewer safety risks, costs less, and could offer the patient more autonomy during travel. However, a study comparing devices found that the efficacy appeared to vary depending on the disease pathology (COPD or interstitial lung disease), ventilatory patterns were different between pulsed-dose and continuous-flow, and there were technological and technical differences in performance between devices. Crucially, the bolus of oxygen delivered was often chosen arbitrarily and not adjusted during exercise.[39]

Initial portable oxygen concentrators have undergone recent improvements to give more efficient and robust devices. Larger concentrators for autonomous home-based filling now provide further choice to patients. Tests of new oxygen concentrators show equivalent clinical efficacy between pulsed-dose delivery of liquid oxygen and pulsed-dose delivery from an oxygen concentrator in exercise tests. However, the wide variation seen between individual patients necessitates titration of the dose,[10] and clinical studies are needed to identify more precise methods of titration with pulsed-dose delivery.

AO provision needs to be tailored to patients' needs, including their level of activity.[40] Recent French recommendations are for liquid oxygen only in active patients needing more than 3 L/min oxygen, whereas portable or transportable oxygen concentrators are recommended for less active patients who need less than this amount. The range of portable oxygen concentrators now available makes it possible to suit the device to the patient's needs for autonomy, their level of activity, and their level of hypoxaemia.

Health Economic Aspects of Long-Term Oxygen Therapy

Doctor Stuart Little

Dr Little presented preliminary findings from a health economic study of the HomeFill oxygen concentrator system in the Scottish health service. The region studied, Dumfries and Galloway, was a largely rural, sparsely populated area where patients were often remote from healthcare resources. Originally, the system for oxygen provision was a mixture of hospitals with a national oxygen provision service, and primary care and community pharmacies with private provision of oxygen delivery devices. In primary care, inappropriate oxygen prescription (e.g. for breathlessness only) was an issue.

An exploratory study (n=22) of oxygen-conserving, pulsed-dose delivery devices in the Dumfries and Galloway region showed a clear increase (40%) in time spent outside the home and a 50% reduction in oxygen cylinders used, thus providing quality-of-life benefits and financial savings. Another small study (n=20) of the HomeFill oxygen concentrator system in the same region found it to be very popular with patients, who reported increased freedom and confidence and decreased concern about supply. The cost reduction to the healthcare system, including reduction in transport and fuel costs, was estimated at 77%.[41]

In 2013, the National Oxygen Project was established in Scotland to provide a nationally coordinated service with a contracted service provider, instead of the previous pharmacy-led, regionally organised system, offering both pre-filled oxygen cylinders and home refillable cylinders (the HomeFill system). This was a more robust system, developed to be more cost-effective, and involved clinicians to ensure a patient-centred service. The reform included development of a single, consistent care pathway. The National Oxygen Project aimed

to benefit patients by providing an accurate diagnosis, ensuring prescription of the most appropriate mode of treatment, offering equal access to treatment for all, focussing treatment on the patient's needs with planned follow-up, and improving quality of life. The system also benefitted the clinician, being consistent and simplified, and offering electronic prescribing and a range of modalities, as well as cost benefits.

A survey of HomeFill users following implementation of the new system gave similar results to the earlier exploratory study. All patients (100% of 450 respondents) found it easy to use and rated the quality of service as 'as good as or better than the previous oxygen service'. In patients who left the home more than four times per week, there was a 50% increase in time spent away from home, and 92% of patients reported an increase in quality of life. The cost reduction compared with the previous system was estimated at 77%.[42] These findings led to a full health economic analysis of the HomeFill system compared with use of DD-size oxygen cylinders. The model extrapolation for Scotland estimated savings of €2 million per year, although this was thought to be an underestimation and a sensitivity analysis suggested savings of €6 million per year.

Q&A session

How many of the audience titrate oxygen therapy at night systematically?

Most clinicians do not titrate oxygen use at night, but prescribe a set amount of oxygen. Those who do are likely to be those for whom home oximeter use is reimbursed, and the use of an oximeter in the home setting is an ideal opportunity for data collection.

How would the panel treat a patient with mild hypoxaemia and exercise dyspnoea?

The NOTT study showed poorer survival in patients with breathlessness using LTOT, but this could be because the breathlessness was linked to other comorbidities that caused increased mortality.

Dr Vivodtzev added that the patient's lifestyle and oxygen needs are important, and there is financial pressure to reduce liquid oxygen consumption. It is worth considering what other sources of oxygen the patient could use, and trialling different ones in the patient with exercise tests. Since different exercise tests have differing oxygen requirements, the patient's oxygen needs should ideally be evaluated in the home or during daily living activities.

Will the Scottish system spread due to its marked economic benefits?

In setting up the Scottish standardised oxygen assessment service, the service providers and the organising team for the national service worked together to develop an efficient, effective service, and consequently the patient response has been good. While one could hope it would set a model for the UK, NHS England works somewhat differently. It is worth noting that the private care and primary pharmacies were resistant to the national reform of oxygen services in Scotland, as they stood to lose revenue from the prescribing of oxygen.

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LONG-TERM NIV IN COPD – WHO AND WHEN?

This symposium took place on 27th September 2015 as part of the European Respiratory Society International Congress 2015 in Amsterdam, Netherlands

Chairpersons and moderators

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Speakers

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Round-table discussion panel

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MEETING SUMMARY

Dr Wijkstra opened this symposium on long-term non-invasive ventilation (NIV) in the treatment of chronic obstructive pulmonary disease (COPD). Dr Köhnlein presented data from a recent randomised controlled trial (RCT) of NIV for the treatment of severe stable COPD.[1] Dr Cheval discussed the use of telemonitoring in French patients with COPD. The meeting concluded with a round-table discussion on the international practice of home mechanical ventilation (HMV) for COPD, moderated by Dr Wijkstra and Prof Windisch with contributions from Dr Köhnlein, Dr Nava, Dr Hart, and Prof Pépin.

Introduction

Doctor Peter Wijkstra

Dr Wijkstra welcomed the audience to the ResMed-sponsored satellite symposium on NIV for COPD. The audience were invited to engage in discussion with the speakers at the end of each presentation.

NIV for Chronic COPD – When and How?

Doctor Thomas Köhnlein

There are currently no universal guidelines for the use of NIV in patients with COPD, but a number of national guidelines exist. For example, the German

Society for Pneumology (DGP) published guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure (CRF) in 2010.[2] These guidelines are expected to be updated in 2016 and an English translation may be downloaded from www.pneumologie.de. The DGP guidelines list five criteria that could lead to chronic NIV in COPD patients with CRF:[2] 1) hypercapnia, respiratory acidosis, and acute exacerbation; 2) hypercapnia and post-acute ventilator therapy; 3) repeated (at least two per year) severe exacerbations needing hospitalisation with respiratory acidosis; 4) chronic elevated daytime arterial carbon dioxide pressure ($PaCO_2$) ≥50 mmHg; 5) nocturnal $PaCO_2$ ≥55 mmHg or partial pressure of transcutaneous carbon dioxide ($PtcCO_2$) increase ≥10 mmHg overnight.

A number of studies have attempted to address the question of whether the provision of NIV to a hypercapnic but stable COPD patient receiving medication and long-term ventilation would provide additional benefit (Table 1).[3-7] Following on from these studies, a recent RCT published in *The Lancet Respiratory Medicine*[1] hypothesised that long-term NIV targeted to reduce hypercapnia would improve survival in patients with advanced, stable, hypercapnic COPD. The trial's primary outcome was overall mortality, and secondary outcomes included changes from baseline in blood gases, exercise capacity, quality of life (QoL), and lung function.[1] Patients were eligible for inclusion if they had been stable for at least 4 weeks with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage IV COPD,[8] were moderately or severely hypercapnic with $PaCO_2$ ≥7 kPa (51.9 mmHg) and had not been acidotic, or had an exacerbation. The 1-year trial used a parallel-group design with the comparator group receiving guideline-based medical treatment and long-term oxygen therapy if indicated, and with the intervention group also receiving NIV for a minimum of 6 hours per day. Power calculations determined that 150 patients were required in each group. Somewhat differently from previous trials, the target of ventilation was reduction of baseline $PaCO_2$ by ≥20%, assessed during spontaneous breathing 1 hour after NIV. Patient disposition and demographics are shown in Figure 1 and Table 2, respectively.

Table 1: Clinical studies of domiciliary NIV for stable chronic obstructive pulmonary disease.

	Casanova et al.[3] 2000	Clini et al.[4] 2002	McEvoy et al.[5] 2009	Díaz et al.[6] 2002	Windisch et al.[7] 2005
Design and size	RCT (n=24 vs 20)	RCT (n=47 vs 39)	RCT (n=72 vs 72)	RCT (n=18 vs 18)	Uncontrolled (n=34)
Age, years	68 vs 64	66 vs 64	69 vs 67	67 vs 67	63
BMI, kg/m^2	25.0 vs 25.0	25.0 vs 26.0	25.4 vs 25.5	25.0 vs 24.9	28.3
FEV_1, L	0.87 vs 0.82	-	0.55 vs 0.63	0.81 vs 0.72	1.03
$PaCO_2$, mmHg	53.0 vs 50.0	55.5 vs 54.0	54.4 vs 52.6	56.0 vs 57.0	53.3
Compliance	5.9 h/day, 11% <3 h/day	9.2 h/night in compliant group (>5 h/night)	4.5 h/day, 60% >5 h/night	3.0 h/day for 5 days/week for 3 weeks	–
IPAP/EPAP, cm H_2O	12.0/4.0	14.0/2.0	12.9/5.1	18.0/2.0	27.7
Mode	Bilevel, spontaneous	Bilevel, timed, back up rate 8	Bilevel, spontaneous	Bilevel, spontaneous	Pressure controlled
Therapeutic target for NIV	Reduced respiratory muscle activity	Reduced CO_2 by day, SaO_2 >90% overnight	Reduced sleep-disordered breathing	Maximum tolerated IPAP during day	Normalisation of $PaCO_2$
12-month survival	78% vs 78%	–	80% vs 72%	–	–
24-month survival	–	83% vs 82%	68% vs 53%	–	86%

BMI: body mass index; EPAP: expiratory positive airway pressure; FEV_1: forced expiratory volume in 1 second; IPAP: inspiratory positive airway pressure; NIV: non-invasive ventilation; $PaCO_2$: arterial carbon dioxide pressure; RCT: randomised controlled trial; SaO_2: arterial oxygen saturation.

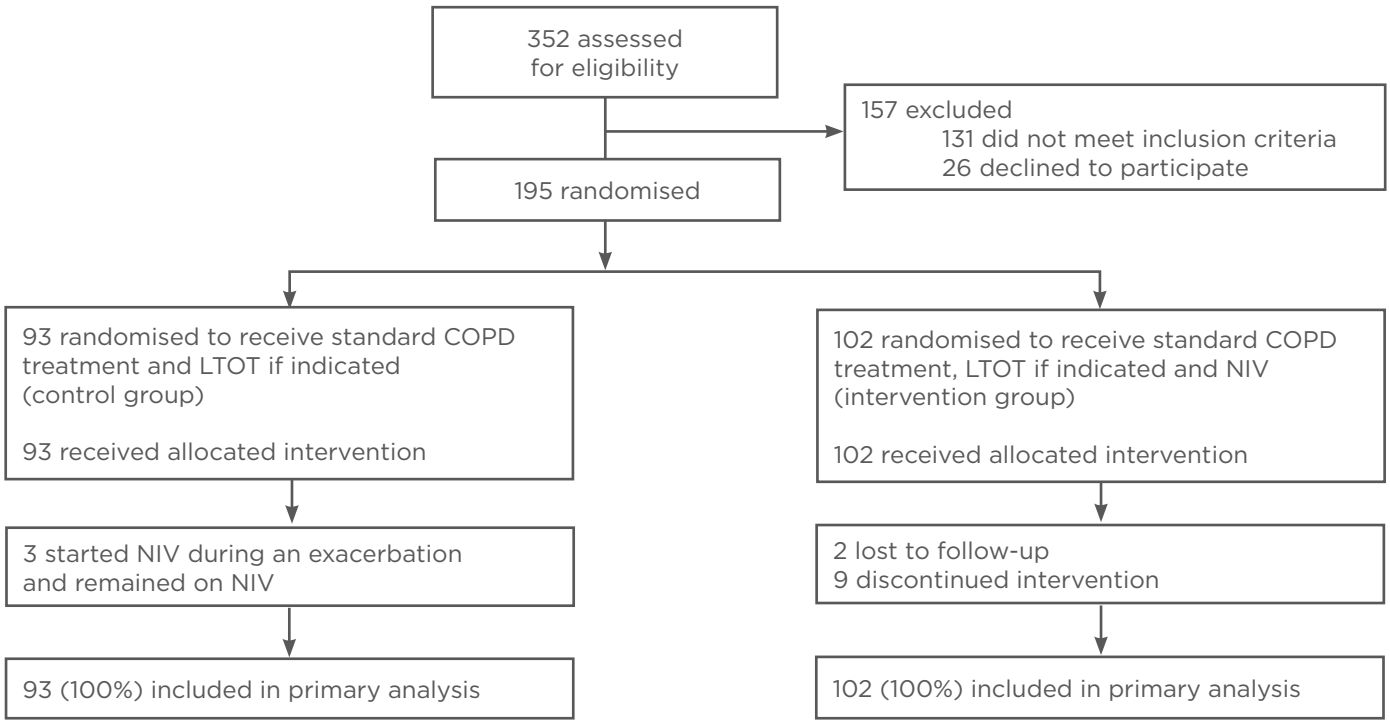

Figure 1: Patient disposition.[1]

COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation.

Table 2: Patient demographics.[1]

	Control group (n=93)	NIV group (n=102)
Age, years	64.4 (8.0)	62.2 (8.6)
Male, n (%)	56 (60)	65 (64)
BMI, kg/m^2	24.5 (5.8)	24.8 (5.8)
FVC, % predicted	53.3 (13.8)	50.4 (13.3)
FEV_1, % predicted	27.5 (8.9)	26.0 (11.0)
FEV_1/FVC, %	41.2 (11.4)	40.4 (11.5)
Residual volume/total lung capacity, %	72.7 (8.9)	73.0 (8.5)
pH	7.39 (0.05)	7.39 (0.04)
$PaCO_2$, kPa	7.7 (0.7)	7.8 (0.8)
PaO_2, kPa*	8.7 (1.9)	8.6 (2.1)
SaO_2, %*	90.8 (5.9)	90.3 (6.2)
HCO_3^-, mmol/L	33.9 (4.1)	34.3 (4.0)
Base excess, mmol/L	8.0 (3.9)	7.8 (3.8)
6-minute walk distance, m	249.6 (145.3)	226.7 (121.2)
Long-term oxygen treatment, n (%)	60 (65)	67 (66)

Data are mean (standard deviation), unless otherwise stated.

*In patients with long-term oxygen treatment, oxygen was applied via nasal cannula at the previously prescribed flow rate.

BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; HCO_3^-: bicarbonate; NIV: non-invasive ventilation; $PaCO_2$: arterial carbon dioxide pressure; PaO_2: arterial oxygen pressure; SaO_2: arterial oxygen saturation.

In the NIV group, the mean inspiratory and expiratory pressures were 21.6±4.7 mmHg and 4.8±1.6 cm H_2O, respectively, and all patients had received pressure support (PS) ventilation with a backup frequency of 16.1±3.6 (range: 2–24) breaths per minute. Using a cut-off value of 14 breaths per minute, 70 (69%) patients were deemed to have had controlled or partially controlled ventilation and the mean daily NIV usage was 5.9±3.1 hours.

$PaCO_2$ was reduced with the use of NIV by approximately 17% within the first 5.3 days and remained stable throughout the observation period. There was a non-significant increase in the NIV group's 6-minute walk distance (approximately 35 m) that met the suggested minimum clinically important difference in almost half of the patients (44%), whereas a significant improvement in FEV_1 (2.8% [0.2–5.4%]; p=0.034) was reported. Improvements in health-related QoL were observed in the General Health Perception component of the SF-36 and were above the minimal clinically important difference of 4.0 in the St George's Respiratory Questionnaire (SGRQ) (5.8 points more for the NIV group than for the control group). Significant improvements were also observed in the NIV group's Severe Respiratory Insufficiency score (5.6 point increase, 95% confidence interval [CI]: 0.1–11.1; p=0.0445). All-cause mortality was statistically lower in the NIV group at 1 year (12% [12 of 102 patients] in the NIV group and 33% [31 of 93 patients] in the control group; hazard ratio: 0.24, 95% CI: 0.11–0.49; p=0.0004) and this advantage was maintained up to at least 2,000 days after randomisation in patients still under observation. The mechanism of this improvement is not clear but the results suggest that a survival advantage appears early and remains throughout the observation period.

In clinical practice, patients with COPD who are treated in intensive care or high-dependency units receiving acute NIV tend to improve and begin breathing spontaneously. However, the question of whether the patient should be placed on long-term HMV once discharged is unclear. A study of patients who had been discharged from intensive care or a high-dependency unit after an acute exacerbation and randomised to NIV or standard treatment showed that, after 1 year, the combined endpoint of readmission for a respiratory cause or death was approximately equal irrespective of home NIV.[9] This study also failed to demonstrate a difference in survival time.[9] The authors postulate that these findings are due to the fact that both patient groups were hypercapnic during their initial hospital stay, both groups saw an improvement in the 3 months following discharge, and then both groups remained normocapnic throughout the observational period.[9] Patients should be re-assessed 3 months after an acute exacerbation to determine whether long-term domiciliary NIV is appropriate.

In conclusion, long-term domiciliary use of NIV in patients with advanced, stable COPD targeted at markedly reducing hypercapnia improves mortality, health-related QoL, and exercise capacity.

Telemonitoring for COPD Patients

Doctor Christine Cheval

The ResMed AirView™ is a clinician-managed telemonitoring platform for patients using continuous positive airway pressure or NIV compatible with Air Solutions' AirSense 10™, AirCurve™, Lumis™, and S9™ series devices. The system's dashboard provides an at-a-glance overview of compliance, unintentional leaks, and other clinical parameters over 90 days. The system provides several different report formats, including compliance only (usage, settings, leaks, and apnoea/hypopnoea index), compliance with clinical parameters, and detailed reports for the last 7 days.

The current trend in France for COPD patients is a reduction in long-term oxygen therapy with an increase in NIV and NIV with oxygen[10] and, due to compliance issues, these patients are ideal candidates for telemonitoring. The Köhnlein study described above is changing the way patients with COPD are ventilated around the world, but is based on a mean hospital stay of 5.6 days.[1] However, the titration period for French patients is limited to a few days, with a follow-up visit 1–2 weeks later. This provides an opportunity for a new treatment pathway: an initial 1-day titration followed by telemonitoring with or without $PtcCO_2$.

When optimising titration, the first task is the control of unintentional leaks.[11,12] The second task is setting the expiratory positive airway pressure (EPAP) level,[12] as the hospital stay is not always representative of home variations, especially in overlap patients. Telemonitoring of NIV enables these parameters to be monitored and adjusted remotely or with the help of homecare providers.

Exacerbation is a major cause of death in COPD and is associated with increased costs. Liu et al.[13] developed a scoring system for predicting a 90-day re-exacerbation in hospitalised patients with acute exacerbations (Table 3). Patients are placed into one of three groups depending on their score (2–6, 7–8, or >9). The higher the score, the greater the risk of an exacerbation in the next 90 days.

A prospective observational study of COPD patients showed that telemonitoring may also provide the ability to predict the occurrence of exacerbations on a regular basis.[14] Data collected included the duration of NIV each day, respiratory rate, and the percentage of inspiratory cycles triggered by the patient. EXACT-PRO® (EXAcerbations of Chronic pulmonary disease Tool) diaries were collected at monthly visits, and if the diary indicated that there had been an exacerbation then this was confirmed by two pulmonologists. Following an exacerbation, the follow-up period was divided into two blocks of 5 days. This proof-of-concept study showed that daily variations in respiratory rate and the percentage of cycles triggered by the patient are predictors of an exacerbation.

In a study of COPD patients treated at home with long-term NIV, a nightly use of >5 hours per day was associated with a better prognosis in the subgroup of 'obese COPD' patients. In contrast, NIV efficacy was rather limited in 'non-obese COPD', and an NIV use of >9 hours per day could predict poor outcomes.[15]

In conclusion, controlling leaks is crucial for successful NIV and recent data suggest that compliance with NIV of at least 5–6 hours per day is necessary to achieve a survival benefit in COPD.[15] New algorithms offer the possibility of auto-adjustable EPAP or PS, allowing a period of home titration. AirView allows remote monitoring of these parameters, enabling physicians to react promptly and take appropriate action. Telemonitoring could potentially help to predict exacerbations and prevent hospitalisation by facilitating early intervention with appropriate treatment. However, more data are required to better define criteria and monitoring methods, and these need to be included in the software. For example, which respiratory rate thresholds should be used, and how often? Telemonitoring is time-consuming and requires a redefinition of the roles and tasks of different stakeholders, e.g. clinicians, nurses, physiotherapists, and homecare providers. This will require a new treatment pathway supported by regulations and reimbursement, combined with economic analyses of the impact of this new approach. Ultimately, there will be a need for patients to become more involved in their treatment.

Table 3: Prediction of short-term re-exacerbation in patients with acute exacerbation of chronic obstructive pulmonary disease.[13]

	–1	0	1	2	3
Age range, years		<65	65–70	71–77	>77
GOLD grade		1	2	3	4
Frequency of exacerbation in previous year		0	1–2	≥3	
Presence of pleural effusion		No		Yes	
Use of accessory respiratory muscles		No	Yes		
Use of NIV		No	Yes		
Use of oxygen		No		Yes	
Use of inhaled corticosteroids	Yes	No			
Use of long-acting β_2-agonists	Yes	No			
Length of hospital stay, days		≤10	11–20	21–30	>30

GOLD: Global Initiative for Chronic Obstructive Lung Disease; NIV: non-invasive ventilation.

International Practice of HMV for COPD

Round-table discussion moderated by Doctor Peter Wijkstra and Professor Wolfram Windisch with contributions from Doctor Thomas Köhnlein, Doctor Stefano Nava, Doctor Nick Hart, and Professor Jean-Louis Pépin.

The session concluded with a lively discussion initiated by questions from the audience. The first topic was the problem of initiation of NIV in the home. The panel concluded that although home initiation of NIV is not suitable for all patients, it may be particularly suitable for patients with neuromuscular disorders such as Duchenne's muscular dystrophy and those with obesity-related respiratory failure. The panel noted that the main goal of telemonitoring is to monitor patients, not to initiate ventilation, and that the information collected needs to be acted upon promptly.

Reduction of CO_2 is critical for the success of NIV, but the panel was divided as to whether this was a direct effect or a surrogate marker of something else, such as a decompensated ventilatory pump. A recent large study in Japan has suggested that hypercapnia may in fact have protective effects.[16] Reducing $PaCO_2$ is an important goal in NIV that drives improvement in exercise tolerance and, ultimately, QoL. These improvements in exercise tolerance may be responsible for the observed survival advantage conferred by NIV.

When questioned on whether the panel would initiate NIV in normocapnic COPD patients during normal clinical practice, the consensus was that NIV was not suitable in these patients and conventional ventilation strategies such as simple PS were more appropriate. Nevertheless, it is important to select a ventilation strategy on a case-by-case basis.

Following this, the subject of whether to stop NIV when a hypercapnic patient becomes normocapnic was raised. The panel noted that it is important to consider whether the patient is becoming normocapnic as a result of the NIV or due to the natural course of the disease. In appropriate cases, NIV time can be reduced gradually over several nights and eventually stopped completely.

The audience was asked to consider whether there was now enough evidence to place all COPD patients on either standard ventilation or NIV. A straw poll revealed that placing hypercapnic COPD patients on NIV as standard is not widespread. The panel agreed that patients with high CO_2 and frequent exacerbations were the right candidates to target since widespread ventilation of hypercapnic patients might be uneconomical.

There is evidence that NIV in patients with COPD improves physiology, QoL, and long-term survival; in the final discussion, the panel members were asked for their views on the future of research in the field. Important topics included the health economics of widespread NIV use, patients with comorbidities, and the correct selection of patients, especially those who do not tolerate NIV or who are not efficiently treated by NIV in terms of the goal of reducing CO_2. Crucially, more basic research is urgently required to understand why chronic NIV in COPD might improve survival in these severely impaired patients.

Meeting Close

Doctor Peter Wijkstra

Dr Wijkstra thanked the speakers for their presentations as well as the audience for their questions and discussion points. With a final thank you to ResMed for having organised the symposium, the meeting was brought to a close.

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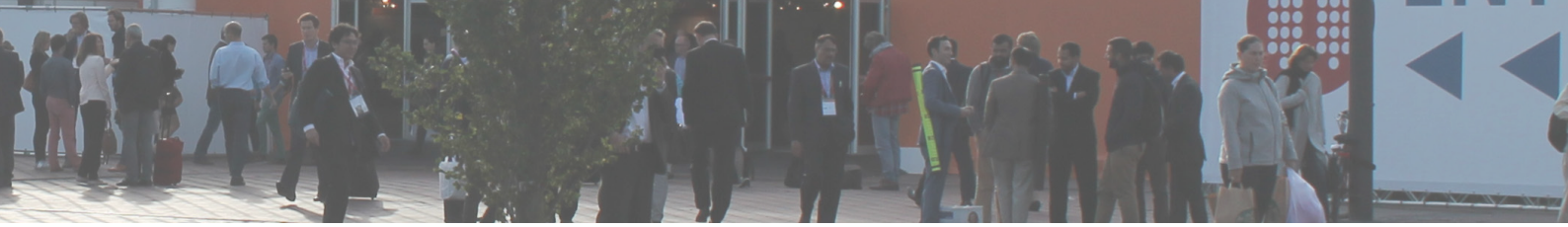
AWARD WINNERS AT ERS 2015

A wide range of prize grants addressing the many different aspects of modern pulmonology were presented at ERS 2015 in recognition of the outstanding research abstracts submitted to the congress. The prizes covered topics such as rehabilitation and chronic care, non-invasive ventilatory support, and bacterial pneumonia, and were presented to the winners during congress sessions with a theme relevant to each of the prizes. The origins of the prize winners reflected the diversity of the delegates attending the meeting and the global reach of the ERS, with 15 different nationalities represented by the winners of the 19 awards. Researchers from European institutions unsurprisingly dominated the list of prize winners at this European congress, but the rest of the world was well represented, with prize winners from the USA, Brazil, and Hong Kong. Of the European prize winners, 12 different European nations were represented, including 2 winners from Spain and 3 from the UK.

The ERS Best Abstract Grant for Healthy Lungs for Life was awarded to Maia Smith for a study demonstrating the lack of an association between the level of physical activity in lung-healthy adolescents and any spirometric lung volume or flow. The study investigated healthy young people from the German GINIplus and LISAplus cohorts (n=1,196), with results standing in contrast to data from chronically ill and elderly cohorts that show an association between physical activity level and lung health. Although the levels of physical activity observed in the adolescent cohort were below WHO recommendations, the spirometric parameters matched values established by the Global Lung Initiative.

There were two winners of the ERS Interventional Pulmonology Travel Grant prize. One of the prizes was collected by Julia D'Hooghe for her abstract describing the use of optical coherence tomography (OCT) to assess bronchial wall thickness before and after bronchial thermoplasty (BT), a novel bronchoscopic treatment that aims to reduce airway smooth muscle in cases of severe asthma. The study employed OCT to compare bronchial wall thickness in three severe asthma patients 3 weeks before, directly after, and 6–10 weeks after BT. The researchers were able to identify and measure separate airway wall layers and demonstrated that the structure of the airway wall was altered directly after BT. The thickness of the bronchial wall was significantly decreased 6–10 weeks after BT (wall thickness as a percentage of total airway area: 60.4±3.8 versus 42.4±5.0 for pre and post-BT, respectively; $p<0.001$). The researchers concluded that OCT is capable of identifying and quantifying airway wall layers and dimensions, and suggest that the technique may be useful as an effect/screening tool for BT.

The other ERS Interventional Pulmonology Travel Grant prize was collected by Youbing Yin for his



abstract describing the use of regional fissure integrity (FI) analysis to improve prediction of outcome following valve-based lung volume reduction therapy. The study investigated 253 patients treated with endobronchial valves using automated FI analysis. Determination of regional FI was shown to yield superior classification results than those obtained from global FI, which the authors suggest may allow the expansion of patient selection for valve implantation, and lead to the development of more targeted and personalised treatments for emphysema.

Anne-Kathrin Brill received the ERS Grant for the Best Abstract in Noninvasive Ventilatory Support for her description of the results from a trial of a pressure-sensing visual feedback system, aimed at improving mask fitting in non-invasive ventilation (NIV). Long-term adverse pressure effects that may compromise the success of NIV can be avoided by achieving a good mask fit, but delivering training in this skill is challenging. A total of 30 healthcare professionals (14 trained in mask fitting, 16 untrained) participated in this randomised crossover trial that compared the results obtained using the I-scan® system with those obtained using standard mask fitting procedures. Compared with standard procedures, a significantly lower pressure was exerted on the nasal bridge using the I-scan system (71.1±17.6 mmHg versus 63.2±14.6 mmHg; $p<0.001$), with significant reductions in the pressure exerted on the nasal bridge observed in both the trained and untrained groups. The participants reported the I-scan system to be easy to use, and the volunteers having the mask fitted perceived the fit as being more comfortable when I–scan was used.

The first ERS Excellence Grant in Clinical Physiology and Exercise was awarded to Ane Arbillaga-Etxarri for a study that reported upon reference equations for predicting the total distance walked by Spanish individuals aged 45–85 years and undertaking an incremental shuttle walk test (ISWT). Due to the costs and infrastructure necessary for incremental exercise tests, ISWTs have begun to be used as a field test to assess maximal exercise capacity. However, there are currently no reference equations for Spanish populations. The study was a cross-sectional, multicentre study carried out in 17 Spanish hospitals and universities, which assessed 568 healthy individuals (48% male; mean age [standard deviation]: 62 years [11]). The resulting reference equations explained 53% of the variance in the total distance walked by healthy Spanish men and women. Variability depended on age, height, weight, and baseline heart rate in men, and on age and weight alone in women. The authors propose to validate the new equations in patients with respiratory disease.

The other prize awarded under the ERS Travel Grant for the Best Abstract in Clinical Physiology and Exercise category was collected by Bruno-Pierre Dubé in recognition of his abstract that reported the reliability of a diaphragm ultrasound for the detection of diaphragm dysfunction in critically ill patients. Measurement of intrathoracic pressure in response to bilateral stimulation of the phrenic nerve is considered the gold standard for diagnosing diaphragm dysfunction, but it is not widely available and is costly. This prospective, single-centre study performed in a medical intensive care unit (ICU) investigated 43 critically ill patients at three key time points: 1) during the first 24 hours of controlled ventilation; 2) as soon as patients could tolerate pressure support ventilation; and 3) before the first spontaneous breathing trial. Diaphragm dysfunction was present in 79%, 85%, and 58% of patients during time points 1, 2, and 3, respectively. There was a significant correlation between the results obtained from phrenic nerve stimulation and those obtained using diaphragm ultrasound at time points 2 and 3 ($r^2=0.88$; $p<0.001$), but not at time point 1. At time points 2 and 3, the ultrasound observation of a diaphragm thickening fraction <30% displayed a sensitivity of 90% and specificity of 100% (AUC: 0.98) for the detection of diaphragm dysfunction.

Long-term adverse pressure effects that may compromise the success of NIV can be avoided by achieving a good mask fit, but delivering training in this skill is challenging.

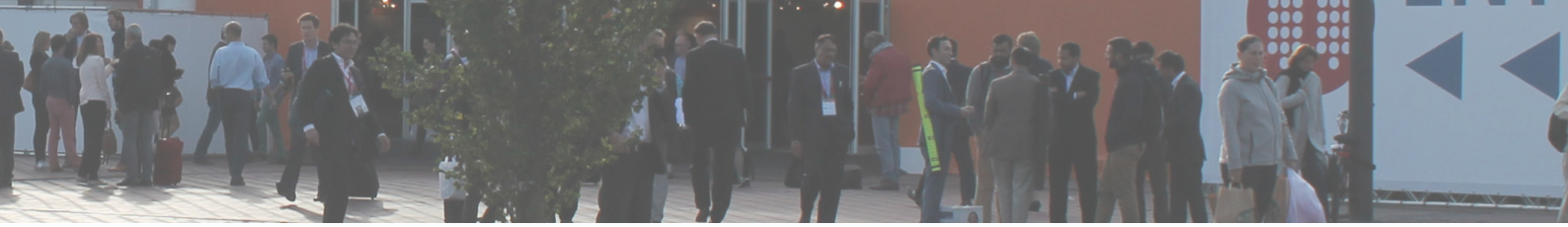
...the new model could prove useful in the study of pathophysiology and novel therapeutic/ preventive strategies for pneumococcal pneumonia.

Rosanel Amaro won the ERS Grant for Best Abstract in Bacterial Pneumonia for her characterisation of pulmonary function in a novel porcine model of severe pneumococcal pneumonia. After surgical preparation, and 4 hours afterwards, viable cultures of *Streptococcus pneumoniae* 19A were instilled into each pulmonary lobe of six anaesthetised pigs. Pulmonary function/mechanics and arterial pressure were assessed every 24 hours, with pneumonia being confirmed at autopsy 72 hours after bacterial challenge. The presence of severe pneumonia was confirmed in five of the six pigs, with pulmonary function/mechanics in these animals significantly worsening throughout the study period. The authors suggest that the new model could prove useful in the study of pathophysiology and novel therapeutic/preventive strategies for pneumococcal pneumonia.

The ERS Young Researcher Grant: Respiratory Infection Aetiological Diagnosis prize was awarded to Alison Dicker for her abstract describing the preliminary data from a longitudinal study of the airway microbiome in 173 patients with chronic obstructive pulmonary disease (COPD). Sputum samples were obtained prospectively at study baseline, at both the onset and the end of each exacerbation, and at 6 months follow-up. Bacterial microbiomes were assessed by 16S rRNA sequencing. A total of 207 sputum samples were obtained (1–6 samples/patient) and the current abstract reports results from the first 45 patients (58 sputum samples). The Shannon Species Diversity indices of the samples ranged from 0.46–3.27, with the less diverse samples predominantly containing *Haemophilus* or *Streptococcus* species. Samples providing *Haemophilus* reads ≥30% were significantly associated with a higher COPD GOLD stage (p=0.016), and regression analysis showed that higher GOLD stages (A–D) were significantly associated with reduced species diversity (p=0.009).

The ERS Grant for the Best Non-CF Bronchiectasis Abstract was awarded to Pieter Goeminne for an abstract describing the impact of acute air pollution fluctuations on pulmonary exacerbations of non-cystic fibrosis bronchiectasis (NCFB). This case-crossover analysis included NFCB patients experiencing an exacerbation and linked the incidence of an exacerbation with data describing the concentration of ozone and particulate matter with a diameter smaller than 2.5 mm ($PM_{2.5}$) near each patient's home address, on the day of the event and 2 days prior. The study included a total of 40 patients (17 male; median age: 68 years, interquartile range: 57–74) who each experienced one exacerbation during the study period. Of these, 30 patients had idiopathic NCFB, 5 had post-infectious NCFB, and 5 had an autoimmune disease. An increase of 1 $\mu g/m^3$ in daily mean $PM_{2.5}$ concentration was associated with a 10.2% increased risk of experiencing an exacerbation in the following 24 hours (95% confidence interval [CI]: 1.6–19.7%; p=0.02), but there was no evidence of an association between ozone levels and NCFB exacerbations.

There were three ERS Travel Grant for Sleep Medicine prizes awarded at the congress. Elizabeth A. Hill's abstract described the results from a prospective, randomised controlled trial (RCT) of the use of continuous positive airway pressure (CPAP) in 28 UK adults with Down's syndrome. Patients exhibiting ≥10 apnoeas/hypopnoeas per hour in bed were invited to participate, with those enrolled randomised to receive either CPAP or lifestyle advice. Patients were reviewed at 1, 3, 6, and 12 months, with those in the lifestyle advice arm offered CPAP at 1 month. There were no significant differences between groups at baseline or at 1 month. At 12 months, three participants had withdrawn and those remaining in the trial were all receiving CPAP. At 12 months, the use of CPAP led to significant improvements in sleepiness (p=0.001 for patient Epworth Sleepiness score [ESS], and p=0.029 for carer ESS), health status, cognitive function, and behavioural/emotional outcomes (p<0.0001, p=0.02, and p=0.008 for 'Disruptive', 'Anxiety/antisocial', and 'Depressive' subscales of



the Developmental Behaviour Checklist for Adults). KBIT-2 verbal (p=0.001) and nonverbal (p=0.011) raw scores and RAND-36 total score (p=0.022) also improved.

Aleksandra Piechuta was another winner of the ERS Travel Grant for Sleep Medicine prize for her abstract reporting the assessment of systemic inflammation in patients with obstructive sleep apnoea (OSA) using a novel scoring system for complications of OSA. The research team observed significant changes in patient comorbidities and constructed their own OSA complications score (OCS) for evaluating the nature and severity of systemic inflammation experienced by OSA patients. The OCS graded the following patient factors on a scale ranging from 0 (lowest impact) to 6 (greatest impact): obesity, diabetes, hypertension, ischaemic heart disease, stroke, and current smoking history. The study investigated 50 OSA patients and found a significant positive relationship between OCS score and apnoea/hypopnoea index (AHI), leukocyte number, C-reactive protein and fibrinogen levels, the number of T cells and HLA DR^+ T cells, and a negative relationship with peripheral oxygen saturation and adiponectin concentration ($p<0.05$, $r>0.3$ in Spearman's test). The authors suggest that the new scoring system may be useful as a quantitative tool in future studies to assess OSA-induced immune alterations.

Weight reduction through lifestyle modification in patients with moderate-to-severe OSA was the topic addressed by Susanna S.S. Ng's abstract. A total of 104 patients using portable home sleep monitoring was included in this parallel-group RCT and randomised to receive either usual care (n=43) or a dietician-led lifestyle modification programme (LMP; n=61) for 12 months; the primary endpoint was reduction of AHI at 12 months. The results showed that there were 16.9% fewer events in the LMP group compared with 0.6% more events in the control group at 12 months (p=0.011). Adhering to an LMP was also more effective in reducing body mass index (BMI) (−6.0% of initial BMI compared with −2.0% in the control group; p<0.001). There were also reductions in daytime sleepiness (as assessed by ESS), a modest improvement in mental health (as assessed by Short Form-36 [SF-36]), and improved eating behaviour (greater intake of protein and fibre) in the LMP group. The changes were observed 4 months after the initial diet counselling appointment and persisted at 12 months.

The authors concluded that the use of nNO may help to potentiate early diagnosis, and thus improve prognosis of PCD patients.

There were two ERS Grant for Best Abstract in Paediatric Respiratory Epidemiology prizes awarded at the congress. The abstract submitted by Panayiotis Kouis described a systematic review and meta-analysis on the use of nasal nitric oxide (nNO) measurements to aid diagnosis of primary ciliary dyskinesia (PCD). The study evaluated nNO using either the velum-closure (VC) or non-velum-closure (non-VC) techniques and found that both were effective compared with diagnosis supported by transmission electron microscopy, high-speed video microscopy, and genetic testing, even in young children. The analysis identified 12 studies, 9 case–control (n=793) and 3 prospective cohorts (n=306), and found a summary sensitivity of 96% (95% CI: 90–98%) and summary specificity of 95% (95% CI: 89–97%) with the VC technique.

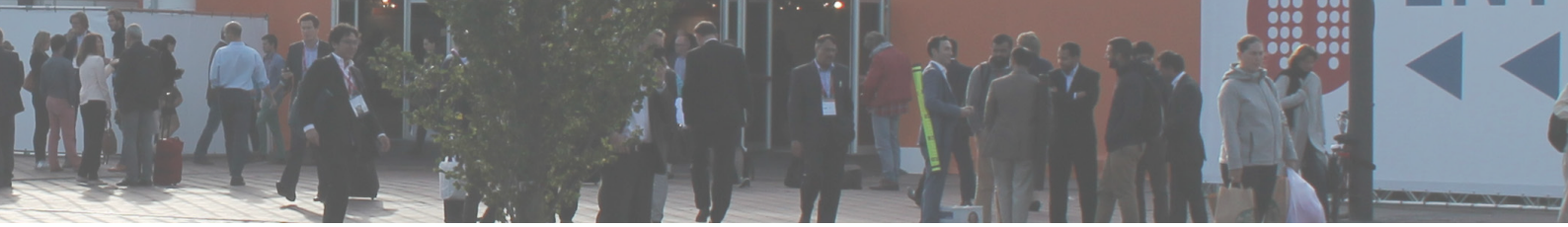
BEST ABSTRACT AWARD WINNERS

For the non-VC technique, the study found a summary sensitivity of 94% (95% CI: 89–97%) and summary specificity of 94% (95% CI: 77–99%). The authors concluded that the use of nNO may help to potentiate early diagnosis, and thus improve prognosis of PCD patients.

The other ERS Grant for Best Abstract in Paediatric Respiratory Epidemiology prize was presented to Maja Popovic in recognition of her study reporting on the association between wheezing at 18 months of age and infant size and velocity of weight gain. The study analysed data collected from questionnaires used in the NINFEA birth cohort study and assessed weight measurements taken from birth up to 18 months of age in 3,600 term, singleton births. The prevalence of wheezing at 18 months was also determined and logistic regression was used to evaluate its relationship with infant size (average weight), weight velocity, and weight tempo (the age that peak weight velocity occurred). Size (odds ratio [OR]: 1.27, 95% CI: 1.08–1.49) and weight velocity (OR: 1.31, 95% CI: 1.13–1.53) were both independently positively associated with wheezing, with only a minimal change in the estimates observed after adjustment for potential confounding factors. There was no association between the weight tempo and the occurrence of wheezing (OR: 1.01, 95% CI: 0.87–1.18).

There were five ERS Grant for Best Abstracts in Rehabilitation and Chronic Care prizes presented at the congress. First prize was awarded to Fanny W.S. Ko for an abstract describing an RCT that evaluated the use of a comprehensive care programme in COPD patients. The results from the RCT show that the implementation of such a programme can reduce hospital readmissions for COPD and length of stay, as well as improve symptoms and the quality of life (QoL) of patients. The RCT compared two groups: one receiving usual care and another receiving a comprehensive, individualised care plan that included optimisation of medication, nurse-led education, physiotherapist support for pulmonary rehabilitation, monthly telephone calls by a respiratory nurse for 1 year, and follow-up at a respiratory clinic by a respiratory specialist once every 3 months for 1 year. The study included 180 COPD patients (n=90 for both groups; mean age: 74.7±8.2 years; 95.6% males; mean FEV1: 45.4±16.6% predicted). Compared with those receiving usual care, the group receiving the comprehensive care programme experienced fewer readmissions (1.56±2.13 versus 2.38±2.14; p=0.0008) and shorter length of stay (7.41±11.29 versus 12.21±12.87 days; p=0.0003), as well as improved mean scores assessing dyspnoea (Modified Medical Research Council dyspnoea scale: −0.1±0.7 versus 0.2±0.6; p=0.033) and QoL (St. George's Respiratory Questionnaire [SGRQ]: −8.5±16.6 versus −0.1±15.7; p=0.002), at 12 months.

The second prize under the category of ERS Grant for Best Abstracts in Rehabilitation and Chronic Care went to Kathryn McDowell, who described the effect of introducing a 6-week exercise programme on the physical function of survivors



of critical illness following discharge from an ICU. This multicentre, Phase II RCT compared the use of the exercise programme with usual care in patients who were ≥18 years of age, had received mechanical ventilation for >96 hours, and were not involved in any other rehabilitation programme. The preliminary results from the trial show that there was no significant difference in the 'physical functioning' subscale of the SF-36 between groups at 6 weeks, but in the exercise programme group there were significant improvements in the 'role physical' subscale of the SF-36, ISWT, Functional Limitations Profile, Chronic Disease Self-efficacy Scale, and readiness to change.

There were also three third prizes in the category of ERS Grant for Best Abstracts in Rehabilitation and Chronic Care. Mariana Sponholz Araujo received her prize in recognition of a study describing the impact of a pulmonary rehabilitation programme on the exercise capacity of patients with lymphangioleiomyomatosis (LAM), which is frequently associated with reduced exercise capacity. The researchers conducted a non-RCT that included 15 LAM patients in the pulmonary rehabilitation programme group and 13 in a control group who received usual care. The trial found that those taking part in the rehabilitation programme displayed significantly improved endurance time during constant work-rate exercise testing (median change: 35% [−3 to 117] versus −7% [−29 to 10]; p=0.04), ΔVO_2 (median: 17% [0.3 to 26] versus −5% [−13 to 3]; p=0.004), 6-minute walk distance (median: 52 m [16–77] versus 16 m [−14 to 27]; p=0.01), SGRQ (median: −8 [−13 to 1.4] versus 2 [−4 to 6]; p=0.05), and muscle strength (median one-repetition maximum: 29% [20 to 77] versus 0% [−1 to 13]; p=0.01). Pulmonary function tests and dynamic hyperinflation did not improve after pulmonary rehabilitation.

The abstract submitted by Charlotte Suppli Ulrik also received a third prize in the ERS Grant for Best Abstracts in Rehabilitation and Chronic Care category, describing an RCT that investigated the use of telehealthcare in COPD patients. The 281 patients included in the study were randomised to receive either usual care (n=140) or usual care with telemonitoring (TM), which comprised the recording of symptoms, saturation, spirometry, and weekly video consultations) as an add-on (n=141). The trial found no significant difference in hospital admissions for COPD between the groups and no difference in the time to first admission or all-cause hospital admissions. Compared with the usual care group, those with TM as an add-on displayed significantly more moderate exacerbations (i.e. those treated with antibiotics/corticosteroid but who did not require hospital admission; 1.21 versus 0.73; p<0.001), whereas the usual care group had significantly more visits to outpatient clinics (p<0.001).

The use of telehealthcare in COPD patients was also the subject of the other third prize awarded under the ERS Grant for Best Abstracts in Rehabilitation and Chronic Care category. Maroula Vasilopoulou's abstract reported on the effectiveness of home tele-rehabilitation on functional capacity and daily physical activity in COPD patients compared with the use of hospital-based maintenance rehabilitation. Six months after completing a 2-month course of supervised pulmonary rehabilitation, tele-rehabilitation (n=47) was shown to be as equally effective as hospital-based rehabilitation (n=48) in terms of maintaining initial significant improvements in 6-minute walking distance, daily physical activity, chronic dyspnoea, and quadriceps muscle strength, which suggests that home tele-rehabilitation may be a useful alternative to hospital-based maintenance rehabilitation in COPD patients.

ASTHMA BEYOND THE BRONCHUS

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Asthma continues to be a large economic and health burden worldwide. Our understanding of asthma and how to effectively treat and manage it has been largely constructed around the assumption that it is the primary condition being managed by those who have it. However, parallel to the growing burden of multiple chronic conditions (MCCs) in the general population is the growing burden of MCCs among those with asthma, especially older adults. Among older adults with asthma, 21% have 1–2 coexisting conditions, 30% have 3–4 coexisting conditions, and 45% have >5 coexisting conditions.[1] Two issues are relevant when we think about asthma beyond the bronchus: 1) what are the most prominent phenotypes; and 2) how do we effectively manage asthma in the context of coexisting conditions?

The presence of MCCs is most pronounced in older adults. Asthma in older adults is typically either: asthma diagnosed in childhood or early adulthood that persists into later life; or new symptoms that appear in later life, which is difficult to diagnose given the high incidence of chronic obstructive pulmonary disease, heart failure, and the greater possibility of differential diagnoses. Whether or not diagnosed asthma is truly asthma when we are thinking about MCCs, the management of respiratory symptoms with other conditions is relevant for a large population. Widely used clinical guidelines for the diagnosis and management of asthma (e.g. GINA, British clinical guidelines, Australian guidelines, US guidelines) identify and list common conditions that accompany asthma, such as obesity, gastro-oesophageal reflux disease, anxiety/depression, food allergy and anaphylaxis, rhinitis, sinusitis, and nasal polyps. Recent observational studies have shown high rates of hypertension and arthritis co-occurring with asthma in both adults and children.[2,3] Certain conditions appear to cluster with asthma, although the mechanisms through which asthma and other conditions occur is unclear. A first step is to identify relevant, commonly occurring clusters or phenotypes of morbidities co-occurring with asthma. A framework developed by Piette and Kerr[4] that has been used widely in diabetes can translate well to the classification of MCC phenotypes with asthma and other respiratory conditions: conditions either concordant (supporting or synergistic) or discordant (conflicting) with asthma care. All current major asthma guidelines contain no information relating to the management of discordant conditions, and there is insufficient evidence for the management of concordant conditions.

There is a lack of evidence in most clinical guidelines to address the clinical interactions of multiple conditions. As a result, clinicians do not have a sufficient evidence-based resource to turn to when addressing the needs of their patients. There are numerous ways to address multimorbidity in clinical practice guidelines. Guidelines can focus on an index condition (e.g. asthma) and select one or more important coexisting conditions to address their combined management. Guidelines can address a pair of conditions in which neither condition is the primary condition. Lastly, guidelines can address multimorbidity in a non-disease-specific way, such as guidelines addressing the coordination of care or self-management.

The combined impact of multiple care needs, and the lack of integration of these needs, means that patients with asthma and MCCs are less likely to receive adequate care. Having other morbidities in addition to asthma has a significant, adverse impact on asthma burden as seen through multiple outcomes.[2,3] The current lack of understanding of MCCs and asthma, and the paucity of evidence included in clinical guidelines, stems from a lack of research. Over the past decade or so, we have seen a large surge in the number of research articles around MCCs in general, although articles on MCCs and asthma remain relatively scarce. Clinical trials have historically excluded patients with MCCs. To a large degree, the current state of our understanding regarding asthma and MCCs, and how to effectively engage in both clinical and self-management, is largely a result of who we are including in our studies, and that needs to change in order to meet the care needs of this growing population.

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PHENOTYPING AND CHARACTERISING PATIENTS WITH AIRWAY OBSTRUCTION

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Throughout the ERS congress, both in formal sessions and in the corridors, there were discussions on the hot topic of 'ACOS' (asthma–chronic obstructive pulmonary disease [COPD] overlap syndrome). Is this a real syndrome and a disease entity separate from asthma and COPD? Is it a clinical phenotype and something that looks like asthma with disease progression, or is it a phenotype that looks like COPD with reversibility, with eosinophilia, with allergy, or any other 'asthma-like' feature?

There was one formal session in which Prof Gary Anderson (Australia) highlighted the underlying mechanisms of asthma and COPD from an immunological perspective; Prof Klaus Rabe (Germany) followed with a view on ACOS from an asthma perspective; and Prof Dirkje Postma (Netherlands) discussed ACOS from a COPD perspective.

As clinicians around the world are aware, GINA (Global INitiative for Asthma) and GOLD (Global initiative for chronic Obstructive Lung Disease) have stated that it is sometimes difficult to determine whether a patient has asthma or COPD in later adult life. Due to this, they have advised that a patient should be defined using several characteristics, and if three or more of these fit with asthma then the patient should be diagnosed with asthma, and similarly if there are three or more that fit with COPD then the patient should be diagnosed with COPD. Finally, if there is an equal number of asthma and COPD features then the patient should be diagnosed with ACOS. The speakers at the ERS congress thought that this advice should be used to raise awareness, but that it remains better to phenotype the patient and not to suggest that ACOS is a definite syndrome by labelling the patient with it.

COPD may develop from longstanding asthma, with remodelling as an underlying mechanism superposed or in parallel with the airway inflammation that is a characteristic of asthma. This condition may reflect COPD 'from the outside' (i.e. irreversible airway obstruction) but still be asthma 'on the inside'. This type of patient will likely deteriorate if anti-inflammatory treatment is stopped and they are treated according to COPD guidelines. We know that there are many types of asthma and, in the current era of the introduction of personalised medicine and the introduction of biologics to treat these asthma subtypes, one needs to more extensively characterise these patients. In the near future, more biomarkers will come to the aid of doctors deciding on which treatment to prescribe or monitoring the effect of treatment. A general label will therefore not help and we should adjust to using patient phenotypes.

In cases of COPD, a very low FEV_1 can be present in patients with and without emphysema. There are many different underlying mechanisms of airway obstruction, again showing that 'the outside' is not reflective of what is 'inside'. Recently, a group of COPD patients was found to have blood eosinophilia. This is not a syndrome (ACOS), but a COPD subtype that may respond to inhaled corticosteroid use with a reduction in exacerbations. One would not state that these smoking patients

with irreversible airway obstruction have asthma simply because they have eosinophilia in peripheral blood. Similarly, COPD with reversibility and COPD with hyperresponsiveness are subtypes, but we do not yet know which treatment helps these patients best and this will not become clear if we lump all COPD patients together.

There are several types of asthma and there are several COPDs, and we have to realise that, when applied, even ACOS is a collection of diseases, each with a specific underlying mechanism and treatment requirement. At the ERS congress, phenotyping was again the message that came clearly from the stage.

INVASIVE PULMONARY ASPERGILLOSIS IN IMMUNOSUPPRESSED PATIENTS

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The most common species of *Aspergillus* causing pathology in humans are *A. fumigatus, A. flavus*, and *A. niger*, although sporadic cases of illness caused by other pathogenic species (e.g. *A. terreus*, *A. clavatus*, *A. niveus*, and *A. nidulans*) have been reported. *Aspergillus* is primarily acquired from the environment by the inhalation of airborne spores. These small spores (usually 2–3 µm in diameter) are easily inhaled and deposited deep into the lungs. The respiratory tract is the main portal of entry (80–90% of all cases) rather than other possible entry sites such as damaged skin, wounds, the cornea, and the ear. In non-immunocompromised patients, *Aspergillus* spp. cause hypersensitivity pneumonitis, Löffler's syndrome, eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, and aspergillomas. Invasive pulmonary aspergillosis (IPA) affects mainly immunocompromised hosts, while chronic necrotising aspergillosis is a chronic destructive disease that develops in patients with chronic lung disease or mild immunosuppression.

The major risk factors for IPA include prolonged (>3 weeks) and severe (neutrophils <500/µL) neutropaenia (usually following chemotherapy) or neutrophil dysfunction (e.g. chronic granulomatous disease), corticosteroid therapy (long-term, high-dose), transplantation (frequently in lung and bone marrow transplantation cases with a higher risk during the first few weeks, or during corticosteroid treatment for graft versus host disease), haematological malignancies (especially leukaemia), cytotoxic therapy, and HIV infection (increased risk with lower numbers of $CD4^+$ cells). Although the majority of IPA cases involve immunocompromised patients, several reports have indicated an increased risk in patients with chronic obstructive pulmonary disease and in patients with chronic liver disease, alcoholism, or diabetic ketoacidosis.

Lung involvement in IPA is characterised by the destructive invasion of lung parenchyma with multifocal consolidation complicated by abscess formation and cavitation. Invasion of blood vessels leads to areas of infarction, haemorrhage, systemic embolisation, and fungaemia leading to haematogenous dissemination to other organs. Disseminated aspergillosis commonly affects the brain, but other sites (e.g. skin, kidneys, pleura, heart, liver) may also be affected. Some patients, especially lung transplant recipients with impaired mucociliary clearance and poor cough reflex, develop tracheobronchial aspergillosis. IPA in immunocompromised patients is characterised by a rapidly fatal progression (usually 7–14 days from onset to death), whereas IPA in immunocompetent patients is characterised by a slow progression (usually 2–3 months from onset to death). The diagnosis of IPA is difficult, with the gold standard being based on histopathological examination of lung tissue and demonstration of *Aspergillus* hyphae in addition to a positive culture.

The stains commonly used to demonstrate the characteristic hyphae are the methenamine silver and periodic acid–Schiff stains, although other fungi may display a similar appearance and therefore a culture obtained from the same site is very important for accurate identification of *Aspergillus*. A histological sample is rarely obtained, however, especially in immunocompromised,

thrombocytopaenic patients. A high clinical suspicion is essential for early diagnosis in high-risk populations.

Among the triazoles, itraconazole has activity against *Aspergillus* spp., although strains of *A. fumigatus* resistant to itraconazole have been described. Itraconazole is, however, attractive for long-term therapy because of its formulation for oral administration. Voriconazole provides higher response rates and better survival than amphotericin B in the treatment of IPA, and for this reason is recommended as first-choice treatment. Echinocandins display *in vitro* and *in vivo* activity against *Aspergillus* spp. Caspofungin has been shown to be effective in the treatment of probable and proven IPA in patients refractory to, or intolerant of, conventional antifungal treatment. There are limited data on the use of anidulafungin and micafungin for the treatment of IPA.

EMERGING REGULATION AND FUNCTIONS OF AUTOPHAGY

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Autophagy is a vital dynamic intracellular stress response pathway that acts as an internal quality control mechanism for the removal of defective or dysfunctional proteins or organelles. Autophagy is a normal physiological process involved in cellular homeostasis and survival mechanisms in normal respiring cells. There are three main types of autophagy: i) macroautophagy, ii) microautophagy, and iii) chaperone-mediated autophagy. Macroautophagy is the most well studied form of autophagy and involves a series of membrane restructuring and translocation events, which result in the encapsulation or engulfment of cytoplasmic contents and organelles by a double membraned structure termed an autophagosome. The autophagosome fuses with, and delivers its contents to, the lysosome, which subsequently facilitates a degradation process to regenerate metabolic precursors that can be used for anabolic pathways. Macroautophagy (hereafter autophagy) is regulated by a number of autophagy-related gene (ATG) products, including the distinctive autophagy marker proteins Beclin 1 (the mammalian homolog of yeast Atg6 that regulates autophagosomal nucleation) and microtubule-associated protein light chain 3 (LC3) (a homolog of yeast Atg8 that is one of the most well-known ATG proteins and is frequently used as a specific marker to monitor macroautophagy experimentally). ATG proteins, including Beclin 1 and LC3B, are responsible for the initiation and execution of autophagy. Until recently, autophagy was merely deemed a nonspecific homeostatic cellular process; however, mounting evidence suggests that a process termed 'selective autophagy' is involved in the delivery of a wide range of autophagic cargo from protein aggregates to whole organelles, such as mitochondria, to the lysosome.[1]

We have previously observed that lungs from patients with chronic obstructive pulmonary disease (COPD) have increased levels of autophagy proteins and autophagosomes.[2,3] However, whether or not this process was selective for specific autophagic targets in the lung was not elucidated. COPD is a complex debilitating lung disease that encompasses a variety of clinical and pathological phenotypes ranging from airway inflammation (chronic bronchitis) to destruction of lung tissue (emphysema).[4,5] The pathogenesis of COPD involves aberrant inflammatory and dysregulated cellular responses of the lung to cigarette smoke (CS) exposure,[4] resulting in the disruption of airway epithelial cell function. Such disruption has been attributed to a reduction in epithelial cell cilia length and airway epithelial cell death, followed by re-epithelialisation by goblet cells, resulting in excess mucus production leading to impaired mucociliary clearance (MCC).[6] Impaired airway

clearance prevents the elimination of particles and pathogens trapped in mucus from the airways, and may promote susceptibility to respiratory infections that exacerbate COPD. Mice exposed acutely or chronically to CS develop inflammation and airspace enlargement, respectively, and frequently represent a physiologically relevant experimental model of COPD.[1,6-8] Using such experimental models, we observed that increased morphological and biochemical indicators of autophagy correlated with cilia shortening both *in vivo* and *in vitro*.[8] We demonstrated CS-induced cilia shortening through an autophagy-dependent mechanism mediated by the deacetylase HDAC6 (histone deacetylase 6). Autophagy-impaired (*Becn1*$^{+/-}$, *map1lc3b*$^{-/-}$, or *Hdac6*$^{-/Y}$) mice resisted CS-induced cilia shortening. Furthermore, cilia components were identified as autophagic substrates during CS exposure. Assessment of airway cilia function using a 3D MCC assay demonstrated that *Becn1*$^{+/-}$, *map1lc3b*$^{-/-}$, or *Hdac6*$^{-/Y}$ mice, or mice injected with the HDAC6 inhibitor tubastatin A are protected from CS-associated mucociliary dysfunction. We concluded that an autophagy-dependent pathway regulates cilia length during CS exposure. Similarly, we found in another study that CS-induced mitophagy, the autophagy-dependent elimination of mitochondria through stabilisation of the mitophagy regulator PINK1 and activation of the programmed cell death pathway known as necroptosis, contributes to emphysematous changes in response to CS exposure in experimental COPD models and in human COPD patient lungs.[1]

Autophagy has been shown to be both protective and injurious in a variety of different models, suggesting that its role in human diseases is complex. In order to accurately measure if autophagy is increased or impaired in experimental systems, the field must consider autophagy as a dynamic cyclic pathway under constant turnover and therefore must consider measuring the activity or endogenous 'flux' of autophagy proteins through the system to complement traditional techniques (such as the detection of autophagosomes via electron microscopy or the measurement of static LC3B-II levels by western blot analysis).[9] In addition to our studies, emerging literature suggests that autophagy 'activity' may play alternative roles in specific lung cell types, depending on the experimental condition.[10,11] Similarly, autophagy may play a complex role in the initiation or progression of lung disease, where in some cases autophagy may be pathogenic[6-8,12,13] and in other cases may be protective,[14,15] therefore making therapeutic targeting of this pathway in the lung a challenging task.

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INFLAMMATORY PATHWAY ACTIVATION BY INTERMITTENT HYPOXIA IN OBSTRUCTIVE SLEEP APNOEA

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Obstructive sleep apnoea (OSA) is a highly prevalent disorder, affecting about 14% of men and 5% of women, and its prevalence is rising rapidly due to the strong association of OSA with obesity. The disorder is characterised by repeated episodes of pharyngeal obstruction during sleep that lead to intermittent hypoxia (IH), sleep fragmentation, and excessive daytime sleepiness. It represents a worldwide public health burden and this is mainly attributed to the significant association of OSA with cardiovascular diseases. The mechanisms underlying cardiovascular disease processes in OSA are still incompletely understood, although there is now strong evidence that the particular form of IH observed in OSA, with repetitive short cycles of desaturation followed by rapid reoxygenation, plays a pivotal role in the development of cardiovascular comorbidities. Research from our group has identified that IH preferentially activates pro-inflammatory pathways mediated by the transcription factor nuclear factor-kappa B (NF-κB). NF-κB is a key player in inflammatory and innate immune responses that, when chronically activated, contribute to atherosclerosis by driving production of inflammatory mediators, which have also been found to be upregulated in OSA populations. The main source organ of the IH-dependent release of inflammatory mediators in OSA is still unknown. However, white adipose tissue (WAT) is a very attractive candidate given the close link between OSA and obesity.

This topic was presented in the flagship Cournand Lecture at ERS Congress 2015 by Dr Silke Ryan, and included new findings, corroborated using a true translational approach, indicating that IH may induce morphological changes of the adipose tissue known to promote inflammation and metabolic dysfunction. Future research will need to focus on the detailed mechanisms of these actions and may identify novel therapeutic targets. The Cournand Lecture commemorates a distinguished French scientist (André Frédéric Cournand) and is awarded every 3 years to the most successful young investigator in any field of respiratory disease.

OBSTRUCTIVE SLEEP-DISORDERED BREATHING IN CHILDREN AGED 2–18 YEARS: DIAGNOSIS AND MANAGEMENT

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Obstructive sleep-disordered breathing (SDB) is not a distinct disease, but rather a syndrome of upper airway dysfunction during sleep characterised by snoring and/or increased respiratory effort secondary to increased upper airway resistance and pharyngeal collapsibility. Obstructive SDB includes a spectrum of clinical entities with variable severity of intermittent upper airway obstruction ranging from primary snoring (snoring without apnoeas, hypopnoeas, desaturation, or arousals) to obstructive sleep apnoea syndrome (OSAS), which is defined as recurrent events of partial or complete upper airway obstruction (hypopnoeas, obstructive or mixed apnoeas) with disruption of normal oxygenation, ventilation, and sleep patterns. About 5–10% of children present with habitual snoring, while 1–4% of children express OSAS, making it a highly prevalent disease in children. The prevalence of OSAS is higher in children with additional risk factors, including obesity, Down's syndrome, etc. Furthermore, OSAS in children is associated with several short-term and long-term complications. A correct diagnosis and treatment of this condition is therefore mandatory.

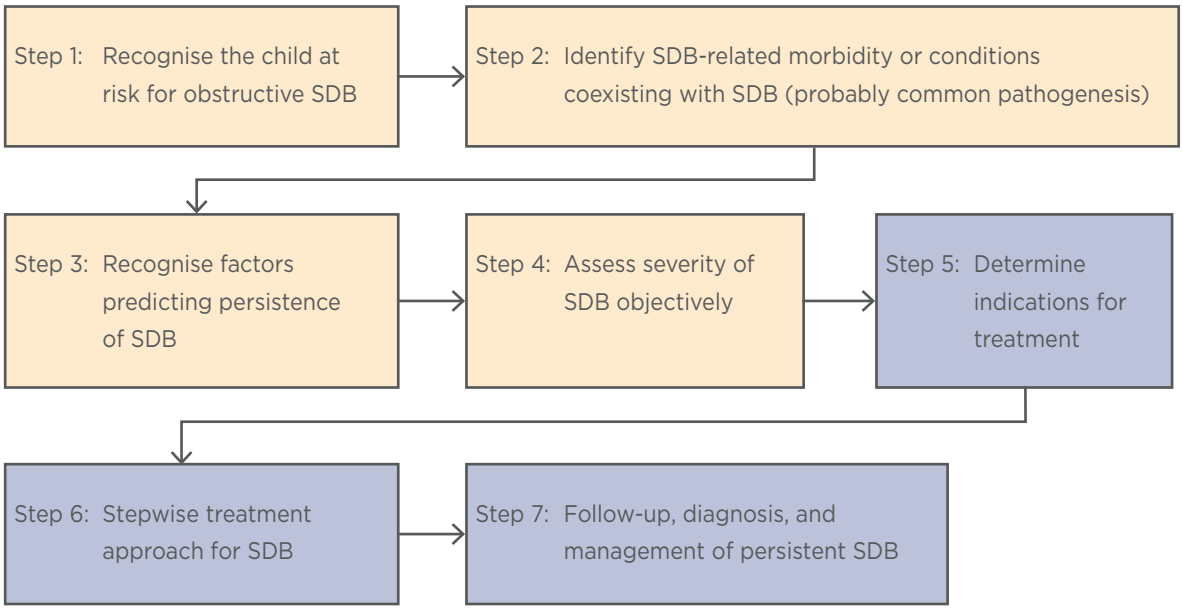

Figure 1: Algorithm for the diagnosis and treatment of obstructive sleep-disordered breathing (SDB) in children and adolescents.

Unfortunately, there is no uniformity in the literature or in clinical practice concerning diagnosis and treatment of this complex condition. Several guidelines exist, but these focus on selected populations and limited diagnostic tools.

The current presentation at the latest congress of the European Respiratory Society (ERS) reviewed a consensus statement of an ERS Task Force entitled 'Obstructive Sleep-Disordered Breathing in 2–18 Year Old Children: Diagnosis and Management'.[1] Compared with previously published guidelines, the unique characteristics of this document are the following:

- It refers to the entire severity spectrum of obstructive SDB, from primary snoring to OSAS
- It discusses conditions other than adenotonsillar hypertrophy and obesity that also predispose to obstructive SDB, including craniofacial abnormalities and neuromuscular disorders
- It takes into account the available diagnostic facilities and accepted treatment policies in different European countries, and describes alternative diagnostic modalities that can be used as alternatives for settings where polysomnography is not available
- It describes a step-by-step diagnostic and treatment approach

The ERS Scientific Committee approved the development of a document on the 'Diagnosis and Management of Obstructive Sleep-Disordered Breathing in Childhood' by a Task Force (TF-2012-09) in April 2012. Experts from several European countries and from countries outside Europe who were active within the ERS participated in the Task Force. The document contains a series of questions formed by the consensus of all members during two face-to-face meetings, with answers summarising the relevant literature. All answers have been incorporated into a stepwise diagnostic and management algorithm (Figure 1). The diagnostic algorithm for paediatric OSAS is divided into four steps: recognition of the child who is at risk for OSAS; identification of comorbidity; recognition of factors predicting persistence of OSAS; and finally the objective assessment of OSAS, in which alternative diagnostic methods other than polysomnography are also described. The treatment algorithm is partitioned into three steps: indications for treatment; stepwise treatment approach ranging from the least invasive to the most invasive treatment; and finally, follow-up, diagnosis, and management of persistent OSAS.

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CAN CATABOLISM AND IMMUNE RESPONSES BE ALTERED WITH PROPER NUTRITIONAL MANAGEMENT IN PATIENTS UNDERGOING MAJOR THORACO-ABDOMINAL SURGERY? – THE OPTIMAL PERIOPERATIVE CARE

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METABOLIC STRESS RESPONSE AND OUTCOMES

Surgical trauma induces a metabolic stress response that is associated with impaired recovery, postoperative complications, and prolonged hospital stay. The metabolic stress response depends on the extent and the type of the surgical procedure, as well as on a number of patient-related factors (e.g. cancer, malnutrition). Modifiable risk factors have recently been targeted in order to prevent a pathological stress response and hence improve outcomes.[1,2]

MEASURES TO MODULATE THE STRESS REPONSE AND TO IMPROVE OUTCOMES

Malnutrition is the most prevalent (approximately 40%) modifiable patient-related risk factor for (infectious) complications. Routine nutritional screening is therefore mandatory for every patient before undergoing major surgery. Patients at nutritional risk should benefit from 7 days of oral nutritional supplements before surgery, while 2 weeks of enteral or even parenteral nutrition are needed to condition severely malnourished patients.[3]

Immunonutrition contains active ingredients (arginine, glutamine, n-3 fatty acids, and ribonucleic acids) with the aim of not only improving nutritional status. These special formulae have also been shown to modify an overshooting postoperative stress response and to improve immune function.[4] Clinical impact has been studied in more than 20 randomised controlled trials (RCTs). Patients receiving perioperative immunonutrition had 50% fewer infections and overall complications; secondary gains were a reduced hospital stay (>2 days) and costs.[5]

As 'prevention is better than cure', the reduction of surgical trauma is an appealing concept that has been confirmed by the impressive results of minimally invasive surgery. Large-scale RCTs (COST, CLASSIC, COLOR, LAFA) demonstrated less pain, faster bowel recovery, fewer complications, and a shorter hospital stay in the laparoscopic groups. Again, one of the underlying mechanisms was a large reduction in the postsurgical stress reponse.[6-8]

MULTIMODAL PATHWAYS ENHANCING RECOVERY

The logical next step was to bundle multiple benefical measures within standardised care pathways aiming to optimise perioperative care and hence improve outcomes. Enhanced recovery after surgery (ERAS) pathways are multimodal concepts aiming primarily to attenuate the postsurgical stress response. The current guidelines recommend more than 20 individual measures with positive effects on stress response and/or outcomes. Important patient-related outcome measures targeted by the ERAS concept are homeostasis, comfort, and prevention/reduction of pain and nausea. Key items to achieve these goals are multimodal opioid-sparing pain management, stringent fluid management, minimally invasive surgery, and early mobilisation and food intake. Furthermore, unnecessary or even deleterious measures such as bowel preparation, prophylactic nasogastric tubes, drains, and urinary catheters for >24 hours can be safely omitted. Improvement of clinical outcomes depends on the application of the intended pathway.[9,10]

A recent meta-analysis of 16 RCTs (2,376 patients) confirmed a significant reduction in overall complications (40%) and hospital stay (2.3 days)

with no (negative) impact on mortality and readmissions.[11] Interestingly, this improvement was mainly due to fewer non-surgical (notably respiratory) complications while surgical morbidity remained unaffected. Furthermore, ERAS pathways have been shown to be cost-effective.[12]

SUMMARY AND CONCLUSION

- Multimodal pathways help to standardise and optimise perioperative care
- Multiple evidence-based measures contribute to modulating an overshooting postoperative stress reponse and thus to enhancing our patients' recovery
- Perioperative nutrition and minimally invasive surgery are key factors
- As a consequence of optimised perioperative care, patients and hospitals benefit from reduced complications, hospital stay, work burden, and costs

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WEANING IN CHILDREN: FROM BASIC PHYSIOLOGY TO A COMPUTER-DRIVEN WEANING PROTOCOL

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Mechanical ventilation is a life-saving therapy and up to 50% of a patient's total time on mechanical ventilation is devoted to the process of weaning. The weaning process starts when the underlying disease for which the patient was ventilated has entered a stabilisation phase, and ends when the patient is able to breathe spontaneously, without any ventilatory support, for at least 48 hours. As in adults, assessment of readiness to wean in children is achieved by initiating a trial of unassisted breathing, i.e. a spontaneous breathing trial (SBT).

In the absence of protocols, patient management during weaning is determined by the availability and experience of the clinical staff. Attempts to standardise weaning have led to the establishment of written protocols. In written weaning protocols, three distinct steps are identified: 1) screening of the clinical condition, including respiratory function, with defined criteria to identify those children who may be eligible for an SBT; 2) trials of spontaneous breathing that are performed at least daily, either with a T-piece, continuous positive airway pressure, or in pressure support ventilation mode; and 3) a 48-hour period following extubation to assess extubation success or failure. It is estimated that a ratio of 10–15% of children failing extubation (indicated by a need for non-invasive ventilation and/or re-intubation) is appropriate in a paediatric intensive care unit (ICU).

In paediatrics, two randomised clinical trials investigating the impact of written weaning protocols have shown some benefit in critically ill children, although another failed to demonstrate any difference in the duration of mechanical ventilation. However, when the weaning strategy is standardised with a written protocol, several factors lead to low protocol compliance, including: 1) availability of caregivers; 2) the physician's unfamiliarity with the protocol; 3) difficulty in communication between respiratory care practitioners and physicians when seeking an order for an SBT; 4) specific reasons cited by the physician for not advancing the patient to an SBT; and 5) lack of stationary unit assignments by respiratory care practitioners performing the protocol.

Another approach to protocol-directed weaning is based on gradual alteration of mechanical ventilatory settings with a computer-driven weaning protocol (CDWP). The level of ventilatory assistance is continuously adapted and gradually decreased to a level corresponding to an SBT. In CDWPs, an SBT is automatically performed and a message is displayed when the patient has passed. CDWPs integrate the clinical knowledge of expert clinicians regarding weaning into a ventilator. As a result, CDWPs solve the issue of low compliance with protocols. A variant of an adult CDWP (SmartCare®, Dräger Medical, Lübeck, Germany) has been evaluated in a pilot paediatric randomised clinical trial and resulted in a decrease of weaning duration when compared with usual care. In a prospective, cross-over clinical trial, another CDWP (IntelliVent®, Hamilton Medical, Bonaduz, Switzerland) succeeded in keeping the children within normal ventilation during the weaning phase. However, both CDWPs need a specific ventilation mode (pressure support ventilation and adaptive support ventilation, respectively), are proprietary to a specific company, and cannot be used in children of all ages (body weight more than 15 kg and 7 kg, respectively). It is clear that CDWPs can do what caregivers cannot, i.e. a continuous assessment of patient breathing status and adaptation of ventilatory support. However, there is still a need to improve the technology and validate its use in children. Another research avenue for CDWPs is their integration into ICU electronic medical records instead of a ventilator.

USING SIMULATION FOR TRAINING AND CERTIFICATION OF TECHNICAL SKILLS

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Growing concerns for patient safety, productivity, and increasing repair costs have challenged the traditional 'see one, do one, teach one' apprenticeship model in which doctors practise on patients.[1-3] Overwhelming evidence indicates that simulation-based training can play a major role in the training of new physicians, but it must be implemented according to the best available evidence.[4] The 'How to reach targeted educational outcomes' workshop at the ERS Congress asked participants to consider the following six statements:

1. Simulation-based training should replace the traditional apprenticeship model for learning clinical skills – FALSE

Pilots who spend many mandatory training hours in the most advanced simulators still start out as co-pilots paired with a more experienced colleague. Medical simulation cannot replace supervised performance of procedures on patients, but should be used to create 'pre-trained novices' who enter the learning curve at a higher level. Simulation-based training is safer, cheaper, and more effective than apprenticeship training in the early part of the learning curve.[5]

2. Every pulmonary department with trainees should have virtual reality simulators and physical phantoms for simulation-based training – FALSE

Every household does not need to have its own gym and every department does not need to have its own simulation centre. The Simulation Centre at

Rigshospitalet, Copenhagen, Denmark, has invested several million euros in simulators, has more than 50 specially trained consultants working as instructors, and trains physicians from 18 affiliated hospitals (Figure 1).[6] Departments and hospitals must collaborate to use the simulation resources and know-how efficiently.

3. The fidelity of the simulators is very important for the learning outcome. Higher realism equals better learning – FALSE

Generally, too much importance is put on equipment – it is not about the tool, but about how we use it. Expensive simulators risk 'gathering dust' if all available resources are spent on equipment without ensuring dedicated and trained personnel for simulation. Simple physical models can be as effective learning tools as virtual reality simulators and evidence indicates that the different training modalities effectively supplement each other.[7,8]

4. Full-day hands-on courses are very effective for learning technical skills – FALSE

It is difficult to learn new technical skills. Mass practise in full-day courses leads to exhaustion and cognitive overload, which reduces the learning outcome compared with distributed learning.[9] If logistically feasible, it is much more effective to practise for 2 hours on four different occasions than to practise for 8 hours in a row.

5. A consultant needs to be present at all times during training to give instructions and offer feedback – FALSE

Imagine arriving at an unfamiliar city for a dinner with a friend. If he meets you at the train station and walks with you to the restaurant then you will arrive quickly but will not be able to find the restaurant again by yourself. However, if you use a map and find your own way then you will remember the location and can navigate there without your friend in the future. Directed, self-regulated learning has been shown to improve retention compared with instructor-led training.[10] As such, instructors should perform demonstrations and give directions, but also allow trainees to practise alone, experiment, and learn from their mistakes. At the same time, feedback is indeed important and trainees should *not* be left alone to figure out the simulation-based training.

6. End-of-course exams are only necessary if required by the authorities, otherwise the time is better spent with extra training – FALSE

All students will agree that exams have a motivating effect. Mastery learning ending with a practical test can ensure basic competency, but is also an efficient learning method. The 'testing effect' of an exam improves retention compared with the same amount of extra training.[11]

Figure 1: The endoscopy room at the Simulation Centre, Rigshospitalet, Copenhagen, Denmark.

In conclusion, trainees must practise before performing supervised clinical procedures on patients. Equipment is just a (small) part of the puzzle. Training periods should be spaced out whenever possible and should allow trainees to find their own way and learn from their mistakes. Finally, those learning should be trained *and* tested!

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A YOUNG MAN WITH NODULES AND ENLARGED LEFT PULMONARY ARTERY

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This abstract reports the case of a young man complaining of acute haemoptysis and shortness of breath. In the emergency room, he showed no sign of respiratory or cardiovascular distress. His chest X-ray showed a dilated left pulmonary artery, as well as nodules and enlarged vessels on the right-hand side. Although there were nodules and sub-pleural opacities, the main finding consisted of vascular abnormalities.

Besides haemoptysis and shortness of breath during exercise, the patient also suffered from chronic headaches and recurrent oral aphthous ulcers. The physical examination was normal except for oral ulcers and acneiform lesions on the back. The haemoglobin level was 11 g/dL, the C-reactive protein level was 35 mg/mL, and the erythrocyte sedimentation rate was 50 mm/h. We performed an enhanced-contrast computed tomography scan that confirmed a left pulmonary artery aneurysm (PAA) 4 cm in size on the left lower lobe, as well as two other aneurysms of right pulmonary branches. These aneurysms were sacculated and partially thrombosed on the circumference. Peripheral condensations due to pulmonary infarcts and a thrombus of the right ventricle were also identified. These lesions are highly suggestive of Behçet's disease (BD).

The diagnosis of BD is based on the new International Criteria for BD,[1] which display good specificity and sensitivity (94% and 95%, respectively) when the overall disease score is ≥4 points. Our patient's signs were: oral ulcers (2 points), vascular lesions (1 point), and pathergy phenomenon (1 point), demonstrating a typical case of vascular BD with pulmonary artery involvement (aneurysms and thrombosis) and right heart thrombosis. Peripheral venous thrombosis and systemic artery involvement could also be observed. These vascular lesions are often associated with oral and genital ulcers and pathergy phenomenon.[1,2] PAAs are the most severe manifestation of BD, with rupture being potentially fatal within a few minutes. Haemoptysis is both the main symptom of PAA (being massive in 26% of patients) and the leading cause of death. PAAs are sacculated

and partially thrombosed, and their constitution is due to massive infiltration of the artery wall by neutrophils, monocytes, and lymphocytes, leading to degeneration of elastic laminae, intima thickening, and thrombosis. Vasa vasorum occlusion, neoangiogenesis of the wall, and thrombi are all striking features.[3,4] BD pathogenesis involves a genetic predisposition, which occurs more frequently in Asians and those from the South Mediterranean region, and environmental factors that activate the immune system through heat shock proteins, such as bacterial infections.[2]

Treatment should be instituted in an emergency. In the case of massive haemoptysis, the feasibility and efficacy of embolisation have been demonstrated using coils, liquid products, or plugs. However, recurrence of haemoptysis is possible.[3] Surgery should not be attempted because of the high risk of mortality, complications, and PAA recurrence.[5] The mainstay of treatment is immunosuppression (IS). In cases with pulmonary artery involvement, the European League Against Rheumatism recommends corticosteroids, administered initially as boluses and then orally, and monthly intravenous cyclophosphamide treatment for 1 year, after which treatment is switched to azathioprine.[2] These recommendations are based on retrospective series and there is a huge need for randomised controlled trials. Anticoagulation is contraindicated in cases of PAA and its efficacy in pulmonary thrombosis has not been demonstrated. Even cardiac thrombosis should be treated with IS first. Colchicine is usually used to treat oral ulcers. Anti-tumour necrosis factor α has been successfully used in cases of resistance of PAA to IS therapy, although there is a risk of tuberculosis.[2]

Our patient, who was treated with steroids and IS, is doing well; the right lung PAA disappeared with total occlusion, while the left lung PAA diminished. Despite the absence of anticoagulation, lung infarcts and the right heart thrombus disappeared. Prolonged IS treatment and follow-up are, however, mandatory as BD evolution is characterised by unpredictable flares. In retrospective series, survival has been shown to depend on treatment group: IS with or without embolisation offers the best prognosis, while surgery and anticoagulation offer the worst. Overall, the prognosis of BD with PAA is still poor, with 26% of cases resulting in death at 7 years, and persistence of symptoms in 40% of cases.[2]

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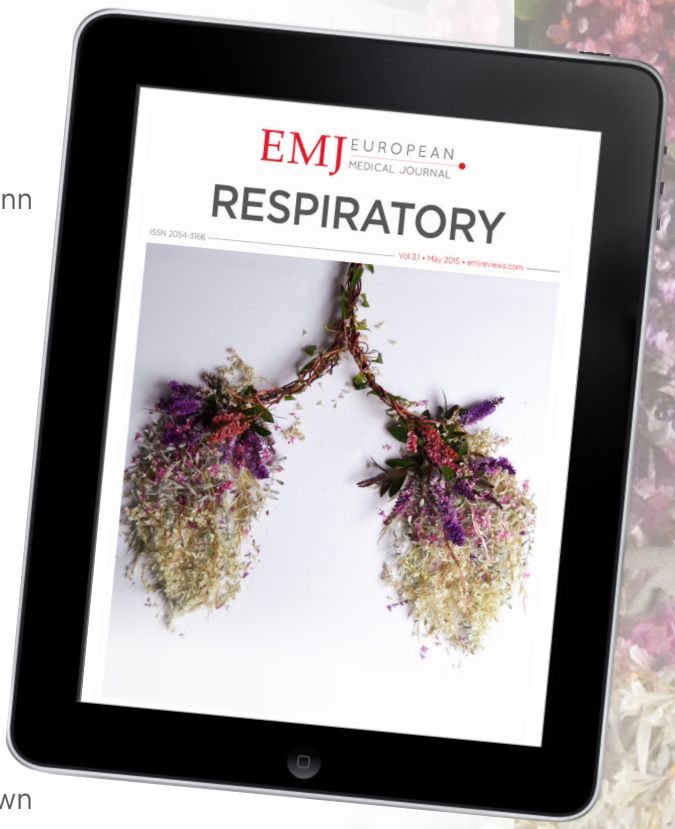

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CHALLENGES OF INHALER USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The mainstay of the pharmacological management of asthma and chronic obstructive pulmonary disease (COPD) is the use of inhaled drugs. This route enables drugs to be delivered to the site of their action, minimising the risk of adverse effects caused by systemic absorption. Drugs that can be administered by the inhaled route include the most commonly prescribed drugs for asthma and COPD, namely short and long-acting β_2 agonists and anticholinergic drugs and corticosteroids. There are two main types of inhalers: pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). pMDIs were introduced in the mid-20th century. The active drug is held in suspension or solution in a canister with a propellant. Proper use of pMDIs requires the patient to apply a series of techniques correctly: i) fire the device, releasing the aerosol very shortly after the initiation of inspiration; ii) inspire slowly and deeply; and iii) hold their breath. Many patients find this procedure difficult. Modifications and add-ons include breath-activated pMDIs and spacers and valved holding chambers; these help to obviate some of the problems with pMDIs. DPIs are breath-activated devices. Following priming, which is different for each device, the aerosol is generated by the patient taking a deep, rapid inspiration. This de-aggregates the powdered drug from its carrier. A prolonged breath-hold is then required. Many studies have shown that errors that may impair the effective delivery of the drug to the lungs, including critical errors, are very common with both pMDIs and DPIs. Such inhaler misuse has been shown to be associated with poorer symptom control and more frequent emergency department attendances. Errors in the use of inhalers can be a consequence of device-related factors, patient-related factors, and health professional-related factors. Minimising inhaler misuse requires the prescribing physician to choose, in cooperation with the patient, the most suitable device for the individual patient. Education and training with subsequent monitoring and re-training are thereafter crucial. There remains a need for more user-friendly devices, which provide constant doses of the active agent, in addition to built-in dose counters and patient feedback.

Keywords: Asthma, chronic obstructive pulmonary disease (COPD), inhaler, pressurised metered dose inhaler (pMDI), dry powder inhaler (DPI), adherence.

INTRODUCTION

Asthma is a chronic respiratory disorder characterised by airway inflammation and hyperresponsiveness, which causes airway obstruction that is reversible in the majority of cases.[1] Asthma results in episodic respiratory symptoms of cough, wheeze, chest tightness, shortness of breath, and sputum production. The aetiology of asthma remains poorly understood, although genetic and environmental factors are both important. Asthma is commonly classified as atopic or non-atopic. The former term implies a causative role of Type 1 hypersensitivity. It affects both children and adults and is common in both sexes. It is estimated that asthma currently affects

300 million people worldwide, and is responsible for 1 in every 250 deaths.[2] There are marked variations in its prevalence between countries, and it is generally more common in developed countries. However, it is increasing in frequency in underdeveloped countries. The economic costs of asthma are considerable: over a decade ago, the total direct cost to the USA was estimated to be $1.5 billion.[3]

The aim of asthma management is disease control. Complete control has been defined as follows: no daytime symptoms; no night-time awakening due to asthma; no need for rescue medication; no asthma attacks; no limitations on activity including exercise; normal lung function; and minimal side effects from medication.[4] International and national guidelines on asthma management stress that inhaled drugs are the mainstay of treatment.[4-6] Drugs that can be administered by this route include short and long-acting β_2 agonists and anticholinergic drugs, corticosteroids, and mast cell stabilisers. A stepwise approach to asthma management is recommended, starting treatment at the step most appropriate to the initial severity of the patient's condition, achieving early control, and maintaining control by stepping treatment up and down as appropriate. For mild intermittent asthma, an inhaled short-acting β_2-agonist is commonly used. If regular preventative therapy is required, evidence suggests that inhaled corticosteroids are likely to be the most effective. In younger children, however, oral drugs such as leukotriene receptor antagonists may be preferred. A rational next step would be to add a long-acting β_2 agonist. The use of mast cell stabilisers and anticholinergic drugs has generally diminished, but may be useful in individual patients.

Chronic obstructive pulmonary disease (COPD) is not a single disease, but rather a heterogeneous collection of disorders whose key defining feature is post-bronchodilator limitation of expiratory airflow by comparison with lung volume.[7] This is associated with chronic inflammation, with mucous plugging, fibrosis, and parenchymal destruction. Airflow is usually measured by the forced expiratory volume in 1 second (FEV_1) and lung volume as the forced vital capacity (FVC). To some extent, the definition is arbitrary and the chosen cut-off for FEV_1:FVC has varied. Both FEV_1 and FVC decrease with age, but FEV_1 does so more rapidly, adding a further complexity to the definition. However, a ratio of <0.7 is most usually used as the cut-off.[7] The two principal disorders constituting COPD are chronic bronchitis and emphysema. There are a number of conditions in which there may be a restriction in expiratory airflow, but which are usually excluded from the definition of COPD. These include cystic fibrosis and bronchiectasis. COPD is the third leading cause of mortality worldwide. Cigarette smoking is the leading cause of COPD but it can occur in those who have never smoked. Cough, mucus production, chest tightness, and shortness of breath on exertion are the main symptoms of COPD, a further characteristic feature of which is the occurrence of exacerbations, often infective.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), established in 1998, has played a leading role in championing improved management of COPD.[8] As with asthma, mainstays of drug treatment are short and long-acting β_2 agonists, anticholinergic drugs, and inhaled corticosteroids. Given that a degree of irreversibility of airflow is, by definition, present in COPD, β_2 agonist bronchodilators have obvious limitations and there is therefore a greater potential role for anticholinergic drugs.[9] The aim of management is the relief of present symptoms and reduction in the risk of future adverse health events.[10,11] A common system is to divide patients into four groups depending on the severity of current symptoms and the severity of future risks. Short-acting β_2 agonists are recommended for current symptom relief in all groups. Such treatment may suffice for those patients with low-risk and mild symptoms (Group A). For those with low-risk but more severe symptoms a long-acting bronchodilator is recommended (Group B). For those assessed as being at increased risk of future events, a corticosteroid in combination with a long-acting β_2 agonist or a long-acting anticholinergic drug are recommended because these reduce exacerbation rates and improve lung function and health status (Group C and Group D).

Inhaled therapy for asthma and COPD seeks to deliver drugs rapidly and directly into the airways (the site of the pathology). This allows high local drug concentrations to be achieved, whilst limiting systemic toxicity. Inhaled therapy can be given via a nebuliser, a pressurised metered dose inhaler (pMDI), or a dry powder inhaler (DPI). Only the latter two of these will be considered in this review.

PRESSURISED METERED DOSE INHALERS

Introduced in the mid-20th century, pMDIs remain the most commonly prescribed device for delivering inhaled therapy. They deliver a fixed medication dose from a pressurised canister containing a mixture of the drug and a propellant. Previously, the propellant was a chlorofluorocarbon, but these have now been replaced by hydrofluoroalkanes. The drug may be held either in a suspension or in a solution. After the aerosol is released, the propellant evaporates and deposits the active drug along the respiratory tract.

The steps that must be followed when using a pMDI are as follows: the cap is removed from the inhaler mouthpiece; the inhaler is shaken (this is not necessary if the drug is in solution); the inhaler is held upright; the patient breathes out maximally; the inhaler mouthpiece is placed between the patient's lips and teeth, with the tongue out of the way of the mouthpiece; the patient starts breathing, and just after fires the inhaler; the patient continues to breathe in slowly and as deeply as possible; the inhaler is removed from the mouth whilst the breath is held for as long as possible (preferably at least 10 seconds); finally, the patient breathes out slowly.[12] Slow inhalation reduces the quantity of drug deposited in the oropharynx, maximal inspiration facilitates peripheral deposition of the drug, and holding the breath for as long as possible facilitates sedimentation and diffusion by Brownian motion. If the device is fired too early (prior to the onset of inspiration) or too late then delivery of the drug to the lungs is markedly reduced. There is much room for error and many patients find using pMDIs difficult.

A number of modifications and add-ons to pMDIs have been developed. With breath-activated pMDIs, airflow at the onset of inspiration triggers release of the inhaler. This overcomes the difficulty many patients have coordinating firing of pMDIs with the onset of inspiration. Spacers (valved holding chambers [VHCs]) were developed to help overcome the same problem.[13] The aerosol is captured in a reservoir before the patient breathes it in. However, the patient is still required to inspire slowly and then hold their breath. Used appropriately, deposition of the drug is reduced in the oropharynx and increased in the lungs. The valve in VHCs prevents expiration into the aerosol. Even with these add-ons, drug delivery to the lungs can still be significantly impaired if there is a long delay between releasing the aerosol and inhalation. Moreover, plastic devices accumulate electrostatic charges, which attracts aerosol particles to the walls of the chamber. Regular cleaning with a household detergent is necessary to counter this. It is not possible for the patient to know when a pMDI is nearly empty, other than by keeping a careful count of the number of doses used.

DRY POWDER INHALERS

DPIs are breath-activated devices. The drug is either housed in a rigid gelatine capsule that is then placed in a holder, or delivery chamber, and released by piercing, or multiple doses are enclosed in a reservoir or in a foil strip. The steps that must be adhered to when using a DPI are as follows: the mouthpiece cover is removed; the patient sits upright or stands; the inhaler is primed according to the instructions for the specific device; the patient exhales completely, away from the mouthpiece; the mouthpiece is placed between the teeth and the lips are closed around it; the patient inhales as forcibly as possible, trying to breath faster as the breath progresses; the inhaler is removed from the mouth; the breath is held for as long as possible; the patient breathes out slowly; and the cover is replaced.[12] The turbulent flow generated by inspiration is crucial for de-aggregating the drug from its carrier. The subsequent size of the aerosol particles varies with the acceleration and the velocity of the airflow achieved during inspiration. In turn, this affects where the particles are deposited in the respiratory tract. Some DPIs have a low internal resistance and require the patient to generate a high inspiratory flow. Others have a higher internal resistance and the respiratory flow required to generate sufficient turbulence is lower. Devices are available to measure the inspiratory flow rates that individual patients can generate.[14]

Whilst DPIs overcome some of the problems of pMDIs, they introduce new ones: some patients, particularly young children and the very old, are unable to generate sufficient inspiratory flow to effectively use DPIs; humidity and environmental temperature changes can affect the de-aggregation of the drug and carrier; and if the patient exhales into the device prior to inhaling, the powder will be dispersed and will tend to clog the tube. These factors differ according to the individual device.

Therefore, it is simplistic to attempt to choose an inhaler based solely on patient age. However, in general the majority of children over 5 years of age can generate sufficient inspiratory pressures to use DPIs.[15]

PROBLEMS WITH EXISTING DEVICES

The Extent of Inhaler Misuse

The incorrect use of pMDIs and DPIs is common.[16] Giraud and Roche[17] devised a system for primary care physicians to assess the adequacy of patients' inhalation techniques for pMDIs. They subdivided failings in any of the steps involved in correct use of the device as either omissions or errors. Omissions include failing to remove the cap, not holding the inhaler correctly, the device not being actuated at the beginning of inspiration, no slow inspiratory flow, >1 puff, and no 5-second breath-holding period at the end of inspiration. Errors included forced expiration, no expiration, inspiration through the nose, actuation of the device at the end of inspiration, and no inspiration. Patients were classified as 'misusers' if at least one error or omission was made. A total of 4,078 adults were assessed and 71% were classified as misusers, with 47% of these showing evidence of coordination difficulties. Molimard and colleagues[18] studied a mixed group of 3,811 adult patients with asthma and COPD who were using a variety of pMDIs and DPIs. GPs were asked to assess the adequacy of the patient inhaler techniques using both generic and device-specific criteria. Errors were considered 'critical' if they could have substantially reduced drug delivery to the lungs. Overall, 76% of patients made errors with pMDIs and these were considered critical in 28%. Depending on the device, at least one error was made with DPIs in 49–55% of patients, which were considered critical in 11–32% of patients.

A subsequent literature review of data from various European studies confirmed very high error rates in the use of inhalers.[19] This review concluded that up to 50% of patients in Europe were not using inhalers correctly. In addition, up to 40% of children were not using spacer devices correctly. Lavorini and colleagues[20] evaluated published data on the errors made with DPIs in patients with asthma and COPD. They found that, depending on the type of inhaler and method of assessment, between 4–94% of patients did not use their inhalers correctly. Although different studies have found marked differences in error rates between different types of inhalers, these are not consistent between studies; a device which performed well in one study may perform poorly in another.[12,20,21]

The problem of poor inhaler technique is not confined to primary care. A multicentre, cross-sectional, observational study of 1,664 adult patients with asthma and COPD attending chest clinics in Italy found evidence of critical mistakes, ranging from 12% of patients for MDIs up to 44% of patients using one particular type of DPI (the Turbohaler).[22]

The Consequences of Inhaler Misuse

There is accumulating evidence that misuse of inhalers contributes significantly to poor symptom control. Giraud and Roche[17] correlated their findings regarding patient's inhalation techniques with asthma instability scores based upon: daytime respiratory symptoms; asthma-related nocturnal waking; exercise-induced asthma; β_2 agonist use; serious exacerbations; and global assessment by the GP of the evolution of the patient's condition during the previous month. They found asthma to be less stable in pMDI misusers than in correct users, with asthma instability scores of 3.93 versus 2.86, respectively ($p<0.001$).

In an Italian study performed in asthma and COPD patients, the finding of critical errors in inhaler technique was associated with an increased risk of hospitalisation ($p=0.001$), emergency department visits ($p<0.001$), use of antibiotics ($p<0.001$), and courses of oral corticosteroids ($p<0.001$).[22] Al-Jahdali et al.[23] reported a cross-sectional study of all patients (n=450) visiting an emergency department with asthma over a 9-month period in two major hospitals in Saudi Arabia. The inhaler technique of each patient was assessed using a checklist, and asthma control over the preceding month was assessed by administering an Arabic version of the asthma control test (ACT).[24] There was evidence of improper device use in 45% of patients. This was associated with uncontrolled asthma ACT scores ($p=0.001$) and three or more emergency department visits ($p=0.0497$). The authors concluded that improper asthma device use was associated with poor asthma control and more frequent emergency department visits.

The Reasons for Inhaler Misuse

Sanchis and colleagues[12] undertook a literature review of the errors observed whilst using pMDIs and DPIs. Only 34% of patients were assessed as

having an overall adequate technique when using pMDIs. Errors were made in every step of the process, with particularly frequent errors involving the need to shake the device, the coordination of firing the device with the start of inspiration, continuing to breathe slowly and deeply after firing the device, and breath holding. With regards to DPIs, the errors made varied significantly depending on the type of DPI. However, common errors occurred in relation to priming the devices, breathing out and away, inspiring forcefully and deeply, and breath holding. Overall, up to 19% of patients were judged to have made critical errors.

A useful method of considering why there is such a high rate of inhaler misuse is to assess those that are device-related, patient-related, and healthcare professional-related.[16] The extraordinary range of available devices is testament to manufacturers' attempts to overcome the problems with existing devices; unfortunately, this factor has become part of the problem itself. Devices differ according to whether the aerosol is generated actively or passively, whether it is held in suspension, solution, or as a dry powder, whether they contain single or multiple doses, are disposable or refillable, and what a 'standard dose' is. A degree of manual dexterity and hand–breathing coordination is required to successfully use all inhalers. Patients differ in the value they attach to their inhalers, the importance they perceive their inhalers to have in controlling their symptoms, and in the consequent quality of their lives. In some cultures, the use of inhaled medication may be considered impolite in public. Some pMDIs contain alcohol that may not be acceptable for religious reasons. The importance of factors such as device aesthetics, medication taste, and ease of cleaning vary greatly between patients. The incorrect use of inhalers has been shown to be significantly associated with irregular clinic attendance and a lack of patient education.[23] Healthcare professionals including physicians, specialist nurses, and pharmacists play a crucial role in choosing which inhaler to prescribe/dispense, and in training patients to use their inhalers correctly, and yet studies have shown that only a minority of such professionals can themselves use inhalers correctly.[25]

Three patient groups deserve special mention: young children, the elderly, and those with learning and/or physical disabilities. Young children may not have the necessary cognitive and motor skills to use inhalers. Even if they do, their maximal inspiratory flow rates may be less than that required for breath-activated DPIs.[16] For these reasons, pMDIs with spacers, face masks, and oral medications are often used in the very young. Licensing issues may also be important to consider because some potentially suitable devices may not have a paediatric licence.

Manual dexterity, hand–breathing coordination, and cognitive functions may all decline with old age and therefore simpler-to-use and larger devices may help to overcome consequent difficulties. For those with disabilities, problems arising from cognitive and memory problems, physical problems, and visual–spatial difficulties may alone or in combination lead to difficulties using inhalers.

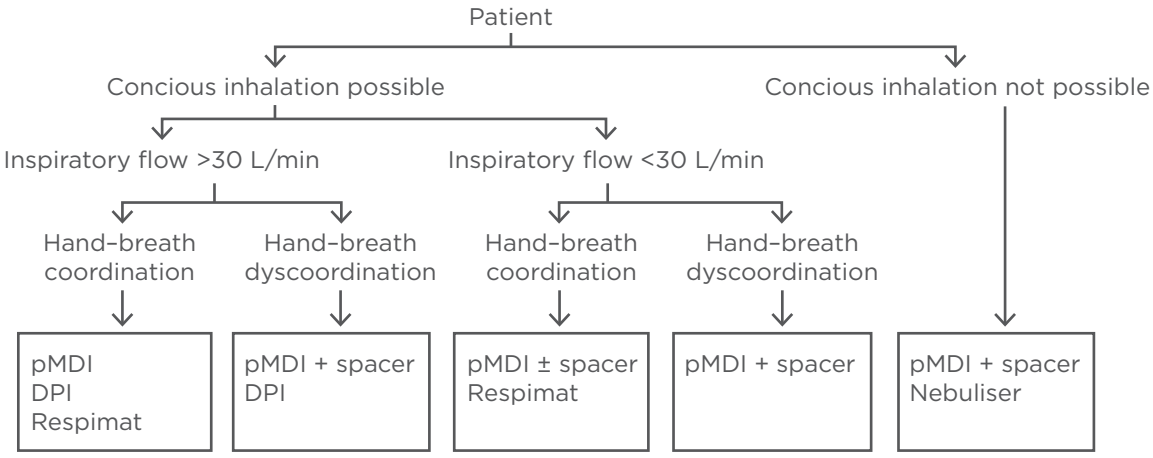

Figure 1: A clinical algorithm that utilises the patient's respiratory flow rate and hand–breath coordination to help physicians choose an appropriate inhaler device.[29]

DPI: dry powder inhaler; pMDI: pressurised metered dose inhaler.

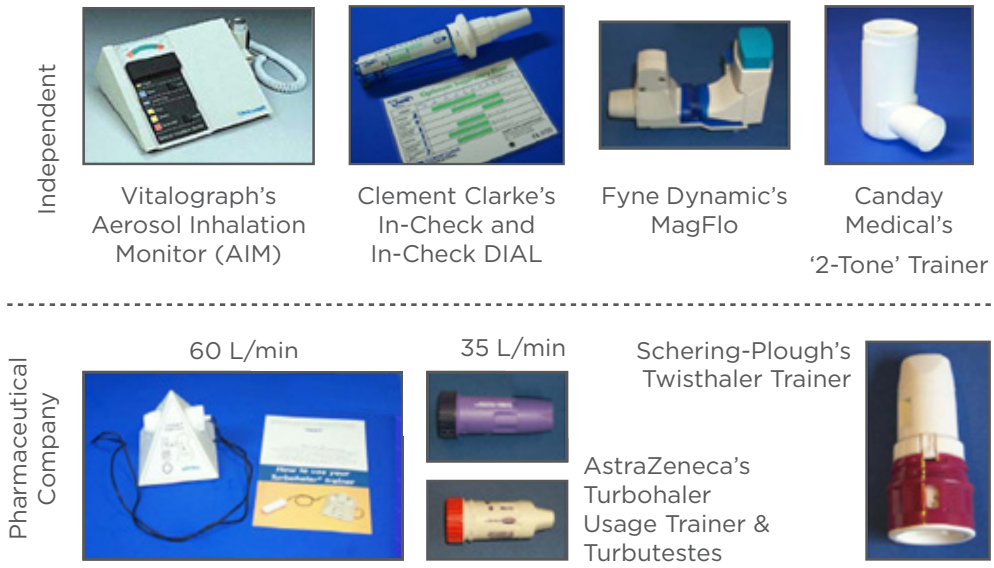

Figure 2: Non-commercial and commercial training tools for inhaler devices.[33]

Overcoming Inhaler Misuse

Overcoming problems with the use of inhalers starts with the prescriber choosing the most appropriate device for the individual patient.[26,27] This must be followed by educating and training the patient in the use of the device (alongside more general asthma and COPD education and training). A system of monitoring should be in place, along with ongoing training, in order to maintain an appropriate level of patient skill.

The key issues to consider when choosing an inhaler is the device(s) with which the patient is already familiar or already using, the patient's preference, their ability to use the device correctly, the availability of devices that can deliver the desired drug, the convenience and portability of available devices, and the familiarity of the physician with potential devices.[28] The opposing breathing techniques needed to correctly use pMDIs and DPIs means that their concurrent use has obvious disadvantages and is discouraged. In practice, however, the use of short-acting β_2 agonists given via pMDIs is so common that many patients do use both types of device concurrently. Algorithms can be of assistance to help physicians make the most appropriate choice of inhaler device (Figure 1).[29]

Educating patients and the families of patients with asthma and COPD about the rationale for the use of inhaled medication, and the problems and pitfalls associated with it, should help them to understand why good inhaler-use technique is likely to be critical to achieving the shared physician–patient goals. This is distinct from training in the use of an individual device. It is important to identify who is responsible for device training. This may be the prescribing physician, a specialist nurse, or the dispensing pharmacist. Whoever is responsible must themselves have appropriate knowledge and skills. It has been demonstrated that training sessions for healthcare professionals are effective.[30,31] Focussed interventions with patients teaching inhaler technique have been shown to be effective in reducing inhaler errors. Physical demonstration of how to use a specific inhaler is more effective than only providing written or verbal instructions.[32] The technique should be explained, demonstrated, and then the patient's technique physically checked. The use of checklists and objective tools to assess correct inhalation patterns for specific devices can be helpful (Figure 2).[33] Training sessions can be provided individually or in groups, and group sessions at school for children may be useful. Inhaler technique tends to deteriorate quickly and regular repetition of training is essential.[34] In addition, patients should have access to written or electronic information to which they can refer between training sessions, particularly if the use of inhaled medication is on an intermittent basis.

If patients continue to show poor technique with a particular device despite appropriate education and training then switching to a different device whose properties are likely to overcome the

patient's specific difficulties should be made. In this regard, the Respimat® Soft Mist™ inhaler is a relatively new type of device that, in a similar manner to pMDIs, delivers drugs as an aerosol. Rather than using a propellant, however, the aerosol is generated mechanically by forcing a metered dose of the drug in solution through a uniquely designed nozzle, which produces a fine mist. The advantages claimed over conventional devices include ease of use with regards to coordination and the improved deposition of the drug in the lungs rather than in the upper airways.[35]

Finally, inhaler devices require intermittent cleaning. Patients should be reminded of the importance of this and asked to follow the manufacturer's instructions. Failure to do so may result in a loss in the efficacy of drug delivery.[36]

THE FUTURE

The 'ideal' inhaler has yet to be designed. Empirically, it would be user-friendly, not require priming or coordination between triggering and inhalation, would provide dose consistency independent of environmental conditions and inhalation manoeuvres, have a dose counter that was based on actual inhalations rather than manipulations, would provide the patient with a clear but not unpleasant perception of drug delivery, and would provide feedback to confirm that a dose had been inhaled, that the technique used was correct, and provide a reminder about adherence.[21]

Manufacturers are exploring the use of new technologies, both intrinsic and extrinsic to the devices, in order to improve compliance. The extrinsic technologies include, for example, phone apps. Some of these may significantly add to the costs of treating asthma, at least in the short term.

CONCLUSIONS

Despite the seemingly alarming statistics regarding how often inhalers are used incorrectly, the fact that they are the preferred method of delivering drugs to treat patients with asthma and COPD is in itself evidence of their overall efficacy. The requirements of any two patients are hardly ever exactly the same. Therefore, it is unlikely that one 'ideal' inhaler would suit all patients. The physician treating patients with asthma or COPD has the luxury of a wide choice of inhalers that, if used correctly, can deliver the active drug to where it is required, minimising the risk of adverse effects. To optimise therapy, however, the choice of which inhaler to prescribe needs to be an informed one and made carefully in collaboration with the patient. Specific training in the use of the device is essential, as is ongoing monitoring and re-training. Clinicians should be willing to switch patients to alternative inhalers if, despite all of this, the patient is unable to use the device correctly.

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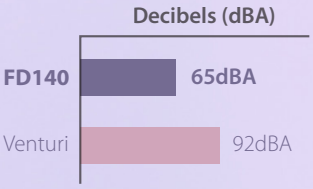

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POSITIVE PRESSURE THERAPIES USED IN THE TREATMENT OF POSTOPERATIVE RESPIRATORY FAILURE – EVIDENCE FOR USE AND FUTURE DIRECTIONS

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ABSTRACT

Postoperative respiratory failure (RF) is a common problem following all types of major surgery, and which has significant implications for morbidity, mortality, and cost to healthcare systems. Although postoperative RF is usually multifactorial in origin, the development of atelectasis perioperatively is a significant contributory factor. A number of different techniques and devices that apply positive pressure to patients' airways, in an attempt to prevent development of atelectasis and RF following surgery, have been studied in this patient group. Non-invasive ventilation (NIV) is considered the gold standard management for prevention and treatment of postoperative RF and is supported by the greatest body of evidence. However, the delivery of NIV requires provision of a critical care bed, has significant economic implications, and is associated with patient compliance issues. Other techniques, such as high-flow oxygen delivered by high-flow nasal cannulae (HFNC), show some promise and are supported by evidence for benefit in related areas, but currently lack supportive evidence in postoperative patients. Positive pressure physiotherapy techniques, such as positive expiratory pressure therapy, offer an inexpensive and accessible alternative to patients, but also currently lack supporting evidence of benefit with regard to clinical endpoints. Future research in the challenging area of postoperative RF should address the potential alternatives to NIV, including the precise role of HFNC, therapies that may be utilised outside of critical care areas, and combinations of existing therapies.

Keywords: Pulmonary atelectasis, postoperative complications, non-invasive ventilation, high-flow nasal cannulae (HFNC), positive expiratory pressure therapy.

BACKGROUND

Postoperative hypoxia is a well-recognised complication of major surgery that may have a detrimental impact on patient outcomes.[1] Postoperative hypoxia due to the intraoperative development of atelectasis may initially be mild, but it frequently progresses to become established respiratory failure (RF),[2,3] which has significant associated morbidity and mortality.[3] Whilst the impact of any intervention on overall mortality in elective surgical populations is often difficult to quantify due to a low baseline risk, the potential to reduce other adverse healthcare-related events has significant implications for improvement of patient outcomes and economic factors.[1]

Established RF is a common reason for invasive ventilation of surgical patients, with up to 20% of all ventilated intensive care unit (ICU) patients being ventilated due to postoperative RF.[4]

Postoperative RF may occur following a wide range of major surgical procedures,[5] including cardiac,[6] thoracic,[7] vascular,[8] and abdominal operations.[9] It is estimated that as many as 40% of patients will develop respiratory problems following abdominal surgery.[10] As such, the management of complications and RF following major surgery is an area of great interest and research focus.

The pathogenesis of postoperative RF is multifactorial in origin with the development and progression of atelectasis, which may begin intraoperatively and be compounded by a multitude of perioperative factors such as patient discomfort, immobility, and fluid shifts, recognised as being pivotal in the development of established postoperative RF.[11] Approaches to postoperative RF management should always include an appropriate analgaesia regime – often multimodal in delivery to allow patient mobilisation and engagement with therapy whilst ensuring maximal patient comfort – as well as specific interventions to prevent and reverse atelectasis.

A number of positive pressure techniques, which may attenuate the process of atelectasis progression and subsequent development of postoperative RF, have been studied in surgical populations. These include the use of non-invasive ventilation (NIV) and high-flow nasal cannulae (HFNC) to deliver humidified, high-flow oxygen to patients, as well as physiotherapy techniques such as the positive expiratory pressure (PEP) valve device.

This review aims to discuss the evidence supporting the use of these positive pressure interventions and discuss potential future avenues for research and practice in this commonly encountered area.

POSTOPERATIVE NON-INVASIVE VENTILATION

In recent years there has been considerable interest in the use of NIV, which encompasses both continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NPPV) support, to prevent and treat RF following major surgery.[12-14] It has been demonstrated that NIV use in selected patient groups may reduce the incidence of postoperative hypoxia, respiratory failure, rates of reintubation, incidence of pneumonia, ICU and hospital length of stay, and potentially mortality.[15-17]

While NIV usage remains a popular and very attractive option for high-risk surgical patients, there are a number of factors that may act to limit its use and potential benefits. As NIV must be delivered via a tight-fitting mask or helmet, problems with interface fit, leakage, and patient discomfort are frequently encountered.[18] Patient non-compliance with therapy, particularly due to poor mask fit, leaks, and patient intolerance, is a common problem that may reduce the benefits of treatment.[19] In addition, due to the high level of monitoring required during treatment and the level of nursing input that is required for patients receiving NIV, it is usually delivered to patients in a critical care environment.[20] Therefore, the question of treating with NIV can become a balance of the costs incurred through equipment, disposables, staffing, and critical care bed provision against the potential savings made by preventing complications and reducing length of stay.

HIGH-FLOW NASAL OXYGEN

High-flow nasal oxygen, which is humidified high-flow oxygen delivered via nasal cannulae, is an emerging therapy for critical care and surgical patients. Conventional methods of oxygen delivery to patients are limited by maximum flow delivery rates of 15 L/min to patients whose maximum inspiratory flow rates may be as high as 120 L/min. This can result in the fraction of inspired oxygen (FiO_2) delivered being inconsistent.[21] HFNC allow delivery of air–oxygen mixtures at inspiratory flow rates of up to 60 L/min, which reduces the amount of ambient air entrainment and allows a more reliable and predictable FiO_2 delivery to patients.[22]

Whilst some debate exists regarding the precise mechanism of action of HFNC, it has been demonstrated to be a safe and effective means of providing respiratory support to patients at risk of or suffering from respiratory failure. It is thought that HFNC therapy derives its beneficial clinical effects from a number of favourable physiological mechanisms, including pharyngeal dead-space 'washout', alveolar recruitment, and reduced airflow resistance, which all promote enhanced respiratory parameters and gas exchange.[23-25] There is also evidence to suggest that the higher flow rates delivered via HFNC generate a variable degree of positive end-expiratory pressure (PEEP), which is quoted as being between 3–7 cm H_20 depending on a number of different patient factors.[26,27] The

mechanism of delivery also allows warming and humidification of inspired gases, which may improve function of the mucociliary system and better clearance of secretions.[28,29]

HFNC have been used with positive clinical effects in paediatric populations for some time.[30] While the evidence base for their use in adult patients is evolving, it is currently less compelling. However, there is emerging evidence that HFNC may be a useful alternative therapy to conventional oxygen therapy or NIV in a number of different clinical situations, where there is actual or pending respiratory failure.[31,32]

Patient comfort and tolerance of therapy with HFNC may be better than in several methods of conventional oxygen or NIV delivery,[33] and, as an intervention, it has the potential to be provided outside of Level 2 and 3 critical care facilities.[34] Therefore, HFNC may potentially provide a viable alternative to NIV use in surgical populations, offer cost savings, and provide patient benefits.

Physiotherapy Techniques

A number of different physiotherapy techniques are widely used in clinical practice to potentially reduce the incidence of respiratory complications in the postoperative period.[35] Physiotherapy techniques are widely utilised and form part of recommendations for the care of postoperative patients both inside and outside of critical care areas due to perceived patient benefits, ease of access, and availability.[36] They are generally well tolerated by patients and improvements in endpoints such as oxygen saturations, chest X-ray (CXR) appearances, and exercise tolerance are frequently observed. However, there is a relative lack of supporting evidence for the clinical benefit of physiotherapy when applied routinely in postoperative groups, or in those with established complications.[37]

Major surgery leads to loss of lung volume and patient immobility in the perioperative period, which in turn predisposes patients to the development of clinically significant atelectasis, secretion retention, chest infections, and possible RF. Postoperative physiotherapy aims to improve lung volume, aid secretion clearance, and improve mobility and levels of physical activity. A variety of different techniques are employed according to clinical need and patient ability, including early assisted mobilisation, exercise, thoracic expansion exercises, incentive spirometry, and airway clearance techniques, in order to attenuate this process and reduce the incidence of respiratory complications.[38]

Lung expansion and sputum clearance treatments are active wherever possible, with patient and therapist working together. However, passive techniques such as positioning and manual therapies such as percussion may be required to improve clearance of secretions[39] in less able or immobile patients. Breathing adjuncts such as PEP therapy, where patients generate an expiratory pressure of up to 20 cm H_20 by breathing against a mouthpiece valve device, may also be used postoperatively to increase functional residual capacity and mobilise secretions.[40] This is especially useful in those with dynamic airway collapse, such as smokers, or those with a history of chronic obstructive pulmonary disease (COPD). Figure 1 demonstrates the CXR changes seen before and after therapy with a PEP device following thoracic surgery.

Physiotherapy in the postoperative period is a multimodal specialty, and for the purposes of this review only positive pressure adjuncts will be further considered.

EVIDENCE FOR USE IN CURRENT PRACTICE

Non-Invasive Ventilation

Treatment with NIV is widely accepted to have beneficial effects on intubation rates and mortality in a wide range of patient groups with acute RF.[41-43] CPAP used prophylactically has been demonstrated to reduce rates of reintubation, pneumonia, and other pulmonary complications following abdominal,[16] vascular,[44] and cardiac surgery.[45] NPPV has been demonstrated to have mortality benefits when used in patients with RF following lung resection surgery.[17] Meta-analysis evidence suggests a mortality benefit associated with NIV usage in mixed postoperative populations.[15]

The decision regarding provision of NIV is often influenced by a number of different patient and organisational factors, including type and duration of surgery, patient comorbidities, and availability of Level 2 critical care beds. No definitive, unifying guidance for the postoperative use of NIV exists and it is often used variably according to clinician preference, or accepted local practice. Despite these issues, however, NIV is widely considered to be

a vital respiratory support therapy for the effective management of established postoperative RF.[46]

High-Flow Nasal Cannulae

Humidified oxygen delivered by HFNC is a relatively new intervention in adult populations, and in recent years the evidence base for its use in a variety of clinical settings where additional respiratory support is required has grown. HFNC have a number of physiological benefits that confer a potential advantage over the use of conventional oxygen therapy. In a recent clinical trial, it was demonstrated that the use of HFNC provided improved oxygenation and 90-day survival in patients with acute hypoxic RF when compared with treatment with NIV.[32] This is a very important finding as the benefits of NIV in hypoxic RF have been questioned for some time, and the emergence of an alternative and complementary therapy in this area is welcomed. HFNC have also been used to beneficial effect in recently extubated critical care patients. When compared with standard oxygen therapy, it was demonstrated that HFNC reduced extubation failure and reintubation rates.[33] It also aided the prevention of severe desaturations and hypoxia during intubations in critical care units.[47]

Use of HFNC has been studied in postoperative populations with some encouraging results. In a recently published, non-inferiority study, Stéphan and colleagues[31] found that the use of continuous HFNC in patients with hypoxaemia following cardiac surgery is as effective as intermittent NPPV in preventing a need for reintubation. A large, European, multicentre, randomised controlled trial is currently recruiting patients to compare the use of HFNC and standard oxygen therapy in patients with mild hypoxaemia following abdominal surgery. It is hoped that the results of this study will further clarify the role of HFNC in hypoxic postoperative patients and help to guide contemporary practice.

The available evidence supporting the use of HFNC would seem to suggest that they are effective in treating hypoxic RF, which is often the predominant aetiology in postoperative populations. However, studies that specifically address the issue of postoperative RF are currently lacking and the efficacy of HFNC therapy compared with CPAP postoperatively has yet to be studied. Concerns also remain regarding the possibility that the use of HFNC may lead to delayed intubation in patients with worsening RF, as has been seen previously with NIV use.[48] This phenomenon may to lead to an increase in mortality in patients treated with HFNC.[49] While there is encouraging emerging evidence to support the use of HFNC in a variety of settings, further work is required to help define their precise role in the management of postoperative RF, as well as the duration and timing of their use.

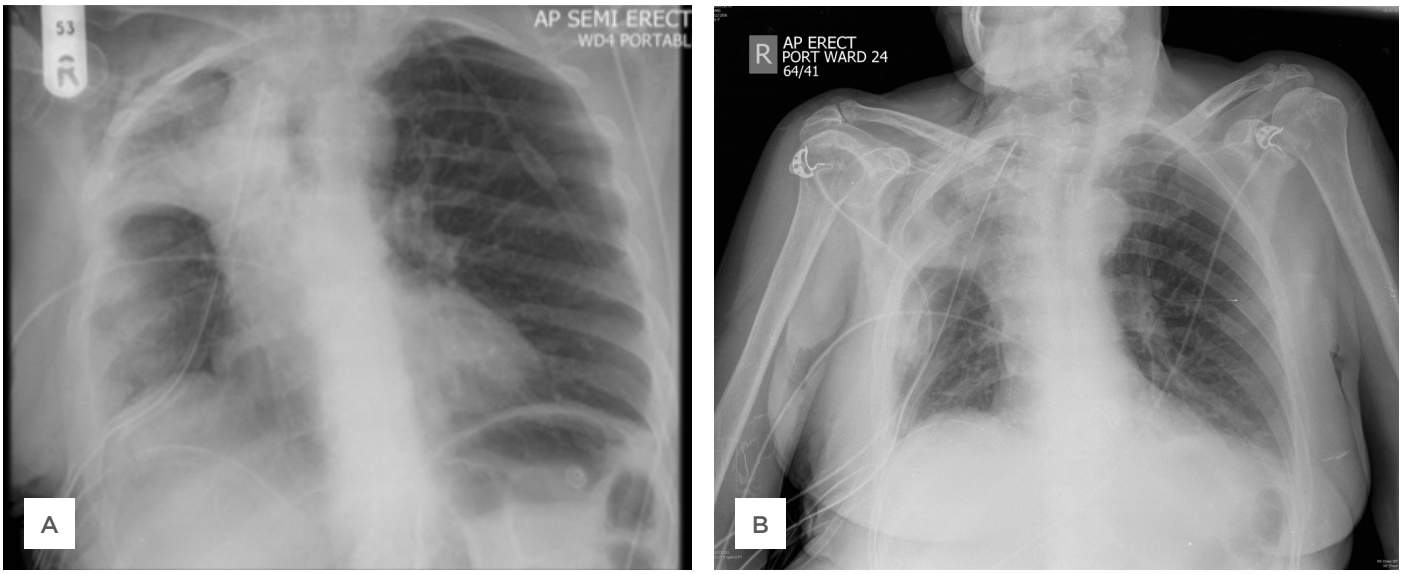

Figure 1: Chest X-ray changes before and after treatment with positive expiratory pressure (PEP) therapy in a patient with respiratory failure following right upper lobectomy surgery. A) Before PEP therapy. B) Increased lung volume and improvement of basal atelectasis after PEP therapy.

Positive Pressure Physiotherapy Techniques

Positive pressure physiotherapy techniques, such as PEP therapy, have been used to support and enhance patient respiratory function in a variety of clinical settings for many years. PEP is established in the physiotherapy treatment of those with bronchiectasis, cystic fibrosis, and COPD. There is little convincing or contemporary evidence available to support the use of PEP postoperatively and, unsurprisingly, its uptake has been more variable in this population.

Early work on breathing techniques in patients following cardiac surgery found that PEP therapy used routinely following coronary artery bypass grafting led to a non-significant tendency towards reduced pulmonary complications compared with standard therapy.[50] The same authors conducted a similar study in a mixed population of cardiac and thoracic patients, but included mask CPAP as a comparative therapy.[51] They found that PEP and mask CPAP have comparable effects on oxygenation, CXR appearances, and measured lung volumes, with participants reporting a greater preference for treatment with PEP therapy. Later work, which compared patients who received PEP therapy with patients who received no physiotherapy following cardiac surgery, found a reduction in atelectasis and improved lung function following PEP therapy.[40]

The evidence base in this area is generally lacking: studies often demonstrate poor methodological quality and conflicting results. Systematic reviews of trials in physiotherapy techniques applied routinely in cardiac,[52] abdominal, and thoracic surgical patients[53] have reported only a small number of trials. These studies often offer scant evidence for the positive benefits of such techniques, and conclude that the role of routine physiotherapy, including PEP, remains unproven. These reviews, however, use data compiled from studies of differing interventions and represent something of a heterogeneous population. Therefore, they draw general conclusions regarding the benefits of many therapy modalities in postoperative patients.

There is certainly no strong evidence to suggest that PEP therapy may not be beneficial when applied routinely. Its role may, however, be of more importance physiologically in those postoperative patients with increased sputum production, or to ameliorate sputum retention, especially in patients with dynamic airway collapse or atelectasis.

Further work studying the relative benefits of individual therapies used both prophylactically and therapeutically, such as PEP, is warranted in postoperative populations. Focus on specific interventions that may be effective against volume loss, sputum retention, and postoperative RF is urgently needed, especially amongst high-risk populations such as those undergoing major surgery and with a history of smoking or COPD.

POTENTIAL DIRECTIONS AND RESEARCH QUESTIONS FOR THE POSTOPERATIVE PERIOD

Theatre Recovery or Ward-Based Therapy

It is attractive, in theory, to consider using NIV for a short period in theatre recovery as a preventative measure. However, many of the studies that have utilised postoperative NIV to good clinical effect have used longer treatment periods – often 12 hours or more. It has been suggested from clinical studies that shorter periods of treatment in post-surgery recovery units do not result in lasting demonstrable clinical benefits to patients.[54] Issues relating to staff training, patient safety, and appropriate levels of monitoring also potentially limit the use of NIV outside of dedicated critical care areas.[55]

The potential to use HFNC outside of critical care areas remains an attractive option, and pilot studies in emergency department settings suggest this may be a feasible and potentially safe option.[34] However, evidence to support the use of HFNC on general wards is currently lacking and concerns exist about delayed treatment escalation to invasive ventilation in patients deteriorating on HFNC.[49] Robust trials are needed to address this issue and examine the safe duration of treatment outside of critical care areas before pursuing this option further in clinical practice.

Combination Therapy

The combination of therapies to produce a maximal clinical effect whilst reducing any additional burden upon critical care services is an attractive and intriguing future direction for research in postoperative populations. Delivery of oxygen via HFNC delivers only a low, and quite variable, level of PEEP to patients, and this level of PEEP is thought to be heavily dependent on patient inspiratory flow rates.[56] It is plausible that combining the known beneficial effects of HFNC

therapy with PEP devices, which would add a higher and more reliable level of PEEP to patients, may result in additional benefits to patients and would potentially have the additional benefit of being available outside of critical care areas. Again, this is an area that currently lacks supporting evidence, but is a potential future avenue for research interest.

DISCUSSION AND CONCLUSIONS

Postoperative RF remains a significant challenge for healthcare providers. This is especially true when considered in the light of an ageing population, increasing demand for provision of services, and higher incidence of significant comorbidities in patients presenting for surgery. At a time when demand for critical care services in general is increasing, the requirement for emergency care provision may mean that elective surgical procedures face cancellation or delay due to a lack of critical care bed capacity. Therefore, any interventions that may reduce the burden of surgical patients on critical care services are of great importance to contemporary practice.

The use of NIV currently has the greatest body of supporting evidence and therefore remains the gold standard for both prophylaxis and treatment of postoperative RF. However, its use as an intervention in surgical patients is relatively resource-heavy and, due to issues of safety, monitoring, and training, it is largely confined to critical care areas. As a result, there exists a definite niche or 'gap in the market' for alternative therapies and approaches, especially those that can be provided in theatre recovery areas or general surgical wards, and which do not mandate occupancy of a critical care bed.

The delivery of humidified oxygen to patients via HFNC represents a very promising and exciting development in the management of postoperative patients. Further work is required to help define the precise role of HFNC in managing postoperative RF, and also to validate the optimum duration of treatment and safety of use outside of critical care areas. Early studies completed in similar and related areas suggest a potential benefit, especially in patients with hypoxaemia. The findings from studies in postoperative populations are eagerly awaited.

PEP therapy is theoretically attractive as it may help to restore lung volumes and clear secretions, especially in high-risk patient groups, and can be delivered at relatively low cost in general ward settings. The evidence base for PEP techniques in postoperative patients is, however, small and conflicting. There is a paucity of contemporary studies reported in the literature, with few trials supporting or refuting the use of this type of physiotherapy postoperatively, or demonstrating an influence on important clinical endpoints. Nevertheless, positive pressure physiotherapy techniques may still have a role to play in selected patient groups and the precise role of PEP in perioperative respiratory management needs to be clearly established.

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Featuring an outstanding line-up, including international speakers and national experts, this meeting offers its delegates cutting-edge developments from all corners of respiratory care: clinical, translational, and basic science. Foci of the meeting include an analysis of the current direction of chronic obstructive pulmonary disease (COPD)-related therapy in the advent of the 50th anniversary of the term COPD, and the latest in rare lung disease phenotypes and research.

46th Union World Conference on Lung Health

2nd–6th December 2015

Cape Town, South Africa

This conference remains part of a global effort to ameliorate the suffering caused by lung diseases, and will feature over 150 sessions, including poster presentations, abstract sessions, and a global TB symposium. With a theme that reflects the changing landscape of global public health and a new era of action, the World Conference on Lung Health, will present the advancing nature of respiratory therapy, especially the challenges faced by low and middle-income countries.

3rd International Workshop on Lung Health: Asthma and COPD: Converging or Diverging Chronicity?

15th–17th January 2016

Monaco, Monaco

The International Workshop on Lung Health, which is endorsed by the European Respiratory Society, is entering its 3rd year. The workshop itself will feature an examination of non-invasive ventilation, with a view to determining the associated successes and failures. Another facet of this event is the recognition of new and upcoming researchers, who will be provided with the chance to gain valuable advice on their research and present their work to a global audience.

Lausanne Airway Course 2016

25th–27th January 2016

Lausanne, Switzerland

The Lausanne Airway course offers a platform for respiratory surgeons, anaesthesiologists, pulmonologists and their colleagues to improve upon a foundation of skills and knowledge, discuss the challenges they face, and further improve the quality of care provided to their patients. The course also represents a valuable experience for medical professionals to network as they are immersed in the sessions with their peers.

X World Congress on Asthma, COPD & Immunopathology

6th–9th February 2016

Dubai, United Arab Emirates

Set within the stunning city of Dubai, this congress will feature a variety of stimulating insights into respiratory medicine, including a discussion into immunotherapy and asthma, as well as an exciting look into neurological diseases that affect the respiratory system. Participants will be awarded the opportunity to learn from, and debate with, an assortment of international speakers, before taking a tour of the one of the world's most beautiful cities.

International Conference: Clinical Update Sleep 2016

26th February 2016

London, UK

Advertised as the largest edition of this conference yet, this 1-day event will include insights in hypersomnia, parasomnia, and sleep-disordered breathing. The organisers promise an exciting and extensive programme delivered through a series of interactive lectures, case studies, and workshops, with an emphasis on multi-disciplinary approaches. Further to this, participants will leave armed with the latest knowledge in sleep disorder management and technology.

German Respiratory Society Annual Meeting 2016

2nd–5th March 2016

Leipzig, Germany

As one of the most well-established events in the field of pulmonary medicine, the annual meeting of this respiratory society will comprise of a fascinating review of the mechanisms and clinical relevance of cardiorespiratory interaction, and an update on the fight against cancer, as well as a combination of other oral and poster presentations and strategies for care. Leipzig will provide the backdrop for this momentous event, a feat the city will surely rise to as it turns 1,000 years old.

European Respiratory Society International Congress 2016 (ERS 2016)

3rd–7th September 2016

London, UK

The ERS International Congress stands among few at the apex of scientific research. Year upon year, the organisers strive to improve upon past congresses, and ERS 2016 should be no different. The EMJ team will be present at the congress to admire and report on the best of the scientific discoveries presented there. The event will feature a wide range of key topics, ranging from the science of, and techniques involved in mucus clearance from the respiratory system, to cystic fibrosis and lung function in paediatric patients. The programme will also feature a multitude of distinguished speakers and scientists, as advances in respiratory knowledge and medicine are propagated for the good of current and future patients.