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RESPIRATORY

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ERS 2018
Paris, France

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Spencer Gore, CEO

Editorial Board

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

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

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

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

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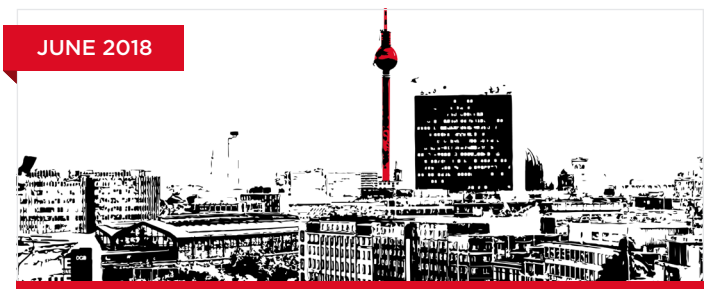
Front cover and contents photograph: Paris, France, home of the ERS 2018. © marina99 / 123rf.com

EMJ Respir.



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Welcome

A very warm welcome to *EMJ Respiratory 6.1*, an eJournal that disseminates top-quality peer-reviewed articles that detail the very latest developments, research findings, and key issues within respiratory medicine. Alongside these articles are, as always, EMJ's comprehensive review of the European Respiratory Society (ERS) International Congress, which encompasses the highlights of the 5-day event and the most pertinent academic news; abstract reviews provided by the authors of the presentations themselves; and interviews with some of the esteemed members of the *EMJ Respiratory* Editorial Board.

"...I would like to take this chance to thank all of you who played a part in this publication, including those who devoted their time to peer-reviewing articles, Editorial Board members, authors, and those working behind the scenes at EMJ."

This year's ERS Congress, which was held in Paris, France, was a fantastic event. I had the opportunity to attend with some of the EMJ team and thoroughly enjoyed the experience. It was an excellent chance to network; attend symposiums, lectures, and debates; and immerse myself in the field of respiratory medicine. A major part of the ERS Congress was the poster presentations, and this journal presents a selection of these in the Abstract Reviews section. The topics covered include a multidimensional approach to chronic obstructive pulmonary disease comorbidities and a phone telesystem to increase treatment adherence in patients with chronic obstructive pulmonary disease exacerbations. This journal also contains an excellent selection of peer-reviewed articles, including an illuminating consideration of paediatric asthma, which is well worth a read.

Once again, I would like to take this chance to thank all of you who played a part in this publication, including those who devoted their time to peer-reviewing articles, Editorial Board members, authors, and those working behind the scenes at EMJ. We are all exceedingly proud of *EMJ Respiratory 6.1* and are confident that the enthralling content will spark countless hours of stimulating debate and discussion, which will no doubt lead to further developments and breakthrough discoveries in the treatment of respiratory conditions. We are already looking forward to joining you all in Madrid, Spain for 2019's ERS Congress!

Warm regards,

Spencer Gore

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear colleagues and friends,

It is my pleasure to welcome you to this latest edition of *EMJ Respiratory*, which contains a compendium of interesting peer-reviewed articles focussing on several aspects of, and strategic approaches for, the management of respiratory diseases.

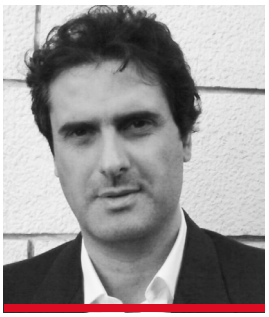
The European Respiratory Society (ERS) International Congress 2018 was held in Paris, France, from 15th–19th September 2018. With >22,000 delegates in attendance, this meeting is the largest congress in respiratory medicine, with an outstanding scientific and educational programme designed to address the needs of researchers, scientists, clinicians, general practitioners, and allied health professionals and allow them to share their opinions and experiences. ERS 2018 represented the perfect forum to learn from the latest studies in the field of pneumology, to meet peers and key opinion leaders from all over the world, and to enjoy many educational sessions. It also acted as a catalyst for producing new collaborations and networks, which will help further the advancement of knowledge and science in this setting.

EMJ Respiratory 6.1 includes a report on asthma, which affects approximately 230 million people worldwide and is the cause of significant morbidity in patients of all age. Current perspectives on the diagnosis and treatment of asthma in children are reviewed, focussing on diagnostic steps, disease phenotypes and endotypes, and novel biologic therapies. A further critical review stresses how physical exercise and breathing strategies are essential components of pulmonary rehabilitation for people with COPD.

As an oncologist, I would like to give a brief introduction to an oncology paper published in this issue. Immunotherapy is an emerging therapeutic modality for the management of cancer, and either increases the strength of the human immune system against cancer cells or counteracts signals produced by cancer cells that suppress immune responses. In this context, the review by Moya-Horno et al. discusses the currently available data and ongoing research on the use of immunotherapeutics for early-stage non-small cell lung cancer.

On behalf of the rest of the *EMJ Respiratory* Editorial Board and the staff of the European Medical Journal, I would like to thank all authors for their efforts in contributing to the publication of this new issue. Finally, I am confident that you will enjoy reading this latest edition of the journal as much as I did; the content is extremely interesting and stimulating!

Yours sincerely,



Dr Antonio Rossi

IRCCS Casa Sollievo della Sofferenza, Italy

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Congress Review

+ Review of EADV 2018 Paris, France, 12th–16th September 2018

Symposium Reviews

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Abstract Reviews

Articles

+ Editor's Pick: Beneath the Skin: The Relationship Between Psychological Distress and the Immune System in Patients with Psoriasis Mahmoud Elsayed, Cody J. Connor
+ A Systematic Review on the Efficacy of Topical Acyclovir, Penciclovir, and Docosanol for the Treatment of Herpes Simplex Labialis Kimberly D.P. Hammer et al.
+ Predicting Response to Omalizumab in Chronic Urticaria Based on Biomarkers Misbah Noshela Ghazanfar, Simon Francis Thomsen

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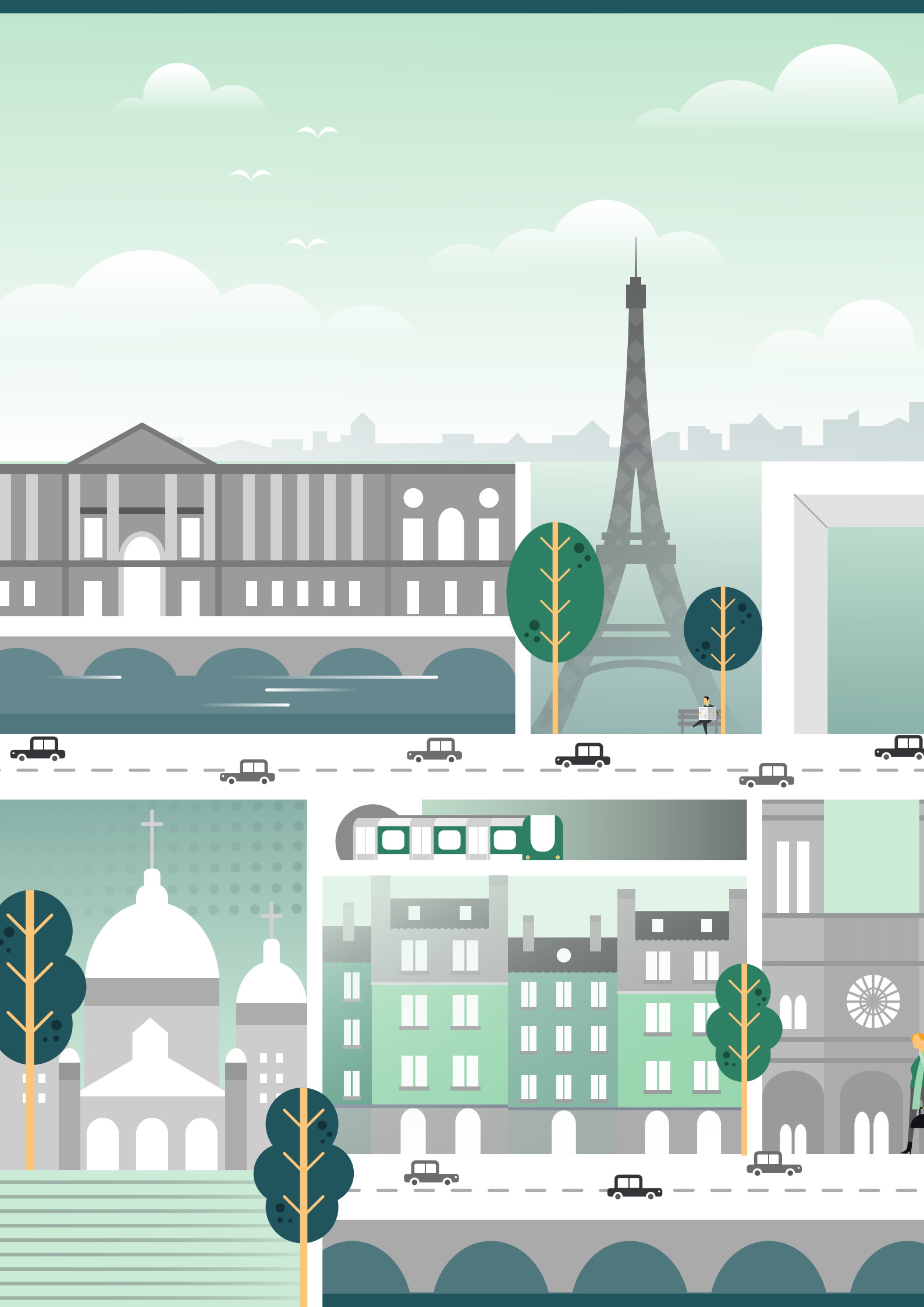


Congress Review

Review of the 28th European Respiratory Society (ERS) International Congress

Location: Paris, France – Paris Expo Porte de Versailles

Date: 15.09.18–19.09.18

Citation: EMJ Respir. 2018;6[1]:12-25. Congress Review.

The 'City of Peace', Paris, France, played host to this year's European Respiratory Society (ERS) International Congress. With the nation bringing forth science, architecture, fashion, and food, the French capital city was the perfect place to celebrate the previous year's records and achievements while also looking to the future, having had "some of the most significant scientific and medical breakthroughs in human history," as stated in this year's opening ceremony.

The opening ceremony welcomed delegates from all over the world to the sound of romantic music: the perfect tribute to the choice of location. France's historical achievements were acknowledged with pride in the initial introduction, one of which included the use of the first gasoline-powered taxi in Paris in 1899. The French motto: "Liberté, égalité, fraternité," which translates as "liberty, equality, fraternity," was reiterated and celebrated not only in the opening ceremony but throughout the event. The motto originated during the French revolution, which brought about the "Declaration of the Rights of the Man" in 1789, a crucial human civil rights document that would later inspire the Universal Declaration of Human Rights.

Prof Mina Gaga, President of the ERS, then took to the stage to pay her respects to the ERS and the success of the previous year. With increased membership, well-attended events, and new strategies for the society being brought into place, the future is looking bright. Prof Gaga noted that the world is changing and, as such, the society and the ERS Congress must change with it. One of these changes includes creating a congress that is more accessible and relevant for patients: "Patients help us share our thoughts about the disease and think that there is always something we can do even if we do not have hope, and so it is so important to include our patients," she said. "We are here for the patient, we are here for the people."

The involvement of patients at the congress included the addition of the European Lung Foundation (ELF) Patient organisation programme. Working tirelessly to bring patients and the public together with respiratory professionals, the organisers of the ELF Patient organisation programme created the World Village at the ERS Congress, a project that brought together patient organisations from all over the world. The activities involved a variety of respiratory diseases for attendees to delve into, focussing on networking, building and strengthening partnerships, and sharing knowledge about future activities around the globe.

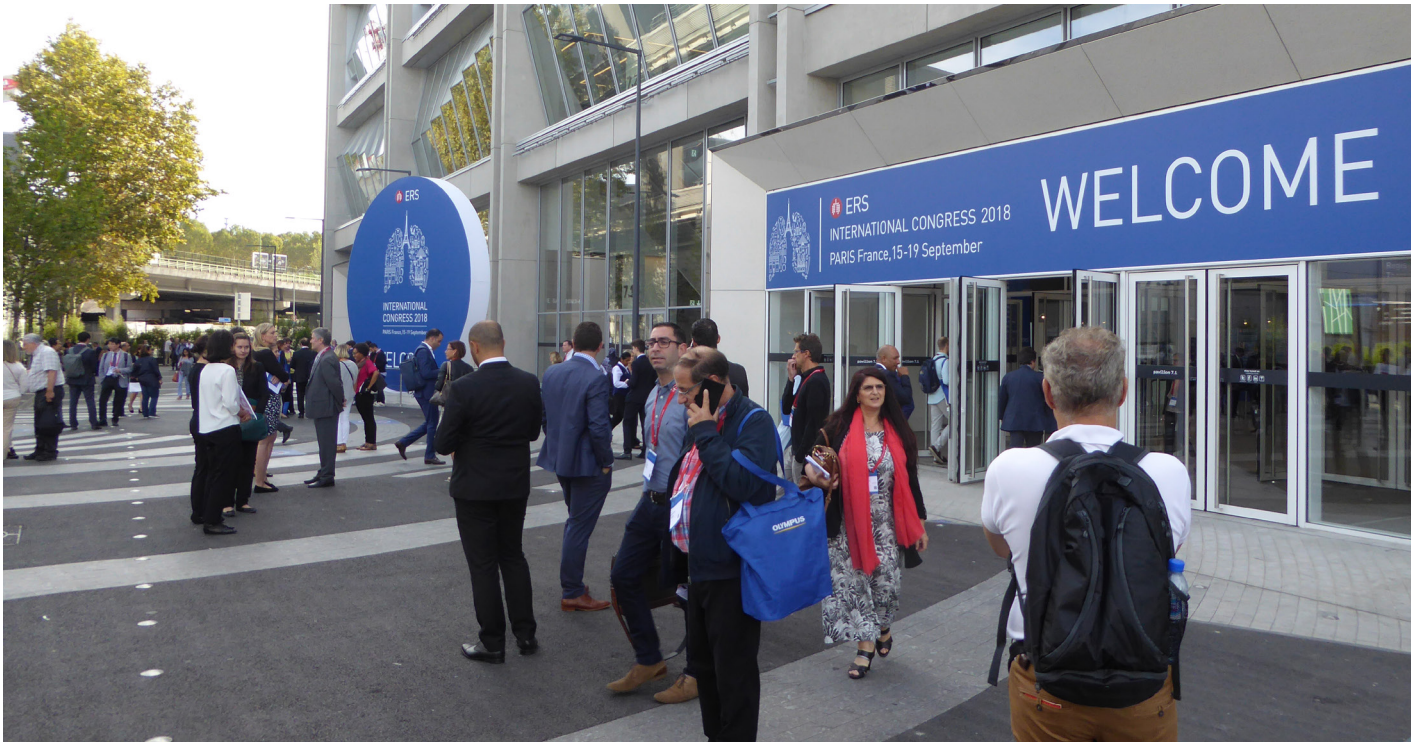
Finishing her opening ceremony speech, Prof Gaga encouraged attendees to "network, learn, teach, and be with friends," before acknowledging the achievements of the most esteemed healthcare professionals by presenting them with awards for their significant contributions to the world of respiratory medicine, including the special ERS Gold Medals.

As the opening ceremony came to a close and the congress was officially in full-swing, attendees reflected on the wonders that were announced and waited in anticipation of what the congress had to offer. Brand new to the ERS Congress was the "Therapeutic breakthroughs: Year in review" session, which covered paediatrics, allied healthcare professionals, thoracic oncology, and respiratory intensive care. This session was a fantastic opportunity for attendees to discuss the most significant therapeutic advances of the last year within these varied fields.

"...network, learn, teach, and be with friends..."

In addition, the "Lungs on Fire" session formed another brand-new event with a twist. This interactive session allowed the audience to diagnose clinical cases with a panel of experts. Multiple choice questions were presented to audience members throughout the session, which consisted of a single moderator in the room with details of each case. This wonderful experience gave attendees the opportunity to challenge themselves with real clinical cases and was perfect for learning and exchanging thoughts and ideas.

With the latest updates, collaborations, and research galore, attendees found themselves, as always, in awe of this imperious event. We look forward to seeing you all at next year's ERS Congress, which heads south to Madrid, Spain.



Access to Green Space During Childhood is Beneficial for Lung Health

RESPIRATORY PROBLEMS, such as asthma and wheezing, are less likely to be experienced by adults if they had access to green space close to their childhood homes. Reported in a ERS press release dated 19th September 2018, the preliminary results of the RHINESSA study indicate the long-term effects of exposure to air pollution on respiratory health.

In a new analysis of lung health in children and adults from seven European countries, green space data from 5,415 individuals aged between 18 and 52 years were investigated, as well as information on air pollution from 4,414 participants. Average annual exposure to particulate matter ($PM_{2.5}$ and PM_{10}) and nitrogen dioxide, in addition to 'greenness' in a 100 m zone around the home (as assessed by the Normalised Difference Vegetation Index), were calculated for the participants from birth until 18 years of age.

When looking at the number of study individuals who experienced reduced lung health, 12.0% had >3 respiratory symptoms, 7.7% had severe wheeze, and 9.4% experienced late-onset asthma. Analysing the data further, $PM_{2.5}$ and nitric oxide increased the probability of late-onset asthma by 6–22% in Bergen, Norway, while exposure to green space at <10 years of age correlated with a 71% lower probability of experiencing wheeze in adults in Tartu, Estonia. Although further analysis is required, the researchers noted that the results showed that exposure to green space during childhood was associated with fewer respiratory problems later in life.

"The ongoing work of the RHINESSA study will, no doubt, produce more interesting and useful results to support these early indications."

As well as allowing physicians to gain a greater understanding of the importance of childhood exposure to air pollution and access to green space, these findings may also impact broader public health and societal regulations. "We believe that our results, seen together with previous results, will be of particular value for city planners and policy-makers," commented Dr Ingrid Nordeide Kuiper, Haukeland University Hospital, Bergen, Norway. When highlighting the implications of these findings for the future of respiratory disease management and prevention, Prof Mina Gaga, President of the ERS, commented: "The ongoing work of the RHINESSA study will, no doubt, produce more interesting and useful results to support these early indications."

Trained Artificial Intelligence More Accurate at Diagnosing Lung Disease Than Pulmonologists

ARTIFICIAL INTELLIGENCE (AI) is increasingly set to revolutionise the modern world across a host of industries and this is certainly true for the field of medicine. New research has demonstrated that a pulmonologist-trained AI programme could outperform human medical practitioners alone when it comes to diagnosing lung disease, as reported in a ERS press release dated 19th September 2018.

A panel of pulmonologists used the results of pulmonary function tests (PFT), which included spirometry, a body box or plethysmography test, and a diffusion capacity test, as well as the respective medical history of 1,430 patients to arrive at an agreed correct diagnosis for each patient; these diagnoses were measured against gold standard guidelines from the European Respiratory Society (ERS) and American Thoracic Society (ATS). These correct diagnoses and their component factors were then used to 'train' the AI programme, with the hope that it would be able to subsequently identify patterns in the training data to correctly diagnose new patients. "When training the AI algorithm, the use of good quality data is of utmost importance," explained Dr Marko Topalovic, Catholic University of Leuven, Leuven, Belgium.

The AI programme was then compared to 120 pulmonologists from 16 European hospitals; both the AI programme and medical professionals received PFT data from 50 randomly selected patients from which to make a diagnosis, measured against gold standard guidelines, as before. The results showed the pulmonologists' diagnoses matched the guidelines in 74% of cases, while the AI's matched in 100% of cases; the correct primary disease was diagnosed in 45% and 82% of cases, respectively.

The researchers were quick to stress that pulmonologists have a broader perspective of each case, since they are working from more than just PFT, and thus are able to diagnose based on a greater number of factors. Dr Topalovic explained: "These results show how AI can serve as a second opinion in pulmonologists when they are assessing and diagnosing their patients."

Besides further studies, the next key step in this process will be using the AI technology in primary care, where general practitioners can use the resulting data to make the correct diagnostic decision.

Targeted Lung Denervation Significantly Improves COPD Patient Health

OPENING obstructed airways of chronic obstructive pulmonary disease (COPD) patients via targeted lung denervation (TLD) can safely reduce respiratory problems associated with the disease. With 4–10% of European adults affected by COPD, these significant results, reported in a ERS press release dated 18th September 2018, will have important implications for patient quality of life and healthcare costs.

TLD involves the delivery of radiofrequency energy to the airways, causing them to relax and widen and decreasing inflammation and mucus production. To investigate the use of TLD in combination with tiotropium, a commonly used anti-cholinergic bronchodilator, the double-blind AIRFLOW 2 Phase II trial randomised patients to receive either the airway opening procedure or a sham procedure.

Presented at the ERS Congress, initial results based on 82 patients (50% male; average age: 64 years) showed that there was a positive benefit of TLD treatment over sham procedure. After 3–6 months of treatment, 71% of sham procedure patients, who did not receive the electrical radiofrequency charge, experienced adverse respiratory events related to COPD, compared to 32% of TLD treatment patients. Furthermore, a >50% reduction in the number of patients hospitalised for respiratory conditions was shown in the treatment arm versus the sham group. As well as being shown to effectively improve respiratory health, TLD was also proven to be acceptably safe, with no TLD-related adverse side effects that required treatment reported and only 5 patients experiencing temporary gastrointestinal effects.

Proudly discussing his team's results at the congress, Dr Dirk-Jan Slebos, University Medical Centre Groningen, Groningen, Netherlands, commented on the implications of TLD for COPD patients: "It offers the ability to significantly reduce symptoms and exacerbations even in patients already on aggressive medical therapy." AIRFLOW 3, a larger Phase III trial, is now in development and will include many more patients to significantly improve COPD patient health. "Better treatments for COPD patients, particularly those with severe disease, are desperately needed and we look forward to the results from the AIRFLOW 3 trial, which we hope will confirm this [TLD] as an effective and safe treatment," commented Prof Daiana Stolz, Chair of the ERS Education Council.

Simple Test Accurately Diagnoses Viral Infections in 50 Minutes

FIFTY minutes is all it takes to diagnose a viral infection using a new test developed by researchers at West Hertfordshire Hospitals NHS Trust, Watford, UK and the University of Hertfordshire, Hatfield, UK. This test, as reported in a ERS press release dated 17th September 2018, could greatly reduce unnecessary hospital admissions and antibiotic prescriptions.

The new service, called point of care respiratory viral testing (POCT), involves swabbing the back of the nostril to collect secretions and inserting the prepared sample into a compact machine called a FilmArray®, which analyses the sample; the entire process is estimated to take around 50 minutes. "The whole process from obtaining a sample from the patient's nose to getting a result should take under 50 minutes, which has a potentially enormous impact on quality of care, improving the patient journey by allowing earlier, informed decision-making about patient management," explained Dr Kay Roy, University of Hertfordshire. This short diagnostic process represents a huge improvement on similar tests using the same technology that would take 2 days to process in a microbiology lab.

"We could make a significant saving for national health services by avoiding unnecessary admissions in patients who may have been otherwise admitted..."

Initial experiences using POCT alongside other diagnostic techniques (such as chest X-ray) have been very positive; of the first 1,075 patients to take the test, 121 were identified as having viral infections, had no evidence of bacterial infection, had normal X-ray results, and had only modest indicators of inflammation. As a result, hospital admission was avoided in 25% of this group, and antibiotic prescription was avoided in 50%; none of the patients in either of these subgroups experienced adverse clinical outcomes. Most of the viral infections diagnosed were influenza (56%), with the remaining viruses including rhinovirus, coronavirus, metapneumovirus, and adenovirus.

Diagnosing these infections early could save healthcare providers thousands in unnecessary hospital admissions and antibiotic prescriptions. "Each respiratory admission can cost around £2,000," explained Dr Roy. "We could make a significant saving for national health services by avoiding unnecessary admissions in patients who may have been otherwise admitted and given antibiotics while waiting up to 2 days for results from the lab."

A randomised controlled trial is now being planned wherein general practitioners will be able to refer patients to a community hub for POCT.

Paracetamol Use Linked to Increased Asthma Risk

TAKING paracetamol in the first 2 years of life has been linked to an increased risk of asthma in teenagers, according to new research from the University of Melbourne, Melbourne, Australia, which was presented in a ERS press release dated 17th September 2018.

The research found that the link between paracetamol use and asthma was strongest among those who had certain genetic makeups, specifically a variant of the glutathione S-transferase (GST) gene, *GSTP1*. In addition, another GST gene variant, *GSTM1*, was found to be linked with reduced lung function.

GST genes code for enzymes that use an antioxidant called glutathione, which is responsible for clearing the effects of toxins around the body and lungs. In doing so, glutathione helps to prevent inflammation and damage to cells. It is known that paracetamol removes glutathione from the body, stopping the beneficial effects it has in preventing damage and inflammation. The researchers hypothesised that those individuals with certain genetic variations or deletions who, as a result, did not have full GST enzyme activity, were more at risk of adverse effects on the lung due to paracetamol use.

The study included 620 children who were chosen based on being potentially at a higher risk of developing an allergy-related disease. The children were followed from birth until they were 18 years old, as part of the Melbourne Atopy Cohort Study. Every 4 weeks for the first 15 months of life, and then again at 18 months, a research nurse rang the family of the child to ask how many days in that period the child had taken paracetamol. At 18 years old, the participants were asked to give a sample of blood or saliva to test for the genetic variants *GSTT1*, *GSTM1*, and *GSTP1*. In addition, the participants were tested for asthma and underwent a spirometry test to assess air inhalation and exhalation when breathing through a mouthpiece.

It was found that the *GSTP1* Ile/Ile variant was associated with a 1.8-fold increased risk of developing asthma by the age of 18 years for each doubling of the days receiving paracetamol when compared to those who had less paracetamol. However, it was also noted that those children with other types of *GSTP1* receiving paracetamol did not have any altered level of risk. In addition, those children who had a dysfunctional version of *GSTM1* had a small but significant reduction in the amount of air they could breathe out in 1 second.

"As we learn more about the genes involved in asthma, and how they interact with the environment and the medicines we use, we hope to learn more about what is best for individual patients."

It is worth mentioning that this link may not necessarily be a result of paracetamol but may rather be a result of viral lower respiratory tract infections in the first 2 years of life that had been treated with paracetamol. The researchers emphasised that further research must be carried out to affirm these results and to determine what is best for patients. "As we learn more about the genes involved in asthma, and how they interact with the environment and the medicines we use, we hope to learn more about what is best for individual patients," said Prof Guy Brusselle, Chair of the ERS council, when commenting on the results.

Air Pollution and Pregnancy: A Greater Understanding

CARBON PARTICLES have been found in placentas for the first time, suggesting that components of polluted air can directly impact a growing fetus via the mother's blood. This new research, revealed at the ERS Congress and reported in a ERS press release dated 16th September 2018, will lead to increased public awareness of the harmful effects of air pollution for pregnant women and ensure appropriate management of air quality.

It has long been known that exposure to air pollution during pregnancy can have a direct impact on adverse birth effects, such as low birth weight, premature birth, and infant mortality, as well as long-term child and adulthood development. "We were interested to see if these effects could be due to pollution particles moving from the mother's lungs to the placenta. Until now, there has been very little evidence that inhaled particles get into the blood from the lung," commented Dr Lisa Miyashita, Queen Mary University of London, London, UK.

Led by Prof Jonathan Grigg, Queen Mary University of London, the research group studied the placentas of five women who had uncomplicated pregnancies and gave birth to healthy babies. A total of 3,500 placental macrophages were examined for carbon particles and 72 small black areas across 60 cells were found. This equated to an average of approximately 5 μm^2 of black on each placenta, which was believed, following electron microscopy, to be composed of tiny carbon particles.

Drawing upon the results of previous research showing that these sooty particles are present in macrophages in the airways, the team concluded that the identification of carbon in the placenta

indicated that inhaled pollution particles can move from the lungs into the circulation and then into the placenta. While it is still uncertain if the particles can be transferred to the fetus, this research suggests a possible mechanism by which unborn babies are affected by air pollution exposure. Stricter policies for cleaner air are therefore recommended to improve health worldwide.

Re-Evaluating the Impact of Childhood Asthma on Adult Life

CHILDHOOD asthma may greatly impact later life, both academically and professionally, suggests new research from Karolinska University Hospital, Stockholm, Sweden, presented in a ERS press release dated 16th September 2018. While the impact of asthma on quality of life is well established, its consequential effects on later life remain unclear, prompting this important study.

In 1996, children aged 7–8 years old from three Swedish districts were invited to participate in the study, with 97% agreement. Follow-ups were conducted at 11–12, 19, and 27–28 years of age, and 59% of participants (n=2,291) were still being studied as of 2015.

"...the key message for families is to try and ensure children stick to their asthma treatments and to speak to a doctor if symptoms are not under control."

The children were assessed for asthma at each follow-up and also the age at which they left education, what their occupation was, and other factors, such as sex, weight, and smoker status. An analysis of this group revealed that those with early-onset asthma (here defined as asthma diagnosed before the age of 12 years that was still present at 19 years) were 3.5-fold more likely to leave school at 16 years than those without asthma, as well as being twice as likely to drop out of university before completing a 3-year course. This group also had a noticeable detriment to their careers, being >50% less likely to enter occupations such as being a police officer, a musician, or a nursing assistant.

The reason for this considerable impact is, at present, unclear, but researchers suggested that asthma may impact school attendance and drive people away from certain professions that may require stamina or could trigger their asthma. "Until we know more about exactly why childhood asthma affects education and job prospects, the key message for families is to try and ensure children stick to their asthma treatments and to speak to a doctor if symptoms are not under control," explained Dr Christian Schyllert, Karolinska University Hospital.

The researchers intend to continue to follow this study cohort for a further decade, as well as examining another group 10 years younger to compare the effects between cohorts.

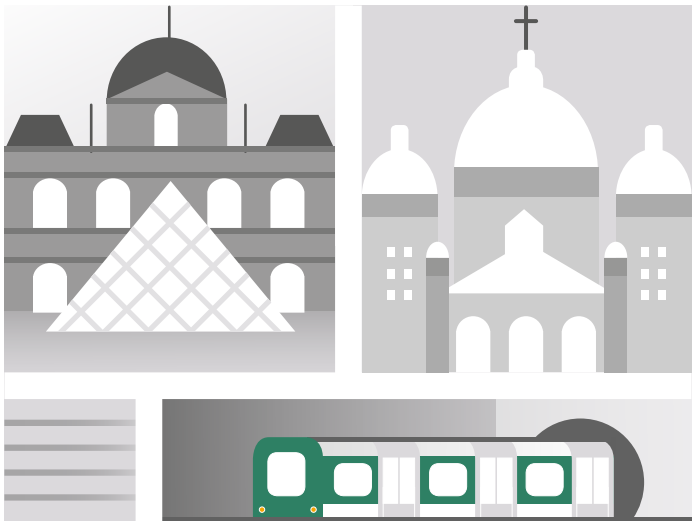
Developing Asthma in Adulthood Associated with Higher Risk of Obesity

ACCORDING to a ERS press release dated 15th September 2018, in addition to obesity being a known risk factor for developing asthma, people with asthma have now been identified as being at an increased risk of becoming obese, suggests research conducted as part of the European Community Respiratory Health Survey.

A total of 8,618 people from 12 countries were recruited into the study in the 1990s, and at the time of enrolment all had a BMI <30 kg/m^2 and were not considered to be obese. Researchers set out to assess the relationship between having asthma and becoming obese 10 years later. The study also analysed those who developed asthma over a 10-year period and their subsequent risk of becoming obese in the following 10 years.

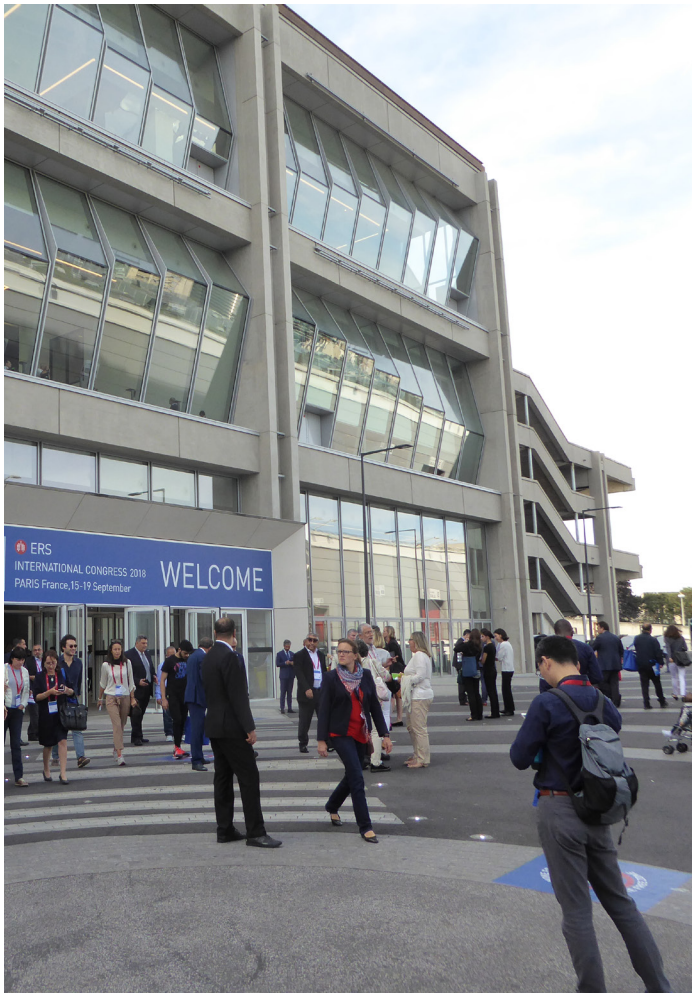
Results showed that 10.2% of people with asthma at the start of the study period became obese 10 years later, compared to 7.7% of those who did not have asthma. Further analysis of the results revealed that the risk of obesity was even greater for those who developed asthma in adulthood, as well as in those who had asthma but who did not have allergies.

"Our findings suggest the relationship between the two conditions is more complicated than we previously realised."



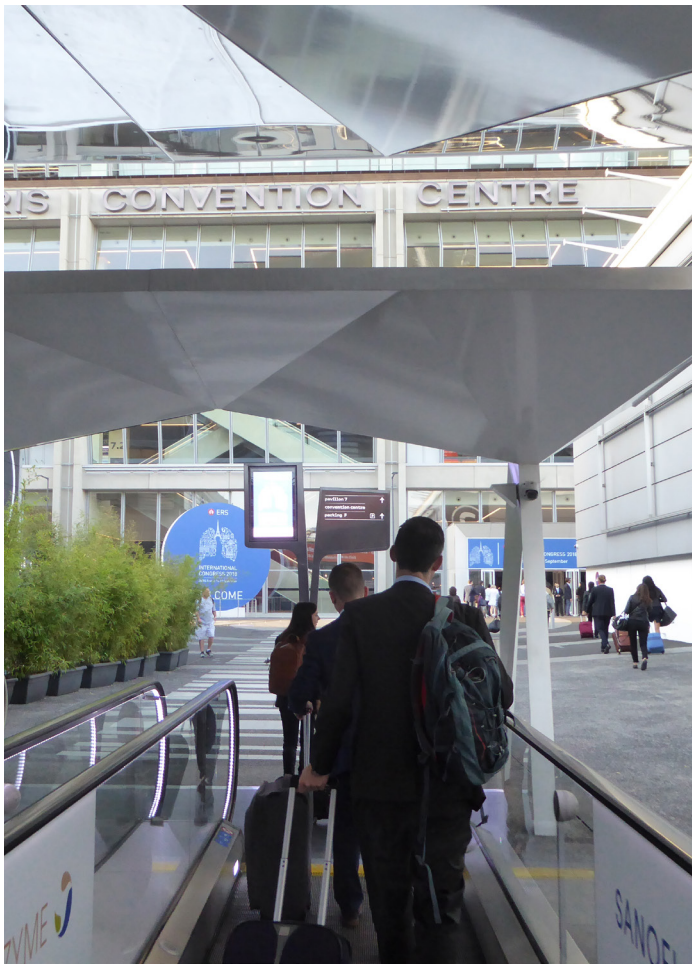
Until now there have been very few studies into whether asthma is a risk factor for obesity. Dr Subhabrata Moitra, ERS Research Fellow, ISGlobal, Barcelona Institute for Global Health, Barcelona, Spain, commented on the importance of the findings and where future research needs to be directed: "Our findings suggest the relationship between the two conditions is more complicated than we previously realised. It is important that we do more work to pick this apart. For example, we do not know why having asthma increases the risk of developing obesity or whether different asthma treatments have any effect on this risk."

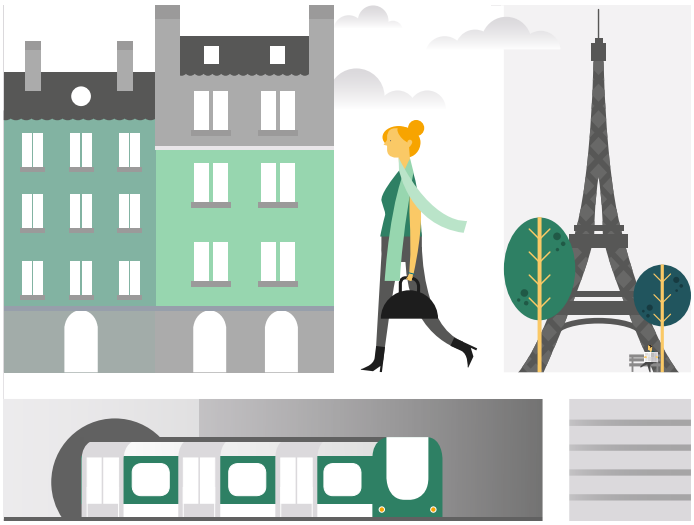
This research is an important step in helping clinicians and healthcare professionals to understand the relationship between obesity and asthma but also raises new questions regarding why the two are linked and what can be done to help patients, who are at the heart of all clinical research.



Treatment for Ureaplasma Infection May Reduce Respiratory Problems in Premature Babies

PREMATURE birth is related to a wide variety of health complications, not least for the respiratory system. Now, new research presented at the ERS Congress and reported in a ERS press release dated 14th September 2018 suggests that the presence of *Ureaplasma* in a premature baby's windpipe is related to the development of serious respiratory disease. Not only that, data also show that treating this infection with a common antibiotic could be an effective option for combating this problem in the future.





"This study shows that Ureaplasma infection is very common in extremely premature infants and clinicians should consider testing for this infection in those newborns who are at risk."

"A key question is whether this bacteria is causing ill health in newborns and, if so, whether eliminating the bacteria improves outcomes for these very small babies," explained Prof Rose Marie Viscardi, University of Maryland School of Medicine, Baltimore, Maryland, USA.

The study examined 121 premature babies born between 24 and 28 weeks' gestation, all of whom were tested for the presence of *Ureaplasma* in their nose and windpipes; half of them were treated with the antibiotic azithromycin (20 mg/kg of subject weight/per day), while the other half received placebo. Of the babies assessed, 36% were found to be *Ureaplasma*-positive, with the highest incidence being found in the most premature babies (45% of those born between 24 and 28 weeks).

The babies found to have the bacteria present in their windpipe were less likely to survive compared to those with the disease present only in their nose or those without the disease (71% versus 90% and 100%, respectively); they were also found to be more likely to develop bronchopulmonary dysplasia (67% versus 50% and 21%, respectively). Finally, the study showed that a 3-day course of treatment with azithromycin reduced the risk of death and severe respiratory disease 1 year after birth compared to placebo (33% versus 86%).

The authors were quick to caution that this study was limited by its small size and larger scale examination is needed before this antibiotic treatment can be more broadly adopted for these patients. Nonetheless, these results should encourage clinicians to look more closely at the impact of *Ureaplasma* infection in premature babies. "This study shows that *Ureaplasma* infection is very common in extremely premature infants and clinicians should consider testing for this infection in those newborns who are at risk," concluded Prof Viscardi.

Macitentan: Safe and Effective for Portopulmonary Hypertension

PULMONARY VASCULAR RESISTANCE (PVR) in portopulmonary hypertension (PoPH) patients can be significantly improved with macitentan treatment, according to results of the PORTICO trial, which were reported in an Actelion Pharmaceuticals Ltd. press release dated 17th September 2018. Presented at the ERS Congress 2018, these results are consistent with those observed in previous trials and suggest a promising treatment option for PoPH patients.

Recognised as the fourth most common form of pulmonary arterial hypertension (PAH), PoPH is associated with cirrhosis and often only diagnosed during liver transplant assessment. In addition, data on PoPH therapies are limited and there are currently no PAH treatments that have been shown to improve cardiopulmonary haemodynamics of PoPH patients in randomised controlled trials.

To address this issue, researchers investigated the safety and efficacy of macitentan, an orally available endothelin receptor antagonist indicated for PoPH, in the first randomised controlled trial of its kind. The PORTICO trial was a placebo-controlled, double-blind study including 85 PoPH patients randomised 1:1 to receive placebo (n=42) or macitentan 10 mg (n=43) once daily during a 12-week period. After the treatment duration, the study's primary endpoint of a reduction in PVR was achieved: the macitentan group showed an overall 35% reduction in PVR compared to placebo (geometric mean ratio: 0.65; 95% confidence interval: 0.59–0.72; p<0.0001). Additionally, macitentan significantly improved mean pulmonary arterial pressure by 5.99 mmHg (p<0.0001) and increased cardiac index by 0.52 L/min/m^2 (p=0.0009) compared to placebo.

Macitentan was also well tolerated in the patient population, aligning with the known safety profile from previous trials, and the most commonly reported adverse events in ≥10% of the participants were peripheral oedema and headache. Since PoPH patients are commonly excluded from PAH clinical trials due to safety concerns, these are promising results for this patient population. In addition, lead investigator Prof Olivier Sitbon, University of Paris-Sud, Orsay, France, concluded: "The findings of PORTICO are relevant because if patients with PoPH can be treated to successfully lower pulmonary vascular pressure and resistance, more patients may be eligible for liver transplant as they will potentially have a better prognosis for this surgery." Improvements in long-term quality of life for PoPH patients may, therefore, also be on the horizon.

"The findings of PORTICO are relevant because if patients with PoPH can be treated to successfully lower pulmonary vascular pressure and resistance, more patients may be eligible for liver transplant..."

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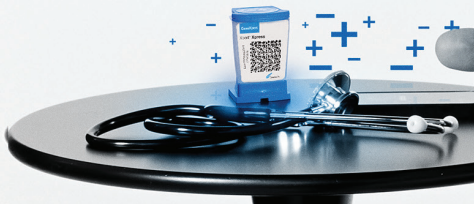

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Interviews

Hear from the newest members of the *EMJ Respiratory* Editorial Board as they discuss their opinions on the latest respiratory developments

Featuring: Prof Dr Catharina Belge, Dr Neil Holden, and Dr Joanna Porter

Prof Dr Catharina Belge

University Hospitals Leuven, Belgium

To begin, was there a single event or person that inspired you to pursue a medical career, and, more specifically, a career in respiratory medicine?

I cannot remember what inspired me to pursue a medical career, but my dream at the age of 3 was to become a doctor. It was difficult for me to choose between paediatrics and internal medicine, but, inspired by my research work as a medical student in the respiratory department, I chose to become a pulmonologist.

How did you begin your career in respiratory medicine, and what does your day-to-day work involve?

In 2009 I obtained my PhD from the faculty of Medicine of the Université Catholique de Louvain. I received a specialist degree in Pulmonology in 2011 and obtained a supplementary master's degree in Pulmonary Vascular Diseases from the University of Bologna in 2012. I started to work in the Department of Respiratory Diseases at the University Hospitals Leuven in the Centre for Pulmonary Vascular Diseases and in the Centre for Sleep and Wake disorders. As an Assistant Professor, I have three main tasks: the clinical part, outpatient clinic and hospitalisations; teaching, in the hospitals and at the faculty of medicine at KU Leuven; and clinical and translational research in the field of pulmonary hypertension.

You are particularly interested in pulmonary arterial hypertension (PAH). Could you explain a little bit about the condition?

PAH is a rare and progressive form of pulmonary hypertension. PAH is haemodynamically defined by a mean pulmonary arterial pressure ≥25 mmHg, a pulmonary artery wedge pressure ≤15 mmHg and a pulmonary vascular resistance >3 WU measured by right heart catheterisation at rest in the absence of other causes of

precapillary hypertension such as lung diseases or chronic thromboembolic pulmonary hypertension.

The pathophysiology of PAH is multifactorial, involving several biochemical pathways and cell types, but all forms of PAH share a common pulmonary vasculopathy, characterised by intimal proliferation, medial hypertrophy, and the development of plexiform lesions. This proliferative and obstructive remodelling of pulmonary blood vessel walls causes a progressive increase in pulmonary vascular resistance, leading to an increased pulmonary arterial pressure, responsible for an increased afterload on the right ventricle. The ability of the right ventricle to adapt to this increased afterload determines the symptoms and prognosis. Ultimately, it is the failure of the right ventricle that is the main cause of death in patients with pulmonary arterial hypertension.

"The work of a respiratory physician is extremely varied: diagnosis, the care of acutely ill patients, practical procedures, education of patients and relatives, and chronic disease management."

The prognosis of PAH patients in New York Heart Association (NYHA) Class IV is particularly poor: if untreated, median survival is around 6 months, compared with 2.5 years for those in NYHA Class III and 6 years for those in NYHA Class II. Even in the modern management era, patients in NYHA Class IV continue to have extremely poor survival.

What causes PAH, and is early detection important?

There are different forms of PAH. In the idiopathic form, no aetiology is known. In the heritable form, there is a genetic mutation. Other forms of PAH are secondary to drugs and toxins, connective tissue diseases, liver disease, HIV, congenital heart disease, or schistosomiasis. PAH is progressive and still not curable, although there are different medications to stabilise the disease. The earlier we can diagnose the disease, the earlier we can start treatment.

Unfortunately, there is often a diagnostic delay: mean time to diagnosis is about 2 years. This has a big impact on patient's quality of life. There is no global screening programme in the population because it is a rare disease. We can only screen in patients with an associated condition, e.g., connective tissue disease.

What are the therapeutic options for PAH?

In most patients we start treatment with oral anticoagulants, if necessary we add diuretics and oxygen therapy. A test is carried out via right heart catheterisation to show if there is reversibility with vasodilators. If so, we start treatment with a high dose of calcium blockers. In the majority of patients, the test is negative. In these patients we prescribe PAH-specific medication that inhibits proliferation of the smooth muscle cells in the lung vessels like endothelin receptor antagonists and phosphodiesterase 5 inhibitors. These very expensive drugs are reimbursed in Belgium under strict conditions.

If the disease is not stabilised under this therapy, we add prostacycline analogues via an intravenous pump; this medication cannot be interrupted and has a great impact on patient's quality of life. In some patients there is an indication for atrial septostomy or lung transplantation. As in other diseases (e.g., cancer), the therapy depends on the severity of the disease. The worse the disease, the more aggressive the treatment should be.

How important do you feel interdepartmental collaboration is when dealing with PAH in a clinical setting?

The management of PAH, which can potentially be fatal, is usually restricted to a few specialised centres. Multidisciplinarity is important in these centres: collaboration between cardiologists and pulmonologists specialised in pulmonary hypertension for echocardiography (for example, in our centre, right heart catheterisation is performed by the pulmonologist) or in the case of congenital heart disease, collaboration with rheumatologists in patients with connective tissue disease. As PAH patients are at high risk under general anaesthesia, a multidisciplinary approach is also very important in case there is a need for surgery.

What are the biggest challenges in PAH?

There is still no medication to cure PAH. Further basic research is necessary; today, therapy focusses on three major pathways, but other targets are in development. As PAH is a rare disease, it should only be treated in experienced hands. Therefore, the European Reference Network (ERN) for rare diseases has been created.

If you could cure one respiratory condition, aside from PAH, what would it be and why?

Aside from PAH, I would like to cure cystic fibrosis. It is a devastating disease, which is not purely a respiratory disease but has a great impact on the lifelong quality of life of young people.

With the increasing number of alternative devices to aid smoking cessation, including vaping devices and electronic cigarettes, have you seen any changes in the type of patients you see, or do you expect there to be a change in the coming years?

I did not see changes due to the use of alternative devices in the patients I see at the centre for Pulmonary Vascular Diseases or in the Sleep Lab. However, with the aging population and the increasing number of obese people, we have seen an increase in patients with obstructive sleep apnoea needing treatment by continuous positive airway pressure. In the pulmonary hypertension population, idiopathic PAH is now frequently diagnosed in elderly patients. The differential diagnosis between PAH and pulmonary hypertension due to left heart disease is more difficult in these patients as they have more cardiovascular comorbidities compared to younger patients. Further characterisation of these patients is required.

Finally, what one piece of advice would you give to a medical student aspiring to pursue a career in respiratory medicine?

Respiratory medicine is an interesting, wide, and diverse area. The work of a respiratory physician is extremely varied: diagnosis, the care of acutely ill patients, practical procedures, education of patients and relatives, and chronic disease management. Choose the speciality you are interested in. The most important attribute is dedication!

Dr Neil Holden

University of Lincoln, UK

What first drove you to pursue a career in respiratory research, and what is it that continues to inspire you to this day?

My first steps into respiratory research were serendipitous. I had volunteered to participate in a year out in the pharmaceutical industry as part of my bachelor's degree. I was placed at Novartis, working within their respiratory research group. The respiratory research bug soon hit me, and I was fascinated by trying to understand the complex signalling pathways that lead to inflammation. In textbooks and lectures, we had always seen these pathways depicted linearly as A+B=C; however, I was soon to learn that nothing in biology is that simple and these pathways exist in an extremely complex network of positive and negative feedback loops. I was soon immersed in the detective work of trying to uncover the intricate network of signalling events that both stimulate and inhibit the inflammatory pathways.

After finishing my year at Novartis, I returned to finish my bachelor's degree. Towards the end of the year, with finals looming, I was planning on taking a year out to explore my options of what to do next when serendipity struck again.

I happened to be walking down a corridor within my department when I spotted a poster advertising PhD studentships in collaboration with Novartis. Upon closer examination, I found that one of the studentships being offered was in collaboration with my supervisor from Novartis on a topic close to what I had worked on: the activation pathway of the proinflammatory transcription factor NF-κB. Now, almost 20 years after my first foray into respiratory research, I am still driven by the same passion: to uncover the complex biology behind asthma and chronic obstructive pulmonary disease (COPD).

"The respiratory research bug soon hit me, and I was fascinated by trying to understand the complex signalling pathways that lead to inflammation."

Losing both of my grandfathers to lung disease when I was very young, one to lung cancer and the other to COPD, and having had the opportunity to meet and talk with both asthma and COPD patients over the years, I consider it both a responsibility and a privilege to be able to make a difference in the lives of these people by furthering the knowledge of these diseases.

You are the module leader for various courses at the University of Lincoln, and lecture on a plethora of different areas, including respiratory pharmacology, virology, airway diseases, and immunology. Do you have a favourite topic that you like to share your knowledge on, and why?

I have found a real passion for teaching many topics through all levels, from first years through to master's degree and PhD students. If I had to pick a single topic that I enjoy the most, it would be teaching students about respiratory viruses.

Virology was my first passion, and my bachelor's degree was in virology at the University of Warwick. I was lucky enough to be taught by Prof Andrew Easton at Warwick, who was an extremely inspiring lecturer. We were taught that if you understand viruses, you understand biology. Viruses affect every form of life on Earth by using the cell's own machinery. The more you delve into the biology of viruses, how they replicate and how they cause disease, the more you understand our own biology.

My own favourite virus (we all have a favourite virus, right?) is respiratory syncytial virus (RSV). This virus predominantly causes bronchiolitis in children <2 years old and is a major cause of hospitalisation in young infants. RSV infections have been associated with the development of asthma, as well as causing exacerbations of both asthma and COPD, particularly in the elderly, whose immunity to RSV has waned. Having spoken to COPD patients, their major fear is catching a respiratory infection and the subsequent effect the infection has on their quality of life. Despite these viruses being fairly minor, in terms of illness in most adults, these infections have a massive impact on people with respiratory diseases.

I am also fascinated by how viruses have driven our evolution. When we sequenced the human genome, the discovery of many viral elements within our DNA was intriguing. Ultimately, my fascination is with how something so simple, just a small piece of nucleic acid and some protein, can have such a massive impact on every form of life.

Before moving to the University of Lincoln, you were working for AstraZeneca in Gothenburg, Sweden. How did you get involved with AstraZeneca and what did your day-to-day activities involve?

After finishing my PhD at the University of Warwick, I was lucky enough to be recruited to the laboratory of Prof Robert Newton at the University of Calgary for my postdoctoral research position. Within Prof Newton's laboratory, I shifted my focus from the pathways that cause inflammation towards trying to understand the anti-inflammatory mechanisms of therapies taken by asthmatics and COPD patients.

Principally, my research focussed on the synergistic behaviours of corticosteroids and β2-adrenoceptor agonists on anti-inflammatory gene expression. Through the research going on at Calgary by Prof Newton and other academics, there were a number of collaborations with various pharmaceutical companies, including

AstraZeneca. Rob was an extremely inclusive supervisor in the lab and made sure all his researchers had the opportunity to meet and present to the various collaborators and build up our contacts throughout the respiratory research community during the process.

Towards the end of my postdoctoral position, I was searching for the next step in my career; I considered both the academic and industrial options. At this time, AstraZeneca were consolidating their respiratory research activities in Mölndal, Sweden, and were looking for respiratory scientists. I happened to reconnect with some of the AstraZeneca contacts I had made in Calgary at that year's American Thoracic Society (ATS) conference who then put me in touch with their recruitment office. After a flight from Canada to Sweden, an interview, and finally a job offer with a decision deadline of the day before my wedding, I moved to Sweden to take up the position of senior research scientist.

My day-to-day activities mostly consisted of acting as the lead biologist on drug development projects. This entailed leading a team of researchers to develop and implement biological assays to test candidate therapies. I also acted as the biological representative for the multidisciplinary project committees, which planned the future direction of the project and reported progress to senior management. Outside of this role, I also became involved in a number of other drug development projects (both in preclinical and clinical development). Using my expertise in various areas, I helped test novel drug candidates by designing and testing new biological assays to screen all the various candidate molecules and select those which could be taken further in the development process.

Why did you decide to change the focus of your career from pharmaceuticals with AstraZeneca to your current academic role?

I loved my role at AstraZeneca and thrived in it, and was promoted to Associate Principal Scientist, but I would say my mind set was always more academic than industrial. During my time at AstraZeneca, I implemented a very successful seminar series that I titled 'The basic biology of...' The idea was to explain the background of relevant biological topics, so they could be understood by anyone. The topics included 'the basic biology of viruses', 'the basic biology of COPD', and 'the basic biology of asthma'. Running this series certainly evoked in me just how much I enjoyed teaching. This was coupled with personal circumstances of having our first child and wanting to raise her nearer to my family. Finally, my old friend serendipity raised its head once again when the University of Lincoln were looking for lecturers with an interest in virology. I would say the most important piece of advice I have ever been given in my career is to never be afraid of exploring any opportunity.

What is it that you enjoy most about teaching students? Have you ever encountered a student that you found particularly inspiring and, if so, what was it about them that stood out for you? How would you encourage academics to nurture these characteristics in other students?

One of the first things that becomes obvious when you start teaching students is just how much teaching pushes your own sphere of knowledge. There is nothing better than being asked a question I do not know the answer to and being forced to expand my own knowledge. This often prompts me to think outside the box and look at problems in a completely different way.

There have been many inspiring students and it is difficult to pick out any one individual. Some of our mature students who have decided to return to education from employment have been particularly inspiring, as often they are balancing studying alongside raising families. I have often found that these are some of the most passionate students who also tend to ask the most difficult questions.

"I loved my role at AstraZeneca and thrived in it, and was promoted to Associate Principal Scientist, but I would say my mind set was always more academic than industrial."

I think, as an academic, the most important thing to remember is that you cannot expect all students to be the same. We have such a diverse group of individuals, it is important that we try to recognise and nurture them as individuals rather than a homogenous group. I believe that the most important characteristic to nurture in students is to be willing to question even the most 'established' fact.

Your research now focusses on COPD and the effects that pulmonary rehabilitation has on anti-inflammatory gene expression in the immune cells of these patients. Can you briefly describe the logistics of this research, and how you hope it will benefit COPD patients in the future?

I have been extremely lucky, since joining the University of Lincoln, to establish a collaboration with Dr Arwel Jones from the Lincoln Institute of Health. Together, we have combined Dr Arwel's expertise from the clinical rehabilitation side of COPD therapy with my expertise in molecular signalling mechanisms.

The aim of our research is to better understand the impact of exercise classes carried out in pulmonary rehabilitation on the immune system of COPD patients. Exercise is known to have a number of potentially anti-inflammatory effects in different populations, but much of the benefits in COPD have been suggested to be the result of improving fitness levels. Our research is examining how exercise changes the immune system of different COPD populations. These studies are designed to highlight the benefits of pulmonary rehabilitation on COPD patients and are aimed at increasing the provision of pulmonary rehabilitation for COPD patients, particularly by identifying the patient subgroups who respond best.

You are also involved in research regarding respiratory syncytial virus, looking into the potential of its inhibition via corticosteroid and β2 agonist combination therapy. What is the most exciting aspect of this research? Why did you decide to pursue research in this area?

My current research on RSV and the effects of corticosteroids and β2-adrenoceptor agonist combination treatment is exciting. The research stems from a recently published paper that showed that children with RSV infections who were treated with a corticosteroid and adrenaline had a lower incidence of hospitalisation than the control group. Since adrenaline is an agonist of the β2-adrenoceptor, I hypothesised that this may be because of the induction of anti-inflammatory genes. I have previously shown that corticosteroids and β2-adrenoceptor agonists can synergistically induce the expression of such genes. Overall, this study is in line with my core interest in anti-inflammatory genes and examining the complex interactions with proinflammatory pathways. We have barely scratched the surface of these mechanisms for resolving inflammation and, in many circumstances, we have not examined the roles of such genes on complex activators of inflammation, such as viral infections.

"I would say the most important piece of advice I have ever been given in my career is to never be afraid of exploring any opportunity."

Is there a line of research ongoing that you are particularly excited about or that you would like to get involved with?

If there were unlimited funds and resources available for me to carry out any research I wanted to, I would certainly concentrate on the expression and function of anti-inflammatory genes.

It is still quite shocking to me that for so many years corticosteroid-induced new gene synthesis was blamed for all the side effects, while blocking the transcription of inflammatory genes directly was suggested to be responsible for the beneficial anti-inflammatory effects of corticosteroids (the transrepression versus transactivation argument). Like many of the most effective medications, corticosteroids work by mimicking and modulating our own endogenous pathways. If I have learnt one thing about biology in my career, it is that evolution has rarely resulted in putting all its eggs in one basket.

Research shows that a huge number of anti-inflammatory genes can be induced by corticosteroids and further increased by combination therapy. This is very exciting as it opens up a completely new door of potential therapies. By understanding the expression and function of these genes in different patient populations we can use these as biomarkers for new therapeutics and design the next generation of anti-inflammatory therapies that are not only more effective but have a safer side effect profile.

"I believe that the most important characteristic to nurture in students is to be willing to question even the most 'established' fact."

If money and logistical concerns were no object, how would you choose to treat COPD patients?

If money was no object, the first thing that we could do is ban cigarettes. This would almost immediately reduce the increasing numbers of COPD patients. However, with existing patients, effective smoking cessation support schemes need to be in place and we need a better understanding of the long term effects of using electronic cigarettes on the lung.

Coupled with smoking cessation, I believe the best thing would be to stop considering these complex diseases (such as COPD and asthma) as single diseases. Personalised medicine needs to be implemented in these patients with a thorough understanding of the underlying mechanisms of their pathology. This would allow specific inhibition of these inflammatory pathways.

We also need to couple pharmacological interventions with other types of treatment, including pulmonary rehabilitation. These interventions need to be implemented as soon as possible after diagnosis with the ultimate aim of slowing down or even halting the progressive destruction of the lungs, rather than trying to treat the disease once it has become too debilitating.

Ultimately, since most COPD exacerbations are caused by respiratory viral infections (e.g., rhinovirus, RSV, and influenza), effective vaccines are needed that cover all possible serotypes and are not made ineffective by such mechanisms as antigenic drift or shift.

As well as performing extensive research, you are a committee member for the British Association for Lung Research (BALR). What does your role with the BALR involve? Would you encourage others to get involved in these kinds of organisations and, if so, why?

My current role in the BALR is as an ordinary member (e.g., a member of the committee without a specific role, such as treasurer or secretary). This role involves a myriad of different activities, including reviewing travel grant applications from junior members, writing articles for the newsletter, and helping to review material before it is released. I would strongly recommend involvement in organisations such as the BALR, as it is a fantastic way to build up a strong network of potential collaborators, grant and paper reviewers, as well as meeting some of the key leaders in the respiratory field. I would say that having a strong supportive network is perhaps one of the most important things for a successful career in scientific research.

"If money was no object, the first thing that we could do is ban cigarettes. This would almost immediately reduce the increasing numbers of COPD patients."

Dr Joanna Porter @DrJoPorter

University College London Hospital, UK

What first interested you in respiratory medicine?

I was attracted to respiratory medicine by the huge unmet need. I started my career as an intensivist, but I missed the long-term interaction with patients. I worked in Rwanda during the genocide in 1994, and while there were a lot of infectious diseases, there were also a large number of respiratory diseases in these very resource-poor settings. So, although I thought I wanted to focus my attention on tropical medicine, I actually saw that respiratory medicine was more practical and of more benefit.

"It was a bit of a gamble, but I am becoming more and more convinced that neutrophils play a much more central role in the pathogenesis of these diseases than previously thought. Watch this space!"

Who has been the most influential person in directing your career path as a respiratory physician?

I could not have become a respiratory physician without the intervention of Dr Jeremy George. Changes to medical training in 1998 meant that trainees had to pick a speciality and be awarded, against fierce competition, a prestigious National Training Number (NTN). I had been involved in intensive care, and other things abroad and in the laboratory, so it was unclear if I was even eligible for a Respiratory NTN. Dr George sat on the panel to decide my fate; he fought my corner and was successful and has since played a huge role in my career at UCLH. Another mentor of mine is Prof Peter Barnes, who I followed to Cambridge and Oxford Medical Schools, but there the comparisons end. Peter has always been an inspirational role model and a constant source of support and sound advice. We are so lucky in UK academic respiratory medicine to have some fabulous women to guide the way; Prof Moira Whyte and the late Dame Margaret Turner-Warwick immediately spring to mind.

One of your specialities is the study of interstitial lung diseases (ILD). How did you first become involved with ILD research and what are you currently working on in this area?

I did my PhD with Prof Nancy Hogg at Cancer Research UK, London. I was interested in leukocyte trafficking and the role of integrins; I then did further work with Prof Alan Hall at University College London on leukocyte transepithelial migration. In 2009, I returned to clinical work and was offered a job running the ILD service at University College London Hospitals. I desperately wanted to work in a more translational area, so I focussed on the role of leukocytes, particularly neutrophils, in ILD. It was a bit of a gamble, but I am becoming more and more convinced that neutrophils play a much more central role in the pathogenesis of these diseases than previously thought. Watch this space!

Children's interstitial lung diseases come in many rare varieties. Why do paediatric cases of ILD differ so much from adult cases, and what unique challenges do they pose for a clinician as a result?

The lung has a limited response to injury and just as there are >200 diseases of the lung that result in ILD in adults, there are a similar number of different diseases in children. For example, a lot of severe genetic diseases will present with ILD in childhood. I confess to not being an expert in these diseases of early life and we have very few patients that transition from the paediatric to the adult ILD service at 18 years of age. This suggests to me that there are very, very different aetiological factors involved in childhood and adult idiopathic lung fibrosis, but perhaps we should look more closely at

the similarities between childhood and adult disease because the pathological processes may well be shared.

"I love teaching and pushing students' boundaries. I particularly enjoy making the case for rheumatoid arthritis being a lung disease: the biggest risk factor for the development of rheumatoid arthritis is smoking!"

What is the relationship between ILD and autoimmune disorders? How have advances in the field of immunotherapy impacted the treatment of ILD?

About one-third of our ILD cases are in the context of an autoimmune rheumatic disease, and it is probable that many cases of idiopathic ILD cases in fact have an autoimmune aspect to them. Therefore, you might then expect these diseases to respond to immunosuppression, and in many cases they do, but by no means do all cases respond in this way. The key distinction to be made when faced with a patient with ILD is the degree of fibrosis versus the degree of inflammation. We might expect immunosuppression to reduce the inflammation but not affect the fibrosis. The advent of novel biologics has stimulated increasing interest in the role of these therapies in modifying lung manifestations. Certainly, the lungs of a patient with an autoimmune rheumatic disease often respond to biological therapies in a very different way to the extrapulmonary disease manifestations. This is an area that is crying out for better organ-specific, treatment-response biomarkers, but it is clearly not straightforward. In addition, new antifibrotics are just beginning to be trialled in these autoimmune diseases, and I hope that in the future patients will be on combination therapy of immunosuppressives or biologics with antifibrotics, depending on where they present on the inflammatory-fibrotic spectrum of ILD. This is where precision diagnosis and treatment will really come into its own.

Pulmonary rehabilitation is an important part of disease management for many patients with chronic respiratory disease. To what extent is this effective in the various forms of ILD?

There is increasing evidence that pulmonary rehabilitation helps to increase 6-minute walk distance, reduce symptoms, and improve quality of life of ILD patients. The evidence base is not as strong as that associated with chronic obstructive pulmonary disorder (COPD), but for those patients that can take part in a class or one-to-one sessions with a physiotherapist, the majority will benefit. Unfortunately, pulmonary rehabilitation is not available for all patients that would benefit, and exercise probably needs to be continued to maintain the effect.

Air pollution is a major health concern in many countries around the world. How can pollution influence pulmonary disease pathogenesis, and what steps need to be taken by policymakers to reduce this burden?

Air pollution, particularly fine particles, is associated with asthma and airway disease and is positively associated with death from cardiopulmonary disease. It may also affect the developing lung. Our Chief Medical Officer, Dame Sally Davies, focussed on pollution in her annual report of 2017. In this report, she made several recommendations, including: "...future UK government national standards for air pollutants, developed within the next five years, should be increasingly stringent and driven by an ambition to protect human health." My own research group has an interest in the role that air pollution plays in the development of restrictive lung disease, which is a relatively under-researched area.

Medicine as a whole is quickly advancing towards multidisciplinary, personalised treatment for a variety of conditions. To what extent is this true for respiratory medicine and what new challenges has it introduced?

I think we are seeing this most clearly for asthma and lung cancer treatments and I hope that we can start to offer a stratified medicine approach

in ILD. This will not only ensure that we offer patients a precise diagnosis and treatment approach, but also means that clinical trials for novel therapies in ILD require smaller numbers of participants to more quickly assess new treatments. Such patient stratification will require more accurate and widely available biomarkers from blood and/or sputum or the use of novel imaging biomarkers, such as fluorodeoxyglucose-positron emission tomography (FDG-PET), other molecular imaging modalities, measurements of tissue density, and perhaps even MRI, as alternatives to surgical lung biopsy.

As a lecturer, what respiratory condition do you find the most challenging to teach to your students?

I love teaching and pushing students' boundaries. I particularly enjoy making the case for rheumatoid arthritis being a lung disease: the biggest risk factor for the development of rheumatoid arthritis is smoking! My own group has worked for some years on the breakdown of immune tolerance in the lungs of patients with rheumatoid arthritis. In particular, we study the production of neutrophil-derived citrullinated histones in the lungs of patients and the subsequent role of these neoepitopes in driving the development of anticitrullinated peptide antibodies that are associated with both rheumatoid arthritis and rheumatoid arthritis-associated lung disease.

What major breakthroughs in respiratory medicine or in the medical field as a whole are you looking forward to in the next decade?

I have been disappointed by the impact of genetics on medical outcomes, even for monogenic diseases that we understand well, such as sickle cell disease. I personally think that an understanding of lifestyle's impact on physical and psychological disease will allow us, if we follow the advice, to live happier, healthier, and more productive lives. My patients always ask what they can do to improve their disease, but the studies are not really out there. In addition, I am very keen on the development of precision medicine in ILD. More precise diagnosis and stratification will ensure that we use the right treatment for the right patient in the right way and at the right time, and thereby avoid harmless and futile medication.

"I personally think that an understanding of lifestyle's impact on physical and psychological disease will allow us, if we follow the advice, to live happier, healthier, and more productive lives."

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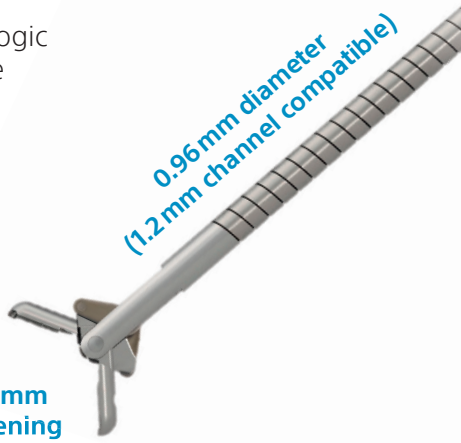

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* Catheter and Specialty Needle Alloys, an abstract from Materials & Processes for Medical Devices Conference & Exposition, Minneapolis, MN, August 10-12, 2009.

** Data on file.

1. Endobronchial Ultrasound-Guided Miniforceps Biopsy in the Biopsy of Subcarinal Masses in Patients with Low Likelihood of Non-Small Cell Lung Cancer. Herth, Felix J.F. et al. The Annals of Thoracic Surgery, Volume 85, Issue 6, 1874 – 1878.

Focussing on the Patient: Future Prospects in Alpha 1 Management

This satellite symposium took place on the 17th September 2018, as part of the 28th European Respiratory Society (ERS) International Congress in Paris, France

Chairpeople: Michael Campos,[1] Joanna Chorostowska-Wynimko[2]

Speakers: Joanna Chorostowska-Wynimko,[2] Miriam Barrecheguren Fernandez,[3] Ilaria Ferrarotti,[4] Timm Greulich,[5] Robert A. Sandhaus[6]

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5. Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Centre Giessen and Marburg, Philipps-University, Member of the German Centre for Lung Research (DZL), Marburg, Germany
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Meeting Summary

With new patient-centric and scientific networks being created, Prof Chorostowska-Wynimko explored how these initiatives, such as the European Alpha-1 Research Collaboration (EARCO) and the European Reference Network-LUNG Alpha1 Antitrypsin Deficiency (ERN-LUNG AATD Core Network), will help to advance the management of alpha 1-antitrypsin deficiency (AATD) patients. EARCO plans to create a registry to gather information from centres across Europe and ERN-LUNG

AATD plans to ensure highly specialised healthcare for AATD patients, including reliable AATD diagnostics across European laboratories.

Explaining in more detail the plans for the new EARCO registry, Dr Barrecheguren argued the case for another AATD registry to gather large-scale data that clinical trials cannot provide. She provided an overview of the new EARCO prospective follow-up registry, to be launched next year, which will integrate existing national AATD registries, enhance long-term follow-up and quality of data, and facilitate research and quality improvements across healthcare systems.

Discussing one of the first initiatives of the ERN-LUNG AATD Core Network, Dr Ferrarotti explored how to align AATD testing across Europe with the creation of European LAB-NET, an initiative first involving six European centres that will co-operate to collect, develop, verify, and make reference materials available for molecular and biochemical tests to correctly diagnose AATD and provide quality control in the laboratory diagnosis.

Dr Greulich reported on a post-hoc pooled analysis from the RAPID-randomised controlled trial (RAPID-RCT) and the RAPID-open label extension (RAPID-OLE) study, which compared the safety and tolerability of adverse event (AE) rates for two different alpha-1 antitrypsin (AAT) dosing patterns, weekly infusions of 60 mg/kg AAT, and bi-weekly infusions of 120 mg/kg AAT. Results showed there were no significant differences for exposure-adjusted event rates (p=0.850), infusion-adjusted event rates (p=0.344), and serious treatment emergent AE (TEAE) (p=1.0); TEAE occurring in the first 24 and 48 hours were comparable for both groups.

Prof Sandhaus presented the results of a telephone survey from the USA AlphaNet organisation of self-infusion practices in 555 patients with AATD. The survey found that 7.9% of respondents self-administered AAT and 92.1% who did not. Of the 44 patients who self-administered AAT, 95.4% reported being very satisfied and 4.6% were satisfied with their treatment.

Rare Lung Diseases in The Spotlight: New European Initiatives

Professor Joanna Chorostowska-Wynimko

In 2012, a group of experts evaluated barriers to accessing therapies for rare lung diseases in Europe and called for greater collaboration and communication between stakeholders (patient groups, physicians, drug developers, regulators, and payers) and better integration of research across countries and continents to address existing challenges.[1]

As one example as to why better collaboration is dearly needed, Prof Chorostowska-Wynimko presented an example from epidemiological research. An epidemiological study of distribution of AATD published in 2004 reported the highest frequency of the *PI*Z* variant in northern and western European countries, while the highest frequency of the *PI*S* variant was described for southern European countries.[2] For both variants, the lowest numbers occurred in Eastern Europe, with a sharp drop occurring along the former iron curtain.[2] However, this cannot be considered to be a true reflection of the frequencies of deficiency alleles, but rather a result of the disparities in the medical care between Eastern and Western Europe. A 2017 updated analysis of *PI*S* and *PI*Z* frequencies no longer showed this East–West divide.[3] Such disparities emphasise the need for better co-ordinated, good-quality research and care for AATD patients throughout Europe.

In April 2018, the European Respiratory Society (ERS) launched the European Alpha-1 Research Collaboration (EARCO) to build a network of AATD researchers and clinicians to guide clinical, research, and translational priorities in accordance with patients' concerns. The initiative comes under the ERS Clinical Research Collaborations umbrella, which supports projects in different respiratory areas with the objective of building and maintaining European multicentre research networks. EARCO has the additional purpose of creating the European AATD EARCO registry to ensure long-term

follow-up, facilitate patient recruitment for research, and improve quality initiatives across healthcare systems. EARCO is chaired by Dr Marc Miravitlles (Spain) and Dr Timm Greulich (Germany) and is run by a steering group of researchers and patient representatives.

The above-mentioned 2012 expert statement identified the need to use a limited number of patients in rare diseases wisely, learn from the model of the Rare Lung Diseases Consortium in the USA, and write consensus documents. With such objectives in mind, the ERS published a statement in 2017 on the diagnosis and treatment of AATD that outlined optimum care provisions in an integrated management programme.[4] Management programme recommendations included primary diagnosis with AAT genotypes and phenotypes, confirmation of AATD diagnosis, disease staging, and properly structured patient follow-up. To help establish such a disease management programme is the major aim of the AATD Core Network that was recently created within the ERN-LUNG.

ERN-LUNG is a non-profit network of European healthcare providers committed to the prevention, diagnosis, and treatment of rare respiratory diseases through patient care and advocacy, education, and research. The AATD Core Network is one of the nine Core Networks within ERN-LUNG, with AATD core centres located in Leiden, Netherlands; Warsaw, Poland; and Pavia, Italy, and supporting partners in Dublin, Ireland; Barcelona, Spain; Homburg, Germany; Birmingham, UK; and Leuven, Belgium. Other ERN-LUNG Core Networks exist for cystic fibrosis, pulmonary hypertension, primary ciliary dyskinesia, non-cystic fibrosis bronchiectasis, mesothelioma, chronic lung allograft dysfunction, and other rare lung diseases.

Benefits of an AATD management programme in the USA have been reported in a number of publications.[5-7] Data from the Alpha-1 Disease Management and Prevention Program (ADMAPP) in the USA comparing patients adhering to the programme (n=1,605) with those who did not (n=1,921) found that adhering patients were more likely to have had a pneumonia vaccine in the last 6 years (p=0.017), flu vaccine in the last year (p<0.001), hepatitis A vaccine ever (p<0.001), hepatitis B vaccine ever (p<0.001), and to exercise (p<0.001).[5] In a second analysis comparing the outcomes for 878 AATD patients, both 12 months before enrolment in ADMAPP and 12 months after, patients showed improvements in mean number of exacerbations (p<0.001), mild exacerbations (p=0.006), moderate exacerbations (p<0.001), and never having experienced an exacerbation (p=0.003).[6] The disease management programme was also cost-effective. Comparing 213 AATD patients assigned to the health management programme with 232 AATD patients not assigned found that the mean total costs were $142,406 for the managed programme cohort versus $167,935 for the comparator cohort (p=0.010), and that the medical costs were $113,051 for the management programme cohort versus $138,045 for the comparator cohort (p=0.021).[7] So far, no disease management programme for AATD in Europe exits. The ERN-LUNG Network recently launched a patient management platform, the Clinical Patient Management System, to facilitate live clinical case discussions between members and enable cross-border consultations.

Future plans include establishing a quality validation programme for standardisation of AATD diagnostics, a network of certified laboratories, and close collaboration between the AATD Core Group and EARCO CRC (that is, the creation of an AATD registry). Initiatives providing good-quality laboratory data should be given the highest priority since they are fundamental for the accurate identification of AATD patients. The ERN-LUNG AATD Core Network also aims to closely collaborate with EARCO and the AATD registry and include strong patient involvement.

Do We Need Another Alpha-1 Antitrypsin Deficiency Registry?

Doctor Miriam Barrecheguren

With an estimated prevalence of 20 people per 100,000 of the population, AATD affects more patients than other well-known rare pulmonary diseases, such as pulmonary arterial hypertension, interstitial lung disease, cystic fibrosis, idiopathic pulmonary fibrosis, and sarcoidosis.[8] AATD is significantly under-

diagnosed,[9] with an average delay in diagnosis of 5.1 years from first presentation of symptoms.[10] A Spanish primary care study demonstrated that the number of AATD determinations was low in relation to chronic obstructive pulmonary disease (COPD) prevalence. Although the number of determinations increased during the study period, the reason not to screen for AATD was not clear in many cases.[11] Results further showed AATD determinations were highest for the 55–64 and 45–54-year old age groups.

A world map of the prevalence of the *Pi*ZZ* AATD genotype estimated there to be 20,611 *Pi*ZZ* individuals in Germany, 17,191 in France, 14,522 in Spain, 11,939 in England, 10,652 in Italy, 4,944 in Portugal, and 4,090 in Denmark.[12] Focussing on the data from Spain, it is notable that only 500–600 individuals have been enrolled in the registry, representing just 3.6% of individuals with *Pi*ZZ*.

A recent ERS statement recommended that the management of AATD patients should be supervised by national or regional expert centres and that those centres should undertake systematic collection of clinical characteristics and disease natural history to enhance knowledge about the evolution and optimal management of AATD.[4] The ERS statement additionally outlined criteria required for rare disease reference centres, including demonstration of a multidisciplinary approach and the ability to perform systematic collection of data in national and international registries. Registries are needed for orphan diseases to further increase knowledge about the disease and promote clinical research, gather epidemiological data, enable the collection of data for sufficiently powered clinical trials, promote collaborations between countries and researchers, and ensure long-term viability.

Since the Alpha-1 International Registry (AIR) was first established in 1997, it has facilitated collaborations between clinicians from 21 countries, integrated and promoted national registries, increased awareness of AATD in countries with low-to-medium prevalence, and enabled recruitment to two clinical trials. The annual accumulation of patients in the AIR registry rose from 519 in 1997 to 4,758 in 2012, when the collection of follow-up data stopped.[13]

As already mentioned in the previous presentation, central to the aims of EARCO, launched in 2017 by the ERS, is the establishment of the EARCO registry. Additional goals for EARCO include building a network of AATD researchers and clinical experts, reaching a consensus on the main research priorities, supporting and encouraging young investigators and clinicians, facilitating applications to industry and European Union (EU) funding sources, and starting standard operating procedures for sample processing and handling.

The EARCO registry, planned for launch in 2019, aims to recruit 3,000 patients with AATD over the first 3 years and gather information from centres across Europe. Data will be integrated with information from pre-existing national registries, allowing registries to grow together. Additional goals include facilitating development of longitudinal follow up, collaborations with other registries (such as the liver registry), and attracting new researchers and clinicians to AATD. These aims are reflected in the broad spectrum of data that will be collected, including sociodemographic and clinical data, with additional information on complementary tests, treatment, symptoms, and exacerbations. Patients will be followed up every 12 months, with emphasis placed on quality control and the uploading of spirometry and blood test results as PDF documents. Opportunities for recording data will be open to all physicians, with direct access from the EARCO website and links to national registries developed for sharing data. Economic incentives are planned to ensure the viability of the registry.

The case for a new AATD registry can be made to increase physicians' awareness of and testing for AATD and enable recording of large-scale data that provides information beyond clinical trials. To conclude, the new EARCO registry will integrate existing national registries, enhance long-term follow-up and quality of data, and facilitate research and quality improvement initiatives across healthcare systems.

As a closing remark, Dr Barrecheguren reminded the audience that in a World Health Organization (WHO) meeting in 1997 recommended that COPD patients should be screened at least once for AAT deficiency[14] and any patients showing abnormal screening results should undergo AAT protease inhibitor typing.

No Lab, No Diagnosis: How to Align Testing for Alpha-1 Antitrypsin Deficiency Across Europe

Doctor Ilaria Ferrarotti

The European Reference Networks are virtual networks involving healthcare providers across Europe and support patients with rare, low-prevalence, and complex diseases. One of the goals of the ERN-LUNG AATD Core Network is to establish a cross-border patient blood sample exchange to detect rare AAT gene mutants and create a quality validation programme across Europe to assess the quality and standardisation of laboratories inside the network. The plan is to establish a network of certified laboratories with AATD Core Network members in Warsaw and Pavia as the reference laboratories.

Laboratory diagnosis of AATD involves both quantitative and qualitative testing. Quantitative testing (evaluating AAT blood concentrations) can take place in any laboratory, while qualitative testing (aiming to correctly identify mutated alleles) can only take place in dedicated laboratories. Where expert laboratories are unavailable, AATD diagnosis cannot be considered reliable. AATD diagnostic laboratories offering state-of-the-art techniques and standard procedures performed by well-trained and dedicated personnel have been shown to reduce costs.[15,16]

Many variations of testing algorithms are possible. Diagnostic AATD testing can be performed on samples including blood, serum, or dried blood spot. Quantitative testing, used to measure AAT concentrations and C-reactive protein, can be undertaken with nephelometry, turbidimetry, ELISA, and immunodiffusion. Qualitative testing includes genotyping (limited to S and Z alleles or addressed to other pathological alleles), phenotyping, sequencing involving only exons, and sequencing involving the whole gene or even next-generation sequencing. In the last 10 years, a number of different algorithms have been proposed for AATD diagnosis by different reference centres that relate to the requirements of different countries and AATD populations.[15,17-22]

Another factor is that cut-off levels for diagnostic AAT serum values have varied. Historically, the AAT serum level was considered to be 11 µM,[23] but more recently levels have moved to between 1.1 g/L[24] and 1.00 g/L.[18] The definition of the appropriate cut-off value will have significant impact on the detection of heterozygotes and rare alleles. While around 95% of diagnosed patients with severe AATD carry the *PI*ZZ* genotype, little is known about the epidemiology of the remaining variants, which are called rare because of their low prevalence and include *PI*I* and *PI*Mmalton*.[25] Clinicians should be aware that AATD is not limited to *Z* and *S* alleles and that rare variants are only apparent if properly investigated. For example, detection of rare variants in the Italian AATD registry increased from 2000–2004 and 2015–2017 due to technological progress and their prevalence exceeds 10% of all individuals with severe AAT deficiency.[26]

In July 2004, a Laboratory Alpha 1-antitrypsin Project workshop for scientists involved in AAT testing held in Stresa, Italy, first considered how to ensure quality control. Quality control consists of different components: pre-analytic (including sample collection, transport, and receipt), analytic (testing), and post-analytic (record keeping and reporting).

The European LAB-NET for AATD has been developed with the objective of introducing a pilot quality control programmes for six leading European laboratories involved in AATD diagnosis. The accuracy of diagnostic procedures will be verified at the laboratories in Marburg, Warsaw, Pavia, Barcelona, Lille, and Dublin, with Pavia and Warsaw providing the reference laboratories for shipping material. The initiative, which started in 2018, has been endorsed by the European Reference Networks and ERS, and is sponsored by CSL Behring.

Alternative Dosing Regimens for Patients with Alpha-1 Antitrypsin Deficiency: Safety of Bi-Weekly Alpha-1 Antitrypsin Therapy

Doctor Tim Greulich

While the recommended and licensed dose of AAT is 60 mg/kg body weight per week,[4]

the clinical reality is that weekly trips to hospitals for augmentation therapy infusions often prove unfeasible for patients. Taking a pragmatic approach, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) guidelines for the management of AATD recommend alternative augmentation therapy dosing regimens, including 120 mg/kg for 14 days, 180 mg/kg for 21 days, and 50 mg/kg for 7 days.[27] Such guidelines raise questions as to whether such alternative dosing regimens maintain sufficient AAT levels. The trough levels, i.e., levels just before the next infusion, should be greater than 0.5 g/L, which is equivalent to 11 µM.

A study evaluating whether steady state minimum concentrations of total AAT can be maintained above the threshold of 0.5 g/L with longer intervals between doses showed that both 100 mg/kg and 120 mg/kg every 14 days maintained serum trough levels >0.5 g/L but that serum trough levels were <0.5 g/L for 150 mg/kg and 180 mg/kg every 21 days and for 250 mg/kg every 28 days.[28] In a Danish trial, where AATD patients were randomised to either AAT 250 mg/kg or placebo albumin 625 mg/kg infusions every 4 weeks, levels of AAT in the active arm were maintained above the 11 µM threshold for an average of 23–24 days, with a mean AAT level of 8.8 µM after 28 days.[29] A simulation model of serum levels undertaken for the RAPID programme showed that for 60 mg/kg weekly the C_{avg} was 21.9 µM and the C_{trough} was 16.3 µM; for 120 mg/g bi-weekly the C_{avg} was 21.9 µM and the C_{trough} was 12.8 µM.[30] The mean plasma concentrations were similar for both regimens and trough levels were maintained above the 11 µM threshold. Data from population pharmacokinetic simulations predicted that trough levels above the 11 µM protective threshold would be maintained in the majority of patients treated with bi-weekly 120 mg/kg infusions.[30,31] (CSL Behring, data on file). Furthermore, a pharmacokinetic model suggested a linear relationship between AAT dose and AAT serum levels within the concentrations investigated.[31]

While a number of studies suggest that sufficient trough levels can be achieved with AAT 60 mg/kg every 7 days and 120 mg/kg every 14 days, little information has been published on the safety of bi-weekly infusions of 120 mg/kg AAT.

In the RAPID-RCT,[32] where 180 AATD adult patients were randomised to AAT (n=93) or placebo (n=87), bi-weekly infusions were allowed under certain circumstances, for example, covering holiday periods. RAPID-RCT was followed by the RAPID- OLE study,[33] where patients originally prescribed placebo could change to augmentation therapy.

In a post-hoc pooled analysis, the safety and tolerability of bi-weekly infusions of 120 mg/kg AAT were compared with weekly 60 mg/kg infusions for patients in both RAPID-RCT and RAPID-OLE.[34] For the analysis, TEAE were defined as an AE not present before initiation of treatment or any AE that worsened in severity following exposure to treatment. Two different measures comparing AE rates were calculated: exposure-adjusted event rates (EAER), defined as all TEAE occurring during the trial divided by the cumulative exposure of the respective group (60 or 120 mg/kg AAT or matching placebo), and infusion-adjusted event rates as TEAE occurring in the 7-day period up to and following a bi-weekly 120 mg/kg infusion or matching placebo (Table 1).[35]

During RAPID-RCT, 75 patients in the AAT group received 333 infusions with 120 mg/kg AAT during 321 sequences and in the pooled dataset of RAPID-RCT and RAPID-OLE studies, 933 bi-weekly infusions during 884 sequences in 137 patients were identified. Results show that the EAER was 5.8844 for patients receiving 60 mg/kg versus 5.7038 for patients receiving 120 mg/kg (p=0.681); for serious TEAE, the EAER was 0.3741 for 60 mg/kg versus 0.4074 for 120 mg/kg (p=0.850). Furthermore, the infusion-adjusted event rates for any TEAE were 0.1041 for 60 mg/kg versus 0.1267 for 120 mg/kg (p=0.3449); for serious TEAE, they were 0.0057 for 60 mg/kg versus 0.0079 for 120 mg/kg (p=1.0). The study showed that TEAE occurring within the first 24 and 72 hours after infusion were comparable between the subgroups. A breakdown of severity of reported TEAE showed that the majority of TEAE were mild or moderate and comparable between the 60 and 120 mg/kg groups.[34]

In conclusion, a post-hoc analysis of the RAPID programme showed that bi-weekly dosing with 120 mg/kg AAT had similar rates and severity of AE to weekly dosing with 60 mg/kg AAT.

Table 1: Pooled data from the RAPID randomised control trial and the open label extension trials- comparing differences in treatment emergent adverse events between weekly AAT (60 mg/kg) and bi-weekly AAT (120 mg/kg).[35]

	AAT (N=137; bi-weekly infusions n=993)					
	60 mg/kg			120 mg/kg		
	Number of events	n (%)	IAER	Number of events	n (%)	IAER
Any TEAE	96	49 (35.8)	0.1086	114	60 (43.8)	0.1290
TEAE within 24 hours	33	23 (16.8)	0.0373	30	22 (17.5)	0.0339
TEAE within 72 hours	53	34 (24.8)	0.0600	57	36 (26.3)	0.0600

IAER: infusion-adjusted event rates; TEAE: treatment emergent adverse events.

Self-Administration of Alpha-1 Antitrypsin Therapy in the USA: Results of an Alphanet Survey

Professor Robert Sandhaus

AlphaNet is a not-for-profit American organisation that provides customised care and innovative disease management for AATD patients. In addition to funding AATD research, AlphaNet provides a comprehensive and structured disease management programme (ADMAPP) designed to optimise AATD outcomes. The overall goal is to reduce exacerbations, improve quality of life, and manage health resources efficiently.

ADMAPP is linked to a prospective outcome study involving >6,000 patients receiving AAT therapy. Currently, 65 regional AlphaNet co-ordinators (who are also AATD patients) provide regular contact with patients, and monthly questionnaires are used to collect data on well-being and care utilisation.

Medical interest in self-infusion was first triggered when it became apparent that patients who needed to travel for work had been teaching themselves to self-infuse. Self-administered home intravenous therapy is already common practice for hereditary angioedema, where it has been shown to deliver a range of benefits including enabling patients to resume normal work and family life (including travel), play an active role in disease management, and experience fewer healthcare visits and fewer episodes of hospitalisation.[36]

AlphaNet has recently undertaken a cross-sectional, observational telephone survey of ADMAPP patients to assess the occurrence of AAT self-administration. To take part, patients needed to be aged >18 years, diagnosed with AATD, and receiving AAT therapy with a human alpha 1-proteinase inhibitor (Zemaira® [CLS Behring, King of Prussia, Pennsylvania, USA] or Respreeza® [CSL Behring UK Ltd., Haywards Heath, UK).[37] Altogether, 555 AATD patients answered the questionnaire, of which 170 (30.0%) were men and 214 (38.6%) women; the remainder (30.8%) did not disclose their sex. The age range of survey participants was 0.9% <30 years, 1.6% 30–39, 7.7% 40–49, 23.6% 50–59, 25.9% 60–69, 10.5% 70–79, and 1.4% >80. The occupation of respondents was students (1.1%), working full-time (14.4%), working part-time (8.5%), and retired (53.7%), with no response concerning employment from 22.3% of respondents.[37]

Results showed that 7.9% of respondents self-administered AAT versus 92.1% who did not. Of respondents who did not self-administer at the time of the survey, 2% reported that they had previously done so, with 30% of these patients reporting that the reason they gave up was due to inability to self-administer independently.[37]

From the survey, the most frequently cited reason for not considering self-administration was satisfaction with an existing regimen

(79.9%). Other reasons cited included lack of confidence (26.2%), physical impairment (3.8%), and fear of needles (5%).[37]

Of the 44 patients who self-administered AAT, 95.4% reported being very satisfied and 4.6% were satisfied. The questionnaire also revealed that significantly more women than men self-administered treatment (p=0.007). Concerning how patients first heard about self-administration, 39.5% learned from other AATD patients, 14.0% from a home or specialist nurse, 7% from a nurse, and 4.7% from a doctor.[37]

The survey showed self-administration training was provided by home nursing agencies (72.1%), patients being self-taught (9.3%), training from hospital nurses (7.0%), and doctors (4.7%). Additionally, 6.9% of self-administering patients had received no training.[37] Of patients who self-administered, 56.4% had received on average 2–3 training sessions. Most respondents (93%) cited greater independence as the biggest benefit of self-administration, with 37.2% saying it allows travel, 32.6% fits their lifestyle better, 2.3% saves time, 2.3% allows more control, 2.3% lowers medical costs, and 2.3% lowers transportation costs.[37]

Overall, 83.7% of patients who self-administered AAT therapy reported that they had experienced no difficulties with self-administration; of those experiencing difficulties, 5 reported infusion-related issues, including selection of infusion sites, ports becoming clogged with scar tissue, intravenous stick injuries, difficulties locating veins, and switching from vein to port.[37]

An unadjusted comparison of survival data from the ADMAPP programme with published historical data seems to imply that AATD patient outcomes have improved over the past 2–3 decades with the advent of augmentation therapy and ADMAPP and further analyses are ongoing to substantiate this finding and calculate the extent of this effect.

To conclude, the survey showed that patients who self-administer AAT therapy are very satisfied, have improved independence, and require limited training to self-administer independently.

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Back to Basics in Asthma and COPD: Optimising the Patient Journey

This symposium took place on 17th September 2018, as part of the 28th European Respiratory Society (ERS) International Congress in Paris, France

Chairpeople: Mika Mäkelä,[1] Giorgio Walter Canonica[2]

Speakers: Mika Mäkelä,[1] Henry Chrystyn,[3] Federico Lavorini,[4] Giorgio Walter Canonica[2]

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Meeting Summary

The objective of this symposium was to build on the guiding principles of asthma and chronic obstructive pulmonary disease (COPD) and to address some of the most frequently encountered challenges in the management of chronic airway disease, using a mix of scientific information and guidance based on clinical practice. Prof Mäkelä opened the symposium by reviewing key achievements from the Finnish asthma, COPD, and allergy programmes. He also highlighted how these co-ordinated educational programmes were responsible for driving an improvement in Finnish public health and reducing the socioeconomic burden of disease. Prof Chrystyn then addressed some of the common misconceptions associated with high-resistance dry powder inhalers;

he explained how the properties of these devices make them suitable for use by a broader range of patients than perceived by many clinicians. Next, Prof Lavorini addressed the real-world use of inhalers by highlighting how specific errors in recent real-life studies are associated with a loss of disease control and how the Easyhaler® (Orion Corporation, Espoo, Finland) meets many of the needs of doctors and patients. Finally, Prof Canonica focussed on precision and personalised medicine in chronic airway disease, with an emphasis on how clinicians can optimise patient adherence and, consequently, treatment in daily practice.

Transforming Asthma and COPD Care: Lessons from Finland

Professor Mika Mäkelä

Over the past few decades, Finland has experienced measurable successes in improving asthma and COPD care, largely due to nationwide and co-ordinated programmes designed to educate healthcare professionals (with a strong emphasis on primary care) and inform the general public.

Early History

The first of these programmes, the 10-year asthma programme, commenced in 1994. It was designed to lessen the burden of asthma on individuals and society through early diagnosis and treatment (with guided self-management as the primary form of treatment); reduction in respiratory irritants, such as smoking; implementation of patient education and rehabilitation combined with normal treatment; an increase in knowledge about asthma in key groups; and promotion of scientific research.[1] Overall, the programme had a considerable impact on healthcare use and disability. By 2003, it reduced the number of hospital days attributable to asthma compared with those in 1981.[1] The total cost of asthma also reduced, from €222 million in 1987 to €191 million in 2013 (a reduction of 14%), despite a three-fold increase in the number of asthmatics from 83,000 to 247,583.[2] The success of the programme has been largely attributed to education, which was central in helping to identify and treat patients and improve guided self-management.

Improvements in COPD Care

The Finnish COPD programme overlapped with the asthma programme and was equally successful in bringing about much needed improvements to COPD care. Using a multilayered approach, this programme was designed to reduce the prevalence of COPD; improve COPD diagnoses (especially in primary care); and reduce the number of moderate-to-severe cases of COPD, hospitalisations, and treatment costs due to COPD.[3] Programme implementation included the provision of information for healthcare professionals and the general population, as well as multidisciplinary education and training. In parallel, the publication of guideline statements and the introduction of tobacco legislation over the same timeframe supported the programme's agenda and helped to ensure its success. In terms of outcomes, the prevalence of COPD remained unchanged over the programme's course, but it was successful on multiple other fronts. For example, smoking decreased in men and women, significant improvements were observed in the delivery of spirometry, and there was a statistically significant reduction in costly hospitalisations (39.7%) between 1997 and 2007.[3]

Targets for the Future

Most recently, the Finnish allergy programme was introduced to address the growing epidemic of allergy. Capitalising on the successes of the asthma and COPD programmes, it has set out a number of ambitious targets, including a reduction in allergies by 20%, work-related allergies by 50%, avoidance diets by 50%, emergency visits caused by asthma by 40%, and allergic disease-related costs by 20%, as well as the availability and use of quality-certified allergy testing centres for all patients.[4] However, rather than seeking to drive behaviour change among healthcare professionals, the allergy programme has targeted patients with allergies and asthma and their families, public health and patient organisations, experts, legislators, and authorities. Full results from the programme, which is due to conclude in 2018, will be disclosed in due course, but results

from the first 8 years have been promising, with improvements reported across all but one indicator.

Overall, the Finnish asthma, COPD, and allergy programmes have shown how the burden of chronic respiratory diseases can be reduced with national consensus and the implementation of regional education and disease awareness campaigns. While sound clinical science is needed as a fundamental basis for education, common sense and the provision of practical information are also needed in equal measure to bring about meaningful change and an improvement in public health.

Making Sense of Dry Powder Inhalers

Professor Henry Chrystyn

Dry powder inhalers rely on the generation of a turbulent airflow energy to sufficiently break-up (known as deaggregation) drug particles from their carrier (typically lactose) within the inhaler formulation. In its simplest terms, this turbulent airflow energy is the product of a patient's inhalation flow and the resistance of a given inhaler.[5,6] Therefore, to generate a set turbulent airflow energy through a dry powder inhaler, either a low inhalation flow through a high-resistance inhaler or a high inhalation flow through a low-resistance inhaler is required.[5]

Turbulent Airflow Versus Peak Inhalation Flow

Peak inhalation flows are lowest through high-resistance dry powder inhalers and highest through low-resistance dry powder inhalers in adults with asthma or COPD, and children with asthma.[7] The opposite is true for turbulent airflow energy, which increases with dry powder inhaler resistance across all patient groups.[7] It is this turbulent airflow energy generated inside an inhaler that is of greater importance than a patient's peak inhalation flow for the deaggregation of the drug particles from their carrier during the operation of a dry powder inhaler.

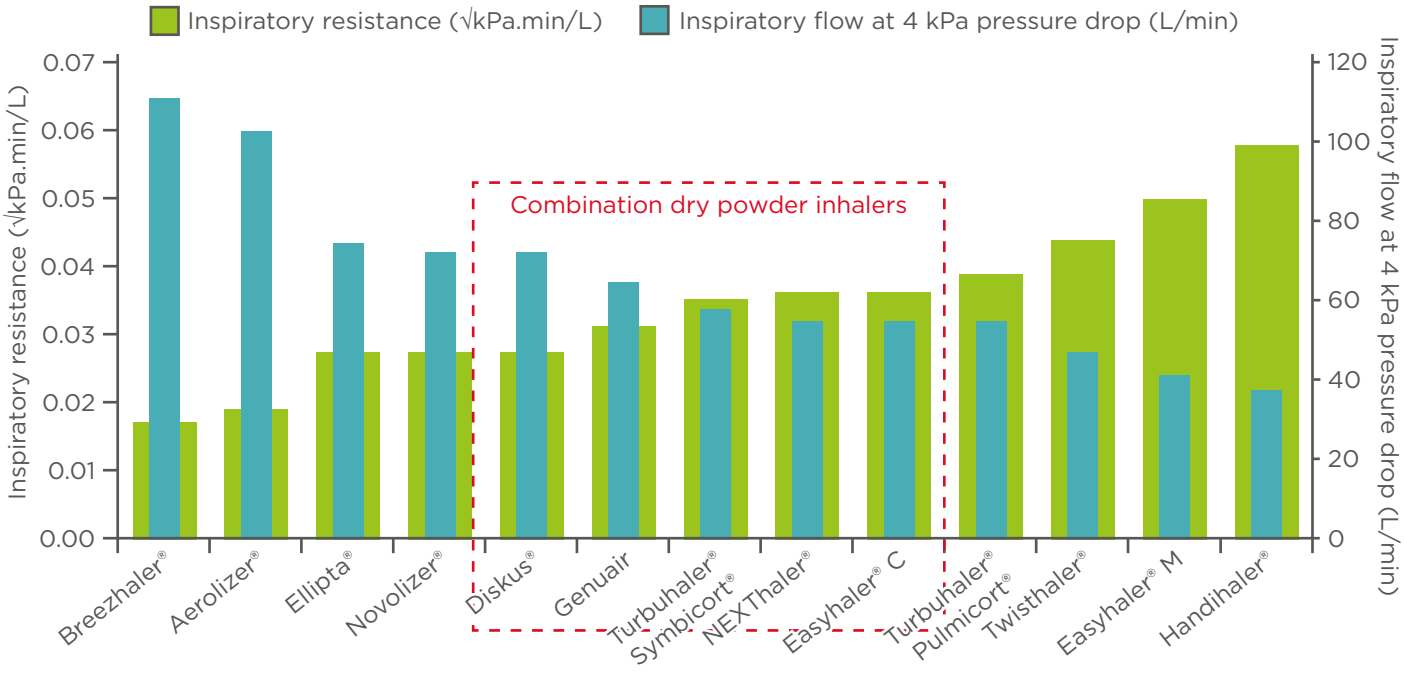

Figure 1: Inspiratory resistance of marketed dry powder inhalers and respective inspiratory flows studied at a pre-set equal pressure drop rate of 4 kPa.

Easyhaler® C: combination; Easyhaler® M: monotherapy.

Adapted from Malmberg et al.[9] and Krüger et al.[10]

The Importance of Inhaler Training

Across the spectrum of dry powder inhalers, only a minority of patients with asthma (adults and children) and COPD are unable to generate peak inhalation flows ≥30 L/min (Aerolizer® [Novartis Pharma AG, Basel, Switzerland]: 1.0%; Diskus® [GlaxoSmithKline, Brentford, UK]: 6.1%; Turbuhaler® [AstraZeneca AB, Södertälje, Sweden]: 4.1%; Spiromax® [Teva Pharma BV, Haarlem, Netherlands]: 1.3%; and Easyhaler: 3.1%),[7,8] which is considered the effective minimum flow rate for dry powder inhalers. Given that most patients can achieve the threshold peak inhalation flow required for correct dry powder inhaler operation, irrespective of device resistance and disease severity, the use of high-resistance dry powder inhalers need not be restricted in patients unable to generate high inhalation flows, such as those with COPD. Dry powder inhalers with higher resistance, such as the Easyhaler, Twisthaler® (Merck Sharp & Dohme Ltd., Hertfordshire, UK), or Handihaler® (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA), require lower inhalation flows than dry powder inhalers with lower resistance to generate equivalent turbulent airflow energies for drug deaggregation through the device (Figure 1).[9,10] With this in mind, clinicians should focus on the provision of adequate inhaler training for patients, rather than placing emphasis on achieving a specific inhalation flow.[11] Figure 1 shows that the resistance of dry powder inhalers that are formulated with fixed-dose combinations of a long-acting β-agonist and corticosteroid are similar.

The inhalation parameters when patients use the Easyhaler make it suitable for all patients generating a range of peak inhalation flows. For example, studies have shown that peak inhalation flows and dose delivery with the Easyhaler are similar to another widely prescribed dry powder inhaler, the Turbuhaler,[9] relative lung deposition with the Easyhaler is similar irrespective of the inhalation flow rate,[9] and interpatient flow variability with the device is smaller to that of other dry powder inhalers.[12] These attributes combine to provide consistent dose emission irrespective of the inhalation flow.[12]

Inhaler Use in Real Life: An Evolving Story

Professor Federico Lavorini

Randomised controlled trials are considered the gold standard of evidence for providing information on treatment efficacy. However, unlike real-life studies, which assess the effectiveness of a treatment under real-world conditions, they can seldom be generalised to a broader population.

Issues with Inhaler Use

According to one analysis, only 1.3% of patients in the real world meet the stringent eligibility criteria for clinical trials in asthma.[13] Patient adherence is also frequently higher in randomised controlled trials than in real-life studies, in which it can fall below 50.0% and reach as low as 8.3%.[14,15] There are many reasons why adherence may be suboptimal in the real world, including poor inhaler technique, incorrect inhaler use, and a lack of understanding of inhaler use.[16]

In a cross-sectional study of >3,500 patients with asthma (CRITIKAL),[17] inhaler errors were found to be common and not exclusive to a specific type of inhaler (Figure 2). Specifically, insufficient inspiratory effort with both the Turbuhaler and Diskus inhalers was associated with an increased likelihood of uncontrolled asthma and exacerbation. By contrast, a lack of knowledge, incorrect preparation, incorrect timing of inhalation, incorrect head position, and hand–breath disco-ordination with pressurised metered-dose inhalers were associated with an increased likelihood of uncontrolled asthma but not exacerbation.[17] Data from a recent real-life French study of almost 3,000 patients have indicated that inhaler handling errors are also frequent in patients with COPD (only 25.4% of whom did not make any error) and are associated with an increased rate of severe COPD exacerbations.[18]

Taken in the context of a systematic review that found inhaler use has not improved among patients over the past 40 years (1975–2014),[19] these results should collectively serve as an urgent call to action for clinicians to ensure that they include patient education as an essential component of disease management.

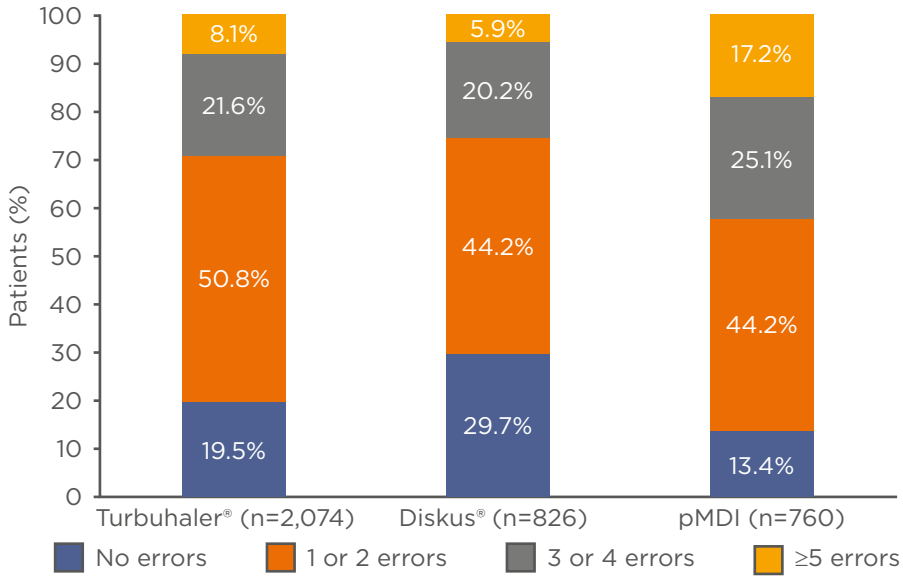

Figure 2: Number of errors made by patients in the CRITIKAL study, grouped by device type.

pMDI: pressurised metered-dose inhaler.

Adapted from Price et al.[17]

Overcoming Challenges

Given that inhaler errors are common in the real world and are associated with poor disease outcomes, it is important that clinicians select the right inhaler for each patient in real life. In practice, an 'ideal' inhaler does not exist. However, the Easyhaler meets a series of five specific criteria designed to accommodate the needs of technologists, doctors, and patients: effective, efficient, engaging, error-tolerant, and easy to teach.

Firstly, the Easyhaler can be considered an effective inhaler. It delivers particle sizes in the respirable range (1.9–4.9 µm) irrespective of inhalation volume or flow rate,[20] and a real-life study has shown that a switch to the budesonide/formoterol Easyhaler significantly improved disease control after 12 weeks in patients with asthma and COPD.[21] Secondly, the Easyhaler is efficient; it requires five essential steps for inhalation. Up to 78% of adult patients displayed correct use after the first visit in a real-life study of 1,016 patients with asthma or COPD in Hungary.[22] Thirdly, the Easyhaler is engaging, with patients expressing a higher degree of satisfaction with the device (72.4%) compared with Turbuhaler (17.3%), pressurised metered-dose inhalers (12.7%), or Diskus (18.0%).[21] Fourthly, the Easyhaler is error-tolerant, meaning that it delivers consistent dose emission irrespective of moisture, vibration, freeze/thaw conditions, and the effects of dropping.[12] Finally, >90% of clinicians have described the Easyhaler as easy to teach, with 98.9% of patients learning the inhaler technique within 10 minutes (Table 1).[21]

Focus on the Patient: What Clinicians Need to Know

Professor Giorgio Walter Canonica

The treatment of asthma and COPD is gradually evolving from a one-size-fits-all approach to one that encompasses both personalised and precision medicine. Although the terms personalised medicine and precision medicine have previously been used interchangeably, they should be considered separate concepts that have a collective role to play in disease management.

Defining Precision Medicine

Precision medicine can be defined as the use of targeted treatment based on the

specific genetic, biomarker, phenotypic, or psychosocial characteristics of an individual patient. In other words, precision medicine targets a particular mechanism of disease.[23,24] Over the years, technological advances in diagnostics and therapeutics have driven the evolution of precision medicine, supported by the growing field of omics, which includes proteomics, transcriptomics, and genomics. These have enabled clinicians to identify disease mechanisms using specific tools, subsequently allowing them to treat such mechanisms with highly targeted treatments, such as antibodies.

Personalised Medicine in Asthma and COPD

By contrast, personalised medicine focusses on the patient rather than the disease mechanism and accounts for the important role of patients in managing their own health. Choosing the correct inhaler for each patient is one aspect of personalised medicine that can have a tangible effect on adherence and, ultimately, control of chronic airway diseases. However, in reality, it is complicated by the fact that clinicians must choose from hundreds of possible inhalation products.[25] It is, therefore, not surprising that patients find the use of multiple inhalers confusing[26] and struggle to use their inhalers properly.[27] In addition, switching from one inhaler to another has been shown to be problematic for patients. One retrospective matched cohort study of 824 patients from the UK found that patients with asthma whose inhaled corticosteroid was switched without an accompanying consultation experienced poorer asthma outcomes compared with controls.[28]

Other challenges to adherence include a lack of patient engagement. Results from the Global Asthma Physician and Patient (GAPP) survey[29] have demonstrated how clinicians and patients have differing perceptions of education provided and received, with 64% of patients and 87% of clinicians reporting that up to half of office visits were devoted to educational issues.

Embracing Personalised Medicine

From a practical perspective, clinicians can incorporate a number of measures into their practice to improve inhaler use in patients switching devices and address the need to improve patient engagement. Firstly, education should be prioritised during clinician–patient consultations and clinicians should explain to patients why they are receiving a new inhaler and provide adequate instructions on how to use it correctly. Clinicians should also factor in frequent assessments of inhaler technique.[30]

These measures would align with patient expectations. A pragmatic survey consisting of face-to-face interviews conducted with a group of >2,000 individuals in Italy revealed that most patients want to be informed about how an inhaler works if they have to change device (86%), would rather maintain the same type of device (81%), and would be willing to change inhaler if their clinician told them to do so (85%).[31]

Overall, nonadherence represents a major barrier to the success of therapy but also an opportunity to improve health and wellbeing in patients with chronic airway diseases. Through better patient engagement, clinicians can help to improve adherence and deliver medicine that is truly personalised and focussed on the patient.

Table 1: Time taken to teach asthma, COPD, and ACO patients how to use the Easyhaler® (asthma: n=617; COPD: n=775; ACO: n=98).

	<5 minutes	5–10 minutes	10–20 minutes	>20 minutes
Total (%)	73.8	25.1	1.1	0.0
Asthma (%)	79.9	18.9	1.2	0.0
COPD (%)	68.6	30.2	1.2	0.0
ACO (%)	76.8	23.2	0.0	0.0

ACO: Asthma–COPD overlap; COPD: chronic obstructive pulmonary disease.

Adapted from Tamasi et al.[21]

Summary

Professor Mika Mäkelä

Disease control in asthma and COPD is achievable in most patients using the inhalers and tools currently at clinicians' disposal. Rather than abandoning the use of inhalers and medications that are supported by sound clinical science and have been successfully used for years, clinicians should reflect on their own practice and ensure that they are performing the basics correctly to promote optimal adherence to therapy. Crucially, patients should be supported in their efforts to remain adherent, and one effective way of doing so is through patient engagement with robust education and training.

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Inhaler Use in Real Life: An Evolving Story
Focus on the Patient: What Clinicians Need to Know
Discussion
Wrap-up

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State-of-the-Art Session: Respiratory Infections

This symposium took place on 17th September 2018, as part of the 28th European Respiratory Society (ERS) International Congress in Paris, France

Speakers: James D. Chalmers,[1] Jakko van Ingen[2]

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Meeting Summary

In recent decades, there has been growing interest in the recognition and management of both bronchiectasis and nontuberculous mycobacteria (NTM) pulmonary disease. More specifically, interest in diagnosing NTM infection in patients with bronchiectasis has dramatically increased. Publication of the European Respiratory Society (ERS) guidelines and results from a number of large clinical trials have resulted in an exciting year for bronchiectasis research. Despite the increased knowledge and expanding options for disease management, a number of challenges persist. There remains a paucity of evidence to support management recommendations, which have not kept pace with the growing attention given to these diseases. To explore these limitations, Prof Chalmers summarised the reasoning behind the new guidelines.

The main objectives of these two presentations were to provide an expert overview of the challenges and achievements in the management of bronchiectasis and NTM pulmonary diseases, as well as predicting future trends. Dr van Ingen called for caution when managing these diseases because neither bronchiectasis nor NTM pulmonary disease can be described as single disease entities and, therefore, cannot be treated as such. The presence of NTM pulmonary disease is often a sign of multiple underlying conditions that must be addressed in tandem with culture conversion. Likewise, bronchiectasis pathogenesis is complex and failure of antibiotic therapy to offer consistent clinical benefit suggests infection is not central to pathogenesis in all patients, and a holistic approach is required. Finally, these interactive sessions uncovered and discussed various aspects and attitudes associated with disease management and highlighted how quality of care may be closely linked to clinical outcomes.

Current Knowledge Gaps in the Treatment of Bronchiectasis and Nontuberculous Mycobacteria Pulmonary Infection

Bronchiectasis is a serious, chronic, progressive pulmonary disease that is common in Europe. Most recent prevalence estimates are >400 cases per 100,000 men and >500 cases per 100,000 women, with a 40% increase in the past decade.[1] Despite this, significant knowledge gaps prevail in key areas, including aetiology and pathogenesis. NTM infection is a considerable challenge for patients with bronchiectasis, with the overall prevalence reported as 9.3% in England, Wales, and Northern Ireland.[2] Hence, there has been a rapid rise in research interest for the treatment and pathogenesis of bronchiectasis, and in the potential involvement of NTM pulmonary disease.

Bronchiectasis and NTM pulmonary disease often coexist and overlap, meaning disease evaluation can be challenging and pathogenesis pathways remain unclear. Combining antibiotic regimens is the current standard therapy for patients with bronchiectasis and NTM infection, but treatment has been predominantly guided by observational data, with just a few randomised controlled trials (RCT) providing evidence. In September 2017, the publication of new ERS guidelines for bronchiectasis was universally welcomed; however, the lack of evidence-based therapy options for patients is an ongoing challenge for healthcare professionals.

Bronchiectasis: The New, The Old, and The Ugly

Professor James D. Chalmers

In the past 12–24 months, bronchiectasis has garnered increasing interest, with the publication of data from the European Bronchiectasis Registry offering an insight into the natural history of bronchiectasis and a greater understanding of the complexities of its heterogeneity, which may provide potential applications in disease management. However, the evidence base has fallen short and, as yet, does not mirror the clinical importance of the disease. One major new development contributing to the growing knowledge of bronchiectasis is the publication of new ERS guidelines for the management of bronchiectasis in adults. The European bronchiectasis guideline was a multinational effort, uniting experts from many different disciplines. The guideline provides recommendations on the key aspects of bronchiectasis management across nine main areas: aetiology, exacerbations, eradication, long-term anti-inflammatories, long-term antibiotics, long-term mucoactives, long-term bronchodilators, thoracic surgery, and respiratory physiotherapy.[3]

Although aetiology may be viewed as a diagnostic effort, the decision was taken to include this topic in management recommendations to emphasise the importance of identifying treatable underlying causes of bronchiectasis. The first step in management is identifying the underlying cause of bronchiectasis and, when a treatable aetiology is identified, having robust guidelines to correctly treat the patient. One of the most controversial areas is management with long-term antibiotics, which has generated a large amount of debate. Years of cystic fibrosis (CF) research have proved the effectiveness of inhaled antibiotics for *Pseudomonas aeruginosa* infection, while data from three small but convincing studies published in the last 10 years have pointed towards the effectiveness of long-term macrolide use in bronchiectasis.[4-6]

Specific guidelines for patients with frequent exacerbations were included because, to date, the best evidence on prophylactic therapy supports exacerbation control. The guidelines emphasise that the first step is optimising airway clearance to reduce exacerbations, as many patients can control their disease with appropriate drainage of secretions from the lung. The next step, treatment of the infection, requires the exclusion of other causes of exacerbations, such as allergic bronchopulmonary aspergillosis or immunodeficiency, because allergic bronchopulmonary aspergillosis, for example, cannot be treated with an inhaled antibiotic. To counter this, a subclassification of bronchiectasis patients was introduced: those with or without *P. aeruginosa* infection. The guidelines recommend inhaled antibiotics

for the treatment of patients with *P. aeruginosa* infection and oral antibiotics, predominantly macrolides, for the treatment of frequently exacerbating patients without *P. aeruginosa* infection. They also recommend avoiding macrolide monotherapy when there is a history of NTM because of the risk of inducing macrolide resistance.

Exacerbation history is a strong predictor of future outcome. One recent study assessed the stability of exacerbation frequency, clinical predictors, and outcomes of patients with frequently exacerbating disease.[7] Patients who have ≥3 exacerbations per year were found to have a probability of >60% of having ≥3 exacerbations in the following year, and this pattern was predicted to extend into Year 3. The study showed that exacerbation frequency is a highly stable characteristic because without intervention, exacerbation frequency will be maintained. The greatest morbidity and mortality rates were also seen in the ≥3 exacerbations group, with a significant difference in 5-year survival rates in this group compared with the rest of the patients.[7] Thus, these patients should be identified as a different subgroup or phenotype and targeted for additional treatment, such as optimising airway clearance, considering other causes of deterioration, and, when appropriate, adding long-term antimicrobial therapy. As with CF, there is evidence that patients with *P. aeruginosa* infection have worse clinical outcomes than those without[7] and that they differ from other patients with bronchiectasis with regard to severity, presentation, and prognosis. Hospitalisation rates for patients with bronchiectasis and *P. aeruginosa* infection are often high because antibiotic resistance means patients must be treated for exacerbations with intravenous agents. Infections with *Haemophilus influenzae* have also been shown to indicate a poor prognosis when persistent and may require more aggressive intervention.[7]

No current clinical trial data demonstrate effective eradication of *Pseudomonas* infection in patients with bronchiectasis, but antibiotic-based eradication is the accepted standard of care for CF patients. On balance and based on clinical practice outcomes, it is believed that eradication should be attempted for patients with bronchiectasis and guidance on treatment regimens has been included in the ERS guidelines. Another challenging area is recommendations for bronchodilators and inhaled steroids. From European registry data, 60–70% of bronchiectasis patients are treated with either inhaled steroids, bronchodilators, or both, although no RCT currently exist showing evidence to support either approach.[8] The ERS guideline recommends that it is reasonable to trial bronchodilators in patients with significant breathlessness, but inhaled corticosteroids are not recommended, except in patients with coexisting asthma or those with chronic obstructive pulmonary disease (COPD).

The vast majority of recommendations in the European guidelines are conditional and most of the strong recommendations are negative, e.g., avoidance of statins for bronchiectasis due to clear evidence of adverse effects with statin use in two RCT.[3] Recombinant DNAase for the treatment of bronchiectasis is not recommended due to results of trials from the 1990s that show it may increase exacerbations, thus, emphasising the difference between bronchiectasis and CF.[3] The only strong positive recommendation in the guidelines states that patients with impaired exercise capacity should participate in pulmonary rehabilitation and take regular exercise due to the beneficial impact on airway clearance, and that physiotherapy is a positive intervention.[3]

The overall message from the guidelines indicates just how weak the evidence base is for bronchiectasis. Historically, there has been some doubt as to whether bronchiectasis is actually a disease.[9] In spite of these debates, it can be concluded that all bronchiectasis patients follow a broadly similar course and, excluding patients who require a specific antimicrobial intervention, like patients with NTM pulmonary disease, may be regarded as a valid group of patients. Indeed, these guidelines were the first to be titled for bronchiectasis, rather than non-CF bronchiectasis.

Some of the more negative trials in bronchiectasis have led to calls for the re-evaluation of the pathophysiology of the disease. In the 1980s, Dr Peter Cole proposed the idea of the 'vicious cycle', in which, because of epithelial dysfunction and mucus hypersecretion, patients develop impaired

ciliary clearance, which causes neutrophilic inflammation, bacterial virulence factors, and lung dysfunction infection, leading to epithelial dysfunction.[10] The natural extension of this is that, if the bacterial infection is cleared using antibiotics, the cycle is broken and other aspects of the disease should improve. Recently, this hypothesis has been tested by assessing whether intervening with antibiotics in patients with high bacterial loads and airway infection improves both rates of exacerbation and quality of life. The Phase III RESPIRE I and II trials[11,12] evaluated the efficacy and safety of ciprofloxacin dry powder for inhalation in patients with bronchiectasis 14 days on and 14 days off or 28 days on and 28 days off over 1 year. The results were conflicting, with RESPIRE I reporting a reduction in time to first exacerbation in the 14-day arm and RESPIRE II showing a non-significant trend to a reduced exacerbation rate in the 28-day arm. In September 2018, an alternative concept for bronchiectasis was published suggesting a more complex model for pathogenesis. The model has been termed the 'vicious vortex': when one pathway is blocked by eliminating bacterial infection the lung destruction continues to affect ciliary function and inflammation persists.[13] Therefore, all aspects may be interdependent, so targeting one aspect in isolation, such as bacterial infection, is likely to only have a modest impact on clinical outcomes.

In light of these updates, where does the solution lie for the effective management of patients with bronchiectasis? Antibiotic therapy is still very important, although one form of intervention is often insufficient. Therefore, the concept of targeting the 'treatable traits' has become more relevant than ever to effectively manage these patients. Antibiotic treatment to combat bacterial infection is still a valid management strategy, but treating the underlying aetiology may be equally as important. Patients with bronchiectasis now require a multimodal treatment approach. Solving the vicious vortex lies in addressing treatable pulmonary, aetiological, extrapulmonary, and environmental traits, whenever possible.

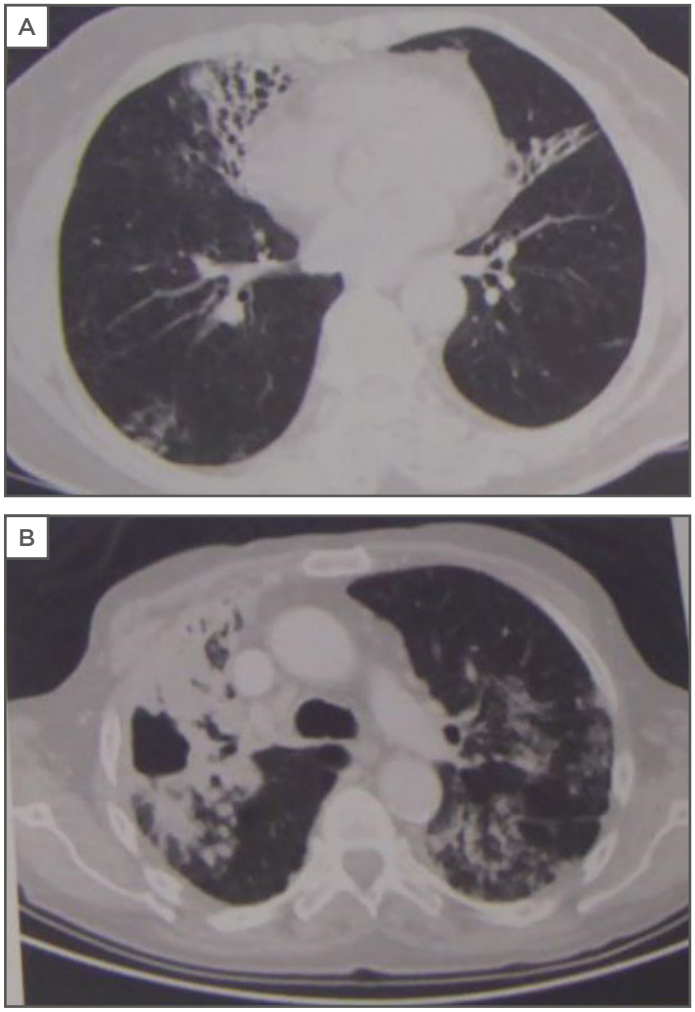

Figure 1: The two separate disease entities of nontuberculous mycobacteria pulmonary infection: nodular bronchiectatic (A) and fibrocavitary disease (B).

Nontuberculous Mycobacteria: How to Treat Difficult Infections

Doctor Jakko van Ingen

"We now leave the safe haven of evidence-based medicine and slowly go down into the abyss when speaking of NTM disease," began Dr van Ingen, referring to the challenges in treating difficult NTM infections. NTM pulmonary disease requires a multidisciplinary approach because, like bronchiectasis, it is not a single disease entity. Instead, it can be described as at least two very distinct entities: fibrocavitary disease that tends to affect those with a history of pulmonary diseases with underlying COPD and silicosis, and nodular bronchiectatic disease

that commonly affects patients who do not have remarkable pulmonary history, except perhaps for bronchiectasis (Figure 1). Currently, both entities are treated in almost the same way, and this requires further consideration.

Dr van Ingen introduced a recent case study of a 59-year-old male with *Mycobacterium avium-intracellulare* pulmonary disease; the patient was an active smoker (35 pack-year history), presented with COPD, and had a Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of II. The patient presented with fatigue, cough, sputum, and weight loss of 9 kg, with 3X sputum acid-fast bacilli+++ and 3X sputum culture indicating *M. intracellulare* infection. In treating NTM pulmonary disease, the practitioner must first assess the patient as a pulmonologist by focussing on environmental and underlying conditions, including smoking cessation. It is clear from studies of tuberculosis that active smoking delays culture conversion and leads to poor treatment outcomes,[14] so the same would apply for *M. intracellulare* infections. As a pulmonologist, the initial step in the management of NTM pulmonary disease can be achieved by asking pertinent questions, such as 'why has the patient developed NTM pulmonary disease?', 'what is the burden of treatment?', and 'does such a treatment burden outweigh the current burden of disease?'. The potential challenges regarding regimen compliance must be addressed for each patient, along with any predictable drug–drug interactions. Any potential role for surgical resection of the worst affected areas must be considered, especially in light of high rates of recurrence and relapse of NTM pulmonary disease.

Current treatment guidelines for NTM pulmonary disease include recommendations published by the American Thoracic Society (ATS)[15] and the British Thoracic Society (BTS).[16] According to these guidelines, *Mycobacterium avium*-complex (MAC) pulmonary disease (MAC-PD) should be treated with rifampin and ethambutol plus a macrolide (RIF-EMB-macrolide) with or without 3 months of intravenous amikacin. For *Mycobacterium abscessus*, an intravenous and oral continuation phase are merited, consisting of amikacin, imipenem, tigecycline, and azithromycin, followed by azithromycin, clofazimine, and 1 or 2 other oral or inhaled agents, guided but not dictated by *in vitro* susceptibility testing.[17] Retrospective analyses of case series have shown that prolonged culture conversion can be achieved using the recommended RIF-EMB-macrolide-based regimen in >70% of MAC-PD patients, but that macrolide resistance and fibrocavitary disease are risk factors for treatment failure and conversion rates drop to 40–50% in these patient categories.[17] It is important to note that macrolide monotherapy should never be administered due to potential development of resistance. Macrolide-fluoroquinolone combinations have also been shown to promote macrolide resistance.[18]

It is interesting to note whether these guideline recommendations are reflected in real-world treatment methods. One survey of five European countries (France, Germany, Italy, Spain, and the UK) and Japan measured guideline adherence for the treatment of NTM.[19] Altogether, 619 physicians (Europe: 446; Japan: 173) participated, covering 1,429 cases (Europe: 1,012; Japan: 417). The key finding from the survey indicated that few MAC patients receive RIF-EMB-macrolide for >6 months. In fact, on average in Europe, only 9% of MAC patients received the guideline recommended regimen, compared to 42% in Japan,[19] which indicates enormous room for improvement. However, it is unknown whether such low levels recorded were due to intolerance rather than a knowledge gap.

Dr van Ingen returned to the previous case study and indicated that this patient was intolerant to rifampicin and discussed alternative treatment regimens. One alternative regimen option is treating with rifabutin, but intolerance may be difficult to anticipate because the drug has very specific toxicities and many interaction challenges. Clofazimine experience in MAC-PD is mainly limited to two combination strategies, each with benefits and weaknesses. Clofazimine-minocycline-clarithromycin combinations were assessed in 22 patients, producing a 64% prolonged culture conversion.[20] The second option, clofazimine-ethambutol-macrolide, was assessed in 90 patients and, while a 100% culture conversion was achieved, there was a 37% relapse rate.[21] Another option to be considered is switching to bedaquiline-ethambutol-

azithromycin, which has shown moderate *in vitro* activity. For example, when assessed in six MAC-PD patients and given with rifampicin, symptomatic improvement was observed.[22] However, microbiological failure also occurred in four patients due to bedaquiline resistance.[22] Therefore, the efficacy of bedaquiline remains very uncertain.

More recently, clinical trial data were published on the use and efficacy of amikacin liposome inhalation suspension (ALIS) for refractory MAC-PD.[23] In 336 patients with refractory MAC-PD, 224 received guidance-based therapy (GBT) plus ALIS, while 112 were treated with GBT alone. Culture conversion occurred in 29% receiving ALIS+GBT versus 9% in those receiving GBT alone ($p<0.001$).[23] While this is an exciting result, it should be noted that in the other 70% of patients, microbiological outcomes were not improved, indicating the extent of the challenge ahead. Such outcomes have not been mirrored when treating *M. abscessus* infection and it may be advisable to consult expert centres for guidance when *M. abscessus* infection presents. This is of particular note in the continuation phase of treatment, when the combination choices noted previously have demonstrated *in vitro* activity against *M. abscessus*. In one study in the USA, 33 of 69 *M. abscessus* patients (48%) treated with individualised treatment regimens based on drug susceptibility results and patient tolerance following ATS/Infectious Diseases Society of America (IDSA) recommendations achieved culture conversion.[24]

Tigecycline, a glycylcycline antibiotic with broad-spectrum antimicrobial activity, now features in guidelines and may slightly improve outcomes. In a study of tigecycline for compassionate use, 16 out of 26 pulmonary cases improved.[25] It should be noted that bacterial subspecies influence clinical outcomes of tigecycline treatment. Across the retrospective case series, 25% of patients treated for pulmonary disease caused by *M. abscessus* subsp. *abscessus* achieved culture conversion, while for disease caused by the macrolide-susceptible *M. abscessus* subsp. *massiliense*, culture conversion was attained in 70–80% of affected patients.[25] Dr van Ingen's case study illustrates the challenges regimen intolerance may pose to treatment and the need to address regimen strengths and weaknesses in each case.

Conclusion

In summary, prevalence estimates for bronchiectasis have increased by 40% in the last 10 years, yet the evidence base supporting diagnosis and treatment has not kept up with the clinical importance of the disease. The recent publication of ERS guidelines for bronchiectasis has offered important guidance on management and, with careful trial design, it is hoped further clinical results will become available to add to the evidence for treatment recommendations. In relation to the model of bronchiectasis pathogenesis, all aspects may be interdependent and, as such, targeting only the bacterial infection is likely to have a modest impact on clinical outcomes.

When treating NTM pulmonary disease, the recent results showing effectiveness of ALIS treatment for refractory MAC-PD are inspiring and multiple trials with clofazimine are ongoing; however, few new developments have occurred for the treatment of *M. abscessus* infection. Therefore, it is always advisable to treat NTM pulmonary disease according to current ATS/IDSA guidelines. In the treatment of NTM pulmonary disease, addressing treatable pulmonary, aetiological, extrapulmonary, and environmental traits, whenever possible, along with infection should achieve more favourable outcomes.

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Discovering Asthma Paradigms in an Evolving Landscape: Expert Perspectives

This symposium took place on 16th September 2018, as part of the 28th European Respiratory Society (ERS) International Congress in Paris, France

Chairperson: Marc Humbert[1]

Speakers: Monica Kraft,[2] William Busse,[3] Ian Pavord[4]

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Meeting Summary

This symposium took place during the 2018 European Respiratory Society (ERS) International Congress in Paris, France and focussed on the disease burden associated with uncontrolled persistent asthma, particularly that driven by Type 2 inflammation; the impact of Type 2 cytokines on the pathophysiology of asthma and other Type 2 inflammatory diseases; current approaches to the assessment and management of uncontrolled persistent asthma; and future aspirations for treatment. Dr Kraft discussed the epidemiology, disease burden, and unmet medical

needs of patients with uncontrolled persistent asthma. These patients have an increased risk of exacerbations, morbidity, mortality, and disease progression. Many patients have evidence of Type 2 inflammation, which constitutes a heavy disease burden and is further impacted by Type 2 inflammatory comorbidities. Prof Busse considered how Type 2 inflammation drives the key pathophysiologic characteristics of asthma. Persistent Type 2 inflammation and airway remodelling contribute to a self-perpetuating vicious cycle of exacerbations and progressive loss of lung function, and, therefore, impact disease progression. Targeting specific Type 2 inflammatory pathway cytokines reduces the pathophysiological impact of asthma and other Type 2 inflammatory comorbidities. Prof Pavord examined the current thinking around the management of uncontrolled persistent asthma driven by Type 2 inflammation. Despite recent advances in patient management, unmet needs remain. Of note, biologics have limitations and some patients are ineligible for currently vailable treatments.

Setting the Stage: The Current State of Uncontrolled Persistent Asthma with Type 2 Inflammation

Doctor Monika Kraft

Asthma is a prevalent and progressive disease characterised by recurring symptoms, variable airway obstruction, airway hyper-responsiveness, and chronic airway inflammation;[1] it constitutes a heavy global burden and public health concern. In 2015, asthma was the most prevalent chronic respiratory disease, affecting an estimated 358 million people and accounting for 397,000 deaths worldwide.[2] Its prevalence is also steadily rising, with an estimated global increase of 12.6% from 1990–2015.[2]

Asthma remains uncontrolled in many patients despite the use of current treatments,[3] with recent European surveys estimating that 45–54% of patients have poorly controlled or uncontrolled asthma.[3] Compared with patients with well-controlled asthma, patients with uncontrolled persistent asthma have an increased risk of exacerbations and hospitalisations; increased morbidity, mortality, and disease progression (as indicated by overuse of short-acting beta agonists);[3-6] reduced and declining lung function;[7] and impaired health-related quality of life.[6] Moreover, uncontrolled persistent asthma is associated with the progressive development of Type 2 inflammatory comorbidities[8] and the high use of oral corticosteroids (OCS).[3] In the TENOR I study[9] of 725 adolescents and adults with asthma, there was a 3.2-fold increased risk of hospitalisation, emergency department visit, or OCS burst in patients with uncontrolled disease versus those with controlled asthma. The same study also showed a significantly decreased post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV_1) for patients with uncontrolled disease versus those without (84.9 versus 67.6; $p<0.0001$).[9] In the cross-sectional European National Health and Wellness Survey, having poorly controlled asthma (n=1,677) was associated with significantly worse mean 12-Item Short Form Health Survey component scores compared with patients with well-controlled asthma (n=1,480) for the physical (39.9 versus 48.0, respectively; $p<0.001$) and mental (40.6 versus 45.0, respectively; $p<0.001$) components.[6] Similarly, in a UK survey, patients (n=246) with poorly controlled asthma reported significantly higher (worse) mean Marks Asthma Quality of Life Questionnaire scores than patients (n=412) with well-controlled asthma (17.5 versus 4.1, respectively; $p<0.001$).[10]

The Global Initiative for Asthma (GINA) 2018 guidelines[11] recommend a stepwise approach to asthma treatment. The recommendations have been updated to include low-dose inhaled corticosteroids as an initial step, along with leukotriene receptor antagonists and tiotropium and/or biologics (anti-IgE, anti-IL-5) as subsequent treatment options. In patients with severely uncontrolled asthma or with acute asthma exacerbations, a short course of low-dose OCS is recommended as an add-on to regular treatment. However, it is not clear whether current therapies impact the risk of disease progression.

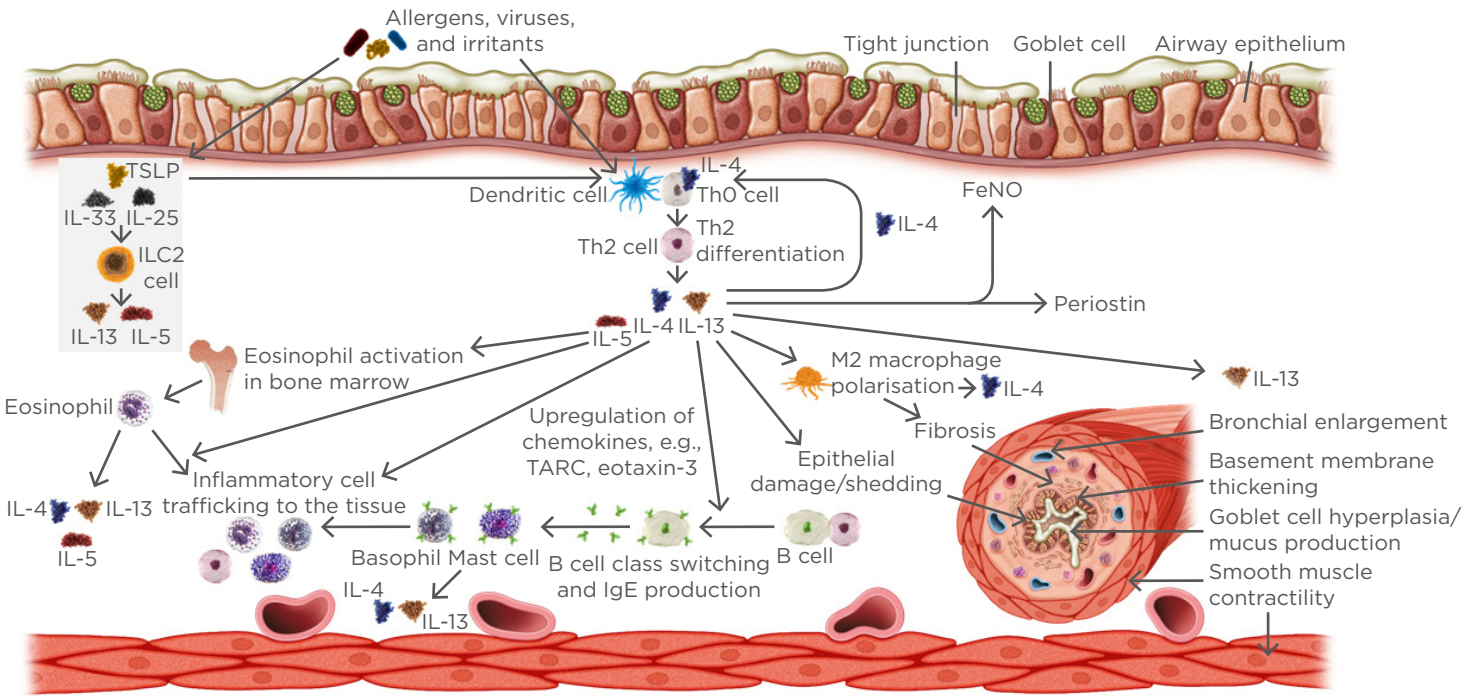

Figure 1: Common effects of Type 2 inflammation in the pathophysiology of Type 2 inflammatory respiratory diseases.

FeNO: fractional exhaled nitric oxide; ILC2: Type 2 innate lymphoid cells; TARC: thymus and activation-regulated chemokine; TSLP: thymic stromal lymphopoietin.

Long-term use of OCS is associated with various adverse effects, including muscle weakness, back pain, osteoporosis, cataracts, glaucoma, diabetes, hypertension, gastrointestinal bleeding, increased susceptibility to infection, and bruising.[12-14] Side effects have also been reported with intermittent OCS use[15] and managing these side effects is associated with a heavy economic burden. Data from the Severe Asthma Registry in Italy showed that among the 62% of patients with severe asthma who were receiving OCS, annual OCS-related events cost 193% more compared to the general population.[16]

More than 50% of patients with asthma have evidence of Type 2 inflammation in the airway,[17,18] characterised by an early onset, the presence of atopic or allergic manifestations and eosinophilia, and responsiveness to corticosteroids.[19,20] Markers of Type 2 inflammation include elevated fractional exhaled nitric oxide (FeNO), serum IgE, eosinophils, and chemotaxins (e.g., periostin, thymus and activation-regulated chemokine, and eotaxin-3).[8,21-23] Type 2 inflammation is associated with a high disease burden. A study in 406 paediatric and adult patients with asthma found that elevated levels of local (FeNO) and systemic (blood eosinophils) Type 2 inflammatory markers correlated with a higher likelihood of moderate-to-severe bronchial hyper-responsiveness (BHR), assessed using the provocation dose of a bronchoconstrictor agonist, causing a 20% fall in FEV_1 (PD_{20}) <0.3 mg. The risk of BHR was greatest when both of these markers were elevated, compared with increased levels of either marker alone.[24] Another prospective study in 304 patients with persistent asthma showed that FeNO levels >300% correlated with increased frequency of exacerbations requiring OCS use.[25]

Patients with asthma driven by Type 2 inflammation are at risk of comorbid Type 2 inflammatory diseases, including allergic rhinitis, atopic dermatitis, chronic rhinosinusitis (CRS) with or without nasal polyps, food allergy, eosinophilic oesophagitis, and aspirin or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease.[26-31] Type 2 inflammation underpins the pathophysiology of Type 2 inflammatory diseases (Figure 1) and Type 2 pathophysiologic features drive the clinical

manifestations of Type 2 inflammatory disease, increasing the disease burden in patients with Type 2 comorbidities. Therefore, it is important that clinicians assess for such comorbidities and address their management, where possible, to maximise the chances of asthma control.

The presence of comorbid Type 2 inflammatory diseases is linked to an increased risk of asthma exacerbations. Data from 118,981 patients with asthma included in the Optimum Patient Care Research Database showed that rhinitis, CRS with nasal polyps, atopic dermatitis, and nasal polyps were all significantly associated with an increased likelihood of asthma exacerbations.[32] Similarly, a study of 709 patients with asthma in the National Heart, Lung, and Blood Institute's Severe Asthma Research Program-3 found that the annual rate of exacerbations in patients with severe asthma was significantly greater in those with comorbid sinusitis versus those without (4.4 versus 2.5, respectively; $p<0.001$).[33] Another study of 79 adult patients with asthma showed that asthma control and lung function were decreased in patients with comorbid CRS with nasal polyps, compared to those without nasal polyps.[34] Since uncontrolled persistent asthma presents challenges for disease control and management, treatments should address the full burden of the disease, from signs and symptoms to comorbidities.

Addressing the Key Issues in the Treatment of Uncontrolled Persistent Asthma with Type 2 Inflammation

Professor William Busse

The pathophysiology of asthma is underpinned by a complex interplay between inflammatory pathways involving multiple cytokines and inflammatory cells.[35] As highlighted by Dr Kraft, >50% of patients with asthma have evidence of Type 2 inflammation in the airway.[17,18] This is characterised by the presence of IL-4, IL-5, and IL-13, which are produced by Th2 cells and innate lymphoid cells in response to allergens, infectious agents, irritants, and pollutants.[35] The components of Type 2 inflammation include airway inflammation, goblet cell hyperplasia, mucus production, smooth muscle contractility and proliferation, and airway remodelling. These components drive the key clinical characteristics of asthma, namely airway hyper-responsiveness, symptoms (e.g., reduced lung function), airway obstruction, and exacerbations.[11,35]

IL-4 and IL-13 are key Type 2 cytokines that drive many of the pathophysiologic features of asthma. For example, IL-13 contributes to goblet cell hyperplasia and increases expression of MUC5AC, which regulates epithelial cell mucus production,[36,37] contributing to airflow obstruction.[38] IL-13 also directly influences airway smooth muscle characteristics, causing increased contractility, decreased relaxation capacity, and potentiating mitogenic effects in the muscle,[39-41] and influences airway fibrosis directly and indirectly via TGF-β.[42,43] IL-4 and IL-13 contribute to epithelial barrier disruption by increasing epithelial permeability[44,45] and are central to airway remodelling.[19,46] Persistent Type 2 inflammation and airway remodelling contribute to a self-perpetuating vicious cycle of exacerbations and progressive loss of lung function, and, therefore, impact disease progression.[19,47]

Asthma is a heterogeneous disease with multiple phenotypes.[19,20,48] In Type 2 asthma, high and low endotypes are recognised, reflecting a spectrum of inflammation.[49] Type 2 cytokines regulate the production of inflammatory biomarkers in asthma. For example, IL-4 and IL-13 induce B cell class switching, which leads to an increase in IgE production and allergic sensitisation of mast cells and basophils that, when activated by specific allergens, cause allergic reactions.[8] IL-5 promotes maturation and activation of eosinophils, and IL-4 and IL-13 contribute to eosinophil trafficking to the lung tissues via adhesion molecules (e.g., vascular cell adhesion molecule-1) and chemokines (e.g., eotaxin-3).[8,50,51] IL-4 and IL-13 also induce FeNO production by airway epithelial cells.[52]

FeNO is a product of airway epithelium that is generated by inflammation and is increasingly recognised as a valuable biomarker of asthma driven by Type 2 inflammation. FeNO is a noninvasive objective measure that is quick and easy to perform. FeNO levels are elevated in asthma characterised by Type 2 inflammation and can remain high despite high-dose inhaled corticosteroid treatment in patients with uncontrolled or unresponsive asthma.[11,52]

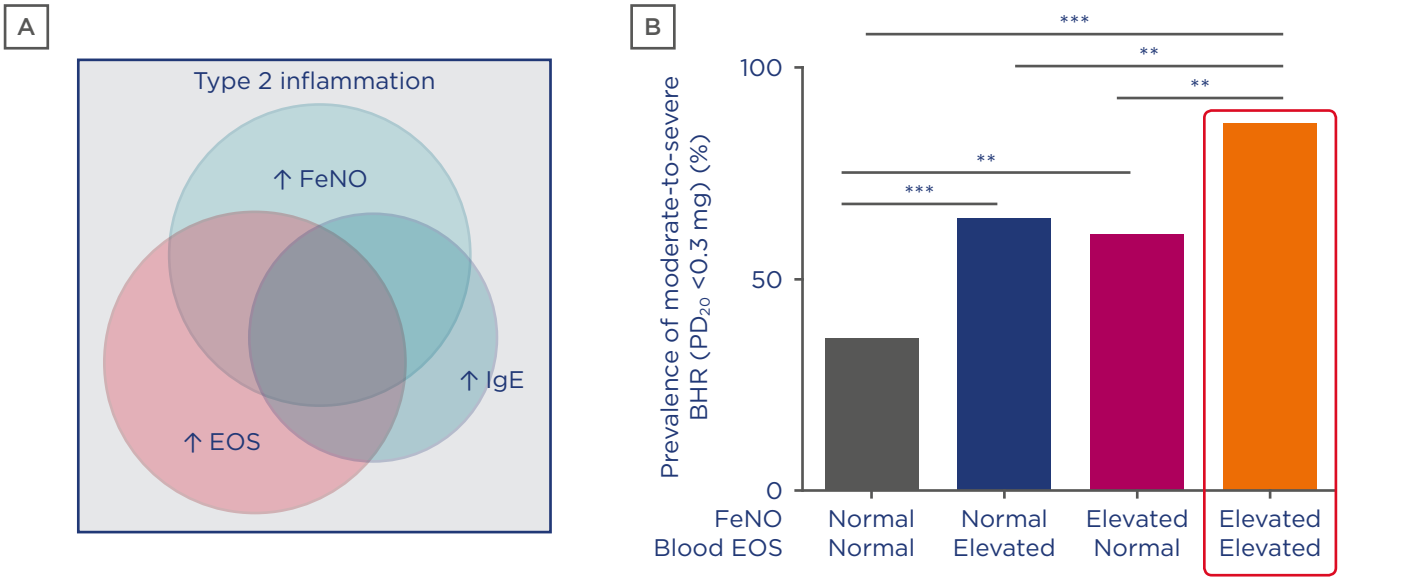

Figure 2: A) Asthma biomarkers are associated with overlapping and distinct disease phenotypes. B) Elevated fractional exhaled nitric oxide and eosinophil Type 2 biomarkers correlate with increased airway bronchial hyper-responsiveness.

**p<0.01; ***p<0.001.

BHR: bronchial hyper-responsiveness; EOS: eosinophils; FeNO: fractional exhaled nitric oxide.

A) Adapted from Spahn et al.,[52] B) Adapted from Malinovschi et al.[24]

FeNO, IgE, and eosinophil biomarkers are associated with overlapping and distinct asthma disease phenotypes (Figure 2A). Evidence shows that elevation of both FeNO and eosinophils has an additive effect on airway BHR (Figure 2B) and leads to higher exacerbation rates than elevation of either biomarker alone,[24] highlighting the value of using a panel of biomarkers to characterise asthma with Type 2 inflammation.

As discussed, Type 2 inflammation also underlies the pathophysiology of a number of inflammatory diseases that can be comorbid with uncontrolled persistent asthma.[8,32] Many of the pathophysiologic features of asthma are also observed in these diseases, and a number of biomarkers are shared.[8,53] For example, in CRS with nasal polyps, the effects of Type 2 inflammation include infiltration of immune cells, mucus production, microbiome alterations, barrier disruption, and tissue remodelling, which are associated with clinical disease manifestations, such as nasal polyps, obstruction, and discharge or post-nasal drip, which can lead to facial pain and a loss of smell.[8,54-56] In allergic rhinitis, Type 2 inflammation is associated with infiltration of immune cells, IgE production and cross-linking, mucus production, and barrier disruption, leading to clinical consequences that include itchy eyes and nose, sneezing, nasal blockage, nasal discharge and post-nasal drip, and rhinorrhoea.[8,57] A consequence of this common pathophysiology is that multiple comorbid Type 2 inflammatory diseases can develop over time.[32,58] Hence, specifically targeting Type 2 inflammatory pathway cytokines reduces the pathophysiological impact of asthma and other Type 2 inflammatory comorbidities.

Management of Uncontrolled Persistent Asthma: Current Considerations and Future Possibilities

Professor Ian Pavord

For every patient, the goals of asthma management are to achieve symptom control,

maintain normal activity levels, and minimise future risk of exacerbations, fixed airflow limitation, and treatment side effects. As discussed by Dr Kraft, GINA advises a stepwise approach to the use of treatments to achieve this.[11]

Patients with uncontrolled persistent asthma driven by Type 2 inflammation have a heavy disease burden associated with reduced lung function, increased exacerbations and hospitalisations, Type 2 inflammatory comorbidities, OCS use, and reduced health-related quality of life.[3,7,9,13,34] Exacerbations have a direct, substantial impact on the economic burden of asthma. Results from a retrospective cohort study of 222,817 patients with asthma showed that the mean total asthma-related healthcare cost per exacerbation increased with disease severity and number of prior exacerbations in the 30 days post-exacerbation.[59]

The basic principles underpinning the management of uncontrolled persistent asthma are correct diagnosis, correct choice and use of treatment, and therapeutic adherence. Other considerations include the patient's risk of exacerbations and the risk of progressive disease and future disability. Careful assessment of patients with uncontrolled asthma is necessary to identify the disease phenotype, taking into consideration objective evidence of asthma (i.e., airway hyper-responsiveness, reversible airflow obstruction, peak expiratory flow variability, and variable wheeze); evidence of airway inflammation (i.e., sputum eosinophilia or neutrophilia, blood eosinophilia, and increased FeNO); and any other factors contributing to their symptoms (i.e., predominant dry cough, fixed airflow obstruction, bronchiectasis, and extrapulmonary factors).[11] Patients with uncontrolled persistent asthma driven by Type 2 inflammation may also have an increased prevalence of overlapping Type 2 inflammatory diseases, which further increases the disease burden and provides additional challenges for disease management.[8,32]

Multiple biomarkers can aid treatment decisions in patients with asthma driven by Type 2 inflammation, including FeNO and blood or sputum eosinophils,[8,11] providing valuable information in addition to clinical assessment. A cross-sectional study of 12,408 patients demonstrated that elevated FeNO and blood eosinophil levels were associated with more asthma attacks and asthma-related emergency department visits compared with normal values,[60] while the inclusion of three biomarkers (FeNO, blood eosinophils, and periostin) in a composite scoring system further differentiated patients on the basis of exacerbations, independent of asthma symptoms.[61] These findings suggest that assessing a panel of Type 2 biomarkers, instead of isolated biomarkers, may better support asthma management.

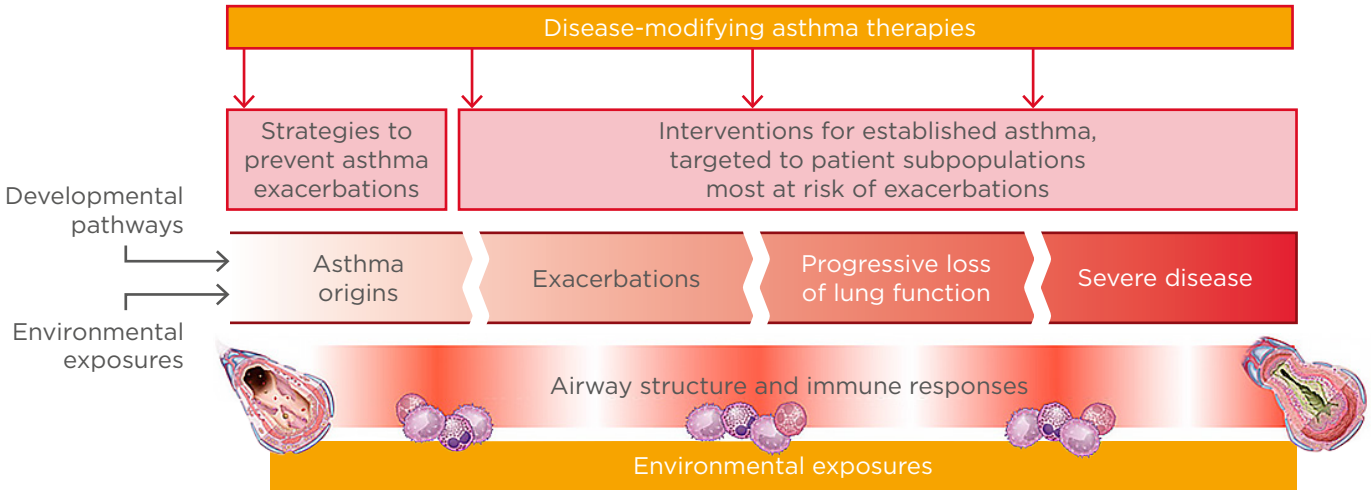

Figure 3: Is there potential to intervene to prevent asthma exacerbations and modify disease progression?

Adapted from Levy et al.[64]

Asthma phenotyping requires consideration of multiple factors, including clinical history and pattern of symptoms, comorbidities, and biomarkers.[48] Patients with severe asthma predominantly have symptoms/airway hyper-responsiveness, Type 2 inflammation/exacerbations, or a mixture of the two.[8,48] Both of these groups require a different approach to management. For example, for patients in whom symptoms/airway dysfunction are dominant (e.g., early symptom predominant or obese female non-eosinophilic asthma), therapy directed at airway hyper-responsiveness (e.g., tiotropium, bronchial thermoplasty), antineutrophil treatment (e.g., macrolide antibiotics), and addressing comorbidities are considered effective approaches. In comparison, for patients in whom inflammation/risk of exacerbation are dominant (i.e., inflammation-predominant asthma), targeted biologic Type 2 therapy should be considered.[8,48]

Four biologic therapies active against Type 2 inflammation are currently licensed in the European Union (EU) and the USA for the treatment of asthma. Omalizumab is a humanised anti-IgE monoclonal antibody (mAb) that specifically binds free IgE in the serum and can interrupt the allergic cascade by preventing binding of IgE with its high-affinity FcεRI receptors on mast cells, antigen-presenting cells, basophils, and other inflammatory cells.[62] The other three licensed biologics target IL-5 signalling, binding to either IL-5 directly (the humanised mAb mepolizumab and reslizumab) or to the IL-5 receptor (the fully human mAb benralizumab), resulting in a depletion of blood and airway eosinophils and basophils.[63] Agents undergoing Phase III clinical testing for poorly controlled/uncontrolled, persistent, or severe asthma include tezepelumab (a human mAb that specifically targets the epithelial cell-derived cytokine, thymic stromal lymphopoietin) and dupilumab (a fully human mAb that specifically binds to the alpha subunit of the IL-4 receptor-alpha). Although targeted therapy based on patient characteristics has led to improved outcomes in patients with uncontrolled persistent asthma driven by Type 2 inflammation, unmet needs remain.

Current biologic therapies are indicated for asthma with an eosinophilic (IL-5) or allergic (IgE) phenotype only, leaving some patients ineligible for treatment and, thus, suboptimally controlled. In addition, these therapies only partially inhibit Type 2 inflammation and may be less effective than biologics that have a broader effect on signalling pathways and iomarkers of Type 2 inflammation. They have also not demonstrated consistent, clinically meaningful improvements in key asthma control goals across a broad range of Type 2 biomarkers, and no therapy addresses all common Type 2 comorbidities.[8]

Tools are now available that offer the potential to prevent asthma exacerbations[64] and modify the course of the disease (Figure 3). Once a diagnosis of asthma is established, patient classification reflects disease heterogeneity and the biological basis of this heterogeneity using clinical and/or molecular phenotypes. Risk factors for abnormal lung growth and poor lung function include low FEV_1, airway hyper-responsiveness, and increased OCS use, which can be modified with treatment.[65] Frequent exacerbations are associated with a progressive loss of lung function and, therefore, reducing exacerbations may prevent or reduce this process.[66] Interventions for established disease could be targeted at patient subpopulations most at risk of exacerbations, for example, patients with uncontrolled persistent asthma driven by Type 2 inflammation.

The era of biologics has raised treatment expectations in asthma and changed future aspirations for treatment. Targeting the underlying pathophysiology of the disease may arrest or reverse progressive loss of lung function and airway structural changes, affording the potential for disease modification in uncontrolled persistent asthma.[64]

Conclusion

Asthma is a prevalent and progressive disease that remains uncontrolled in many patients, despite the use of current treatments. Many patients with uncontrolled persistent asthma have evidence of Type 2 inflammation. Persistent Type 2 inflammation and airway remodelling contribute to a self-perpetuating vicious cycle of exacerbations and progressive loss of lung function, and, therefore, impact disease progression. These patients are also at

risk of comorbid Type 2 inflammatory diseases, which further contribute to the heavy burden of disease. Type 2 inflammation is complex and heterogeneous and encompasses multiple asthma phenotypes. Asthma phenotyping requires consideration of multiple factors, including clinical history and symptom pattern, comorbidities, and multiple biomarkers, such as FeNO, IgE, and eosinophils.

Targeting specific Type 2 inflammatory pathway cytokines reduces the pathophysiology of asthma and other Type 2 inflammatory comorbidities. However, despite recent advances in the management of uncontrolled persistent asthma driven by Type 2 inflammation, unmet needs remain. Of particular note, existing biologics have some limitations and not all patients are eligible for currently available treatments.

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Assessment of Efficacy of Omalizumab Retreatment in Patients With Severe Asthma

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INTRODUCTION

Omalizumab is a recombinant humanised monoclonal anti-IgE antibody currently approved in the USA and Europe for treating inadequately controlled allergic asthma. Previous data have shown the high efficacy of omalizumab in severe asthma. However, factors that may affect response to therapy, relapse rates after drug discontinuation, and efficacy of retreatment remain unclear. This study aimed to evaluate the efficacy of retreatment on relapsed disease.

Methods

Patients who were treated with omalizumab at least 2 years ago at first treatment and were also retreated at least 1 year ago were included in the study. Patients with adverse effects causing discontinuation of first treatment were excluded. Social demographic data, laboratory findings, pulmonary function tests, asthma attack, hospitalisation due to asthma attack, systemic corticosteroid usage, asthma control test, and adverse effects during retreatment were recorded.

RESULTS

Twelve patients were included in the study. There were 8 female patients and the mean age of all patients was 57.4±11.9 years. The most popular reason for stopping omalizumab treatment was following the patient's wishes (n=7). The retreatment dosage of omalizumab was found to be decreased ($p>0.05$). Mean duration of time from discontinuation of first treatment to retreatment was 12.2±9.7 months. Two patients did not respond to retreatment.

Table 1: Outcomes after omalizumab treatment.

	Before retreatment	After retreatment	p value
Pulmonary function tests			
FEV_1 (% predicted)	56.9±25.2	61.5±18.3	>0.05
FEV_1/FVC (%)	62.7±13.8	64.0±11.6	>0.05
Hospitalisation (all reasons); n (%)	11.0 (91.7)	5.0 (41.7)	<0.05*
Hospitalisation (due to asthma attack); n (%)	9.0 (75.0)	3.0 (25.0)	<0.05*
Emergency room visits due to asthma; n (%)	12.0 (100.0)	5.0 (41.7)	<0.05*
Number of patients that needed systemic corticosteroid treatment; n (%)	11.0 (91.7)	2.0 (16.7)	<0.05*
Asthma control test	16.2±2.7	22.1±2.0	<0.05*

*Significant p value.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

After retreatment, asthma control test was improved (16.2±2.7 versus 22.1±2.0 [p<0.05]). Emergency room visits, number of asthma attacks, hospitalisation due to asthma attack, and the number of patients needing systemic corticosteroid treatment were also decreased after retreatment (p<0.05) (Table 1).

Two patients who were retreated with a lower dosage of omalizumab than at first treatment did not respond to retreatment with omalizumab, despite responding at first treatment. Regarding the adverse effects of treatment, there was no difference between first treatment and retreatment.

CONCLUSION

Omalizumab retreatment is effective and well-tolerated in patients with severe asthma who have benefited from initial omalizumab treatment.

Polymetallic Dust-Induced Pneumoconiosis: An Experimental Study

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Bronchoalveolar lavage, experimental study, morphology, oxidative activity, phagocytic activity, pneumoconiosis.

Citation: EMJ Respir. 2018;6[1]:72-73. Abstract Review No. AR2.

AIM

Dust load and oxidative stress play a leading role in the development of pneumoconiosis.[1,2] The aim of this study was to examine the role of macrophages and oxidative activity in the development of pneumoconiosis in the rat model.

METHODS

Polymetallic dust (PD) from the grinder work place contained Fe (39.2%); SiO_2 (21.3%); Mg 8.5%; Cr and Al (2.0%); C and Mn (1.0%);

Zn, Ti, Co, Cu, Zr, and Pb (<1.0%); and traces of Cd and W. Morphology signs and cytology of bronchoalveolar lavage fluid (BALF) in 120 Wistar rats' lungs after single (SII), double (DII), or triple intratracheal instillation (TII), with a 1-month interval of PD, were examined on the 3rd, 7th, 14th, and 30th day, and 3, 6, and 12 months after exposure. The phagocytic activity of alveolar macrophages (PAAM), and spontaneous (CLsp) and stimulated (CLst) luminol-dependent chemiluminescence were investigated.

RESULTS

Upon examination on the 3rd and 7th day after SII PD exposure, erosive bronchitis, bronchiolitis, pneumonia, and perivascular lymphocytic infiltration had developed. Granulomas of macrophages were numerous from the 14th. After 1 year DII and TII of PD resulted in pneumoconiosis, i.e., macrophage granulomas of foreign bodies, lymphocytic infiltration, focal sclerosis, and irregular emphysema, observed after 6 months.

After SII BALF neutrophilia, maximum levels of CLsp and CLst were observed on the third day ($p<0.05$ for all parameters), while lymphocytosis and maximum levels of PAAM were observed on the fourteenth day (both $p<0.05$) (Figure 1). PAAM and CLst continued to increase up to Month 3 ($p<0.05$). After DII and TII of PD, BALF lymphocytosis and increased PAAM, CLsp, and CLst levels were revealed up to Month 6 ($p<0.05$ to all parameters in TII cases).

CONCLUSION

Only DII or TII of PD may result in experimental pneumoconiosis, which demonstrates the impact of prolonged dust exposure. Activation of macrophages and their oxidative activity is important in pneumoconiosis pathogenesis.

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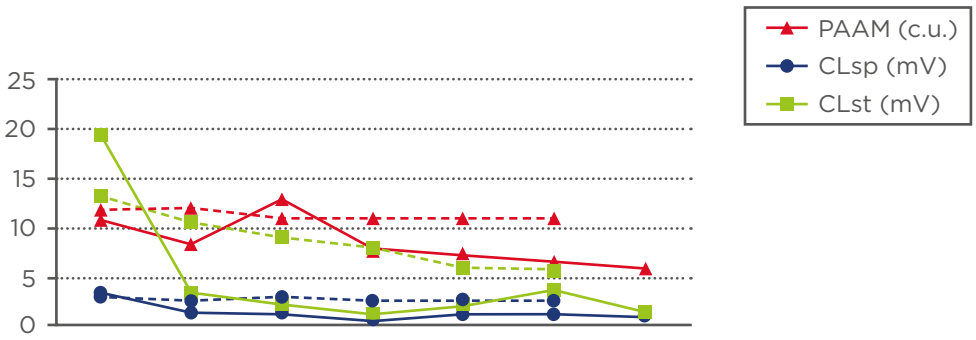

	Day 3	Day 7	Day 14	Month 1	Month 3	Month 6	Year 1
PAAM (c.u.)	10.8	8.5	12.9	7.8	7.3	6.5	6.0
CLsp (mV)	3.5	1.5	1.4	0.8	1.3	1.4	1.2
CLst (mV)	19.3	3.4	2.4	1.3	2.4	3.8	1.5
PAAM (c.u.)	11.9	12.0	11.0	11.0	11.0	11.0	NR
CLsp (mV)	3.0	2.8	2.9	2.7	2.7	2.7	NR
CLst (mV)	13.1	10.5	9.0	8.0	6.0	5.6	NR

Figure 1: PAAM, CLsp, and CLst in rats' BALF and SII (—) and TII (- -) of polymetallic dust.

BALF: bronchoalveolar lavage fluid; CLsp: spontaneous luminol-dependent chemiluminescence; CLst: stimulated luminol-dependent chemiluminescence; NR: not recorded; PAAM: phagocytic activity of alveolar macrophages; SII: single intratracheal instillation; TII: triple intratracheal instillation.

Daily Physical Activity in Patients with Severe Eosinophilic Asthma and the Effect of Anti-IL-5 Therapy

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Keywords: Biologic therapy, mepolizumab, physical activity monitoring, severe eosinophilic asthma.

Citation: EMJ Respir. 2018;6[1]:74-75. Abstract Review No. AR3.

Severe asthma, with an estimated prevalence of 5–10% in the total asthma population, impacts considerably on morbidity, mortality, and socioeconomic cost;[1] however, biologic therapies are revolutionising the management and outcomes for patients with severe asthma. In the eosinophilic phenotype of severe asthma, anti-IL-5 therapy enables reduction of asthma exacerbations and steroid use, better control of asthma and health-related quality of life, and improved lung function.[2,3]

Daily physical activity (DPA) in adult patients with asthma remains overlooked. Limited evidence demonstrates reduced levels of DPA in asthma populations,[4,5] but studies examining the potential effect of available therapies are missing. The authors believe that this is an important missing link in the management of severe asthma as higher adherence to physical activity is associated with favourable outcomes, including better overall asthma control, reduced exacerbations, and reduced healthcare use.[6]

Therefore, we aimed to investigate the overall levels of DPA in patients with severe eosinophilic asthma and whether anti-IL-5 therapy, on top of existing, maximal, and optimised asthma treatment, may improve DPA in this patient population. A prospective, observational study of continuous patients who fulfil the definition of severe asthma[1] and the criteria for mepolizumab therapy (blood eosinophils ≥150 cells/μL at screening or ≥300 cells/μL in the past 12 months) is ongoing.[2] Patients have their DPA recorded for 7 consecutive days using triaxial accelerometery (DynaPort MoveMonitor; McRoberts, The Hague, Netherlands) prior to treatment and at 6 months after mepolizumab (Nucala; GlaxoSmithKline, London, UK) therapy (100 mg subcutaneously once every 4 weeks).

Ten patients have been studied to date (10 women; age: 59±10 years; Asthma Control Test score: 14.6±4.3; pre-bronchodilator forced expiratory volume in 1 second [FEV_1]: 1.45±0.70 L [62±25% predicted]; FEV_1/forced vital capacity ratio: 61±16; IgE: 185±174 IU/mL; eosinophils: 346±108 [4.8±1.8%]; daily beclomethasone-equivalent inhaled corticosteroid dose: 1,146±479 μg). Daily moving time (walking, stair climbing, and cycling) was limited to 78±36 minutes, step count to 6,311±3,023, and movement intensity to 1.80±0.19 m/s^2 (units of acceleration). Weekly time in moderate-to-vigorous-intensity physical activity (MVPA; ≥3.0 metabolic equivalents) was 452±200 minutes. The current data on daily step count agree with previous evidence[4,5] in that patients with severe asthma fall into a low-active population.[7] Movement intensity in the current cohort compares with that of older patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).[8] Only one patient fulfilled current recommendations for weekly physical activity.[9]

Four patients completed 6-month mepolizumab therapy. Daily moving time increased by 11% (from 101±23 to 112±20 minutes) and almost reached statistical significance (p=0.05). Changes in daily steps, movement intensity, and weekly time in MVPA did not reach statistical significance (all p>0.15); however, data must be interpreted with caution because of the small cohort size. Of note, weekly time in MVPA increased by >100 minutes (from 585±124 to 692±72 minutes) and daily steps by >600 (from 8,930±1,887 to 9,562±2,015), thus reaching the minimal important difference in COPD patients after pulmonary rehabilitation.[10]

In conclusion, this novel study shows significantly reduced indices of DPA in patients with severe eosinophilic asthma. Our preliminary results lend promise that anti-IL-5 therapy may be beneficial in DPA in patients with severe eosinophilic asthma, although a larger data sample is certainly required to adequately test this hypothesis. Nonetheless, the possibility that a single, add-on intervention, such as anti-IL-5 therapy, may succeed in improving such an important patient-centred and challenging outcome that reflects concrete behavioural patterns, like DPA, is exciting and worth further consideration.

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A Simple Multifunctional Tool for Integrated Care for Chronic Obstructive Pulmonary Disease

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Chronic obstructive pulmonary disease (COPD), discharge bundle, exacerbations, integrated care, palliative care.

Citation: EMJ Respir. 2018;6[1]:75-77. Abstract Review No. AR4.

ABSTRACT

National and European initiatives to drive quality improvement in chronic obstructive pulmonary disease (COPD)[1,2] have led to integrated care models.[3,4] There is, however, no consensus on what these should comprise, and this remains a matter of debate and discussion. We presented our experience at the European Respiratory Society (ERS) International Congress 2018 in Paris, France, to illustrate how the successful integration of care requires the engagement of, and communication between, several healthcare providers and between the acute units, primary care, and community hospital settings. The same body of chest physicians, nurses, and allied healthcare professionals, whom the patient will see in the acute hospital and in the community clinics, also form part of the palliative service, where severely affected patients are discussed in a multidisciplinary forum and, where applicable, reviewed towards the end of life. This allows continuity of care across sites to be delivered. Patients can also self-refer themselves back into the system if they have

been discharged and always remain at the centre of all decision-making.

In West Hertfordshire, UK, we introduced an integrated and seamless care pathway on 1st August 2017, based on the use of a simple double-sided *pro forma*, shared across all healthcare providers. Frontline staff in the emergency department can initiate the process, which is then carried forward by the specialist respiratory nurses during hospital admission and upon discharge, to be continued in the community. The tool encompasses all aspects of care, as well as functioning as a discharge bundle to ensure specific areas such as smoking cessation, palliative care (PC), and medication adherence are addressed and that the respiratory team is informed. Furthermore, the tool serves as a guide for COPD management, supported by an ongoing educational programme. An important measured outcome was the impact of this management on COPD exacerbations.

Symptom control is a frequently underestimated challenge in severe COPD,[5] causing recurrent hospital admissions. PC needs to be reviewed and advanced care planning may help achieve better symptom management. We demonstrate how integration of respiratory and PC services can facilitate this process with regular team discussions and timely referral to psychology and well-being services.

In the last year, >300 COPD exacerbations over the winter months were managed in the community alone with 1,013 COPD admissions in our acute hospital. After implementation of the service, a statistically significant reduction was noted in length of hospital stay in the winter of 2017 compared to 2016. Nonelective readmissions within 30 days after discharge were lower in 2018 compared to 2017. Also, COPD assessment tool score and symptom scores (measured using the integrated PC outcome scale) improved on receiving an integrated PC and respiratory intervention, such as the breathlessness service (Figure 1). Overall, 49.35% improved their anxiety score and 16.88% achieved the minimally clinical important difference of a reduction of ≥4 points.

We discussed with delegates at the ERS Congress how our approach, using the pathway throughout the patient journey and linking services across both acute and community sites, has led to the success of this model in improving quality of care and achieving the outcomes above. Although the feasibility of our model depended on a large pool of available staff, the initial investment has reaped benefits in a short time.

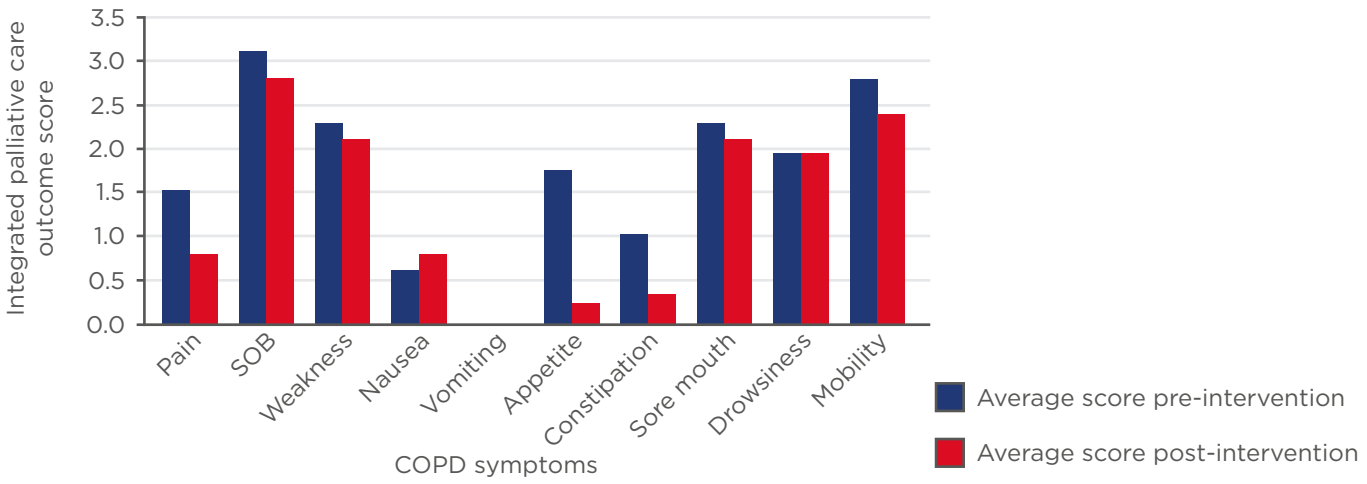

Figure 1: Comparison of symptom scores in severe chronic obstructive pulmonary disease patients before and after integrated palliative care and respiratory interventions.

Integrated palliative care outcome score for symptoms performed before and after specialist combined respiratory and palliative care intervention.

COPD: chronic obstructive pulmonary disease; SOB: shortness of breath.

Looking to the future, we are excited about the opportunities and ventures that will allow further growth of our model, such as digital health platforms to improve patient self-management.

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A Multidimensional Approach to Chronic Obstructive Pulmonary Disease Comorbidities

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Chronic obstructive pulmonary disease (COPD), comorbidities, health-related quality of life, multidimensional indexes.

Citation: EMJ Respir. 2018;6[1]:77-78. Abstract Review No. AR5.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide and is predicted to be the third leading cause of death by 2020.[1] Most COPD patients have at least one comorbid condition that further complicates the evolution and management of the disease. COPD is currently regarded as a systemic condition and is linked to several comorbidities with major clinical importance, including cardiovascular, metabolic, and gastrointestinal complications.[2] At least one comorbidity of clinical relevance is found in 78.6% of COPD patients, two in 68.8% of patients, and ≥3 in 47.9% of patients, with cardiovascular comorbidities being the most predominant.[3] This underlines the need for multidimensional assessment and complex management of COPD patients.[4] The aim of the study was to evaluate and analyse the prevalence and clinical significance of COPD comorbidities in Moldova.

METHODS

The study was conducted in 435 patients with COPD. Spirometric data were analysed, including forced expiratory volume in 1 second, forced vital capacity, and a ratio of both, and were assessed by multidimensional indexes, including BODE, ADO, BODEx, CODEX, and DOSE.

RESULTS

The results showed that 38.62% of patients had heart failure, 50.11% had hypertension, 23.45% had coronary artery disease, 10.11% had diabetes, 1.15% had renal failure, 3.22% had rheumatoid arthritis, 4.83% had depression, 4.37% had cognitive impairment, 29.89% were obese, and 3.22% had cachexia. Only 24.65% of patients did not have any comorbidities. Patients with one comorbidity represented 23.73% of the study sample, two comorbidities

were present in 24.19%, and ≥3 comorbidities were present in 27.42%. The Charlson Comorbidity Index (CCI) had a medium negative correlation with 6-minute walking distance (r=-0.37; p<0.001) and a weak correlation with the rate of exacerbations (r=0.17; p=0.016). CCI had a strong correlation with ADO (r=0.75; p<0.001), a moderate correlation with BODE (r=0.30; p<0.001), and a weak correlation with BODEx, CODEX, and DOSE (Figure 1). CCI also had a medium correlation with St. George's Respiratory Questionnaire activity (r=0.36; p<0.001), impact (r=0.34; p<0.001) and total (r=0.37; p<0.001) scores, and the overall quality of life assessed by St. George's Respiratory Questionnaire and CCQ.

CONCLUSION

COPD patients often have one or two comorbidities of clinical significance that are predominantly cardiovascular and metabolic in nature. These two groups of disease commonly coexist together and potentially share underlying pathophysiological pathways. COPD patients with comorbidities tend to have a poorer health-related quality of life and, as shown by this study, such comorbidities can be assessed by multidimensional indexes, such as ADO, BODE, and others.

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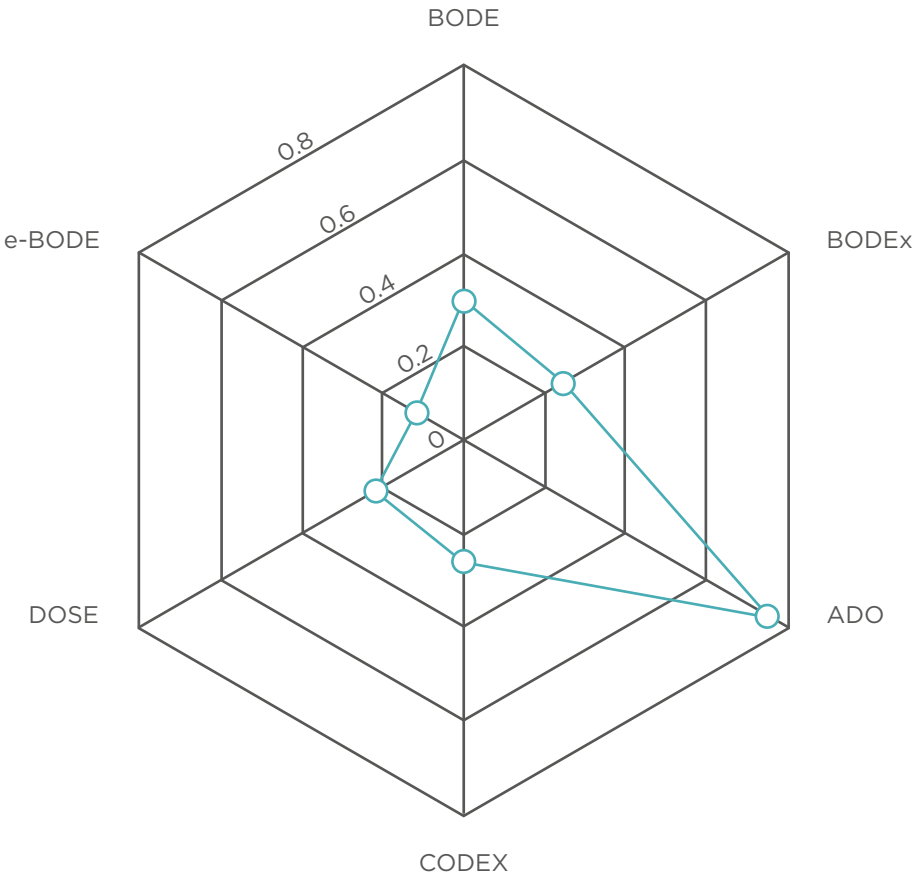

Figure 1: Correlation between multidimensional indexes and the Charlson Comorbidity Index in the study population.

Does Talc Increase Risk of Subsequent Non-Draining Septated Pleural Effusion after Indwelling Pleural Catheter Insertion?

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Keywords: Indwelling pleural catheter (IPC), pleural effusion, talc pleurodesis.

Citation: EMJ Respir. 2018;6[1]:79-81. Abstract Review No. AR6.

BACKGROUND

Current management of recurrent pleural effusion is symptomatic. Indwelling pleural catheters (IPC) reduce the initial length of hospital stay[1,2] but require repeated domiciliary drainage. Talc pleurodesis is a potential one-time definitive procedure but has a modest failure rate. In cases of talc pleurodesis failure, IPC insertion is usually advocated with the consequence that a subset of patients with IPC *in situ* will have previously received ipsilateral intrapleural talc.

Non-draining symptomatic septated IPC-related pleural effusions (NSSIPE) complicate up to 14% of IPC insertions, and may require further procedures, including those aimed at disrupting septations.[3-6] Given the larger pleural tumour bulk and greater area of pleural involvement with mesothelioma than with other malignant pleural effusions (MPE),[7] mesothelioma may be associated with increased risk of fibrin deposition and septation formation.

This study aimed to assess whether prior failed talc pleurodesis is associated with increased risk of NSSIPE.

METHOD

IPC insertion records from January 2008–April 2017 were analysed retrospectively. Standard management in our unit during this time was to offer patients with recurrent pleural effusion a choice between chest drain insertion with talc pleurodesis or IPC insertion.

NSSIPE was defined as a symptomatic pleural fluid collection with septations evident on pleural ultrasound in the context of a non-draining patent IPC.

RESULTS

There were 202 recorded IPC insertions. The non-MPE group included 21 patients with a mean age of 70 years (standard deviation [SD]: 10.8 years) and 29% (n=6) were female. In this group, the underlying causes were attributed to hepatic hydrothorax (3% overall), benign pleuritis (3%), heart failure (2%), and others (2.5%). The MPE group consisted of 181 patients with a mean age of 68 years (SD: 13.9 years; p=0.4) and 48% were female (n=87; p=0.09).

There was no statistically significant difference between rates of NSSIPE in patients who had received prior talc and those who had not, as well as between patients with mesothelioma MPE and those with non-mesothelioma MPE (Figure 1).

DISCUSSION

Non-draining MPE are associated with a higher concentration of pleural fluid lactate dehydrogenase and systemic C-reactive protein, indicating an association between increased

pleural fluid metabolic activity and systemic inflammation.[4,5,8] The aim of giving talc is to induce an inflammatory response within the pleural space, leading to adhesion formation between the visceral and parietal pleura, with subsequent pleurodesis.

The results of this study raise interesting questions. For example, in cases of failed talc pleurodesis, why is it that talc is not associated with increased rates of NSSIPE? It may be that if a patient is unable to mount an adequate immune response to talc, and, therefore, has failed talc pleurodesis, then the patient is also unable to mount an adequate immune reaction to talc to form adhesions and septations within the pleural space.

These results are limited by the retrospective study design and the relatively small number of NSSIPE. Further analyses will investigate whether the stage of tumour at which talc was given influenced rates of NSSIPE, and further studies are required to investigate whether the pleural space in certain patients is inherently resistant to different forms of pleurodesis.

CONCLUSION

Talc pleurodesis remains an important alternative to IPC insertion in recurrent pleural effusion. The risk of NSSIPE is not increased in patients with a prior talc pleurodesis attempt. Therefore, the risk of subsequent NSSIPE should not dissuade patients from choosing talc as a primary treatment for recurrent pleural effusion.

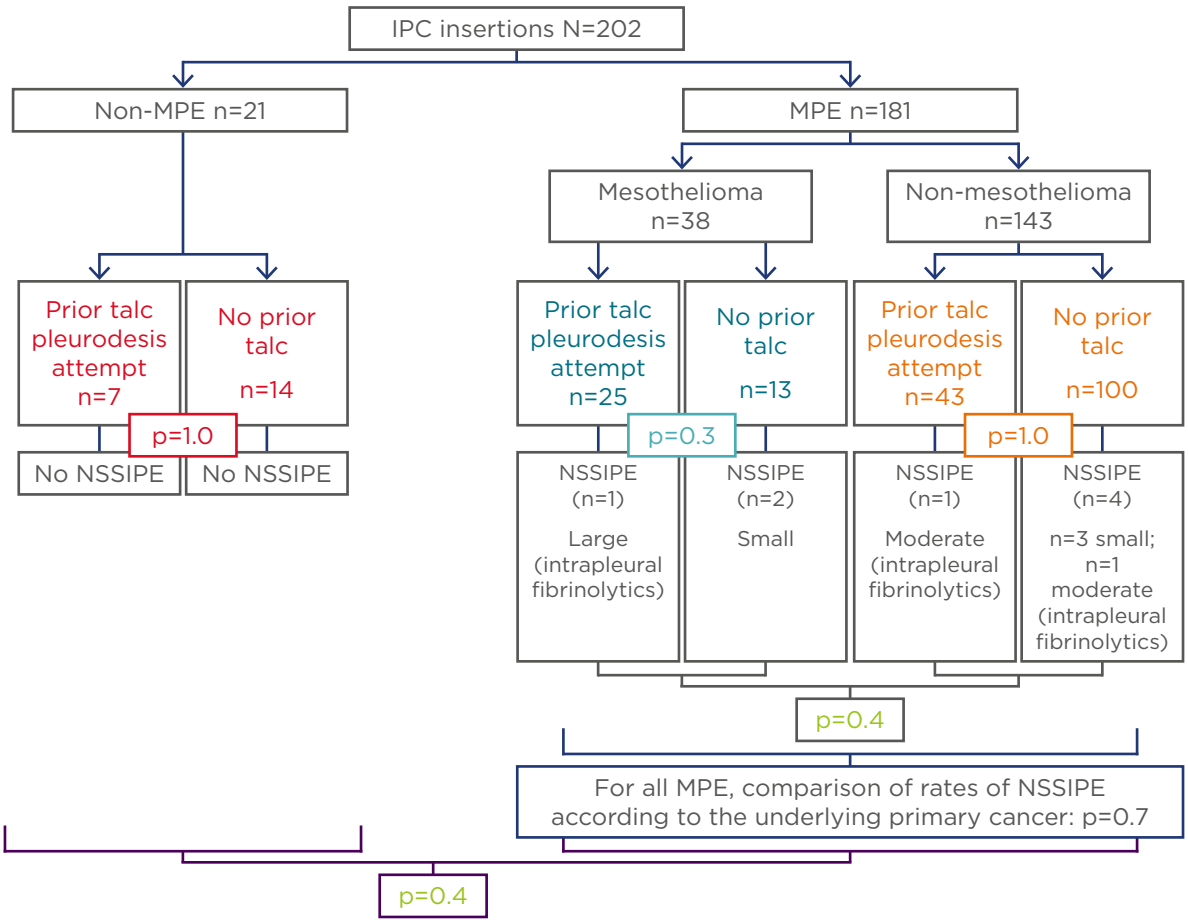

Figure 1: Rates of non-draining symptomatic septated indwelling pleural catheter-related pleural effusions in patients who had received prior talc and those who had not, as well as rates in patients with mesothelioma malignant pleural effusion and those with non-mesothelioma malignant pleural effusion.

IPC: indwelling pleural catheters; MPE: malignant pleural effusion; NSSIPE: non-draining symptomatic septated IPC-related pleural effusions.

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Pneumothorax Induction with a Boutin Needle without Ultrasound Guidance During Local Anaesthetic Thoracoscopy

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Keywords: Boutin, lung cancer, pleura, thoracoscopy.

Citation: EMJ Respir. 2018;6[1]:81-82. Abstract Review No. AR7.

Pleural disease is an increasingly common presentation and it has been estimated that up to 15% of patients have a metastatic pleural effusion at autopsy.[1] Local anaesthetic thoracoscopy (LAT) is becoming widely available throughout the UK. Biopsies can be taken for diagnosis whilst offering talc poudrage as a treatment in the same sitting.[2] LAT also has the advantage of being used in a patient cohort that has been deemed unsuitable for general anaesthetic. Some centres require a sizable pleural effusion prior to performing LAT. When there is little or no pleural fluid present, a Boutin needle can be used to collapse the lung by inducing a pneumothorax, thus enabling LAT[3] and leading to a decrease in the number of patients requiring video-assisted thorascopic surgery (VATS). To date, there are limited data on the use of the Boutin needle and its impact on clinical care.

All patients undergoing LAT at the Hampshire Hospitals NHS Foundation Trust, Winchester, UK, also undergo assessment with thoracic ultrasound. If there is little or no fluid seen, then a two-part cutting 2 mm Boutin needle (Novatech SA, La Ciotat, France) is used to gain access through the chest wall, without direct ultrasound guidance. The blunt 2 mm Boutin needle is then used to induce a pneumothorax; this is assessed audibly by the insufflation of air. The blunt Boutin needle is used as a depth gauge to assess the size of the pneumothorax. Blunt dissection and placement of the trocar are undertaken, and LAT is then completed.

A total of 245 LAT performed by our service were retrospectively reviewed. Thirty-eight (15.5%) patients had insufficient fluid and induction of a pneumothorax was attempted with a Boutin needle. Twenty-seven of the 38 (71.05%) attempted pneumothorax inductions were successful. Ten of the cases where induction of a pneumothorax was unsuccessful were noted to have adhesions. This retrospective review of our service demonstrated that the Boutin needle can be successfully used to induce a pneumothorax

when there is little or no pleural fluid present with a low complication rate, enabling LAT.

Our experience with the Boutin needle was presented at the European Respiratory Society (ERS) International Congress 2018. There was debate regarding the use of the Boutin needle versus blunt dissection and finger sweep to induce a pneumothorax in this patient cohort. Blunt dissection and finger sweep does not allow for the depth of the pneumothorax to be fully assessed and may increase risk to the underlying lung when a trocar is introduced. Discussion concluded, which we advocate the development of a guideline for inducing a pneumothorax prior to LAT. Either with blunt dissection or with a Boutin needle, because there are multiple different approaches, not only within each country but worldwide. This may be difficult due to the lack of data on the induction of a pneumothorax preceding a LAT when little or no fluid is present. Further assessment of different centres' techniques is required.

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Innovating the Treatment of Chronic Obstructive Pulmonary Disease Exacerbations: A Phone Telesystem to Increase Action Plan Adherence

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Keywords: Chronic obstructive pulmonary disease (COPD), COPD exacerbations, exacerbation recovery, healthcare utilisation, self-efficacy, self-management, telesystem, Written Action Plan adherence.

Citation: EMJ Respir. 2018;6[1]:82-84. Abstract Review No. AR8.

RATIONALE

Chronic obstructive pulmonary disease (COPD) exacerbations are major contributors to the burden of the disease, reducing patients' quality of life, leading to hospitalisations and increasing mortality.[1-3] Prompt treatment accelerates recovery and prevents hospitalisation.[4] To achieve prompt treatment, patients need to identify when their symptoms are worsening and seek medical attention. These skills are known as self-management strategies.[5,6] When supported by a Written Action Plan and communication with a case manager coaching the patient, self-management strategies can prevent up to 40% of COPD-related hospitalisations.[7] However, Written Action Plan adherence rates remain low, with studies reporting adherence

<50%.[8] Adherence can be improved through more frequent communication, particularly telephone calls from case managers, at the cost of an increased amount of time spent supporting patients.[9] Telehealth technologies are a promising strategy to enhance communication with healthcare professionals in severe COPD patients.[10] The objectives of our study were to determine whether the use of an interactive phone telesystem increased Written Action Plan adherence to manage exacerbations, which can further reduce hospitalisations in patients from a specialised centre with routine COPD self-management intervention practices.

METHODS

Pilot Study

Forty patients from the COPD clinic at the Montreal Chest Institute, McGill University Health Centre, Montreal, Canada, were enrolled in an initial study. Patients received regular automated phone calls from the telesystem and could contact the telesystem at any time. The telesystem issued alarms to case managers during acute exacerbations. Nurse case managers accessed telesystem call information through a secured online database. Patients kept a symptom diary, recording dates of symptom worsening, treatment use and contact with healthcare professionals. Detailed data from patients' behaviours during exacerbations were recorded monthly by a third party. Adherence was defined as the patient's ability to initiate their Action Plan medication by themselves and/or contacting their case manager within 72 hours.

Implementation Scaling-Up Study

The telesystem was then implemented on a large scale to cover >250 patients from a COPD clinic. Healthcare use was assessed with hospital databases.

RESULTS

Thirty-three patients completed the 1-year initial study (12 males/21 females; mean age: 69.0±6.9 years; post-bronchodilator forced expiratory volume in 1 second [FEV_1]: 41±13% predicted). A total of 93 symptom-based exacerbations were reported, with the majority of patients reporting ≥2 exacerbations during the year of initial evaluation. Fifty-three percent of patients initiated their Action Plan medication by themselves and 38% contacted their case manager within 72 hours. Overall Action Plan adherence, which includes taking medication as prescribed in the Written Action Plan and/or contacting a healthcare professional within 72 hours, was observed in 72% of exacerbation cases. Exacerbation recovery time was significantly faster for those episodes in which patients adhered to their Written Action Plan (10±6 days for adherent versus 16±10 days for non-adherent patients; p<0.001). Following the large-scale implementation, the use of the telesystem was extended to the caseload of the COPD clinic for a total of 256 patients (117 males/139 females; mean age: 70±9 years; prebronchodilator FEV_1: 0.42±0.20% predicted) enrolled in the telesystem. After 1 year of telesystem use, we observed a significant decrease in the number of patients with ≥1 respiratory-related emergency room visits and COPD-related hospitalisations (Table 1).

CONCLUSION

Patients already on a self-management programme from a COPD clinic using the COPD telesytem demonstrated higher Action Plan adherence rates than previously reported. The large-scale implementation of the telesystem resulted in a further reduction of COPD-related hospitalisations.

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Table 1: Healthcare utilisation before and after telesystem enrolment.

	Before enrolment	After enrolment	p value
Patients with ≥1 respiratory-related ER visit	120	110	<0.001*
Patients with ≥1 COPD-related hospitalisation	75	65	<0.001*
Respiratory-related ER visits	243	234	0.519
COPD-related hospitalisations	143	108	0.138
Number of hospital days for a COPD-related diagnosis	1,387	1,352	0.258

*p<0.05 was considered statistically significant.
COPD: chronic obstructive pulmonary disease; ER: emergency room.

Adherence Rate to Inhaled Therapies and Factors Affecting Adherence in Elderly Patients with Chronic Obstructive Lung Diseases

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Keywords: Chronic obstructive lung diseases (COLD), elderly, inhaler treatments, Mini-Mental State Examination (MMSE), Test of Adherence to Inhaler Treatment (TAI) assessment.

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BACKGROUND

Adherence to treatment is essential in chronic diseases, especially in chronic obstructive lung diseases (COLD). Poor adherence to the treatment regimen and improper use of inhaler devices lead to adverse clinical outcomes and an unnecessary use of healthcare resources.[1] In a recently published study, Japanese researchers showed that the adherence rate to inhaled medicines was lower than for oral medicines in patients with COLD, suggesting patients experienced problems using the devices.[2] Nonadherence to the treatment regimen and inadequate inhaler technique are important causes of therapy failure, especially in elderly patients. A study showed the overall

prevalence of using inhalers correctly was 31% and no improvement was observed over time.[3] For these reasons, we evaluated adherence rates of our patients, including whether they used inhaler devices properly and the underlying reasons if they did not.

MATERIALS AND METHODS

Patients ≥65 years old were classified as elderly, while patients <65 years of age were classified as non-elderly. A questionnaire was answered by patients with COLD within a scheduled time period. Cognitive functions of the patients were evaluated by the Mini-Mental State Examination (MMSE) and disease control status was assessed using an appropriate disease-specific questionnaire. The adherence to inhaled therapy and inhaler device use were evaluated by the Test of Adherence to Inhaler Treatment (TAI) questionnaire. The first 10 components of the TAI are designed to identify nonadherent patients, while the last two items identify compliance with treatment regimen and proper device use.

RESULTS

The study recruited 135 patients (69 asthmatics and 66 chronic obstructive pulmonary disease [COPD] patients). The elderly group consisted of 54 patients and the non-elderly group was composed of 81 patients; the groups had a similar sex distribution. The proportion of patients with COPD was higher than those with asthma in the elderly group. Dry powder inhalers were the most commonly used device among COLD patients for chronic therapy (40.0%), while the second most common was separated capsules (22.2%). MMSE score was lower in the elderly group than in the non-elderly group (27 versus 28; p=0.022), but the rate of cognitive impairment was similar between the groups. Adherence level according to TAI-10 was 25.9% and overall disease control rate was 35.4% in the whole study group. The adherence scores according to TAI-10 were higher in the elderly group than in the non-elderly group (median: 49 versus 47; p=0.004) and there was also a higher adherence rate in the elderly group (37.0% versus 18.5%; p=0.016). Each component of the TAI was higher in COPD patients than in asthmatics and the differences were statistically significant. In addition, unconscious noncompliance rate was higher in the elderly than in the non-elderly according to items 11 and 12 (70.4% versus 55.6%; p=0.083). Seventy patients (51.9%) made critical errors when using inhaler devices and the elderly group and COPD patients made more critical errors (p=0.005 and p=0.020, respectively). No difference was found in critical errors according to the type of inhaler device. Logistic regression analysis showed that age and being informed about the disease were associated with critical errors. For example, being ≥65 years old increased the risk by 2.536-fold and not being informed about the disease increased the risk by 2.254-fold (p=0.015 and p=0.029, respectively).

CONCLUSION

Adherence to inhaled drugs is lower than that of other treatment methods in chronic diseases. The reasons for this may include both the requirement for compliance with the treatment regimen and the proper use of inhaler devices. In this study, a high critical error rate was found in elderly patients, especially those with COPD, independent of the type of inhaler device.

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VIEW MORE ABSTRACTS ONLINE ←

The National Institute for Health and Care Excellence (NICE) Updated Guidance on Endobronchial Valves: What Was Behind the Decision and What Does it Mean for Pulmonologists?

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Disclosure: Prof Shah has been involved in several clinical trials investigating endobronchial valves and the host institution (Royal Brompton Hospital) has been reimbursed for clinical trial expenses. He is also a coapplicant for two National Institute for Health Research (NIHR) grants evaluating endobronchial valves in randomised clinical trials and serves as a consultant for Pulmonx.

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In December 2017, the National Institute for Health and Care Excellence (NICE) updated its interventional procedures guidance, titled 'Endobronchial valve insertion to reduce lung volume in emphysema',[1] to support the routine use of endobronchial valve therapy for emphysema. The NICE guidance states: 'Current evidence on the safety and efficacy of endobronchial valve insertion to reduce lung volume in emphysema is adequate in quantity and quality to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.' NICE is the latest organisation to include endobronchial valves in its chronic obstructive pulmonary disease (COPD) treatment pathway, following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report for the diagnosis, management, and prevention of COPD;[2] the German Society for Pneumology and Respiratory Medicine (DGP) guidance;[3] and the Australian and New Zealand guidelines for the management of COPD;[4] however, what does this mean to us as respiratory physicians?

Let us start by looking at emphysema. The British Lung Foundation (BLF) estimates that 1.2 million people in the UK are living with diagnosed COPD and almost 30,000 patients die from the disease every year.[5] Roughly one-third of COPD patients have the emphysema subtype of COPD, presenting with destruction of the lung parenchyma.[6] These patients are chronically breathless, making even the most simple daily activities, such as washing, eating, walking, and household chores, difficult and often leading to patients becoming housebound and depressed. In fact, the quality of life of emphysema patients is commonly worse than Stage IV lung cancer patients.[7]

Current emphysema treatments range from conservative medical management to invasive lung volume reduction surgery and, ultimately, lung transplantation. Strategies involving

endobronchial valves, namely bronchoscopic lung volume reduction (BLVR), provide a less invasive, nonsurgical approach to treatment. During BLVR, tiny endobronchial valves are implanted via a bronchoscopic procedure in the airways of the more diseased areas of the lung (target lobe) to block air from entering. This allows the target lobe to collapse, reducing overall hyperinflation, improving breathing mechanics, and enabling healthier areas of the lungs to expand and take in more air.

We have been using endobronchial valves to treat emphysema for almost 18 years and have been closely involved in developing the extensive body of clinical evidence available today for the leading endobronchial valve, the Zephyr® Endobronchial Valve (Pulmonx Corp., Redwood City, Califonia, USA). The Zephyr Endobronchial Valve is available in four sizes: 4.0, 4.0 LP (for an airway diameter of 4.0–7.0 mm), 5.5, and 5.5 LP (for an airway diameter of 5.5–8.5 mm).

Ideally, the treatment target during BLVR is the most diseased lobe of the lung. However, the VENT study,[8] which was the first randomised clinical trial of the Zephyr Valve, provided important insights regarding appropriate patient selection for this therapy, specifically the need to treat patients with little-to-no collateral ventilation between the target lobe and the adjacent lobe and to achieve total lobar occlusion.[8] Collateral ventilation in the human lung refers to the ventilation of alveolar structures through passages or channels that bypass the normal airways.[9] In the presence of collateral ventilation, the occluded lobe fails to achieve atelectasis because of continuous air entering the lobe through the collateral channels. The availability of diagnostic tools, such as the Chartis® Lung Assessment System (Pulmonx Corp.), which provides a physiological measure of airflow from a lobe occluded with a balloon[10] and/or quantitative CT assessment of fissure integrity (a surrogate for collateral ventilation),[11] enables the selection of patients who are most likely to benefit from this therapy. In our experience, the use of these tools generally achieves a 70% response rate in improving lung function and, more importantly, a clinically meaningful response, with patients being able to take part in the activities that matter to them with less breathlessness.

The NICE committee further noted that "there are different devices available for this procedure, and that the published evidence shows they may have different efficacy profiles."[1] NICE assessed four randomised clinical trials[12-15] of the Zephyr Valve, which showed consistent improvement in breathing function, exercise capacity, and quality of life, and one randomised controlled trial conducted for another valve, the IBV Valve (Spiration Inc., Redmond, Washington, USA),[16] which showed statistically significant improvements in the coprimary endpoints (the number of patients with both a reduction in target lung volume and improvement in forced expiratory volume in 1 second). However, for the participants of the latter study, changes in quality of life and lung function were modest, not clinically meaningful, and not significantly different from patients in the placebo group, possibly because the treatment was non-lobar.[16]

The efficacy data for the Zephyr Valve are comparable to that of lung volume reduction surgery (Figure 1) but with lower morbidity and mortality,[17-19] making valves the first choice treatment option. The Zephyr Valve is also removable, thus allowing the procedure to be reversed if a patient does not respond or has complications. BLVR with a Zephyr Valve does not negate the option of surgical lung volume reduction, if desired. NICE recommends that patient selection for BLVR with valves should be performed by a multidisciplinary team experienced in managing emphysema, which should typically include a chest physician, radiologist, thoracic surgeon, and a respiratory nurse.

The benefits provided by any treatment must be balanced against the safety profile associated with the procedure. The most frequent side effects associated with BLVR with a Zephyr Valve are pneumothorax (up to 26%) and COPD exacerbations (up to 77%) in the periprocedure period.[1,11,12] Targeted lobar deflation likely causes inflation of the ipsilateral lobe, which can lead to a tear of the already compromised parenchymal tissue of the emphysematous ipsilateral lobe, resulting in a pneumothorax, which is managed with standard techniques. Most pneumothoraces occur within the first 2–3 days postprocedure; as a result, a minimum of a 3-night hospital stay is recommended for patients undergoing BLVR with valves.

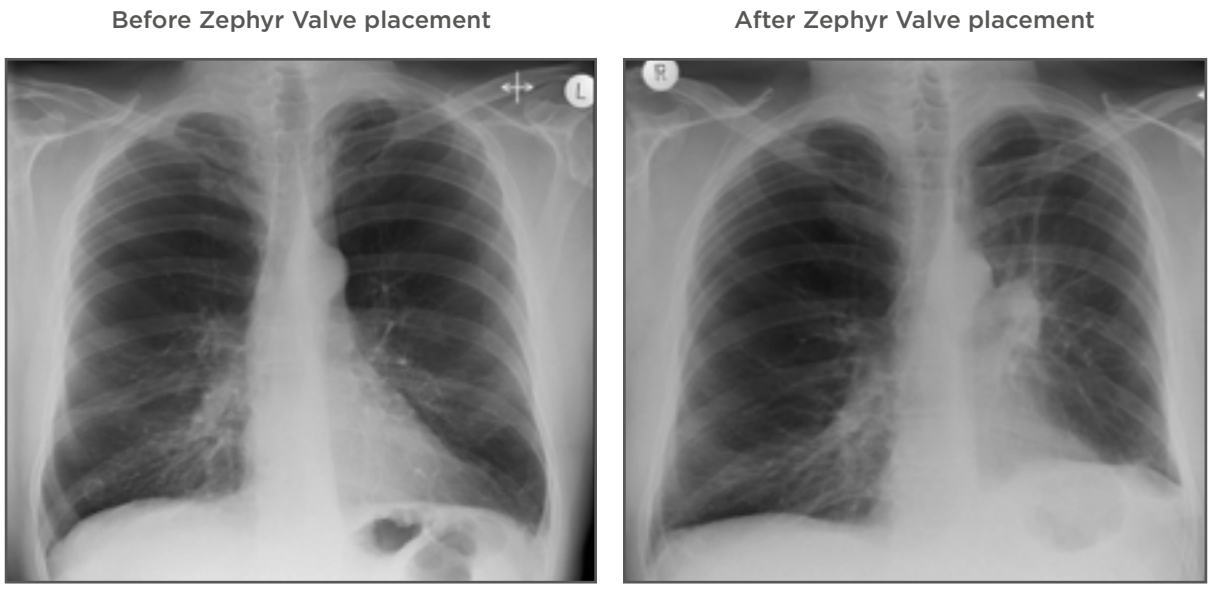

Figure 1: Chest X-ray images before and after Zephyr® Valve treatment.

The chest X-ray images highlight the reduction in hyperinflation and return of the diaphragm to a near-normal position with Zephyr Valve placement.

Images courtesy of Hugo Goulart de Oliveira, Porto Alegre, Brazil.

In this severely affected emphysema patient group, the overall benefit–risk profile is in favour of valve therapy. NICE agrees with this assessment, stating that there are no serious concerns about its safety.[1] Patients considering this treatment option should be informed of the potential risks and benefits of the procedure to make an informed decision.

While many physicians are satisfied with the available data on valves, NICE required a preponderance of consistent data before recommending valves as a treatment option. Their detailed assessment of all available data allowed NICE to reach the same conclusion as physicians: patients treated with endobronchial valves experience tangible benefits through improvements in their lung capacity, quality of life, and/or level of breathlessness.

This NICE decision is a huge step forward because health authorities will now recognise that BLVR with valves is an effective therapy and has the potential to meaningfully improve lung function, dyspnoea, exercise capacity, and quality of life for emphysema patients. General practitioners should consider referring patients with COPD who present with breathlessness while performing normal day-to-day activities, such as walking or doing light chores, despite medical management, for further evaluation and potential consideration for this treatment. While the NICE recommendation for the routine use of valves does not guarantee that health authorities will fund the therapy, it certainly facilitates the process and can be very meaningful to pulmonologists and patients. More recently, in June 2018, the U.S. Food and Drug Administration (FDA) also approved the Zephyr Valve for the bronchoscopic treatment of adult patients with hyperinflation associated with severe emphysema in regions of the lung that have little-to-no collateral ventilation,[20] validating its safety and efficacy.

Previously, when I have applied for exceptional funding to treat patients with valves, I would apply for funding for 20 well-selected patients and receive approval for only a few. Now, with the NICE recommendation, it will likely be much easier; I now expect to get approval for perhaps 16 or 17 patients out of 20. The UK health authorities generally follow the lead of NICE and, therefore, this decision has large potential to increase patient access to this important technology. As a physician who has been involved with valves since the beginning,

it is very gratifying to have seen the positive trajectory for this treatment over recent years. It is even more exciting to see the life-changing impact it can have for patients and their families. I applaud NICE on their decision and encourage private insurers to take the lead in making this technology available to improve the lives of very sick emphysema patients.

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Asthma in Childhood: Current Perspectives on Diagnosis and Treatment

EDITOR'S PICK

Asthma in adults and children is a complex cluster of disease phenotypes linked to specific endotypes. This emphasises the importance of precision in diagnosis and administration of more personalised treatments. In this narrative review by Uwaezuoke et al., the current perspectives on the diagnosis and treatment of asthma specifically in childhood are evaluated, with a focus on diagnostic steps, disease phenotypes and endotypes, and novel biologic therapies.

Antonio Rossi

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Abstract

This narrative review aims to appraise the current perspectives on the diagnosis and treatment of asthma in childhood, with a focus on diagnostic steps, disease phenotypes and endotypes, and novel biologic therapies. Asthma in children and adults is now regarded as a complex cluster of disease phenotypes linked to specific endotypes. Unravelling asthma heterogeneity is key to understanding the pathogenic mechanisms of the disease and developing novel treatment strategies that are tailored according to these phenotypes and endotypes. This will make for a more precise diagnosis and more personalised treatments. There is currently no gold-standard method for making the diagnosis of asthma due to the non-specific nature of asthma symptoms; respiratory symptoms and airflow limitation need to be carefully evaluated to establish a causal relationship with the disease. Although corticosteroids and bronchodilators still constitute the recommended step-wise pharmacological based therapy in both childhood and adult asthma, novel biologic therapies targeting type 2 immunity have been proven effective in severe childhood and adult asthma and will likely lead to improved disease outcomes.

INTRODUCTION

Asthma is currently characterised, in functional terms, as an inflammatory disorder linked to airway hyper-responsiveness that leads to symptoms.[1] The disease has thus been defined as a chronic inflammatory disorder of the airways involving many cells and cellular elements, which are associated with airway hyper-responsiveness leading to non-specific symptoms, such as recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, especially at night or in the early morning. These episodes (or exacerbations) are usually associated with widespread, but variable, airflow obstruction within the lung, which is reversible either spontaneously or with treatment.[2] Asthma is one of the leading non-communicable respiratory diseases in children globally.[3,4] In the UK,[5] the USA,[6] and China,[7] asthma is reported to be a major cause of childhood morbidity with rising prevalence rates seen in developing countries, including China.[7] Although the reason for this trend is not clear, the environmental pollution arising from industrialisation in these countries has been suggested as a major risk factor,[7] especially considering that the disease occurs following a genetically driven abnormal response of the immune system to environmental air-borne allergens.[8] However, both genetic (atopic) and non-genetic (non-atopic) asthma forms do exist: the latter being the more common form of presentation in adult patients.[9]

In children and adults, asthma is a heterogeneous disorder in which the asthmatic phenotype, including its clinical features, and the underlying endotype are complex and represent the myriad of host (gene)–environment interactions, which take place over different spatial scales and timescales.[10] The heterogeneity of the disease is particularly evident following clinical presentation, as well as in the nature and severity of airway inflammation and remodelling. Thus, asthma is no longer regarded as a single-disease entity, but rather as a complex cluster of disease phenotypes.[8]

Multiple phenotypes have now been identified, which are based on different cellular and molecular mechanisms from the heterogeneity of its immunology.[10] For instance, major inflammatory phenotypes, such as eosinophilic, neutrophilic, mixed complex inflammation, and pauci-granulocytic phenotypes, have been described from sputum cytological examination.[11] Further discoveries have been made that have identified molecular phenotypes in keeping with high type 2 T cell immunity and low type 1 T cell immunity asthma.[12] At present, a better understanding of the mechanisms of asthma immunopathology has led to the classification of the disease as either eosinophilic asthma (allergic and non-allergic), non-eosinophilic asthma (pauci-granulocytic and neutrophilic type 1 and type 17 T cell), or mixed granulocytic asthma.[10]

Unravelling the heterogeneity of asthma is a prerequisite for appreciating the pathogenic mechanisms of the disease and developing novel treatment strategies that are tailored according to phenotypes and endotypes. This will make for a more precise diagnosis and the provision of more personalised treatments. Although corticosteroids and bronchodilators still constitute the recommended step-wise pharmacologic agents in both childhood and adult asthma,[13] novel biologic therapies targeting type 2 T cell immunity have undergone trials and have been proven to be effective in severe childhood and adult asthma.[14,15]

This narrative review aims to appraise the current perspectives on the diagnosis and treatment of asthma in childhood. Specifically, the review discusses the progress made so far in the phenotyping and endotyping of the disease, as well as the emergence of novel biologic and other therapies.

LITERATURE SEARCH STRATEGY

The PubMed database was searched for original research and review articles published within the last 20 years, to the day the search was carried out (10th September 2018). The search was conducted by combining the key term 'asthma' with each of the following descriptors: 'childhood', 'diagnosis', 'spirometry', 'peak expiratory flow rate', 'phenotypes', 'endotypes', 'type 2 immunity', 'type 1 immunity', 'biologic therapy', and 'pharmacologic therapy'. Articles were selected in line with the specific objectives of the present review. The selected review

articles consisted of both narrative and systematic reviews. Duplicated papers were excluded, while the remaining articles formed the bulk of the published literature used to produce this review.

ASTHMA DIAGNOSIS: ASSESSING SYMPTOMS AND AIRFLOW LIMITATION

Assessment of pulmonary function should complement symptom evaluation in the diagnosis of obstructive lung diseases, such as asthma.[16] In fact, there is no gold-standard method for making a diagnosis of asthma; the symptoms and variability of airflow limitation are the parameters often evaluated during diagnosis.[10] As a result of the non-specific nature of asthma symptoms, respiratory symptoms need to be carefully evaluated to establish a causal relationship between the presented phenotype and the disease.

Spirometry is a useful tool for assessing air flow limitation, especially in older children (aged ≥6 years) and adults: populations that can easily understand and co-operate with the procedure.[17] While it is not commonly used in younger children, some preschool children have been shown to undergo acceptable spirometry as well.[18] The procedure provides an objective evaluation of airflow limitation and reversibility, which makes it a useful tool for measuring bronchial responsiveness in suspected cases of asthma, as well as in diagnosing and differentiating obstructive from restrictive lung diseases.[19] Using spirometry involves the correct interpretation of the values of forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the ratio of FEV_1 to FVC obtained from the spirometer.[20] Asthma and other obstructive lung diseases are associated with a reduction in FEV_1 relative to FVC and consequently a low FEV_1:FVC ratio. Nevertheless, spirometry is limited as an evaluation tool in asthma. For instance, many intermittent and mild or stable asthmatics may have normal FEV_1 and FVC values between acute exacerbations. Thus, the procedure is more useful as a monitoring tool since a sudden decline in FEV_1 or other measures in the same patient can signal poor asthma control, even with normal baseline values.

While limited, spirometry is useful for the assessment of air limitation reversibility after the administration of a bronchodilator. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) define this reversibility as an increase in FEV_1 of ≥12% from baseline and an absolute FEV_1 increase of ≥200 mL; an elevation of FVC by ≥200 mL also constitutes reversibility.[21] It has been suggested that postbronchodilator spirometry should not be done in all patients with normal baseline values unless asthma is strongly suspected on clinical grounds.[22] For instance, a recent study, which reported a postbronchodilator improvement in 3.0% of 1,394 patients with normal baseline results,[23] further corroborates this recommendation,[22] while also highlighting the poor sensitivity of FEV_1 as a variable in evaluating the disease.

When spirometry fails to demonstrate significant reversibility of airflow limitation and clinical suspicion of asthma remains strong, broncho-provocation testing (usually with methacholine) is recommended.[24] Despite the predictive ability of a positive methacholine-challenge test for asthma in patients with atypical symptoms or normal baseline values, false-positive results are also obtainable. The high negative predictive value of broncho-provocation testing with methacholine makes it a useful test for excluding the diagnosis of asthma, since negative results are rarely false-negatives.[24] Adequate standardisation of this test is vital to enable the best differentiation between normal airway responsiveness and airway hyper-responsiveness, as well as to compare results between different methods.[25] Thus, standardisation documents have recently been updated by the ERS to achieve these objectives.[25] It is also important to note that pharmacologic agents may inhibit airway responsiveness to methacholine through one of the following mechanisms: specific antagonism (e.g., antimuscarinic agents), functional antagonism (e.g., other bronchodilators, especially β agonists), or an anti-inflammatory effect (e.g., corticosteroids).[25] An understanding of the effects of these pharmacologic agents on the outcome of the methacholine challenge test is therefore essential as it will aid in guiding the appropriate washout periods from therapeutic interventions that inhibit airway responsiveness: an important aspect of the standardisation.[25]

Spirometry is also useful for the assessment of disease severity and reversibility of airflow in order to guide therapy. Generally, asthma symptoms do not correlate with disease severity. Asthma symptoms poorly reflect airflow reversibility and may lead to inaccurate assessment of the degree of airflow limitation.[26] This disparity between symptoms and disease severity and airway reversibility is confirmed by the findings of a study that showed that the majority of the evaluated asthma patients had FEV_1 and FEV_1/FVC values that were not directly related to self-reported disease exacerbation or subjective measures of disease severity or treatment response.[27] In comparison to the assessment of asthma symptoms, spirometry provides a more objective approach to assess asthma severity and response to treatment. The Global Initiative for Asthma (GINA) guidelines recommend the use of spirometry every 1–2 years or more, and at the initial evaluation, after treatment is initiated and symptoms are under control, and during periods of progressive deterioration or improvement of symptoms.[28] In resource-poor settings, where spirometers are not readily available, measurement of peak expiratory flow rate using the peak flow metre may be an acceptable alternative.[20] Airway constriction leads to lower peak flow readings. Changes in recorded values can be used to determine lung function, the severity of asthma symptoms, and therapy. Some asthma patients may benefit from regular peak flow monitoring, especially if the process is conducted simultaneously with the review of asthma symptoms and the frequency of reliever medication use. The measurement of peak expiratory flow rate requires training in the correct use of the peak flow meter while values are affected by confounders such as the patient's sex, age, and height. Thus, the wide range of 'normal' values makes it a less recommended test to evaluate asthma.

Finally, spirometry may also be useful for predicting asthma exacerbations. For instance, FEV_1 values, in comparison with parent-completed or patient-completed questionnaires, were reported to have a strong association with the risk of asthma exacerbations in children.[29] In summary, spirometry remains an important objective tool to measure lung function, which facilitates asthma diagnosis when used together with symptom evaluation. It should be performed in all patients in whom asthma is suspected, both at the point of diagnosis and subsequently at intervals, to evaluate disease progression.

ASTHMA PHENOTYPES, ENDOTYPES, AND BIOMARKERS

Although childhood asthma has previously been classified into two main phenotypes, namely allergic asthma and non-allergic asthma,[30] several novel phenotypes have now been identified from latent-class and cluster analyses,[31-36] with considerable overlaps of clinical features in phenotypic cluster groups.[31] During early childhood, the onset and pattern of wheezing over time has often been used to define asthma phenotypes, whereas in older children variables like atopic status and risks, decline in pulmonary function, or exacerbation risks have been incorporated into the designation of phenotypes, making prediction of treatment outcome possible.[37]

Taking several factors into consideration, diverse phenotypes of childhood asthma have been described by many studies. For instance, two prospective cohort studies, which evaluated long-term outcomes of early childhood phenotypes, have identified phenotypes based on asthma onset,[33] and patterns of wheezing.[34] In the BAMSE cohort study outcomes at age 8 and 16 years,[33] phenotypes were classified into never asthma, early transient asthma, early persistent asthma, and late-onset asthma. Decline in pulmonary function typically occurred in all the designated phenotypes except the never asthma phenotype. The Melbourne Atopy Cohort Study[34] placed children into five groups (never/infrequent wheezers, early transient wheezers, early persistent wheezers, intermediate-onset wheezers, and late-onset wheezers) based on the pattern of wheezing at 12 and 18 years of age. The persistent wheeze phenotype was characterised by reduced growth in prebronchodilator FEV_1 over adolescence, with the intermediate-onset wheezers showing irreversible airflow limitation by 18 years of age.

Furthermore, classification of childhood asthma phenotypes via cluster-analysis study has been

conducted.[31] This study, from the Childhood Asthma Management Program (CAMP), defined five cluster phenotypes on the basis of atopy burden, airflow limitation, and history of exacerbation. In cluster 1, the phenotype is described as mild asthma with low atopy, obstruction, and exacerbation rate; in cluster 2, the phenotype is atopic asthma with low levels of obstruction, and medium rates of exacerbation; cluster 3 refers to atopic asthma with high levels of obstruction, and medium rates of exacerbation; in cluster 4, moderately atopic asthma with high levels of obstruction and high exacerbation rates is the identified phenotype; while cluster 5 describes highly atopic asthma with high levels of obstruction and high exacerbation rates.[31] The prediction of bronchodilator response can easily be made from these phenotypic clusters: cluster 1 shows the lowest response while cluster 5 is characterised by highest bronchodilator response. Interestingly, heterogeneity in therapeutic response to inhaled steroids versus placebo or nedocromil (a mast cell stabiliser) was also observed between the phenotypic groups.[31] For instance, during asthma exacerbations, clusters 1, 2, and 3 showed better response to inhaled steroids compared with the administration of nedocromil or the placebo, whereas cluster 4 responded better to either steroids or nedocromil than to placebo; but there were no differences in the responses to these therapeutic interventions by cluster 5.[31]

To underscore the current diversity in phenotyping childhood asthma, it is important to mention other notable classifications. In the MeDALL project, Garcia-Aymerich et al.[32] studied large populations of children at 4 and 8 years of age from seven European population-based birth cohorts using latent class and cluster analyses. Researchers concluded that allergy-related diseases in children (asthma, rhinitis, and eczema) are more accurately grouped together as an allergic comorbidity cluster, than as three distinct diseases. Thus, this cluster consists of phenotypes, including asthma only, asthma and allergic rhinitis, asthma and atopic dermatitis, and asthma with atopic dermatitis and allergic rhinitis. Interestingly, a decline in pulmonary function from birth to 16 years was observed in the asthma with atopic dermatitis and allergic rhinitis phenotype but not in the other phenotypes.[38] Further classification of severe childhood asthma into sub-phenotypes reveal differences compared with severe asthma in adulthood.[37,39] For instance, eosinophilic airway inflammation occurs in both childhood and adult severe asthma. Male predominance and severe atopy are the hallmarks of severe asthma in children, whereas adults with severe asthma are predominantly non-atopic females with aspirin sensitivity and nasal polyposis.[39] Additionally, both children and adults have airway remodelling, but this is worse in adults with severe asthma who also exhibit fixed airway obstruction. In a prospective Brazilian study,[40] a therapy-resistant asthma sub-phenotype was described in children with severe asthma, characterised by low FEV_1 and high fractional exhaled nitric oxide (FeNO). Similarly, in adults with severe asthma, a sub-phenotype identified as frequent exacerbators, also showed high FeNO, but these individuals had a history of smoking.[41] Despite the abundance of work, more research is required to link these phenotypes with underlying immunopathology and genetics.

Given that asthma is a heterogeneous and genetically complex disease, it is likely to have several specific endotypes linked to distinct clinical characteristics, different underlying molecular aetiologies, and distinct therapeutic responses.[1] Progress in understanding the pathophysiological mechanisms of the disease have resulted in the identification of biologically distinct variants.[42] The definition of asthma endotypes will lead to precision in disease classification and the identification of biomarkers that fulfil conventional diagnostic or prognostic criteria.[1] Furthermore, grouping patients into endotypes will enable effective preventive measures and identification of appropriate individualised treatments.

The traditional concept of clinical asthma is predicated by the Th2 inflammation hypothesis. It is believed that exposure to allergens propels eosinophilic inflammation and tissue injury resulting in airway hyper-responsiveness and mediator release, which are responsible for asthma symptoms.[1] Thus, two distinct endotypes have been recognised: Th2-high and Th2-low asthma. Classification depends on the expression of the Th2 cytokines, including genes encoding for IL-4, IL-5, IL-9, and IL-13, as well as the treatment response to inhaled corticosteroids (ICS).[43]

Although the Th2 inflammation hypothesis presents a molecular framework underpinning the associations of atopy or IgE and eosinophilic-linked lung inflammation with asthma, the hypothesis is now being challenged on the basis of some observed discrepancies.[1] For instance, the Th2 inflammation model predicts that eosinophilic inflammation should propel airway hyper-responsiveness, but no obvious relationship has been observed,[44,45] and there is also non-concordance between atopy and airway hyper-responsiveness.[46] Consequently, a new model for childhood asthma endotype has been proposed. In this new model, distinct endotypes arise through variable interplay of the components: asthma symptoms frequently result from the interaction between altered lung function (FEV_1, airway hyper-responsiveness, and airway smooth muscle) and immunopathologies (airway remodelling and inflammation), while modifying processes (BMI, diet, and *in utero* exposures), acute asthma exacerbations, cigarette smoke, and environmental irritants impinge on lung function and remodelling and inflammation.[1]

Although the classification of endotypes in childhood asthma is still developing, the presence or absence of a Th2-molecular imprint has therefore enabled the linkage of asthma endotypes with phenotypes in order to identify patients who would respond or fail to respond to treatment with ICS.[47,48] As recent updates shed more light on asthmatic pathogenesis, disease classification has now been able to link phenotypes to endotypes based on airway and serum biomarkers, for example, specific IgE, Th2 cytokines (early-onset allergic phenotype); eosinophilia, IL-5 (late-onset eosinophilic phenotype); sputum neutrophilia, IL-8 (neutrophilic phenotype); and FeNO (smoking-induced phenotype).[47] A potential nexus exists between observable disease characteristics (phenotype) and underlying pathobiology (endotype) or biomarkers, as well as some potential personalised therapeutic options. In the future, endotypes may be used together with specific biomarkers to predict responses to targeted therapy.[47,49] For instance, Cowan et al.[50] reported that a noninvasive panel of inflammatory biomarkers in steroid-naïve asthmatics predicted clinical responsiveness to ICS.[50] The authors specifically measured FeNO values, sputum eosinophil counts, and urinary bromotyrosine levels. Notably, the combination of high FeNO values and high urinary bromotyrosine levels had the best predictive ability for a favourable response to ICS.[50] Urinary bromotyrosine is a noninvasive biomarker of eosinophil-catalysed protein oxidation, which has been shown to measure asthma control and predict disease exacerbations in children,[51] while FeNO is considered a biomarker of Th2 inflammation and atopy rather than a marker for evaluating severe asthma.[52] Currently, FeNO is seen as a useful marker of asthma severity, recognising specific asthma phenotypes (such as allergic asthma in childhood and smoking-induced asthma common in adults), predicting efficacy of standard corticosteroid and biologic therapies, as well as evaluating patients with allergic rhinitis at risk of asthma.[53] A recent retrospective study further confirms the ability of FeNO (in combination with blood eosinophil count) to identify patients with frequent asthma exacerbations and to stratify the appropriate therapy for Th2 inflammation-predominant severe asthma.[54] Blood eosinophil count is considered the best evaluated biomarker, the most applied in clinical practice, and, until recently, the most promising of all blood biomarkers.[55] Aside from blood eosinophil count, using other blood biomarkers for asthma diagnosis has not been encouraging. It may be trite to recall that the major biomarkers used in investigating the disease are generally present either in the sputum (e.g., sputum eosinophils and neutrophils), exhaled breath (e.g., FeNO), or in blood (e.g., blood eosinophils, IgE, and periostin). Several Th2-high asthma biomarkers have been extensively evaluated and validated: especially FeNO, blood eosinophil count, and serum periostin.[56] However, there is still a lack of biomarkers for Th2-low asthma. Therefore, characterising the Th2-low endotype essentially requires the absence of any known biomarkers of Th2-high asthma, as some investigators recently used these cut-off points (IgE ≥100 IU/mL, blood eosinophil count ≥300/µL, and FeNO ≥30 ppb) to define high levels of Th2 immune activation: grouping patients as having either a high Th2 immune profile (≥2 raised Th2 biomarkers) or a low Th2 immune profile (≤1 Th2 biomarkers).[57] This method appears logical until a validated Th2-low biomarker that can be used in clinical practice is discovered.

Table 1: Novel biologic therapies currently found to be effective in moderate-to-severe asthma in childhood.

Study	Biologics	Outcomes
Hanania et al.,[64] 2013	Omalizumab (anti-IgE)‡	Significant decrease in protocol-defined exacerbations (PO).
Busse et al.,[65] 2011	Omalizumab (anti-IgE)*	Significant decrease in asthma-symptoms days (PO) and decrease in exacerbations (SO).
Teach et al.,[66] 2015	Omalizumab (anti-IgE)**	Significant decrease in exacerbations (PO) and improved IFN-α responses to rhinovirus.
Ortega et al.,[14] 2016; Ortega et al.,[67] 2014	Mepolizumab (anti-IL-5)†	Significant decrease in exacerbation rate by about 50% (PO) and significant increase in FEV_1 by 100 mL/significant decrease in ACQ (SO).
Castro et al.,[15] 2015	Reslizumab (anti-IL-5)‡	Significant decrease in exacerbation rate by 60–80% (PO) and significant increase in FEV_1/significant decrease in ACQ (SO).
Bleecker et al.,[62] 2016	Benralizumab (anti-IL-5R)‡	Significant decrease in exacerbation rate by about 50% (PO) and significant increase in FEV_1 by 110 mL/significant decrease in ACQ.

†Trialled in adults and children (>12 years); ‡Trialled in adults and children (12–75 years); *Trialled in children, adolescents, and young adults (6–20 years); **Trialled in school children (6–17 years).

ACQ: asthma control questionnaire; FEV_1: forced expiratory volume in first second; IL-5R: interleukin 5 receptor; PO: primary outcomes; SO: secondary outcomes.

PHENOTYPE AND ENDOTYPE-DRIVEN (BIOLOGIC) THERAPIES

Novel treatments, which are based on disease pathobiology, may offer a more effective option for managing severe asthma in patients who do not respond to conventional therapies such as corticosteroids and bronchodilators. These patients have an elevated airway eosinophil count which is characteristic of Th2 inflammation.

Biologic therapies that target the Th2 signalling pathway and eosinophils constitute a paradigm shift in the treatment of severe asthma.[58] Examples of these treatment options include the anti-IL-5, anti-IL5R, and anti-IgE therapies. Most of these biologic therapies have undergone successful Phase III trials in adult asthma,[59-61] and in both adult and childhood asthma (Table 1).[14,15,62-67] Firstly, omalizumab (an anti-IgE), the first monoclonal antibody therapy for severe asthma, is currently licensed for moderate-to-severe allergic asthma in adults and children (>6 years) with IgE >30 IU/L.[10] Omalizumab has been observed to reduce exacerbations and hospital admissions in adults and children,[63] while another study showed that the therapeutic response was predicted by elevated high Th2 immunity biomarkers (namely high FeNO, serum periostin, and blood eosinophils) rather than IgE concentration.[64] It also reportedly reduced virus-associated exacerbations.[65,66] The drug particularly improved IFN-α responses to rhinovirus in school children.[66] Recently, omalizumab has been added to Step 5 of treatment in the latest GINA recommendations, which include other therapeutic options like tiotropium and oral corticosteroids.[13] It has been noted that omalizumab is more likely to be useful in patients exhibiting high levels of Th2 inflammatory biomarkers, such as FeNO, blood eosinophil count, and serum periostin,[68] which corroborates the findings of the previous study.[64]

Secondly, mepolizumab (anti-IL-5) has been found to significantly reduce exacerbation rate by 50% as well as increase the FEV_1 in adults and children (>12 years) with moderate-to-severe asthma.[14] Another anti-IL-5 monoclonal antibody which has been trialled in childhood and adult moderate-to-severe asthma is reslizumab; the drug was also noted to have significantly reduced the exacerbation rates and increased the FEV_1.[15] Finally, treatment with benralizumab (anti-IL5R) was found to have resulted in similar primary and secondary outcomes with a significant reduction in exacerbation rates and increase in FEV_1.[62]

OTHER CURRENT TREATMENT OPTIONS

Despite the prospects biologic therapies hold for personalised treatment and improved outcomes in children with moderate-to-severe asthma, the traditional pharmacologic therapies with bronchodilators and corticosteroids remain effective. The step-wise pharmacologic treatment with these classes of drugs as recommended by GINA is still the current practice.[13] If symptoms and exacerbations are not controlled, drug and dose adjustments are made as per the steps.

In this treatment approach for adults, adolescents, and children (≥6 years), the Step 1-recommended drug for all ages is the inhaled short-acting β agonist (e.g., salbutamol or terbutaline) acting as reliever medication. Alternatively, a regular low-dose ICS is added to reduce asthma symptoms, exercise-induced broncho-constriction and exacerbation risk, and halt the attendant decline in pulmonary function. For Step 2, regular low-dose ICS is recommended, with as-needed short-acting β agonist for all ages: another option being regular low-dose ICS and long-acting β agonist (LABA) for adults and adolescents. In Step 3, low-dose ICS and LABA are recommended for adults and adolescents. ICS and maintenance and reliever therapy are recommended for the same age groups in Step 4, while referral for assessment is advised for children. Referral for further assessment is recommended in Step 5.

Another currently proposed treatment option for asthma are the macrolide family of antibiotics. The beneficial effects of macrolides in asthma are thought to be related to either their anti-inflammatory action and/or their inhibitory action on the airway virobiome and microbiome.[69] For instance, low-dose azithromycin reduced the rate of exacerbations in patients with noneosinophilic asthma.[70] Furthermore, as an add-on treatment to medium-to-high-dose ICS plus LABA, it resulted in reduced exacerbation rate and quality of life improvements in patients with uncontrolled, persistent asthma.[71] Recently, Stokholm et al.[72] reported in their randomised, double-blind, placebo-controlled trial that azithromycin alone reduced the duration of episodes of asthma-like symptoms in children aged 1–3 years, and also suggested that this antibiotic potentially has a role in acute management of exacerbations.[72] However, there is a cautious optimism about its use because of the risk of microbial resistance, as well as the limited evidence about its role in severe asthma.

Another group of medications currently used in mild or severe asthma in children is the leukotriene modifiers.[73] Leukotrienes (LT), namely cysteinyl LT (CysLT) and LTB_4, are potent lipid mediators that play an important role in the pathophysiology of asthma phenotypes: with two identified receptor subtypes for CysLT ($CysLT_1$ and $CysLT_2$), activation of $CysLT_1$ receptor results in increased airway smooth muscle activity, microvascular permeability, and airway mucus secretion, while LTB_4 may be involved in the development of airway hyper-responsiveness, severe asthma, and asthma exacerbations.[73] Despite the less effective action of $CysLT_1$ receptor antagonists such as montelukast, pranlukast, and zafirlukast when compared to ICS, they can either be administered orally as monotherapy in patients with persistent mild asthma or in combination with ICS in patients with more severe asthma.

CONCLUSIONS

The current concept regarding asthma is that of a heterogeneous and genetically complex disease with several phenotypes having unique clinical characteristics linked to endotypes with different underlying mechanisms and distinct responses to treatment. Better understanding of the pathophysiologic mechanisms of the disease has resulted in the identification of these endotypes. Definitions of asthma endotypes will lead to precision in classifying disease and identifying biomarkers that meet formal diagnostic or prognostic criteria, as well as enable identification of appropriate individualised treatments. Thus, biologic therapies which may in future represent a paradigm shift from the traditional pharmacologic therapies will lead to improved disease outcomes in moderate-to-severe childhood asthma (in which they are currently indicated). However, the drawbacks to their routine use in children include their parenteral form and high cost of treatment.

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Noninvasive Ventilation: Challenges and Pitfalls

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Abstract

Noninvasive ventilation (NIV) is frequently used in patients with acute respiratory failure and its success is dependent on the underlying cause of the condition. When used for cases with a more rapid, reversible nature, like cardiogenic pulmonary oedema or acute exacerbations of chronic obstructive pulmonary disease, early intervention before patient deterioration is a key factor in success. Gastric distention-associated anastomose leakage after bariatric surgery is overestimated and the success of NIV trials in patients with encephalopathy has a strong association with the triggering cause rather than the severity of a coma. Immunocompromised patients mostly benefit from a short period of ventilation and more invasive ventilation is associated with excessively high mortality independent of the cause. In other diseases with parenchyma inflammation or infection, little success with NIV has been shown. Limiting ventilator-induced lung injury in these patients is another issue and is mostly achieved with heavy sedation or paralysis. Since NIV failure increases the risk of mortality, determination of a failing patient is of paramount importance. Clinical and laboratory surrogates of muscle fatigue can also be assessed. Adequate pressure support and positive end-expiratory pressure levels vary and the haemodynamic status of the patients must be considered. Ventilator–patient asynchrony increases NIV failure. Unfit interfaces also result in asynchrony, which will inevitably lead to failure, and observing waveforms can address this issue. The aims of this review were to understand the mechanism of NIV that leads to its failure or success, to become aware that delaying the appropriate therapy increases mortality, and to elucidate that spontaneous breathing can be a double-edged sword in some circumstances.

INTRODUCTION

Noninvasive ventilation (NIV) has been used for many years and its use has been steadily rising in the last two decades. Apart from substantial evidence supporting its use in specific clinical problems, like cardiogenic pulmonary oedema or acute exacerbations of chronic obstructive pulmonary disease (COPD), there are many controversies regarding the use of NIV as a first-line ventilatory support therapy in other types of acute respiratory failure (ARF), such as community-acquired pneumonia or acute respiratory distress syndrome (ARDS). As NIV failure may increase mortality, it is essential to have a good understanding of the respiratory pathophysiology before generalising the success of the procedure to other situations.

When the cause of the ARF is reversible and there is a need for ventilator support (i.e., the

patient shows signs of muscle fatigue), NIV is often initiated. It can be used to avoid intubation and its complications, to reduce work of breathing (WOB), to prevent atelectasis, to assist the failing heart, and to enable time for the treatment of the underlying disease.[1] However, reverting from spontaneous negative-pressure ventilation to positive-pressure ventilation (PPV) has its consequences, and the underlying pathology of the ARF is a significant factor in the success of NIV.

POSITIVE-PRESSURE VENTILATION AND HEART–LUNG INTERACTIONS

Traditionally, the lung can be divided into three Zones of West; although this is an oversimplification and there are many more factors influencing ventilation and perfusion in the lungs, it is helpful to understand and predict changes with interventions.[2] In Zone 1, there is ventilation but no perfusion, which is termed dead space ventilation. In a healthy lung, there is no Zone 1 and most of the lung consists of Zone 3, so perfusion in the lungs is independent of the pressure within the alveoli. PPV increases alveolar pressure and may enlarge Zone 1, thus leading to dead space ventilation. NIV, especially with full face masks, also increases apparatus-associated dead space.[3] These two factors may lead to CO_2 accumulation, which may not be overcome by increased minute ventilation. In situations when the respiratory pattern becomes rapid and shallow, this also must be considered.

PPV also induces right ventricular (RV) dilatation and increases its afterload, thus increasing the work performed by the RV. In cases where RV workload has risen, like pulmonary thromboembolism, pulmonary hypertension, or an RV infarct, one must be careful about the deleterious effects of PPV. Hypoxaemic pulmonary vasoconstriction also increases pulmonary vascular resistance (PVR) and RV workload, so a precise balance between these two endpoints must be considered.[4]

PVR has two main components, alveolar vessels and extra-alveolar vessels, and is lowest at the functional residual capacity. Below this volume, towards residual capacity, hypoxaemic pulmonary vasoconstriction increases together with PVR and, with increasing lung volume, the alveolar pressure increases and compresses the alveolar vessels, again increasing PVR.

Increases in intrathoracic pressure are reflected as an increase in right atrial pressure, and this impedes venous return to the heart. Decreased venous return to the right ventricle decreases left ventricular preload, which may reduce the cardiac output of the left ventricle. Increased PVR and RV dilatation push the interventricular septum against the left ventricle, impairing its preload further. Therefore, in haemodynamically unstable patients, instituting PPV may lead to circulatory collapse. Adequate hydration can limit these effects, but a strict negative fluid balance may be harmful to these patients because West Zone 3 becomes West Zone 2, which makes alveolar perfusion dependent on alveolar pressure, increasing the ventilation–perfusion mismatch further.[5]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Acute exacerbations of COPD patients have an increased WOB, muscle fatigue, and respiratory acidosis. The pressure support delivered with NIV helps to unload respiratory muscles, and the external positive end-expiratory pressure (PEEP) applied to the lung assists the patient to overcome intrinsic PEEP (iPEEP). Mechanisms leading to iPEEP include an increased time constant for expiration due to expiratory flow limitation in COPD patients and a short expiratory time resulting from the higher respiratory rate. Inability to exhale the volume in the alveoli leads to dynamic hyperinflation, which disrupts respiratory mechanics. When the patient initiates a breath, first the excess alveolar pressure must be overcome, then a negative pressure must be generated to create a gradient between the airway, referred to as zero pressure in a spontaneously breathing subject, and the alveoli, allowing gas flow to the lungs. This extra load leads to respiratory muscle fatigue and is a significant contributor to increased WOB in COPD patients. External PEEP application may reduce the gradient between intra-alveolar pressure and the airway opening pressure. In a patient with an iPEEP of 10 cm H_2O and a PEEP of 5 cm H_2O, the patient must first level their excess pressure with the airway opening pressure (assumed to be 5 cm H_2O) when the

ventilator is still in the expiratory phase and is thus unable to assist. If external PEEP is increased to 8 cm H_2O, the new gradient between the intra-alveolar pressure and airway opening pressure becomes smaller. In this way, applying external PEEP to assist patients in initiating a breath is a common method. iPEEP is measured in a no-flow state, namely with expiratory hold, and is hard to perform in a spontaneously breathing patient. Thus, observing the expiratory flow waveform and the point where the patient initiates a breath, and its distance from the zero line, will help identify internal PEEP and its response to external PEEP. Other than this, changing pressure support levels and/or mandatory ventilation frequency or the I:E ratio will also address this issue. It is important to keep in mind that applying external PEEP to assist the patient in triggering the ventilator does not modify the dynamic hyperinflation unless a greater external PEEP value than iPEEP is set. If a higher external PEEP is used, this will increase dynamic hyperinflation and can exacerbate the working conditions of the respiratory muscles.[6] It is evident that a 'one size fits all' level of 5 cm H_2O PEEP will have a different effect on every patient and must be titrated. Analysing flow waveforms on the ventilators would address this issue.

In a large retrospective study, NIV was associated with better outcomes compared to invasive mechanical ventilation (IMV) in acute exacerbations of COPD.[7] On the contrary, another study of 9,716 COPD patients in the UK showed higher mortality in NIV patients.[8] The investigators emphasised the importance of careful patient selection with milder respiratory acidosis and early start of therapy; severe acidosis (i.e., pH <7.26) and delayed treatment initiation led to NIV failure. Other risk factors associated with NIV failure were weak cough reflex and excessive secretions, hypercapnic coma, and patient–ventilator asynchrony.[9]

COPD without acidosis should not be treated with NIV to prevent the development of acidosis, and the mainstay of the therapy should be medical.[10] A group of patients with COPD presenting with a recent onset of shortness of breath with mild acidosis (i.e., pH >7.30) were randomised to a standard therapy of inhaled beta-agonists, inhaled ipratropium, and/or steroids, or to NIV therapy; there was no reduction in worsening respiratory distress rate, though there were crossovers in the study. The authors also showed an almost 50% intolerance to NIV sessions. This study suggests that without overt respiratory distress or severe respiratory acidosis, initiation of NIV has no advantage over conventional medical therapy.[11]

ENCEPHALOPATHY

Due to a lack of airway protective reflexes and co-operation, severe hypercapnic encephalopathy is considered a contradiction to NIV. Milder hypercapnic encephalopathy in patients with COPD exacerbations (Glasgow coma scale [GCS] >10) can rapidly improve with NIV; however, a lower GCS, an APACHE II score ≥29, a respiratory rate ≥30, and a pH <7.25 on admission have been shown to have a risk of failure >70%.[12] Pressure control ventilation or a high back-up rate can be used to reach the desired alveolar ventilation. Also, more CO_2 binds to haemoglobin at lower oxygen saturation, increasing the CO_2-carrying ability of the venous blood. This is known as the Haldane effect and means that blood oxygen saturation levels of 88–92% should be targeted.[13]

In other types of encephalopathies with hypercarbia, such as neuromuscular diseases associated with respiratory failure, the following must be considered before initiating NIV therapy: ability to clear secretions, the absence of agitation or agitations managed with conscious sedation, and expertise in NIV.[14] A study conducted by Díaz et al.[15] showed even higher success in patients with GCS ≤8 compared to GCS >8. However, the groups were not homogenous, and the more comatose patients had more NIV-responsive diseases like COPD (69.5% versus 25.5%). Overall, the outcome of NIV therapy in encephalopathy is dependent on the underlying cause rather than the level of encephalopathy.

CARDIOGENIC PULMONARY OEDEMA

Acute respiratory failure in cardiogenic pulmonary oedema (CPO) is due to muscle fatigue induced by an increase in WOB resulting from sudden flooding of the alveoli, an increase in airway resistance, a drop in the lung volume,

and a decrease in oxygen diffusion capacity. Application of PEEP recruits alveoli, decreases venous return, and decreases left ventricular afterload, improving stroke volume. These are translated into a favourable effect and NIV is therefore recommended. In CPO, NIV is associated with a reduced need for intubation and decreased mortality.[16] In addition, NIV in patients with acute coronary syndrome and ARF is not associated with an increased risk of cardiopulmonary events when compared with medical care.[17]

The ventilation mode, whether continuous positive airway pressure (CPAP) or bilevel positive airway pressure, is dependent on the underlying cause. Hypercapnic patients can benefit from increased alveolar ventilation and CPAP is effective in hypoxaemic patients, though a typical clinical presentation is uncommon. The superiority of one mode over the other has not been shown and the choice should be made separately for every patient.[17]

IMMUNOCOMPROMISED PATIENTS

A variety of conditions can affect immunocompromised patients and lead to ARF, such as opportunistic infections, drug-induced toxicity, and malignancy-related pulmonary damage. Immunocompromised patients are considered high-risk and extremely high mortality is associated with IMV; therefore, irrespective of the cause of the ARF, these patients may benefit from a trial of NIV to avoid complications related with IMV.[18] However, a study including 115 ARF patients showed that a high-flow nasal cannula was associated with better outcomes compared to NIV. The authors associated this result with better patient tolerance and an absence of ventilator-induced lung injury (VILI).[19]

HYPOXAEMIC RESPIRATORY FAILURE

The response to NIV in hypoxaemic ARF patients can change with the underlying cause and comorbidities. In pneumonia patients without previous history of cardiac or pulmonary diseases, NIV was associated with a faster improvement compared to oxygen therapy in the arterial oxygen partial pressure (PaO_2):fractional inspired oxygen (FiO_2) ratio and a reduced intubation rate.[20] However, the higher mortality rate in the rescue noninvasive group showed that delaying therapy worsens outcome. Another study also found improvement in oxygenation with NIV in community-acquired pneumonia patients compared to standard oxygen therapy, but oxygenation levels declined as soon as the NIV was stopped.[21] It is possible that applying CPAP to lungs recruited collapsed alveoli caused by the inflammatory process and exudative flooding; however, once the positive pressure was removed, this effect was lost. The authors suggested that CPAP should be applied over longer intervals to allow time for antibiotics to have an effect.[22]

In patients with comorbidities, success rates were higher than the former group.[22] On the contrary, no reduction in mortality or length of hospital stay compared to venturi mask was found in another study in patients with community-acquired pneumonia.[23] Concern in these patients comes from higher mortality associated with NIV failure compared with immediate IMV.[22] Patients should be selected with utmost caution and immediate IMV should be performed if the NIV fails to achieve the target (i.e., improved oxygenation).

Patients with ARDS also have a high rate of NIV failure, and the pressure levels needed to treat ARDS can be an indication for IMV. In an early study conducted in hypoxaemic patients, CPAP slightly improved oxygenation compared to oxygen therapy alone.[24] The authors also suggested that the assessment of oxygenation at 1 hour of therapy (i.e., PaO_2:FiO_2 <200) can be used as a marker of severity.[24]

If NIV is selected for ventilatory support in hypoxaemic ARF patients, appropriate PEEP levels must be applied. There is great debate regarding what the appropriate PEEP level is, and the clinician must choose one of the several conflicting results from the studies conducted on this topic.[25,26] Higher PEEP levels increase leaks and patient discomfort. It is also suggested that NIV should be reserved for patients with milder hypoxaemia (i.e., PaO_2:FiO_2 >200).[27] NIV in this setting was associated with higher tidal volumes compared to IMV. Also, lower PEEP levels were applied in the NIV group, which can be adjusted to a certain limit, compared to

invasive ventilation. This leaves increasing FiO_2 as the only option to improve oxygenation. The result was higher mortality in NIV failure patients compared to severe ARDS patients managed with invasive ventilation.[27] Also, a high tidal volume after 1 hour of NIV therapy was independently associated with mortality at Day 90.[28]

Higher PEEP application in NIV is linked with poor patient tolerance and increased leaks through the interface. The helmet interface has been used to address the problems of face mask application in hypoxaemic patients. In a study by Patel et al.,[29] the helmet interface was shown to significantly reduce intubation rates (by >40%) and mortality compared to a face mask in hypoxaemic respiratory failure patients. The authors attributed this effect to continuous and better application of higher PEEP rates, though the difference between the groups was only modest (8 cm versus 5 cm H_2O).[29]

NONINVASIVE VENTILATION AND LUNG INJURY

When the underlying pathology necessitating support is an injured lung, some receptors, such as the juxtacapillary receptors or central and peripheral chemoreceptors, may stimulate the respiratory drive.[30] Whereas a healthy lung can tolerate considerable increases in tidal volume, as seen in exercise, lungs with pre-existing injury are susceptible to VILI.[31] Ventilation-induced lung injury can be divided into two categories: VILI and patient self-inflicted lung injury.[31] The concept of 'baby lung' is well established and measures have been taken to reduce the overdistention of the already-aerated alveoli. Protective ventilation with lower tidal volumes according to body weight can limit this overdistention, though it is an indication of a patient's healthy lung size. Limiting driving pressure (the ratio of tidal volume to respiratory system compliance) also reduced mortality in ARDS patients.[32] The transpulmonary pressure (TPP) is the alveolar pressure minus the intrapleural pressure and increases in TPP can lead to VILI.[33] The TPP swings are similar for a given tidal volume, whether controlled, spontaneous, or partially assisted.[31] In an inhomogeneous lung, the TPP swings can be regionally different[34] and they are not always well reflected by a global measurement of tidal volume or TPP. A strong patient effort in patients with a higher respiratory drive may lead to the pendelluft phenomenon, which over-distends the more compliant alveoli.[35] Limitation of tidal volumes may reduce lung injury, but this is hard to accomplish in severe patients. Moreover, in controlled ventilation, alveolar pressure is higher than the end-expiratory pressure during most of the respiratory cycle. This is not the case in spontaneous breathing, during which the alveolar pressure can drop below the end-expiratory pressure. With the increased vascular permeability seen in patients with injurious lung, thus having a higher respiratory drive, it increases the risk of pulmonary oedema.[36] Therefore, these findings show that spontaneous breathing with higher tidal volumes can amplify lung injury, hence this is termed patient self-inflicted lung injury.[31]

Assisted spontaneous breathing has many advantages compared to controlled ventilation, including preserved diaphragmatic activity,[37] better ventilation–perfusion distribution,[38] better haemodynamics,[39] and a reduced need for sedatives.[31] On the other hand, the potential of increased respiratory drive to harm the lungs has been described in experimental conditions,[40] and research has shown a reduced mortality in controlled ventilation patients.[41] Decreased ventilator dys-synchrony, decreased respiratory drive, reduced atelectotrauma, and direct anti-inflammatory effects of cisatracurium were proposed to explain these findings. Also, in a recent study, the use of neuromuscular blockade resulted in decreased inflammatory markers, which was partly attributed to a reduction in epithelial and endothelial injury.[42] While the use of neuromuscular blockade should be considered in severely hypoxaemic patients, relevancy of injured lung and increased alveolar stress are important. All these proposed mechanisms also apply to milder patients with lung injury, in whom NIV may be considered as a favourable intervention. The risks of patient self-inflicted lung injury should be weighed against the short and long-term consequences of heavy sedation and paralysis.[43]

In a study conducted in subjects with acute hypoxaemic respiratory failure, patients failing

NIV have been shown to have higher tidal volumes.[44] Controlling tidal volume in these patients is almost impossible without high levels of sedation and often paralysis, which is mostly achieved with invasive ventilation.

Respiratory drive is sometimes assessed through respiratory rate, though it is not reliable. A high respiratory drive can be evaluated by oesophageal manometry, diaphragm ultrasound, electrical activity, electromyography, or by asking the patient if they have 'air hunger'.[30]

Recently, the 'mechanical hypothesis' was put forward.[45] In an inhomogeneous lung caused by inflammatory oedema, the forces acting on alveoli with different elasticity can be entirely different and the TPP can be doubled in these injured regions. Decreasing the inhomogeneity can be achieved by two manoeuvres: prone positioning and/or PEEP.[46] The former is clearly indicated in moderate-to-severe ARDS, and it is usually performed with IMV. Prone positioning with NIV was applied with success, though it has many limitations and needs specific expertise.[47] PEEP may decrease lung inhomogeneity through limiting lung collapse, increasing lung volume and, thus, reducing WOB.[48] On the other hand, increasing PEEP also increases the mechanical power applied to the lung parenchyma, facilitating VILI.[45] It can also disturb the perfusion. Indeed, it is known that cardiac output and shunt are related; a decrease in cardiac output decreases the shunt.[49] An increase in PaO_2 but a reduction in SvO_2 with PEEP increases shows that the improvement in oxygenation is not related to the recruitment of the collapsed alveoli.[50]

COMPLICATIONS OF NONINVASIVE VENTILATION

One of the complications of NIV is gastric distention, but it is likely to be overestimated. The tone of upper and lower oesophageal sphincters in a healthy person are 40 cm H_2O and 32 cm H_2O, respectively.[51] The fear of starting NIV after bariatric surgery is justified by gastric distention and anastomose leakage and supported by few case reports.[52] In a review which included 11 studies of 5,801 patients undergoing bariatric surgery, 1,293 (22%) of patients received PPV and only 11 cases of anastomose leak were reported, yielding a rate of 0.8%, which was the same as in patients who did not receive PPV.[53]

Other studies have shown no relation between anastomose leakage and NIV after bariatric surgery in obstructive sleep apnoea syndrome patients.[54,55] Nevertheless, sphincters may not function properly in some patients and can be as low as 11 cm H_2O.[56] Caution to high airway pressure is advocated in these patients.

Skin breakdown is a frequent complication of NIV and has been reported to occur in up to 48% of NIV patients.[57] It ranges from transient erythema to skin necrosis and increases a patient's intolerance to a mask. The use of total face masks or helmets and interchanging between different types of masks are suggested if an NIV session will be long.[58]

Table 1: Problems associated with patient selection for noninvasive ventilation.

Problem	Justification
Neurologic disorders	Reduced respiratory drive Risk of aspiration
Unstable haemodynamics	Risk of collapse
Deformities or recent facial surgery	Helmet interface can be used
Recent upper gastroesophageal surgery	Anastomose leakage Attention given to airway pressures
Severe hypoxaemia	Higher airway pressures are necessary
Inability to clear secretions	Bronchoscopy can be performed

Box 1: Predictors of noninvasive ventilation failure in acute respiratory failure.[47]

Higher illness severity score (SAPS >34).
Presence of ARDS or CAP.
Failure to improve oxygenation after 1 hour of treatment (PaO_2:FiO_2 ratio ≤175).
Higher respiratory rate under NIV.
Need for vasopressors.
Need for renal replacement therapy.
Lower arterial pH at baseline (in COPD).

ARDS: acute respiratory distress syndrome; CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease; FiO_2: fractional inspired oxygen; NIV: noninvasive ventilation; PaO_2: arterial oxygen partial pressure; SAPS: Simplified Acute Physiology Score.

HOW TO UNDERSTAND IF A PATIENT IS FAILING

The intensive care patient population can be heterogeneous, and it is logical to trial NIV in patients with respiratory failure unless a clear contraindication or potential harm is present. Problems associated with patient selection are given in Table 1.

The importance of detecting failing patients cannot be overemphasised because it is shown that delaying IMV increases mortality.[22,59,60] Close evaluation is necessary after initiating NIV therapy and laboratory values can also assist managing clinicians. Accessory respiratory muscle involvement, such as the sternocleidomastoid muscle, is associated with increased WOB and respiratory drive, and diminishing activity of the sternocleidomastoid muscle can be used as a surrogate for adequate pressure support level.[61] Predictors of failing NIV are summarised in Box 1.[41] Several studies have also addressed this situation.[62-64] Minimum improvement in PaO_2:FiO_2 after 1–2 hours of NIV, higher illness severity at admission, and higher respiratory rate were found to be indicators of NIV failure.[65]

If adequate oxygenation, relief of dyspnoea, or a decrease in respiratory rate cannot be achieved within 1 hour or the neurologic condition deteriorates, proceeding to intubation is necessary. Ventilator asynchrony is another major factor for NIV failure, but it has been shown that a clinician's ability to recognise this issue is low.[66] Meticulous attention to flow and pressure waveforms is required after every change in the ventilator setting to improve patient outcomes. Appropriate interface selection is also crucial because leaks will cause an insensitive trigger, affecting patient tolerance and synchrony.[65]

CONCLUSION

The relative success of NIV in respiratory failure patients with hypercarbia compared to hypoxaemic patients can be due to the more rapid reversible nature of the hypercapnic disease, such as muscle unloading and changes in the workload of the heart. The more time taken for the reversal in parenchymal infection, inflammation, or ARDS may necessitate more extended ventilatory support and careful observation of the patient. Favourable effects of NIV have been demonstrated in a select group of patients with CPO, patients with acute exacerbations of COPD, postoperative patients with atelectasis, and immunocompromised patients, though some concerns are inherent in most cases. It would be wise to select patients carefully according to observed pathophysiological changes.

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Anti-Programmed Death Receptor 1 Signalling Immunotherapy as a Part of Curative Intent Strategies for Stages I-III Non-Small Cell Lung Cancer

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Abstract

Surgery provides the best chance of a cure for patients with early stage non-small cell lung cancer (NSCLC) and plays an important role in the multimodal treatment for locally advanced disease. However, many patients still relapse despite intended curative surgery, and no major advances in systemic therapy for resectable NSCLC have been achieved in the last decades. The incorporation of immunotherapy for the treatment of metastatic Stage IV NSCLC and the recent data on the efficacy of cancer consolidation with the anti-programmed death-ligand 1 (PD-L1) antibody durvalumab after concurrent chemoradiation for unresectable Stage III NSCLC open new opportunities for the use of immune checkpoint inhibitors in earlier stages of the disease. Multiple ongoing clinical trials are exploring the safety and efficacy of immunotherapy in Stage I–III resectable NSCLC, either as a postoperative (adjuvant) strategy or before surgical resection (neoadjuvant). The neoadjuvant setting is particularly interesting, as it represents an ideal chance to develop translational research.

Herein, the authors summarise the main ongoing research and available data on the use of anti-PD1/PD-L1 antibodies for Stage I–III NSCLC.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide.[1] Survival strongly depends on the stage of disease at presentation, which was recently revised for the eighth edition of the tumour, node, and metastasis (TNM) classification for lung cancer.[2] According to staging, early NSCLC is defined as Stage I–II, while locally advanced (non-metastatic) disease refers to Stage III, which represents a highly heterogeneous group of patients with different tumour extent and controversial management based on the combination of surgery, chemotherapy (CT), and radiotherapy (RT).

Surgery offers the best chance of survival for patients with early stage and locally advanced resectable NSCLC. However, 5-year survival rates decline from 77–92% for Stage IA patients to 36% for Stage IIIA patients, with many patients experiencing disease relapse during postoperative follow-up.[3]

The use of immune checkpoint inhibitors that reverse cancer immunotolerance and enhance antitumour immune response has demonstrated durable remissions for a subset of patients with metastatic Stage IV NSCLC, in both the first[4-10] and second-line setting in recent years,[11-14] with a manageable safety profile. These immune checkpoint inhibitors include monoclonal antibodies directed against programmed cell death protein 1 (PD1) (nivolumab, pembrolizumab), PD-ligand 1 (PD-L1) (atezolizumab, avelumab, durvalumab), and the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) (ipilimumab, tremelimumab). The Phase III PACIFIC trial[15] comparing durvalumab versus placebo following concurrent chemoradiation in patients with unresectable Stage III NSCLC showed a significant improvement in progression-free survival (PFS) with the anti-PD-L1 antibody as consolidation therapy. The improvement was consistent across all patient subgroups that were analysed, irrespective of baseline expression of PD-L1 on tumour cells. Durvalumab was reasonably well tolerated with a manageable safety profile.[15] Based on PFS data, in February 2018, the U.S. Food and Drug Administration (FDA) approved durvalumab for the treatment of patients with locally advanced, unresectable, Stage III NSCLC who have not progressed following chemoradiation therapy. A statistically significant overall survival benefit was also determined by an independent data monitoring panel at an interim analysis in May 2018,[16] providing additional evidence of the clinical benefit that durvalumab can offer NSCLC patients in this setting. The use of durvalumab after chemoradiation is a new standard of care for unresectable Stage III NSCLC patients. After concurrent therapy, this has been the first major advance in Stage III NSCLC in the past decade.

Based on the efficacy of immunotherapy (IT) in advanced NSCLC, earlier stage disease is the next frontier for immune checkpoint inhibitors. Multiple clinical trials are currently ongoing to test their role in Stage I–III resectable NSCLC, either as postoperative (adjuvant) strategy or preoperative resection (neoadjuvant). In this review, the authors summarise the key ongoing research and available data on the use of anti-PD1/PD-L1 antibodies for Stage I–III NSCLC.

ANTI-PROGRAMMED CELL DEATH PROTEIN 1/PROGRAMMED CELL DEATH PROTEIN LIGAND 1 IMMUNOTHERAPY IN INOPERABLE STAGE I–II NON-SMALL CELL LUNG CANCER

Surgery is the standard of care for Stage I–II NSCLC patients who are medically fit. Stereotactic body radiation therapy (SBRT) can be an alternative strategy for those patients who are medically inoperable or refuse surgery.[17,18] The efficacy of IT is being investigated across studies in this setting. A currently ongoing Phase I trial is evaluating atezolizumab in combination with SBRT in patients with inoperable Stage I NSCLC.[19] Another Phase I/II trial for patients with Stage I NSCLC who have been deemed medically inoperable or who have refused surgery is also testing the safety and tolerability of definitive SBRT combined with concurrent and adjuvant avelumab.[19]

The concurrent use of anti-PD1/PD-L1 antibodies with RT has the potential benefit of boosting the abscopal effect, a phenomenon in the treatment of metastatic tumours where localised radiation triggers systemic antitumour effects outside the scope of the localised treatment.[20] Abscopal effects after SBRT have been reported in both renal cell carcinoma and melanoma.[21-23] For patients unsuitable for surgery with early stage NSCLC, nivolumab is going to be tested in the Phase II STILE trial[24] on completion of SBRT, although this trial is not yet recruiting.

ANTI-PROGRAMMED CELL DEATH PROTEIN 1/PROGRAMMED CELL DEATH PROTEIN LIGAND 1 IMMUNOTHERAPY AS ADJUVANT TREATMENT AFTER SURGERY IN STAGE I–III NON-SMALL CELL LUNG CANCER

In patients with completely resected Stage II or IIIA NSCLC, adjuvant platinum-based CT improves survival and is currently considered the standard of care.[25] In contrast, no significant improvement of adjuvant CT has been observed for resected Stage I NSCLC, although results from a subgroup analysis indicate that it would be reasonable to consider adjuvant CT for larger tumours (≥4 cm).[25] The use of adjuvant RT after successful R0 resection is still under debate, but recent studies have demonstrated clinical benefit in patients with N2 nodal stage diagnosed surgically.[26,27] Particularly in patients with clinically unforeseen N2 disease that have undergone complete resection, adjuvant CT and RT are still insufficient to provide optimal outcomes. Several clinical trials are currently recruiting patients with completely resected NSCLC to assess the efficacy of adjuvant anti-PD1/PD-L1 antibodies. Many of these trials allow for the combination of immune checkpoint inhibitors with adjuvant CT and/or RT (Table 1).[28-33]

One possible caveat for the adjuvant use of IT is that optimal lung cancer surgery requires mediastinal lymphadenectomy while tumour-associated lymphatic vessels and lymph nodes could play an important role in antitumour immune response regulation.[34,35] Neoadjuvant use of IT might circumvent this problem.

ANTI-PROGRAMMED CELL DEATH PROTEIN 1/PROGRAMMED CELL DEATH PROTEIN LIGAND 1 IMMUNOTHERAPY AS NEOADJUVANT TREATMENT IN RESECTABLE NON-SMALL CELL LUNG CANCER

Preoperative CT (also referred to as induction or neoadjuvant CT) has proven as effective and better tolerated than postoperative (adjuvant) CT in resectable NSCLC.[36,37] Neoadjuvant CT has the potential to reduce tumour size, eradicate micrometastasis, and improve patient compliance with treatment compared to adjuvant CT. In general, patients with Stage IB, II, or IIIA resectable NSCLC may be treated with neoadjuvant CT before surgery.[38] So far, there is little data on the efficacy of IT for resectable NSCLC and it is unknown whether the benefit is greater as a neoadjuvant or adjuvant strategy.

Based on mice models of breast cancer, neoadjuvant IT demonstrated a greater efficacy compared with adjuvant IT in preventing metastasis following primary tumour resection.[39] In this preclinical study, the authors evaluated and identified sustained peripheral tumour-specific immune responses that underpinned the outcome.

Patients with early stages of NSCLC may have a more intact immune system and reduced tumour conal heterogeneity compared to advanced disease, leaving a window of opportunity for immune checkpoint inhibitors to enhance systemic host immunity.[40] The presence of a tumour in the neoadjuvant setting is important as a source of neoantigen to prime the immune response, and neoadjuvant IT may contribute to T cell activation and expansion before the primary tumour is surgically removed, which may ultimately lead to an effective long-term systemic surveillance of micrometastasis. The neoadjuvant setting is particularly interesting too, as it allows identification of the effects of IT on pathologic tumour response.

In April 2018, Forde et al.[41] published the results from a pilot study evaluating two neoadjuvant doses of the anti-PD1 antibody nivolumab in untreated resectable (Stage I, II, or IIIA) NSCLC.

Table 1: Clinical trials of adjuvant anti-programmed death receptor 1/programmed death-ligand 1 immunotherapy in non-small cell lung cancer.

Clinical trial	Phase	Setting	Intervention	Status
ANVIL[28] NCT02595944	III	Completely resected Stage IB (≥4 cm), II, or IIIA	Nivolumab for up to 12 months (adjuvant CT and RT allowed)	Recruiting
RECIST[29] NCT03053856	II	N2 positive treated with neoadjuvant concurrent chemoradiation followed by resection	Pembrolizumab for up to 24 months	Not yet recruiting
MK-3475-091 KEYNOTE-091 PEARLS[30] NCT02504372	III	Completely resected Stage IB (≥4 cm), II, or IIIA	Pembrolizumab for up to 12 months (adjuvant CT allowed)	Recruiting
IMpower010[31] NCT02486718	III	Completely resected Stage IB (≥4 cm), II, or IIIA	Platinum-based CT followed by atezolizumab for up to 12 months	Recruiting
BR.31[32] NCT02273375	III	Completely resected Stage IB (≥4 cm), II, or IIIA	Durvalumab for up to 12 months (adjuvant CT allowed, adjuvant RT allowed only in N2 disease)	Recruiting
NCT03130764[33]	II	Completely resected Stage IB (≥4 cm), II, or IIIA	Durvalumab for up to 12 months plus four doses of tremelimumab (adjuvant CT allowed)	Withdrawn (principal investigator transferred)

CT: chemotherapy; RT: radiotherapy.

This study demonstrated that preoperative PD1 blockade was feasible, had acceptable side effects, did not delay planned surgery, and induced a major pathologic response in 45% of resected tumours, even when preoperative radiologic imaging failed to demonstrate tumour shrinkage. Tumour mutation burden correlated significantly with pathologic response, and neoadjuvant treatment induced expansion of tumour-specific T cell clones in peripheral blood.[41]

The association between pathologic response to neoadjuvant CT and survival in resectable NSCLC has been addressed in some retrospective studies.[42,43] As PFS and overall survival are long-term endpoints for early-stage lung cancer trials and it takes years for data to mature, future studies are needed to validate pathologic response after neoadjuvant therapies as a surrogate endpoint for survival.

Currently, neoadjuvant IT for resectable NSCLC is under investigation in several clinical trials and data from these trials are eagerly awaited (Table 2).[44-59] The Phase II NADIM trial evaluating preoperative nivolumab plus CT for resectable Stage IIIA NSCLC, followed by adjuvant nivolumab after surgery, conducted by the Spanish Lung Cancer Group, reported its first results in June 2018 at the American Society of Clinical Oncology (ASCO) Annual Meeting.[44] Forty-three patients were enrolled in the trial and 22 underwent surgery. Thirteen cases (59%) achieved a complete pathologic response, four cases (18%) had a major pathologic response (defined as <10% viable tumour cells in the resection specimen), and five cases (23%) had a partial response.[60]

DISCUSSION

The benefit of immune checkpoint blockade in early stage and resectable, locally advanced NSCLC remains unknown. Several clinical trials are underway exploring the role of adjuvant and neoadjuvant IT in this setting. Although preclinical data in breast cancer mice models suggest that neoadjuvant IT strategies have a better efficacy than adjuvant IT strategies in preventing metastases after primary tumour resection, the optimal approach in resectable NSCLC needs to be confirmed.

Table 2: Clinical trials of neoadjuvant anti-programmed death receptor 1/programmed death-ligand 1 immunotherapy in non-small cell lung cancer.

Clinical trial	Phase	Setting	Intervention	Status
NADIM[44] NCT03081689	II	Resectable Stage IIIA N2	Nivolumab plus platinum-based CT before surgery followed by adjuvant nivolumab	Enrolment completed
NA_00092076[45] NCT02259621	II	Resectable Stage IB (≥4 cm), II, or IIIA	Three doses of nivolumab with or without ipilimumab once	Recruiting
CheckMate 816[46] NCT02998528	III	Resectable Stage IB (≥4 cm), II, or IIIA	Nivolumab plus platinum-based CT versus nivolumab plus ipilimumab	Recruiting
MK3475-223[47] NCT02938624	I	Resectable Stage I or II	Pembrolizumab	Recruiting
NEOMUN[48] NCT03197467	II	Resectable Stage II or IIIA	Pembrolizumab twice	Not yet recruiting
TOP 1501[49] NCT02818920	II	Resectable Stage IB (≥3 cm), II, or IIIA	Pembrolizumab twice before surgery followed by four doses of adjuvant pembrolizumab (adjuvant CT and RT allowed)	Recruiting
MK-3475-671 KEYNOTE-671[50] NCT03425643	III	Resectable Stage IIB or IIIA	Four doses of pembrolizumab plus platinum-based CT before surgery followed by 13 doses of adjuvant pembrolizumab	Recruiting
NCT02987998[51]	I	Resectable Stage IIIA	Three doses of pembrolizumab plus chemoradiation before surgery followed by adjuvant pembrolizumab	Recruiting
PRINCEPS[52] NCT02994576	II	Resectable Stage IB (≥4 cm), II, or IIIA non-N2	Atezolizumab once	Recruiting
LCMC3[53] NCT02927301	II	Resectable Stage IB, II, IIIA, or selected IIIB, including T3N2 or T4 without mediastinal invasion	Atezolizumab twice before surgery followed by adjuvant atezolizumab for up to 12 months	Recruiting
NCT02716038[54]	II	Resectable Stage IB, II, or IIIA	Atezolizumab plus platinum-based CT	Recruiting
IMpower030[55] NCT03456063	III	Resectable Stage II, IIIA or selected IIIB (T3N2 only)	Four doses of atezolizumab versus placebo plus platinum-based CT before surgery followed by 16 doses of adjuvant atezolizumab	Recruiting
IONESCO[56] NCT03030131	II	Resectable Stage IB (>4cm) or II	Three doses of durvalumab	Recruiting
NCT02904954[57]	II	Resectable Stage I (>2 cm), II, or IIIA	Durvalumab with or without concurrent SBRT before surgery followed by adjuvant durvalumab for up to 12 months	Recruiting
NCT02572843[58]	II	Resectable Stage IIIA N2	Platinum-based CT followed by durvalumab twice and then surgery followed by adjuvant durvalumab for up to 12 months	Recruiting
NCT03237377[59]	II	Resectable Stage IIIA	Durvalumab versus durvalumab plus three doses of tremelimumab concurrently with thoracic RT	Recruiting

CT: chemotherapy; RT: radiotherapy; SBRT: stereotactic body radiotherapy.

In the neoadjuvant setting, some published data[41] may change future clinical practice in non-metastatic NSCLC. Pathologic response to neoadjuvant IT may serve as a surrogate endpoint for predicting survival in resected NSCLC, but further validation is warranted.

Until now, the expression of PD-L1 assessed by immunohistochemistry is the commonly used biomarker for selecting NSCLC patients most likely to benefit from immune checkpoint inhibitors. However, tumour responses to anti-PD1/PD-L1 antibodies have also been described in patients with PD-L1-negative tumours, suggesting that other factors related to tumour microenvironment beyond PD-L1 expression may determine the response to IT.[61] Tumour mutational burden and IFN-γ, among others, are emerging biomarkers of response to immune checkpoint blockade[62,63] and immune-related gene expression signatures are under development. The ongoing trials on the neoadjuvant use of anti-PD1/PD-L1 antibodies for resectable NSCLC patients may facilitate a comprehensive exploratory characterisation of the tumour microenvironment and the changes in tissue-based biomarkers that might correlate with pathologic response.

Substantial efforts are also needed to address many questions regarding the use of immune checkpoint inhibitors in Stage I–III NSCLC, such as the ideal timing of IT in relation to surgery, method of CT and RT delivery, the optimal dose, schedule, and duration of therapy. The PACIFIC trial[16] evaluating durvalumab after chemoradiation in unresectable Stage III NSCLC showed benefit, even though only 40% of the patients assigned to the intervention arm completed the 12 months of planned therapy, suggesting that perhaps optimal duration of therapy could be <1 year. The NADIM trial,[44] which evaluated preoperative IT with CT for resectable NSCLC, used three cycles of nivolumab before surgical treatment. The current trials focussing on combining checkpoint inhibitors with CT and RT are expected to help to better define optimal schedules.

CONCLUSION

In view of the efficacy results of IT in metastatic and unresectable NSCLC, earlier stage disease is the next frontier for immune checkpoint therapies. A number of clinical trials are currently investigating the efficacy and safety of anti-PD1/PD-L1 antibodies in Stage I, II, and resectable III NSCLC, either as adjuvant or neoadjuvant strategy, alone or in combination with CT and/or RT. Data from these trials are eagerly awaited while optimal endpoints are being defined.

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Alternative Exercise and Breathing Interventions in Chronic Obstructive Pulmonary Disease: A Critical Review

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Abstract

Interventions such as exercise training and breathing strategies are components of pulmonary rehabilitation for people with chronic obstructive pulmonary disease (COPD); however, the conventional mode of gym-based exercise training may not be optimal for all individuals with COPD, and adaptive breathing strategies may be beneficial in reducing dyspnoea, but the current evidence is limited. Uptake and completion rates of pulmonary rehabilitation are suboptimal, so alternative interventions need to be considered. This review examines the current scientific evidence on alternative exercise and breathing interventions from systematic reviews, experimental and observational studies, clinical trial registries, and grey literature. Alternative interventions are assessed for the effect on exercise capacity and quality of life with the aim of guiding the development of strategies to increase training uptake and completion. Systematic reviews of tai chi, yoga, minimal or no equipment exercise, water-based exercise, inspiratory muscle training, and singing demonstrated positive effects on exercise capacity and/or quality of life compared to no training, with some interventions demonstrating comparable outcomes to conventional training. Some positive outcomes have been demonstrated for whole-body vibration, single-limb partitioning, and Nordic and downhill walking; however, further research is required to compare these interventions to conventional training. The most recent interventions examined include exer-gaming, virtual reality, dancing, and laughing; controlled studies are still required to determine the effect on patient outcomes. Although further research is needed to compare alternative exercise and breathing interventions with conventional exercise training, results to date are promising, suggesting that people with COPD will have more options that may help to improve training uptake and adherence.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is recognised as a complex condition with effects extending beyond the respiratory system, including systemic manifestations[1] and other comorbidities.[2] This increased recognition and understanding of the multifactorial consequences of COPD and coexisting symptoms has led to a greater awareness of the importance of exercise training to reverse, manage, and/or improve physical function and health-related quality of life (HRQoL).[3] Exercise training traditionally consists of a variety of land-based (most typically gym-based) lower and upper limb endurance and strength exercises to improve muscle function, reduce dyspnoea, increase exercise capacity, and improve HRQoL;[3] however, the definition of exercise as an "activity requiring physical effort, carried out to sustain or improve health and fitness"[4] lends itself to more than just the conventional modes of exercise training characteristic of pulmonary rehabilitation (PR) programmes worldwide, such as cycling and treadmill walking.[5] Alternative exercise training modes, such as water-based exercise (WBE) training and tai chi, have now also been used to improve exercise capacity and HRQoL in people with COPD.[6,7]

Breathing strategies are another component of PR for people with COPD. Breathing strategies focus on retraining to slow the respiratory rate through prolonged expiration[3] and, traditionally in PR, using breathing retraining strategies to reduce dyspnoea, such as yoga breathing or pursed-lips breathing.[3] Breathing retraining extends to more than just these breathing strategies and could be achieved through singing or laughing.

Uptake and completion rates of PR are suboptimal,[8] and the presence of comorbidities has been attributed to the non-completion of PR.[9] Incorporating the values and preferences of people with COPD is essential in evidence-based decision making and delivering patient-centred care.[10,11] Therefore, there is now growing interest in investigating alternative exercise and breathing interventions in people with COPD, which may address these issues.[12-14]

Table 1: Literature search process.

Process	Description
Search period	Up until April 2018.
Search terms	Terms used in a recently published PR Clinical Practice Guideline,[16] with the addition of search terms related to each intervention.
Search strategy	Identified SR published within the last 10 years to support each intervention (if available) using CINAHL, Medline, Embase, CENTRAL, and PEDro. Identified experimental or observational trials published since the most recent SR end search date (if applicable) using the same search strategy. Searched clinical trial registries, including the Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, and the WHO trials portal for study protocols. In the case of none of the above being available, researchers searched conference abstracts, narrative approaches and commentaries (such as editorials and letters), social media posts (e.g., Twitter hashtags and users), and contacting authors of and leads from any identified information regarding an intervention.
Hierarchy for reporting of evidence (determined a priori)	1. SR and RCT published since the SR end search date and RCT listed on clinical trial registries. 2. RCT (where no SR were identified which met inclusion criteria) and RCT listed on clinical trial registries. 3. Any source of evidence of information (where no RCT were identified) and RCT listed on clinical trial registries.

PR: pulmonary rehabilitation; RCT: randomised controlled trial; SR: systematic review; WHO: World Health Organization.

The purpose of this study was to identify, highlight, and critically review current and new literature investigating alternative exercise and breathing interventions in people with COPD that aimed to improve exercise capacity and/or HRQoL. The results will help guide the development of strategies to increase the uptake and completion of exercise training.

METHODS

An alternative exercise intervention was defined as an activity that required physical effort other than conventional cycling and walking exercises recommended for people with COPD.[3] An alternative breathing intervention was defined as an activity that required physical effort other than the conventional yoga breathing or pursed-lips breathing typically included in PR programmes.[3] These interventions were identified by a number of sources, including expert consensus, review of published narratives, expert reviews of PR and exercise training, and texts of PR. The primary inclusion criteria for this review was that, in people with COPD, the alternative exercise and breathing interventions needed to be supervised and be an activity that required physical effort.[4] The secondary inclusion criteria were studies that included an outcome measure of exercise capacity (peak, endurance, or functional exercise capacity) and/or HRQoL, with a study duration of at least 4 weeks.[15] Studies were excluded if the mode of training was provided as an adjunct to conventional PR (not in isolation) or were not available in English.

The literature search process is detailed in Table 1.[16] Multiple types of literature were considered (in a hierarchical nature) to ensure all identified alternative interventions were highlighted to provide information on the current state of evidence (planned, in progress, or currently available). Literature searches were undertaken by one review author for each alternative intervention. A second author reviewed the results of each search and consensus was reached by discussion to ensure no pertinent studies were overlooked.

RESULTS

Fourteen interventions that met the primary inclusion criteria were identified, including tai chi, yoga, minimal or no equipment exercise, WBE, whole-body vibration (WBV), single-limb partitioning, Nordic walking (NW), downhill walking (DW), exer-gaming, virtual reality, dancing, inspiratory muscle training (IMT), singing, and laughing. The description and rationale underpinning each alternative exercise intervention is presented in Table 2,[6,7,17-29] with breathing interventions presented in Table 3.[30-33]

Alternative Exercise Interventions

Tai Chi

A Cochrane review published in 2016 included 12 randomised controlled trials (RCT) (N=811) investigating tai chi training of 6–52 weeks duration.[7] Assessing 6 studies (n=318), compared to no exercise training, tai chi demonstrated a larger improvement in 6-minute walk distance (6MWD) (mean difference [MD]: 27 m; 95% confidence interval [CI]: 11–49 m).[7] In one study (n=60), a comparison of tai chi and breathing exercises versus breathing exercises alone found no superiority for functional exercise capacity or HRQoL.[7] No adverse events were reported.[7] An additional 12-week RCT comparing tai chi to PR was published in 2018, with comparable improvements in exercise capacity and HRQoL immediately following a 12-week intervention.[34] At 3 months post intervention, there was a significant difference in HRQoL favouring tai chi.[34]

Clinical trial registry searches found four RCT with a tai chi programme duration ranging from 12–24 weeks: tai chi versus conventional exercise versus usual care; tai chi versus group walking versus usual care; tai chi versus conventional exercise; and tai chi versus breathing exercise versus education. The study protocols of two of the four trials have been published.[35,36]

Tai chi training is safe and feasible in people with COPD. Tai chi has different styles, each with its own characteristics and forms. Exercise intensity, duration of practice, and length of programme often varies between styles. New trials will provide more insight into the effect of tai chi compared to active training interventions, and future trials are required to determine the long-term benefits.

Table 2: Description and rationale for alternative exercise interventions.

Intervention	Description	Rationale
Tai chi	An ancient Chinese martial art consisting of a series of slow but continuous movements of the body, which incorporates elements of strengthening, balance, and postural alignment; it emphasises use of the mind or concentration to control breathing and circular body motions to facilitate flow of internal energy (i.e., 'qi') within the body.[17]	Tai chi is recognised as an exercise of moderate intensity that emphasises the integration of diaphragmatic breathing into its slow, circular, and rhythmic movements, which mimic the controlled breathing techniques used in the management of COPD.[7]
Yoga	An ancient practice from the East, which often consists of exercise (asanas), controlled breathing (pranayama), meditation, relaxation, and concentration.[18]	Yoga involves holistic methods to enhance mind–body co-ordination.[19]
Minimal or no equipment exercise	PR programmes in which the intervention required only minimal equipment (i.e., no bikes, treadmills, or weight machines) or where low resources (e.g., body weight, theraband, or hand weights) were used.[20]	Most studies of the effectiveness of PR have been performed in large centres with well-equipped gymnasiums; low cost programmes with minimal equipment may improve the availability of PR.[20]
Water-based exercise	Exercise in water with the body submersed and the head out of water.[6]	In a water environment, buoyancy supports the body weight and reduces mechanical impact on the body, muscle work is increased due to water turbulence and resistance to movement in all directions, and warm water improves blood flow to muscle, all of which are features that may enable a higher intensity and duration of exercise, especially in people who have difficulty completing a land-based exercise training programme.[6]
Whole-body vibration	Standing on a vibration platform, which produces oscillating mechanical vibrations to the subject,[21] while performing static or dynamic exercises.	The platform generates vertical vibrations or uses a side alternating mode;[21] the oscillations are transmitted to the body and stimulate muscle spindles to produce muscle contractions.[22]
Single-limb partitioning	Partitioned exercise, for example, cycling with one leg at a time.[23]	One-limb exercise is half the load of two-limbed exercise but places the same metabolic demands on the targeted muscles, but it reduces the ventilatory load, enabling an increase in work capacity.[23]
Nordic walking	Outdoor walking performed using specially designed Nordic poles with rubber tips designed to be shock absorbent and slip resistant.[24]	Walking with Nordic poles increases muscle use and walking speed and generates higher intensities of work than standard walking on ground with no change in dyspnoea.[25]
Downhill walking	Walking on a treadmill that has been adjusted to create a 10% negative incline.[26]	Eccentric muscle work induced by downhill walking produces higher muscular stress with lower metabolic cost (lessened symptoms of dyspnoea and fatigue) compared to level ground walking.[26]
Exer-gaming	The use of interactive video games that combine game play with exercise.[27]	Elevates energy expenditure and may offer the same health benefits as conventional exercise.[27]
Virtual reality	Sophisticated computer-generated simulation of a three-dimensional virtual or imaginary environment that can be interacted with in a seemingly real way using special electronic equipment such as a headset; the participant can be fully immersed in the gaming experience.	Interactive exercise sessions may increase access to limited supply PR programmes and boost independence in completing exercises at home.[28]
Dancing	Complex body movements synchronised to music.	Dance sessions may be of sufficient intensity to provide a training stimulus for improvements in muscle strength and endurance with potential psychosocial benefits.[29]

COPD: chronic obstructive pulmonary disease; PR: pulmonary rehabilitation.

Yoga

A systematic review (SR), including studies published up to June 2017, included a total of 10 trials (8 RCT and 2 non-RCT) (N=312) investigating yoga training of 12–36 weeks duration.[19] Yoga with or without education was compared to controls, including usual medical care, PR, or education.[19] In six studies of 312 participants, yoga demonstrated a larger improvement in 6MWD compared to controls (MD: 22 m; 95% CI 10–34 m). Improvement was also found regarding the St George's Respiratory Questionnaire (SGRQ) total score in three studies

of 105 participants compared to controls (MD: -3.81 points; 95% CI: -6.65 to -0.97 points).[19] No adverse events were reported.[19] An additional RCT of 12 weeks of yoga training compared to PR was published in 2017, with comparable improvements in exercise capacity and HRQoL after intervention.[37] Clinical trial registry searches did not find any further trials meeting the inclusion criteria.

Evidence to date indicates that yoga is safe and feasible in people with COPD. Despite evidence of improvements in exercise capacity and HRQoL, these did not reach the minimal important difference (MID) for 6MWD[38] or SGRQ total score.[39] In addition, non-RCT were included in the SR,[19] and some studies investigating yoga training included controlled breathing (pranayama) only, while some studies included exercise, meditation, and relaxation in addition to controlled breathing.[19] Similarly to tai chi, yoga has many different forms and styles, which can easily be modified to suit individual needs; however, the exercise intensity may vary between styles. These variations limit the ability to draw a clear conclusion on the effect of yoga training in people with COPD.

Minimal or No Equipment Exercise

A SR has shown that PR with little or no equipment improved exercise capacity and HRQoL when compared to no training in people with COPD.[20] In the eight studies reviewed (N=285), there were significant improvements reported in HRQoL and both 6MWD and incremental shuttle walk distance,[20] with only the 6MWD reaching the MID.[38] The training provided included ground-based walking, NW, and different modes of strength training, including free weights, therabands, sit-to-stand exercises, and stepping,[20] rather than the conventional exercise training that uses bikes, treadmills, and weight machines.[3,5] The frequency of supervision provided ranged from three times per week to once per month, and the programmes were home-based, varying in length between 4–12 weeks.[20] A Cochrane review protocol was published in 2017[40] and clinical trial registry searches revealed one RCT from Switzerland examining the effects of a long-term home-based exercise training programme using minimal equipment versus usual care.[41]

These results provide support for supervised exercise training using minimal or no exercise equipment when compared to no exercise training in people with COPD. Further research with larger cohorts and comparison of supervised training with no equipment to conventional exercise training will strengthen the evidence.

Water-Based Exercise

A Cochrane review published in 2013 included five RCT (N=176) investigating WBE training of 4–12 weeks duration compared with no exercise training and/or land-based exercise (LBE) training.[6]

Table 3: Description and rationale for alternative breathing interventions.

Intervention	Description	Rationale
Inspiratory muscle training	A technique used to increase respiratory function by improving the performance of the muscles involved in inhalation using threshold devices.[30]	Inspiratory muscle weakness is related to increased dyspnoea and reduced exercise tolerance.[31]
Singing	The production of musical words or sounds with the voice, which can be performed individually or in a group (choir), and can be arranged or improvised.[32]	Singing uses diaphragmatic breathing, altered posture, and improved breathing co-ordination.[32]
Laughing	A physical reaction consisting typically of rhythmical, often audible contractions of the diaphragm and other parts of the respiratory system in response to certain external or internal stimuli.	During laughter there is a predominance of expiration over inspiration, which should result in an elimination of air accumulated with normal breathing; it is also thought to aid the clearance of respiratory secretions.[33]

Compared to LBE training, WBE improved the endurance shuttle walk distance (MD: 313 m; 95% CI: 232–394 m) and the fatigue domain of HRQoL.[6] Other aspects of HRQoL were not significantly different between WBE and LBE.[6] One minor adverse event was reported.[6] An additional RCT of 6 months that compared WBE and LBE training was published in 2018, with comparable improvements in exercise capacity and HRQoL between the two training groups.[42] Clinical trial registry searches did not locate any further studies.

One trial in the aforementioned Cochrane review specifically included people with COPD with physical comorbidities, such as musculoskeletal conditions, joint replacements, neurological conditions, and obesity,[43] indicating WBE may be particularly suitable for people with physical limitations to exercise on land. WBE may not be acceptable to all people with COPD, with two studies reporting that three participants refused to consider WBE.[6] Conversely, two studies reported participant subjective preference for an exercise training environment, with WBE preferred by the majority over LBE (49% versus 37%, respectively).[6]

WBE is safe and improves exercise capacity and HRQoL, with a greater effect on improving endurance exercise capacity over LBE training. Long-term effects of WBE have not yet been investigated.

Whole-Body Vibration

Three SR,[21,22,44] with a combined total of six studies, have been published on WBV for people with COPD; however, all reviews included studies of <4-weeks duration and thus did not meet the criteria for inclusion in this review. Despite this, the three reviews reported no serious adverse events from WBV.[21,22,44]

Four RCT of at least 4-weeks duration of WBV have been published. Significant improvements in 6MWD of 80 m (95% CI: 68–92) following a 6-week WBV training programme involving static work of the lower limbs on a vibration platform were found when compared to lifestyle and physical activity advice alone.[45] Smaller improvements in 6MWD were also shown in a small (N=11) 12-week cross-over pilot study with a comparison group of no intervention,[46] and in a 3-month WBV programme compared to breathing retraining and calisthenics.[47] However, following a 3-month training period comparing WBV to resistance training, there were no differences between groups for 6MWD.[48] Improvements in HRQoL also did not reach significance between WBV and comparison groups.[46-48] A review of the clinical trial registries identified four studies currently recruiting participants with COPD for WBV, with a further eight studies listed as having completed recruitment.

The role and benefit of WBV in COPD appears promising for improving functional exercise capacity, with further research occurring. This may assist in determining the optimal mode, frequency, and duration of WBV delivery.

Single-Limb Partitioning

One RCT[34] and one small non-controlled study[49] investigated one-legged cycling for people with COPD. Both studies demonstrated that a 7-week or 8-week one-legged cycling programme improved peak oxygen uptake.[23,49] In a pragmatic feasibility trial of implementing one-legged cycling training as the principal aerobic exercise activity in PR, the 6MWD improved by a mean of 72 m (95% CI: 45–98), and a change in HRQoL above the MID was found.[50]

Clinical trial registry searches identified one RCT of single-limb resistance training compared to two-limb resistance training. Given the two previous studies in the area were published nearly a decade ago, the results of this study will add new knowledge to this area.

Nordic Walking

One RCT was identified investigating NW in people with COPD. A 12-week training programme of NW compared to no training in people with COPD (n=60) showed an increase in 6MWD[24] with the results maintained at 9 months follow-up and with a 92% completion rate.[24] A search of the clinical trial registries did not find any further studies.

Although the evidence is limited, the available study reported that supervised NW was safe, suggesting it may be an accessible and low-cost mode of training that may enhance long-term adherence to exercise and could

be ideal for people with COPD who prefer to exercise outdoors. Further studies are required to confirm or refute this hypothesis.

Downhill walking

One RCT investigated DW in people with COPD.[51] Thirty-four people were randomised to 12-weeks of DW or conventional level walking.[51] Similar improvements were observed between the two groups for change in 6MWD and cycle endurance.[51] More participants in DW (94%) exceeded the 6MWD MID[38] compared to level walking (65%).[51] Importantly, fewer symptoms were reported during DW training.[51] No further trials were found on the clinical trial registries. This one study provides evidence of an effect of DW on exercise capacity. Further studies are warranted to confirm and further examine the effect of DW.

Exer-Gaming

One uncontrolled study using gaming technology has been reported in people with COPD using the Nintendo Wii Fit programme, which allows participants to complete endurance training of the upper and lower limbs (e.g., jogging-based movements) as well as functional upper and lower-limb exercises (e.g., squat, stepping activities, and boxing).[27] Eighteen participants with moderate-to-severe COPD completed training in the home environment with exercise on most days per week over a 12-week period.[27] A significant increase in endurance shuttle walk test time of 131±183 seconds, a significant increase in the total score of the Chronic Respiratory Disease questionnaire, and no adverse events were reported.[27] Searches of clinical trial registries yielded no further studies. This preliminary evidence suggests that exer-gaming as a form of exercise training is feasible and may be effective in this population.

Virtual Reality

Given that virtual reality technology is relatively new to the gaming world, no peer-reviewed publications or clinical trial registry listings examining the feasibility or effectiveness in people with COPD were identified. However, a virtual reality application has been developed by researchers at Manchester Metropolitan University, Manchester, UK for people with COPD.[28] The app contains a virtual beachside training environment where participants can interact in an exercise class, performing exercises from the comfort of their own homes. This application is currently being evaluated for ease of use and acceptability by people with COPD.

Dancing

There is currently no evidence on the effect of dancing in people with COPD. However, a recent pilot study (N=5) indicated three expert-led dance sessions may provide a suitable training intensity for people with COPD.[29] People with chronic lung diseases, including COPD, have also expressed interest in participating in dance-based PR.[52] Dance in COPD will be an emerging field of research, with investigators in Canada currently examining the feasibility of dance as an intervention.[53] It is anticipated that findings from this study will inform design for a future RCT.

Alternative Breathing Interventions

Inspiratory Muscle Training

In a recently published SR of IMT, 29 RCT, non-RCT, and cohort studies investigated constant-load threshold IMT with a duration range of 4 weeks–12 months compared with sham IMT, general exercise training, incentive spirometry, education, respiratory muscle stretch gymnastics, expiratory muscle training, and usual care.[45] IMT significantly improved 6MWD which surpassed the MID.[30] The meta-analysis result from nine studies for HRQoL failed to reach a statistically significant improvement.[30] One further RCT has been published since the end search date for the SR. Eight-weeks of IMT compared to sham training control significantly increased endurance exercise time.[54]

Clinical trial registry searches found numerous research activity in this area with 11 studies currently recruiting participants, and an additional two studies not yet recruiting. Effects of IMT in HRQoL need to be examined further, as well as determining the optimal prescription for IMT training.

Singing

A Cochrane review published in 2017 included three RCT (N=112) investigating singing for

6–24 weeks duration compared with control (film workshop, handcraft work, or no intervention).[32] In two studies (N=52), compared to the control group, singing improved HRQoL (SF-36 Physical Component Summary score MD: 12.64; 95% CI: 5.50–19.77), but not SGRQ total score.[32] Singing had no impact on exercise capacity.[32] No adverse events or side effects were reported, and no studies examined long-term outcomes.[32] Clinical trial registry searches located one study currently recruiting participants to 10-weeks of singing training compared to PR.

Qualitative research studies have reported high satisfaction with singing by people with COPD;[55] however, the optimal dosage to achieve positive outcomes is yet to be determined.[32]

Laughing

There is currently no evidence on the effect of laughing in people with COPD. However, a single laughter intervention improved cheerfulness,[56] and a sense of humour has been associated with an enhanced HRQoL in people with COPD.[33] Clinical trial registry searches revealed no studies on this intervention.

DISCUSSION

This review investigated the research around novel interventions of exercise and breathing to improve exercise capacity and/or HRQoL in people with COPD. SR of tai chi, yoga, minimal or no equipment exercise, WBE, IMT, and singing have demonstrated positive effects on exercise capacity and/or HRQoL compared to no training, with some interventions demonstrating comparable outcomes to conventional exercise training. Some positive outcomes have been demonstrated for WBV, single-limb partitioning, NW and DW; however, further research is required to compare these interventions to conventional exercise training. The newest exercise and breathing interventions to be examined include exer-gaming, virtual reality, dancing, and laughing, and controlled studies are required to determine their effect on patient outcomes.

The purpose of identifying alternative exercise and breathing interventions is to widen the options available to people with COPD to improve their exercise capacity and HRQoL. In rural and remote locations, and in centres with limited funding and facilities, lack of conventional exercise equipment may be a barrier to setting up conventional PR programmes, as well as a barrier for patients when asked to perform home exercise. Minimal or no equipment training could address these problems. People with physical comorbidities, such as musculoskeletal conditions, often find conventional gym-based exercise difficult or aggravating to their condition, so the appeal of reduced weight-bearing training, such as WBE,[43] or breathing interventions, such as singing, may be appealing. Preliminary evidence on sophisticated gaming technology suggests that it can be effective for people with COPD[27] and may help to engage people in exercise training, but more studies are required to verify these results.

Limiting factors to implementing some alternative interventions are the need for specialised equipment and skilled personnel. For example, a limitation to the use of DW as part of an exercise programme is the need to have a specialised treadmill. More research is needed in this area to determine if DW using ramps and hills would provide the same training effect as conventional treadmill training. Specialised equipment is also required for NW and WBV, access to technology is required for exer-gaming and virtual reality, and WBE requires access to a pool. Specialised personnel or training of existing PR staff in new skills is required to deliver tai chi, yoga, NW, singing, and dancing.

There are some limitations to the evidence reviewed in this paper for the different interventions. It is unclear whether this evidence can be applied to people with different severities of COPD or those on long-term oxygen, or use these interventions for maintenance of health outcomes after completion of conventional training. Some of the evidence is from non-controlled studies, and not all studies compared the alternative intervention to conventional training; therefore, it cannot be concluded that these alternative interventions can replace conventional training. Rather, the evidence presented here supports new interventions that could be offered to improve exercise capacity and HRQoL in people with COPD. Furthermore, this review did not examine

the issue of delivery of the interventions in different environments, such as hospital centres, community centres, and the home environment. Future steps would be needed to investigate the feasibility of offering and implementing these alternative interventions in different settings and to determine the acceptability of these interventions in routine clinical PR practice. Certainly, this issue has been established for some alternative interventions such as no equipment exercise,[57] single-limb partitioning,[50] and WBE.[58]

It is well established that PR should encompass patient-tailored therapies that are individually designed to improve the physical condition of people with COPD, and meet the unique needs of the patient, including disease severity, complexity, and comorbidities.[3] With emerging evidence on alternative interventions, clinical practice needs to move beyond offering only conventional exercise training options. The provision of a menu of interventions to improve exercise capacity and HRQoL for people with COPD gives patients options that may be better suited to their physical capacity and preference. It is well established that, in certain global areas, the access to conventional exercise training is suboptimal.[8] Offering options and a choice of interventions may increase the appeal of exercise training and improve the rates of referral, uptake, and retention. Additionally, more options and a flexible model would allow patients to select their preferred intervention and to transfer between different interventions to improve their physical condition whilst maintaining their level of interest in exercise training.

CONCLUSION

The results of the studies reviewed have shown that different exercise and breathing interventions are safe and effective in improving exercise capacity and/or quality of life in people with COPD. In many cases further research is needed to compare the interventions to conventional exercise training, but the results to date are promising, suggesting that in the future people with COPD will have greater options available for exercise training and breathing interventions, and may be offered a choice of ways to manage their condition, which may lead to increased uptake and completion of training.

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