EMJ RESPIRATORY

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+ ERS INTERNATIONAL CONGRESS 2020

+ EDITOR'S PICK

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+ INTERVIEWS

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Contents

"Always open access, always at the forefront; please enjoy the following pages, and I hope that this content adds value to your medical practice, whatever your role in the field."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

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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Congress Notice

Staff members attend medical congresses as reporters when required.

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EMJ Respiratory 8.1

Welcome

Dear Readers,

Another issue of unmissable articles, abstracts, and interviews awaits inside *EMJ Respiratory 8.1* as we bring the latest news from the European Respiratory Society (ERS) International Congress, as well as our own selection of peer-reviewed articles on the hottest topics in the field, to make sure you keep up with the latest in the field of respiratory.

A pandemic will always have the capacity to affect all medical specialties, but the coronavirus disease (COVID-19), being a respiratory condition, has put an unprecedented strain on pulmonary healthcare professionals. It is therefore imperative that accurate and timely medical research is disseminated at the present time, and this is where EMJ come in; this is our promise to you.

"It is therefore imperative that accurate and timely medical research is disseminated at the present time, and this is where EMJ come in; this is our promise to you."

Our Congress Review of the 30th ERS meeting provides the highlights from the >450 scientific and educational sessions, including late-breaking abstract summaries on topics such as personalised asthma care, 'long COVID' and lung damage, and a novel app that measures night-time coughing to predict asthma deterioration.

Alongside the congress content, *EMJ Respiratory 8.1* also offers exclusive interviews with ERS 2020 Award Winners; our editorial team spoke to Dr Dina Brooks, ERS Assembly Lifetime Achievement Award Winner, and Prof Greet Van den Berghe, ERS Gold Medal in ARDS Winner, about their areas of expertise and their most valuable learnings from the COVID-19 pandemic so far.

Always open access, always at the forefront; please enjoy the following pages, and I hope that this content adds value to your medical practice, whatever your role in the field.

Spencer Gore

Chief Executive Officer, EMG-Health

PRESENT IN ~50%[a] TO 70%[b] OF YOUR ADULT ASTHMA PATIENTS,

TYPE 2 INFLAMMATION IS HIGHLY HETEROGENEOUS AND A PREDICTOR OF RISK FOR FUTURE EXACERBATIONS[1-4]

IDENTIFY

Type 2 inflammation in asthma

HETEROGENEITY

Encompasses several phenotypes[2]:

- Allergen-driven
- Mixed eosinophilic and allergen-driven
- Eosinophilic

SIMPLE IDENTIFICATION

Identifiable by one or more of the following criteria[5]:

- ✓ Elevated EOS
- ✓ Allergen-driven
- ✓ Elevated FeNO
- ✓ OCS-dependency

EOS, eosinophils; **FeNO**, fractional exhaled nitric oxide; **OCS**, oral corticosteroid.

TARGET

Cytokines IL-4, IL-5 and IL-13 are key drivers of type 2 inflammation in asthma[6-8]

	IL-4	IL-13	IL-5
Th2 cell differentiation	●		
B-cell class switching and IgE production	●	●	
Eosinophil recruitment and trafficking to tissue	●	●	●
Eosinophil differentiation in bone marrow			●
Mucus production and goblet cell hyperplasia		●	
Smooth muscle hypertrophy and tissue remodeling	●	●	

IL-4 and IL-13 have distinct and overlapping roles with a broad impact on asthma symptoms[7,8]

TREAT

TO REDUCE

Exacerbations

Oral corticosteroids

TO IMPROVE

Lung function

Quality of life

Target and treat type 2 inflammation holistically to achieve optimal asthma control[1,5]

[a]N=205.
[b]N=37.

References: 1. Dunican EM, Fahy JV. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. *Ann Am Thorac Soc*. 2015;12(suppl 2):S144-S149. **2.** Rogliani P, Calzetta L, Matera MG, et al. Severe asthma and biological therapy: when, which, and for whom [published online ahead of print December 25, 2019]. *Pulm Ther*. doi:10.1007/s41030-019-00109-1 **3.** Fahy JV. Type 2 inflammation in asthma-present in most, absent in many. *Nat Rev Immunol*. 2015;15(1):57-65. **4.** Peters MC, Mekonnen ZK, Yuan S, Bhakta NR, Woodruff PG, Fahy JV. Measures of gene expression in sputum cells can identify TH2-high and TH2-low subtypes of asthma. *J Allergy Clin Immunol*. 2014;133(2):388-394. **5.** Global Initiative for Asthma. Difficult-to-treat & severe asthma in adolescent and adult patients, 2020. https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf. Accessed April 14, 2020. **6.** Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35-50. **7.** Robinson D, Humbert M, Buhl R, et al. Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy*. 2017;47(2):161-175. **8.** Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. *Nat Rev Immunol*. 2008;8(3):193-204.

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Foreword

Dear Readers,

It is a great pleasure for me to welcome you to the new issue of *EMJ Respiratory.* This year has been trying for all healthcare professionals around the world, but perhaps particularly those in the field of respiratory. Many have dedicated their lives to fighting the coronavirus disease (COVID-19) pandemic on the frontline and progressing research into the disease. One lesson, among many, from this year is the importance of collaboration and sharing scientific knowledge, which are both fundamental goals of *EMJ Respiratory*.

Adapting to the new world we are currently living in, the European Respiratory Society (ERS) made the decision to hold their annual congress virtually this year. Furthermore, an additional day was added to the scientific programme to disseminate what is known so far about COVID-19. The virtual ERS International Congress exemplified the agility of the respiratory field and showcased key advancements in respiratory medicine over the last year through live presentations, thousands of e-posters, and satellite symposia, a review of which is included in the following pages.

Complementing the congress review, ERS Award Winners Prof Dina Brooks and Prof Greet Van den Berghe provide insight into their respective expertise in pulmonary rehabilitation and intensive care medicine.

Inside this issue there are also articles from respiratory experts discussing topics such as the risk factors for severe COVID-19 in the article by Hussain et al., the cellular networks in lung immune homeostasis by Borger, and sleep quality during noninvasive and invasive ventilation by Ugurlu et al.

My Editor's Pick for this issue is the paper by Chen et al. Asthma, a highly prevalent comorbidity during pregnancy, if uncontrolled, can be associated with alterations in placental function and fetal growth. The interesting paper by Chen et al. provides the clinical management of asthma during pregnancy to prevent adverse outcomes for the fetus, the barriers in the education of health professionals, and the importance of self-management skills, especially in this current COVID-19 pandemic period.

I hope you all enjoy reading *EMJ Respiratory*, an issue that I believe to be of interest to you all.

Dr Antonio Rossi

Medical Director, Therapeutic Science & Strategy Unit, IQVIA, Milan, Italy

Congress Review

Review of the virtual European Respiratory Society (ERS) International Congress 2020

Location: ERS International Congress

Date: 6th–9th September 2020

Citation: EMJ Respir. 2020;8[1]:12-24. Congress Review.

THE 30th anniversary of the European Respiratory Society (ERS) meeting was set to be a spectacle in Vienna, Austria, but no one could predict what the year had in stall for us. In response to the ongoing coronavirus disease (COVID-19) pandemic, the ERS made the decision to hold the 30th ERS International Congress virtually. Even with this unexpected turn of events, the society put together a platform that showcased research and facilitated discussion and interaction, which was attended by over 33,000 delegates.

In the 'Welcome to 30th Congress' section of the platform, the ERS President Thierry Troosters welcomed attendees to the event. Amongst many of his encouraging words, Prof Troosters highlighted how many professionals in the respiratory field had dedicated their lives to fighting the COVID-19 pandemic on the frontlines or have been involved in researching pharmacological and nonpharmacological treatments for the many patients affected by the disease. He further noted that: "The pandemic also showed the pivotal role of links to other country and regional societies. We exchange knowledge and help each other with dissemination of science around the pandemic in many of the disease areas covered by the society."

The scientific programme evolved to fit with the platform, with some sessions being available in multiple languages such as English, Spanish, and German. The society also added a day dedicated to the knowledge that is known so far about COVID-19, including COVID-19 prevention, management, and the impact on those with pre-existing lung conditions. In his welcome message, Prof Troosters thanked those who contributed to the meeting: "I'm grateful to those who have taken time, despite overburdened agendas, to contribute to the sharing of knowledge and initiation of scientific projects, moving the field forward at light speed."

Another new addition to the scientific programme this year were ALERT sessions,

"I'm grateful to those who have taken time, despite overburdened agendas, to contribute to the sharing of knowledge and initiation of scientific projects, moving the field forward at light speed."

which combined the breaking news from recent, unpublished randomised clinical trials in easy-access sessions. Furthermore, 'Live from the Clinic' sessions showed experts performing live procedures such as endoscopies, which was only possible due to the digital format.

Thousands of e-posters and abstracts were presented, which provided insight into the latest developments across all aspects of the respiratory field. Included in the following pages are summaries of a hand-selected collection of abstracts, written by the presenters themselves.

Prof Troosters acknowledged that we should not draw too much attention away from the ongoing efforts in preventative health, using smoking as an example, which has killed 15 times as many people in 2020 as COVID-19, adding that air pollution is still a pertinent issue for respiratory health. Even though the congress was held virtually this year, and thus had a very minimal carbon footprint, the society had great plans to hold a green face-to-face meeting, showcasing their commitment to minimising their ecological footprint.

Weighing in on the positives, Prof Troosters reminded attendees that: "The coronavirus has put some of our projects on hold, but facilitated others, for example, the transition towards a virtual format for our consultations, rehabilitation programmes, or even our congress. We will not waste this crisis and continue to build on the good things that came out of it."

We look forward to being able to attend what will sure to be another great meeting next year in Barcelona, Spain, until then, please enjoy the following review of the 30th ERS International Congress.

ERS 2020 REVIEWED →

Personalised Asthma Care: Should we Prescribe According to Genetics?

GENETIC differences between children and adolescents with asthma may aid treatment selection for these patients; this is according to a study conducted at the University of Dundee, Dundee, UK, the results of which were reported at the ERS International Congress 2020 on the 8th September 2020.

In total, 241 patients aged between 12 and 18 years were enrolled in the trial. They were all being treated for asthma by their general practitioner and were randomly assigned to either a group that received treatment according to existing guidelines, or to a group that utilised personalised medicine techniques, in which they received treatment according to their genotype. To determine their genotype, the participants' inner cheek cells were tested for different versions of the β-2 adrenergic receptor *ADRB2* gene.

The β-2 adrenergic receptor is a common pharmacological target of asthma treatments, but previous research has shown that one in seven children have one or two copies of the altered versions of this gene; this can lead to the medication having a negative effect on patients symptoms. Therefore, the personalised medicine group of this trial were treated with montelukast, rather than salmeterol.

Participants were followed for 1 year, during which quality of life, the severity of their symptoms, and the extent to which asthma limited their normal activities were assessed (on a scale of 1–7). When comparing the average scores for quality of life between the two groups, there was only an improvement of 0.16 seen in the personalised group. However, when specifically looking at those with two copies of the altered *ADRB2*, they found a 0.42 improvement.

Prof Mukhopadhyay, Brighton and Sussex Medical School, Brighton, UK, and leader of the study team, is hopeful about the implications of the results, especially as the genetic test kits cost $20 USD: "These results are very promising because they show, for the first time, that it could be beneficial to test for certain genetic differences in children with asthma and select medication according to those differences."

"These results are very promising because they show, for the first time, that it could be beneficial to test for certain genetic differences in children with asthma and select medication according to those differences."

'Long COVID': Heart and Lung Damage Could Improve with Time

CORONAVIRUS disease (COVID-19) has caused long-term heart and lung damage in many patients, but this has been shown to improve over time, as evidenced by a prospective follow-up study by researchers from the Tyrolean region in Austria. These results were presented at the ERS International Congress 2020 on 7th September 2020.

Conducted between 29th April and 9th June 2020, the study included 86 patients hospitalised with COVID-19 who were followed up at 6, 12, and 24 weeks, as well as after their discharge from the hospital. Clinical examinations, laboratory tests, CT scans, and echocardiograms were all carried out at every follow-up visit. The average age of participants was 61 years, 65% were male, 65% were overweight or obese, and almost 50% were current or former smokers.

At 6-weeks follow-up, 65% of the patients had at least one persistent symptom, the most common being breathlessness and coughing (47%). Using CT scanning, it was observed that 88% of patients had lung damage, deemed by the presence of ground-glass opacities. Echocardiogram analysis also showed that 59% of patients had dysfunction of the heart's left ventricle. At 12-weeks follow-up, some recovery was seen because lung damage was visible in 56% of participants and only 39% reported breathlessness. The 24-weeks follow-up has yet to be performed.

Dr Sabina Sahanic, The Medical University of Innsbruck, Innsbruck, Austria, and one of the authors of the study, summarised the findings: "The bad news is that people show lung impairment from COVID-19 weeks after discharge; the good news is that the impairment tends to ameliorate over time, which suggests the lungs have a mechanism for repairing themselves."

She concluded: "Knowing how patients have been affected long-term by the coronavirus might enable symptoms and lung damage to be treated much earlier and might have a significant impact on further medical recommendations and advice."

"The bad news is that people show lung impairment from COVID-19 weeks after discharge; the good news is that the impairment tends to ameliorate over time"

Bronchitis in Early Years as a Prediction Tool for Middle-Age Lung Health

LUNG problems in later life can be reliably predicted if the patient had bronchitis at least once before the age of 7 years; this is according to findings from the Tasmanian Longitudinal Health Study, which were released at the ERS International Congress 2020 on 4th September 2020.

Enrolled as children, 8,583 participants who were born in Tasmania in 1961 and started school in 1968 had their lung function initially assessed using a spirometer. The researchers took note of how much air they could breathe out forcibly in 1 second and the total volume of air exhaled, as well as establishing if they had been diagnosed with bronchitis or asthma by the age of 7 years.

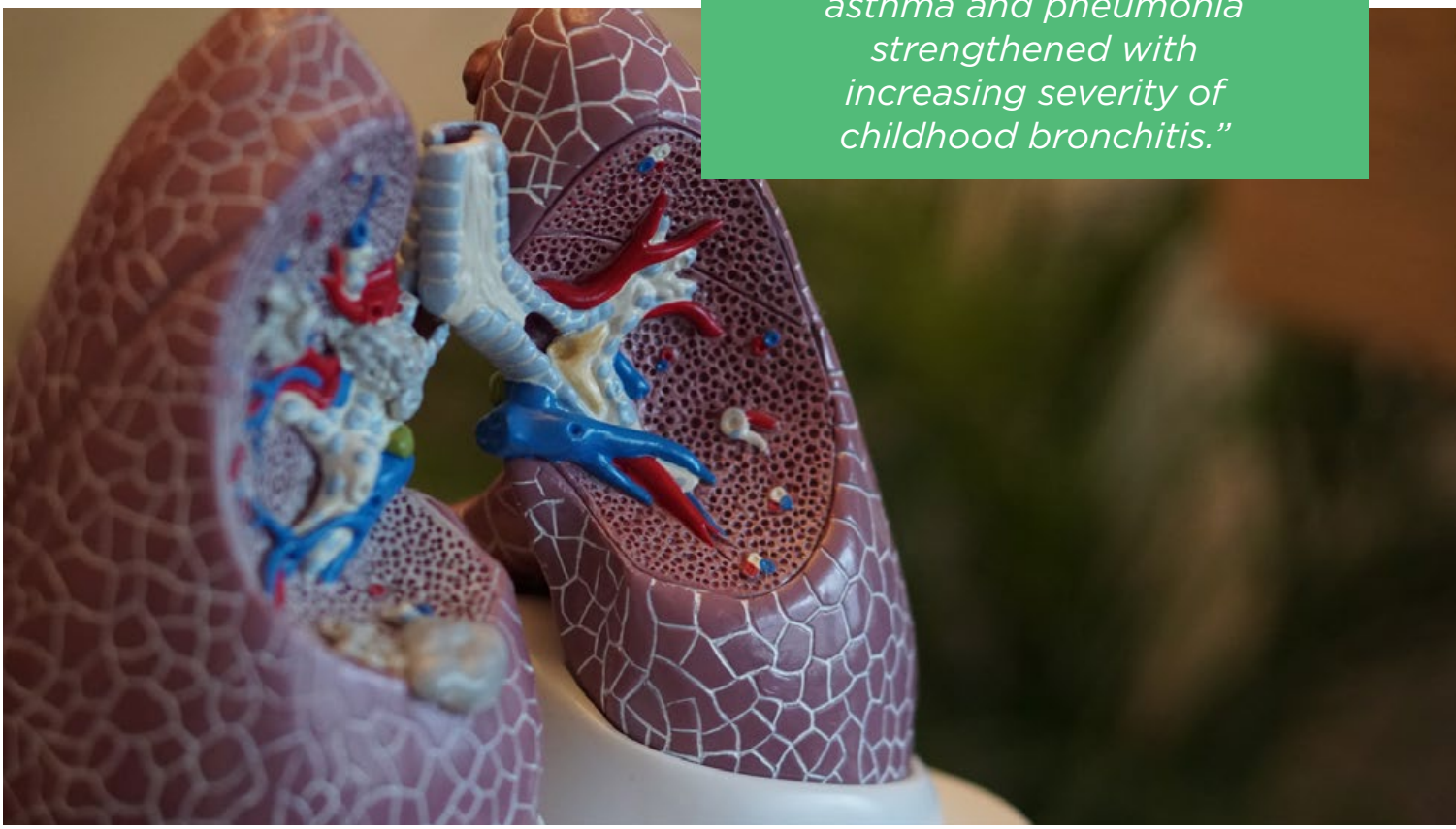
The participants were followed up for an average of 46 years. In 2014, a total of 5,729 participants responded to a further survey and between 2012 and 2016, 3,609 participants completed an additional survey and 2,629 underwent a clinical examination that again used a spirometer to access lung function.

Nonrecurrent, recurrent, or protracted recurrent episodes of bronchitis before the age of 7 years was associated with a 1.4-fold, 2.0-fold, and 3.2-fold increased risk of pneumonia, respectively, by the time participants reached the average age of 53; a 1.3-fold, 2.7-fold, and 6.4-fold increased risk of ever having asthma, respectively; and a 1.3-fold, 2.0-fold, and 4.5-fold increased risk of currently having asthma, respectively.

Dr Jennifer Perret, a researcher at the University of Melbourne, Melbourne, Australia, analysed the findings: "The associations with asthma and pneumonia strengthened with increasing severity of childhood bronchitis."

However, she did stress that the results should be interpreted with caution: "There was no statistically significant link between childhood bronchitis and chronic bronchitis in middle-age. This was an unexpected finding and further study would be informative. We are currently exploring these associations."

"The associations with asthma and pneumonia strengthened with increasing severity of childhood bronchitis."



"We need to do all we can to support smokers to quit completely using evidence-based means."

What is the Cancer Risk of 'Social Smoking'?

MORE smokers are cutting back on their daily smoking, but the mortality and cancer risks of 'social smoking' remain substantially higher than for nonsmokers. News from a study by Columbia University Irving Medical Center, New York City, New York, USA, was presented at ERS International Congress 2020 on 1st September 2020.

'Social smokers', defined as those who smoke <10 cigarettes per day, represent an increased proportion of smokers in the USA, from 16% up to 27%, as many smokers have cut back or combined smoking with vaping. However, the risks from social smoking have not previously been well understood. Researchers analysed data from 18,730 people across ethnicities as a sample of the general population of the USA, to compare risk between social smokers, heavier smokers (>20 cigarettes per day), and nonsmokers. Participants, with an average age of 61 years, were followed for an average of 17 years.

The study found that, compared to nonsmokers, social smokers were 2.5 times more likely to die from respiratory diseases and 8.6 times as likely to die from lung cancer, even when controlling for age, sex, race, level of education, and body weight. Death from respiratory disease or lung cancer occurred in 3.3% and 4.7% of social smokers, respectively, compared with 10.1% and 12.9% of heavier smokers, and 1.8% and 0.6% of nonsmokers.

Addressing the value of these findings for clinicians at ERS International Congress 2020, Prof Jørgen Vestbo, Chair of the European Respiratory Advocacy Council and Professor of Respiratory Medicine, University of Manchester, Manchester, UK, emphasised: "It's clear that there is no safe level of smoking. This large study is important because it shows that smoking less will probably not have the effect that people are hoping for. We need to do all we can to support smokers to quit completely using evidence-based means."

Flavourings and Solvents Mix to Form New, Toxic Chemicals in e-Cigarettes

e-CIGARETTES have propelled into common use as a 'safe' alternative to tobacco smoking; however, recent evidence is questioning the real safety of these devices and the associated e-liquids. The case for such tobacco alternatives being unsafe was further supported by research presented at the ERS International Congress 2020 and reported in a press release dated 3rd September.

Flavourings are routinely added to e-liquids, and, according to manufacturers, are safe because they are vaporised by the e-cigarette; however, a recent study reported that they form new toxic chemicals by combining with the solvents, for which there are severe safety concerns.

In the toxicological studies, the researchers exposed cells that line the bronchi to chemicals that are commonly used as flavourings, for example vanillin and cinnamaldehyde, and explored the possible compounds formed when mixed with propylene glycol and vegetable glycerine, the main solvents used in e-liquids. "We consistently observed that the new chemicals formed from the flavours and e-liquid solvents were more toxic than either of their parent compounds," noted author of the study Prof Sven-Eric Jordt, Duke University School of Medicine, Durham, North Carolina, USA.

"We consistently observed that the new chemicals formed from the flavours and e-liquid solvents were more toxic than either of their parent compounds"

Additionally, TRPV1 and TRPA1, sensory irritant receptors in the bronchi responsible for numerous inflammatory responses, were activated by the new chemicals. Activation of these receptors can lead to issues in both the cardiovascular system, such as increased heart rate and irregular heartbeat in the predisposed, and pulmonary system, such as coughing and breathing difficulties due to increased secretions throughout the airways.

Upon further investigation, the researchers found that the newly formed chemicals caused the cells lining the bronchi to die, even if the chemicals were at low concentrations. Prof Jordt commented: "This is the first demonstration that these new chemicals formed in e-liquids can damage and kill lung cells and probably do this by damaging their metabolism."

In addition to listing the original chemicals, Prof Jordt called for manufacturers to list the chemicals formed when the flavourings are mixed with solvents. Furthermore, he noted that additional research into the toxicological properties of these chemical products should be conducted, and regulators to be aware of their safety profile to assess the level of risk to health from e-cigarettes, with the aim for manufacturers to reduce the concentration of such chemicals in their product.

Heavy Metal Exposure in the Womb Associated With Childhood Asthma

CADMIUM is a heavy metal and its use is restricted in the European Union (EU) due to its known hazards to human health; however, exposure to cadmium can occur because it has been widely used in batteries and pigments, and is present in tobacco. According to new research presented at ERS International Congress 2020 and in a press release dated the 3rd September, higher concentrations of cadmium in the umbilical cord blood of newborns may increase the risk of developing childhood asthma and allergies.

In the study, the quantities of cadmium, manganese, and lead were measured in 706 females and their babies at the maternity units in Nancy and Poitiers in France. Blood samples were taken from the mothers during pregnancy and babies from their umbilical cord after delivery. During the 8-year follow-up period, the researchers noted if any of the children had developed asthma, allergic rhinitis, eczema, or food allergies, accounting for family medical history and smoking status of the parents.

At the time of delivery, the average level of cadmium in the mothers was 0.8 µg/L and in the cord blood was 0.5 µg/L. For cadmium, higher levels in the umbilical cord of babies (>0.7 µg/L) were associated with a 24% increased risk of developing asthma. Interestingly, lower levels of cadmium (<0.3 µg/L) were associated with a 44% increase in risk of developing a food allergy. Manganese levels were linked to risk of eczema, a known risk factor for developing asthma: levels of >1.1 µg/L in the mother's blood was associated with an increased risk of developing eczema, compared with levels <0.5 µg/L.

"Our study doesn't tell us why this might be the case, but it could be that cadmium is interfering with babies' developing immune systems and we think this can have an impact on their allergic reactions in childhood," hypothesised the research presenter Prof Isabella Annesi-Maesano, Institut national de la santé et de la recherche médicale (INSERM) and Sorbonne Université, Paris, France.

Prof Daiana Stolz, ERS Education Council Chair, University Hospital Basel, Basel, Switzerland, commented on the findings: "It's particularly worrying to know that cadmium and other metals might be reaching unborn babies via the umbilical cord." She added that this study, along with the already known dangers of cadmium, supports extremely tight regulations of the use and disposal of products containing heavy metals.

"It's particularly worrying to know that cadmium and other metals might be reaching unborn babies via the umbilical cord."

Novel App Measures Night-Time Coughing to Predict Asthma Deterioration

COUGHING at night, measured via a novel smartphone app, can indicate the severity of asthma progression according to research presented at ERS International Congress 2020 and a press release dated 25th August 2020.

"Smartphones have lots of potential to monitor different symptoms and detect changes early," stated research lead Dr Frank Rassouli, Cantonal Hospital St Gallen, St Gallen, Switzerland. The research group aimed to utilise technology and simple interventions to improve the management of chronic lung diseases such as asthma. Dr Rassouli noted that: "Until now, we haven't had a reliable tool for measuring peoples' asthma symptoms overnight, so we know very little about night-time coughing and what it means."

The study recruited 94 patients with asthma being treated at two Swiss clinics. Patients visited their clinics at the beginning and end of the study, where they were assessed on their usage of asthma treatments and symptoms, which included shortness of breath and the impact of asthma on their daily lives. For 29 days, patients slept with a smartphone in their bedroom and the app prompted them to report their night-time symptoms and measured the noise of their night-time coughing.

Analysis of the data showed that while there was a discrepancy in the amount of night-time coughing from patient-to-patient, there was a strong correlation between increased night-time coughing over the course of 1 week and subsequent worsening of asthma symptoms. "Our results suggest that night-time coughing can be measured fairly simply with a smartphone app and that an increase in coughing at night is an indicator that asthma is deteriorating," Dr Rassouli explained. He further stated that monitoring asthma is pivotal because early recognition of worsening symptoms would allow clinicians to adjust medication accordingly and prevent asthma attacks. This study showcases a potential new and easily accessible way to monitor signs of deteriorating asthma, and with this success the researchers are planning to test the same technology on patients with chronic obstructive pulmonary disease.

"Our results suggest that night-time coughing can be measured fairly simply with a smartphone app and that an increase in coughing at night is an indicator that asthma is deteriorating"

Low Levels of Air Pollution Linked to Asthma in Babies and Adults

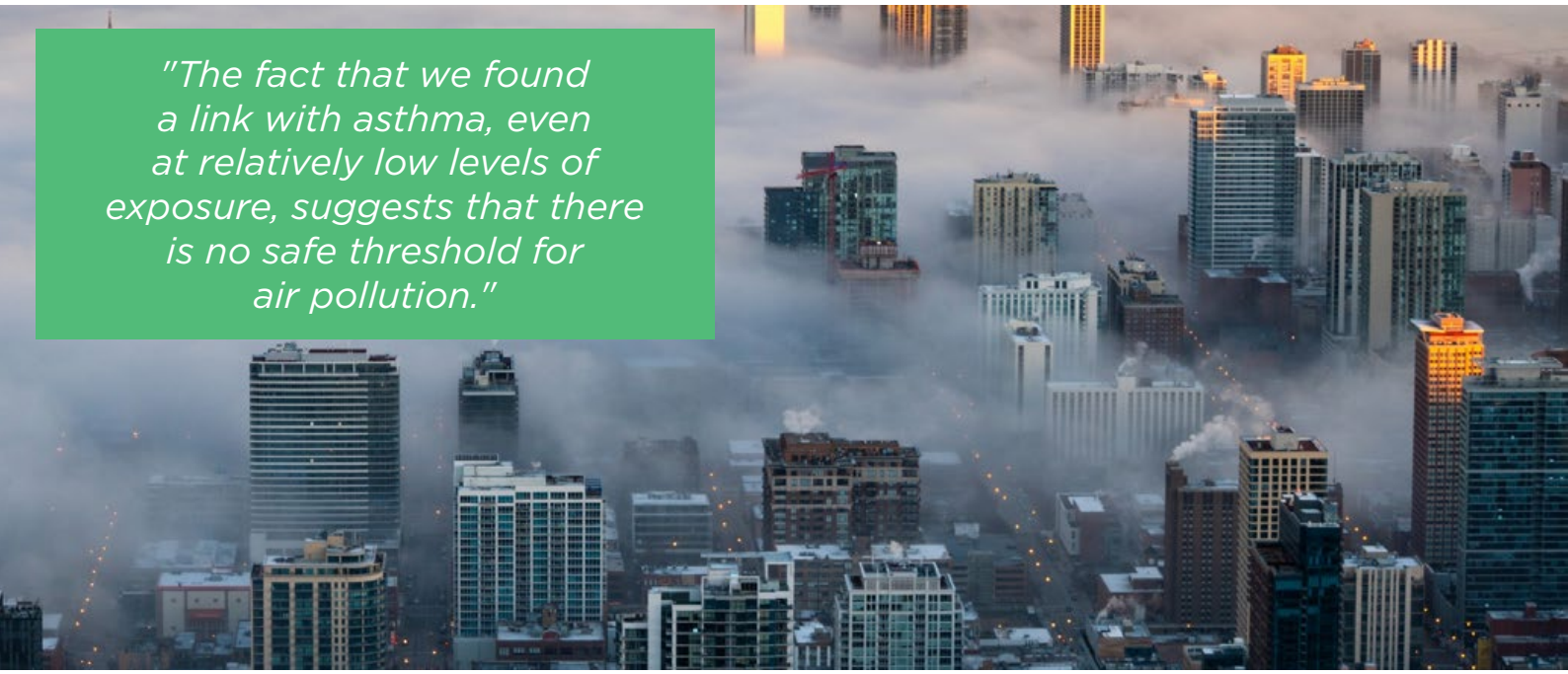
BABIES raised in areas of higher levels of air pollution develop poorer lung function as children and teenagers, and adults exposed to low levels of air pollution over a prolonged time are more likely to develop asthma. These findings from two studies were reported at the ERS International Congress 2020 and in a press release dated 25th August 2020.

In the first study, lead by Dr Qi Zhao, IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany, 915 children from Munich and Wesel in Germany were tested for their breathing capabilities at the ages of 6, 10, or 15 years. Forced vital capacity and forced expiratory volume in 1 second were measured and compared with estimates of the levels of pollution in the areas the children lived in their first year of life. Factors associated with poorer lung function, such as whether the children's mothers smoked, were considered. Results found that the higher the babies air pollution exposure was, the worse their lung function was when they grew up. Dr Zhao concluded that: "Our results suggest that babies who grow up breathing polluted air, even at levels below European Union (EU) regulations, have poorer breathing as they grow into children and adults. This is worrying because previous research suggests that damage to lungs in the first year of life can affect respiratory health throughout life."

A separate study found that adults were also at risk. The study, which analysed 23,000 Danish nurses, found a correlation between long-term exposure to air pollution and the likelihood of being diagnosed with asthma. Levels of nitrogen dioxide (NO_2) and particulate matter smaller than 2.5 microns ($PM_{2.5}$) were compared to the levels of road traffic noise where the nurses lived, accounting for factors including smoking and obesity. While no link was found to noise pollution, air pollution increased the likelihood of asthma diagnosis. A 29% rise in asthma risk was associated to each 6.3 µg/m³ increase in $PM_{2.5}$ and a 16% rise in asthma risk for each 8.2 µg/m³ increase in NO_2.

Compared to many European cities, the nurses were exposed to relatively low levels of air pollution; approximately 18.9 µg/m³ and 12.8 µg/m³ for $PM_{2.5}$ and NO_2, respectively, and current European standard for $PM_{2.5}$ and NO_2 are 25.0 µg/m³ and 40.0 µg/m³, respectively. Researcher Dr Shuo Liu, University of Copenhagen, Copenhagen, Denmark, asserted: "The fact that we found a link with asthma, even at relatively low levels of exposure, suggests that there is no safe threshold for air pollution. This is strong evidence that our regulations on air pollution need to be stricter if we want to prevent cases of asthma."

"The fact that we found a link with asthma, even at relatively low levels of exposure, suggests that there is no safe threshold for air pollution."



Lung Microbiome Fungal Diversity Linked to Disease Severity

FUNGI present in the lung microbiome may regulate the inflammatory response in acute respiratory distress syndrome (ARDS), with less diversity linked to poorer outcomes. A study of mechanically ventilated patients was presented at ERS International Congress 2020 and in a press release dated the 24th August 2020.

Despite being outnumbered by bacteria as a part of the lung microbiome, fungi are known to play a role in activating and regulating immune responses. Researchers at the University of Pittsburgh, Pittsburgh, Pennsylvania, USA, analysed 202 mechanically ventilated patients from October 2011 to September 2019; 21% had a diagnosis of ARDS. Next-generation sequencing of the DNA of the tracheal secretions of the patients revealed about 100 different species of fungi. Although species diversity was low in all of the samples, for those patients where one species dominated the samples, diversity was very low.

"it provides evidence for a relationship between the lung microbiome and clinical outcomes in critical illness."

ARDS was associated with very low species diversity; shock, sepsis, and organ failure were associated with lower fungal diversity among the patients with ARDS. Reduced diversity was found to be associated with more severe lung injury, more intensive treatment, and elevated levels of the protein pentraxin-3 (an indicator of inflammation and disease severity).

Noel Britton, University of Pittsburgh, an author of the abstract, highlighted the value of the study: "The association of lower fungal diversity with clinical markers of disease severity is an important finding because it provides evidence for a relationship between the lung microbiome and clinical outcomes in critical illness." Discussing the future implications of the findings, Prof Tobias Welte, ERS Past President, and Hannover University School of Medicine, Hannover, Germany, said: "The finding from this study, that less diversity in the mycobiome is linked to worse outcomes for patients with ARDS, is fascinating. It's too early to know what this might mean for patients and their doctors, but it has the potential to lead to new diagnostic tests and better treatments."

Electronic Alerts Improve Asthma Management

ELECTRONIC alerts can improve prescribing and asthma management in general practice. A UK study presented at ERS International Congress 2020 revealed the impact of an electronic alert system in general practitioner (GP) records.

Excessive prescription and use of short-acting reliever inhalers, such as salbutamol, can be an indicator of poorly controlled asthma, is a risk factor for asthma attacks, and has been implicated in asthma-related deaths. These short-acting reliever inhalers address asthma symptoms but do not improve the underlying inflammatory cause.

The study included 18,244 patients with asthma at 132 general practices in north-east London, UK, and involved adding an automatic, electronic alert that appeared on GP screens when accessing the electronic patient records for patients who had received three prescriptions for short-acting reliever inhalers within a 3-month period. The alert recommended an asthma review for the patient, to assess symptoms and improve asthma control.

This intervention resulted in a 6% reduction in excessive prescribing of reliever inhalers in the 12 months following the first inclusion of the alerts, with asthma reviews increasing by 12% in the 3 months after the alerts. Within 6 months of the alerts being introduced, repeat prescribing of short-acting β2 agonists reduced by 5% and exacerbations requiring oral steroid treatment reduced by 8%.

The value of these findings, and the intervention approach used, were highlighted by Dr Shauna McKibben, Institute of Population Health Sciences, Queen Mary University of London, London, UK, and clinical nurse specialist in asthma and allergy at Imperial College Healthcare NHS Trust, London, UK: "Excessive short-acting β2 agonists use is only one indicator for poor asthma control but the risks are not well understood by patients and are often overlooked by healthcare professionals. Further research into the development and robust evaluation of tools to support primary care staff in the management of people with asthma is essential to improve asthma control and reduce hospital admissions."

"Within 6 months of the alerts being introduced, repeat prescribing of short-acting β2 agonists reduced by 5% and exacerbations requiring oral steroid treatment reduced by 8%."

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References: 1. Chorostowska-Wynimko J. Disease Modification in Emphysema Related to Alpha-1 Antitrypsin Deficiency, COPD: Journal of Chronic Obstructive Pulmonary Disease. 2016;13(6):807–815; doi: 10.1080/15412555.2016.1178224. **2.** Chapman KR, Burdon JGW, Piitulainen E, et al; Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;386(9991):360–368; doi: 10.1016/S0140-6736(15)60860–1 **3.** Respreeza® SPC, May 2019, www.swissmedicinfo.ch **4.** Boerema DJ, An B, Gandhi RP, et al.; Biochemical comparison of four commercially available human α1-proteinase inhibitors for treatment of α1-antitrypsin deficiency. Biologicals. 2017;50:63–72. doi: 10.1016/j.biologicals.2017.08.010. **5.** Prolastin® SPC, July 2017, www.swissmedicinfo.ch **6.** Alfalastin® SPC, September 2018, http://agence-prd.ansm.sante.fr/php/ecodex/extrait.php?specid=60153239

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CMD-RPZ-0109

The Treatment of Severe Respiratory Disorders in Challenging Times

This industry symposium took place on 7th September 2020, as part of the virtual European Respiratory Society (ERS) International Congress 2020

Chairpeople: Tobias Welte,[1] Marco Idzko,[2] Timm Greulich[3]

Speakers: Michael Larbig,[4] Maria Sucena,[5] Felix Herth,[6] Robert Sandhaus,[7] Alice Turner,[8] Dave Singh,[9] James Chalmers[10]

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2. Department of Pneumology, Medical University of Vienna, Vienna, Austria
3. Department of Internal Medicine and Pneumology, University Hospital Marburg, Marburg, Germany
4. Clinical Pharmacology and Translational Development, CSL Behring, Bern, Switzerland
5. Pulmonology Department, Centro Hospitalar Universitário do Porto, Porto, Portugal
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7. Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, Colorado, USA
8. Institute of Applied Health Research, University of Birmingham, Birmingham, UK
9. Medicines Evaluation Unit, University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK
10. Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK

Disclosure: Prof Welte has received consulting fees for lectures and participating on advisory boards from CSL Behring, Biotest, Boehringer Ingelheim, AstraZeneca, Novartis, GlaxoSmithKline, Bayer, Pfizer, and Grifols; and has received research funding and participated in clinical trials as a principal investigator for Boehringer Ingelheim, GlaxoSmithKline, Novartis, Roche, Zambon, and AstraZeneca. Prof Idzko has received consulting fees for lectures from CSL Behring. Prof Greulich has received consulting fees for lectures and advisory boards from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, and Novartis; grants and consulting fees for lectures and advisory boards from Grifols; and grants from the German Centre for Lung Research (DZL), CSL Behring, Grifols, and Kamada. Dr Larbig is a full-time employee at CSL Behring AG, Switzerland. Dr Sucena has received consulting fees for lectures and participating in advisory boards from CSL Behring, Grifols, Boehringer Ingelheim, and Novartis. Prof Herth has received consulting fees for lectures and participation on advisory boards from Olympus, Pulmonx, BTG, Uptake, Broncs, BSI, and Erbe Elektromedizin. Prof Sandhaus receives a salary as the Medical Director of AlphaNet. Dr Turner has received grants from the Linde REAL fund Chiesi, AstraZeneca, the American Thoracic Society (ATS) Foundation, and the Alpha-1 Foundation; and nonfinancial support from GlaxoSmithKline and Boehringer Ingelheim. Prof Singh has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards, and research grants from various pharmaceutical companies including Apellis, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Johnson and Johnson, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Skyepharma, Teva, Theravance, and Verona. Prof Chalmers has received research grants from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Pfizer, Grifols, Bayer, Polyphor, and Insmed; and consultancy, congress travel, or speaker fees from GlaxoSmithKline, Bayer Healthcare, Aradigm Corporation, Grifols, Pfizer, Boehringer Ingelheim, Napp, and Insmed.

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Meeting Summary

Prof Welte opened the symposium by describing the key roles of hypercoagulation and inflammation in the course of severe coronavirus disease (COVID-19). This was complemented by Dr Larbig's talk that introduced CSL312, a new human monoclonal antibody targeting coagulation factor XIIa, which aims to target both hypercoagulation and inflammation. Prof Idzko followed with a discussion about the challenges of treating respiratory conditions such as alpha-1 antitrypsin deficiency (AATD) during the COVID-19 pandemic. Dr Sucena explained that many patients had been unable or unwilling to attend health centres to receive alpha-1 antitrypsin (AAT) therapy, putting them at risk of increased morbidity. In response, Prof Herth discussed the use of self-administered AAT to ensure that patients receive regular therapy. Prof Greulich described the difficulties in providing robust evidence for the positive impact of AAT therapy on mortality, and Prof Sandhaus introduced a recent observational study that overcomes some of these problems, with findings that suggest AAT therapy results in improved survival rates and a slower decline in quality of life (QoL). Finally, Profs Idzko, Singh, and Chalmers emphasised that better treatments are needed for other respiratory conditions, and introduced drugs that are currently under development to address this need; these include a new antibody intended to treat a broad range of the severe asthma population (CSL311; CSL Behring, King of Prussia, Pennsylvania, USA) and nebulised IgG to treat non-cystic fibrosis bronchiectasis (NCFB) (CSL787; CSL Behring). Overall, advances continue to be made in the treatment of severe respiratory conditions, despite the difficulties posed by the current COVID-19 pandemic.

Challenges of Treating Lung Disease Caused by COVID-19

Professor Tobias Welte and Doctor Michael Larbig

Prof Welte described COVID-19, caused by the new coronavirus strain severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as a disease that primarily affects the respiratory epithelium. The virus enters the bloodstream at an early stage and the course of COVID-19 is then dictated by damage to the vascular endothelium and vascular leakage.[1] This means that unlike classic acute respiratory distress syndrome, severe COVID-19 is more likely in patients with endothelial dysfunction, such as those with diabetes, obesity, or arterial hypertension, compared with patients with respiratory diseases in general.[1]

Repair mechanisms in the vascular endothelium can lead to hypercoagulation that may cause thrombosis, leading to pulmonary emboli and affecting gas exchange. Recent research has shown that capillary thrombosis is a major pathomechanism of severe COVID-19 disease at the microvascular level.[2,3]

Drugs currently under investigation for COVID-19 treatment fall into three groups:

- Antivirals, such as remdesivir, aim to reduce the viral load, which may drive the early stage of COVID-19.
- Anti-inflammatories aim to reduce the hyperinflammatory burden, which is a consequence of the host immune response to endothelial damage.[4] This immune response is driven by lymphocytes but also involves mediators such as cytokines.[3-6] Patients with severe disease have been shown to have very high concentrations of cytokines, suggestive of a cytokine storm.
- Anticoagulants, such as heparin, aim to counteract the coagulation recently shown to be involved in COVID-19 disease.[6-8] It remains

to be seen whether anticoagulants with more specific targets than heparin could be used to reduce right–left shunting on the pulmonary level, which would reduce hypoxaemia and the need for mechanical ventilation in severe COVID-19.[9] For example, CSL312 is a new drug that targets factor XIIa and is currently being tested in a Phase II clinical trial.[10]

Targeting Factor XII in COVID-19 Disease

Dr Larbig explained that factor XII becomes activated upon contact with damaged tissues, and in turn activates factor XIIa, which initiates the kallikrein–kinin system.[11] This results in inflammation, vasodilation, and capillary leakage, which can cause fluid accumulation in lung tissue.[11] Factor XIIa also triggers the complement system and the intrinsic coagulation cascade, which can lead to thrombosis (Figure 1).[10,11] In addition, *ex vivo* human lung tissue models have shown that factor XIIa has proinflammatory properties.[12]

Growing evidence suggests that vascular leakage, pathological thrombosis, proinflammation, and complement activation may play a role in COVID-19,[3,13,14] making factor XIIa a viable target for this disease. Human monoclonal antibody CSL312 has the potential to block the pathology triggered by activated factor XIIa, but to investigate whether it can influence disease progression in patients with severe COVID-19 disease, high-quality scientific data are needed. Despite the difficulties of conducting a controlled, randomised clinical trial during the current pandemic, investigators in many countries have shown that it is possible, and a placebo-controlled trial of CSL312 is currently underway in patients with COVID-19.[10]

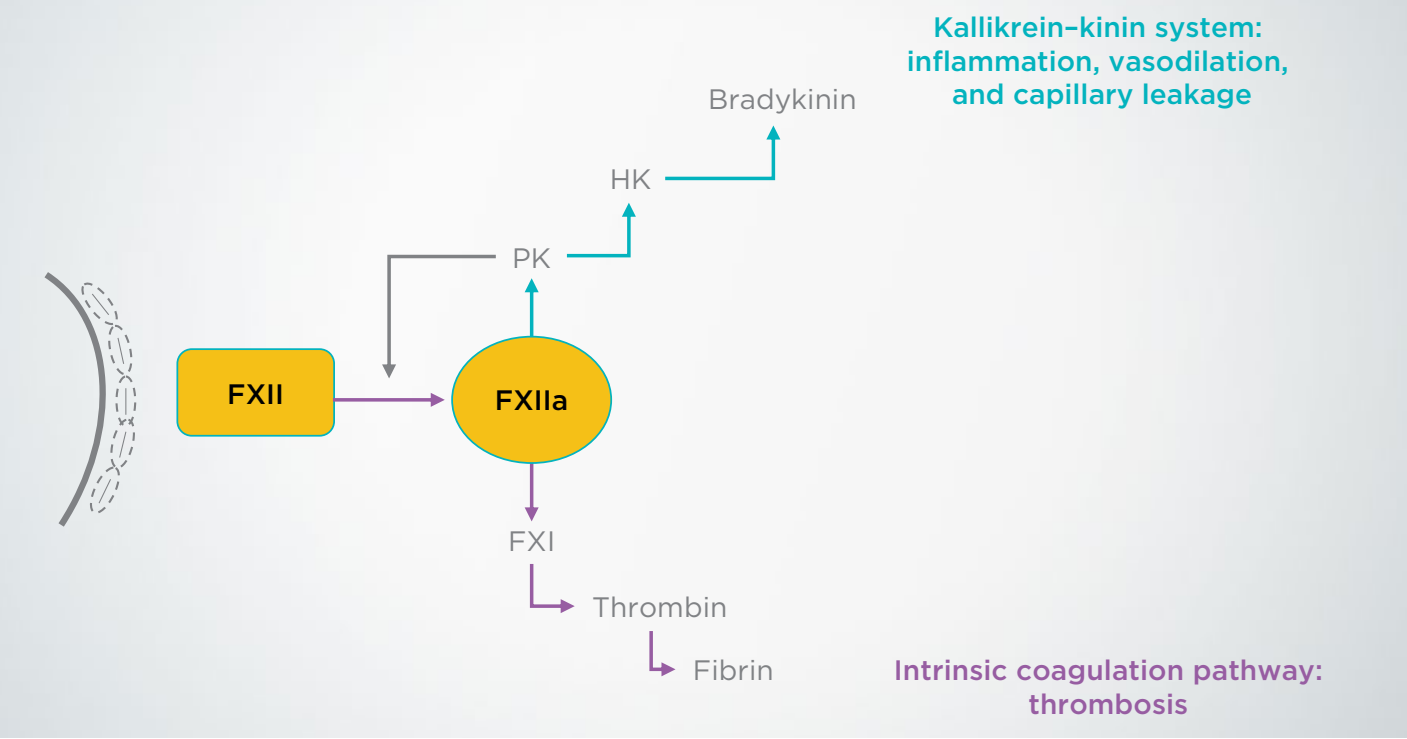


Figure 1: Mechanisms of action of factor XIIa on the immune system.

FXI: factor XI; FXII: factor XII; FXIIa: factor XIIa; HK: high molecular weight kininogen; PK: prekallikrein.

Adapted with permission from Weidmann et al.[11]

Questions and Answers

Q: When do you expect to see preliminary results from the CSL312 trial targeting COVID-19 patients with severe pneumonia?

Prof Welte explained that many studies are currently underway to investigate potential treatments for COVID-19, but that few drugs have been found to be effective. He believes that addressing the coagulation pathway is one of the most promising ways to treat COVID-19 and emphasised that preliminary data from the CSL312 trial should be available in early 2021.

Q: What is the biggest challenge in treating COVID-19 patients with severe pneumonia?

Prof Welte replied that these patients have hypoxaemia and most require mechanical ventilation. Unlike other respiratory infections, patients with a severe course of COVID-19 need ventilation for weeks rather than days, and this increases the risk for cardiovascular and renal complications as well as secondary infections.

Q: Do you have any recommendations for protecting medical staff from COVID-19?

Prof Welte explained that in his hospital, double-masking was introduced from the beginning of the pandemic, preventing hospital-acquired infections. He recommends that in outpatient situations, social distancing, the use of face masks, and regular disinfection of the hands should be used to minimise transmission of the virus, as for any infectious disease.

Treatment of Alpha-1 Antitrypsin Deficiency in Times of COVID-19

Professor Marco Idzko, Professor Timm Greulich, Doctor Maria Sucena, and Professor Felix Herth

Prof Idzko highlighted that the treatment of severe respiratory diseases, such as AATD, is challenging during the COVID-19 pandemic. While there is a need to protect medical staff by introducing additional safety measures for diagnostic procedures, such as the lung function test,[15] it is crucial to continue treating patients.

AATD is a genetic disease that results in reduced circulating levels of AAT (also known as α-1 protease inhibitor), a protein that protects lung tissue against the inflammatory enzyme neutrophil elastase.[16] Patients with AATD are more susceptible to infection and structural damage of the lung, as well as liver disease caused by hepatocyte inclusions formed from misfolded AAT.[16] Treatment options include regular AAT therapy to restore circulating levels of the protein.

Prof Greulich explained that although the risk of severe COVID-19 disease has not been assessed in patients with AATD, the fact that they are already severely ill means that they are more likely to have a poor outcome from COVID-19 than healthy patients. This makes it difficult to treat patients in many European countries because treatment is performed in health centres and attending these appointments will increase the risk of contracting SARS-CoV-2. In addition, the COVID-19 pandemic may restrict the resources available in these centres. If AAT therapy is interrupted, patients with AATD are at increased risk of lung infections, loss of lung density, and liver damage.[16]

Alpha-1 Antitrypsin Deficiency Treatment in Portugal During the COVID-19 Pandemic

Dr Sucena explained that the first case of SARS-CoV-2 infection in Portugal was confirmed on 2nd March 2020, and within a very short time frame, Portugal had to reorganise its national health service (Serviço Nacional de Saúde [SNS]) to focus on managing the COVID-19 pandemic. This meant that patients without COVID-19 had restricted access to hospitals and other health facilities: personal appointments were replaced with phone calls, day hospitals were closed or had their activities reduced, and bronchoscopies were only performed in urgent situations.

Although there were very few confirmed COVID-19 cases in patients with AATD in Portugal, Dr Sucena emphasised that the pandemic had

a major impact on patients across the country because AAT treatment is only available in public day hospitals. During the first few weeks of the COVID-19 pandemic, AAT therapy was often cancelled, or patients were referred to alternative centres. Where treatment was still available, some patients chose not to attend because of the perceived risk of infection.

Health facilities in Portugal began to reopen to patients without COVID-19 in early May 2020, but as SARS-CoV-2 still exists in the general population, the SNS must evolve to manage COVID-19 while also caring for other patients. The course of the COVID-19 pandemic over the next few months will dictate the availability of AAT therapy to patients with AATD.

Prof Greulich highlighted that other countries are likely to face similar problems. The cancellation of appointments for patients with AATD will have left healthcare professionals unsure of the best way to care for their patients. Although some face-to-face appointments can be replaced by virtual appointments, other approaches are needed for treatment.

Alpha-1 Antitrypsin Deficiency Self-Administration in Germany and Austria During the COVID-19 Pandemic

A proportion of patients with chronic diseases have always been unwilling to attend appointments in health centres because of infection risk anxieties, and this problem has been exacerbated by the COVID-19 pandemic. However, for patients with AATD who are unable or unwilling to attend health centre appointments, a human AAT therapy (Respreeza®, CSL Behring) is licensed in Europe for at-home self-administration.[17]

Prof Herth emphasised the importance of selecting the right patients for self-administration of AAT therapy. Patients need to be physically and mentally fit, without significant comorbidities, and they should have the necessary motivation to learn how to self-administer their treatment. Prof Herth explained that in his preselected population, self-administration is suitable for 30–50% of patients with AATD. Many of these patients have been receiving intravenous AAT therapy for several years and are already familiar with the procedure. Training suitable patients is the next step, and guidance and support is offered for this process, including guidelines to help patients learn the required techniques (Figure 2).

Prof Herth explained that the use of self-administered therapy by his patients guaranteed that they would receive their treatment on time every week, which has been extremely helpful during the COVID-19 pandemic.

Questions and Answers

Q: What is the legal situation for AAT therapy self-administration?

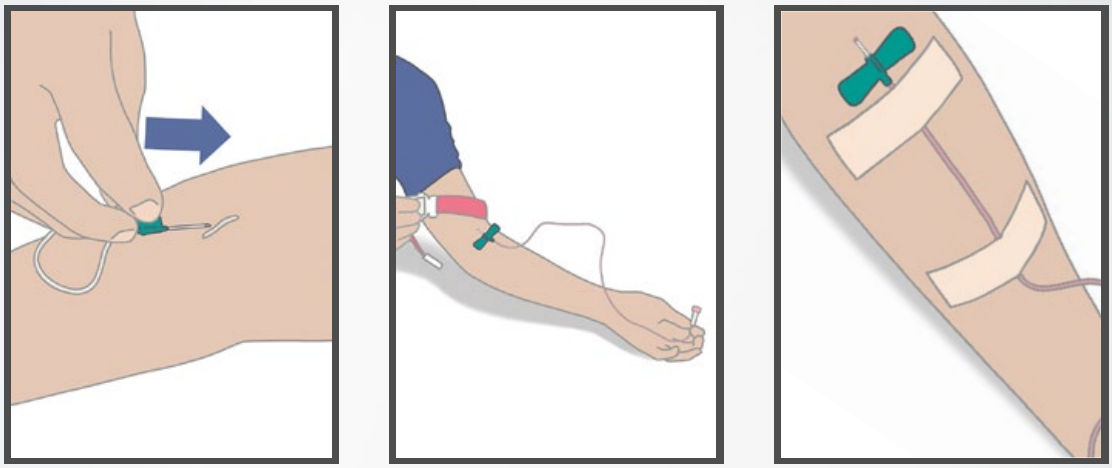
Prof Herth advised healthcare professionals to conduct well-documented, thorough training to protect staff legally.

Q: How many training sessions do you think are required for AAT therapy self-administration?

Prof Herth explained that this varied depending on the patient; for some, one training session might be enough, but generally about three sessions are required. If patients are still uncertain about the techniques, they can perform their initial infusions under the supervision of a healthcare practitioner in a medical centre.

Q: What, if any, adverse events might occur during AAT infusion?

AAT therapy has been used for many years, and for this reason, Prof Herth explained, physicians know that adverse events are unusual. Provided that patients have undergone adequate training, self-administration at home is as safe as administration in a health centre. Should an adverse event occur at home, the patient can stop the infusion.



Key points:

- Work under aseptic conditions
- Reconstitute the concentrate
- Infuse the drug appropriately
- Take care of the infusion site and veins
- Document the infusion

Figure 2: Part of a step-by-step training guide for self-administration of alpha-1 antitrypsin therapy.

The Impact of Alpha-1 Antitrypsin Deficiency Therapy on Mortality

Professor Timm Greulich, Professor Robert Sandhaus, Doctor Alice Turner, and Professor Tobias Welte

With many patients with AATD going untreated during the current pandemic, it is important to consider the impact that AAT therapy has on their overall mortality. Prof Greulich explained that an early study of AATD mortality using the National Heart, Lung, and Blood Institute (NHLBI) registry in the USA indicated that patients (N=1,129) who received intravenous AAT therapy had a lower risk of mortality compared with those who did not receive therapy (risk ratio: 0.64; 95% confidence interval: 0.43–0.94; p=0.02).[18]

More recently, an international, double-blind, randomised, placebo-controlled trial (RAPID) was conducted in 2015 to compare lung density in patients with AATD (N=180) who received AAT therapy with those treated with placebo.[19] Over the 2-year study period, only four deaths were reported: one in the AAT group and three in the placebo group. The small number of patients in this study makes it difficult to derive important findings regarding mortality; a comparative study of mortality in patients with chronic obstructive pulmonary disease (COPD), for example, included >6,000 patients.[20] To overcome this problem, more recent studies have used retrospective national registry data from around the world to investigate outcomes in patients receiving AAT therapy.

A Comparison of Outcomes Between AAT-Naïve and AAT-Treated Patients with AATD-Related Lung Disease Using Retrospective Data

Prof Sandhaus introduced a recent observational study that compared mortality, lung transplantation, and QoL data between matched patients with AATD-related lung disease in UK and USA national registries.[21] Patients in the UK registry were treated with standard of care (control cohort), while those in the USA received standard of care plus plasma-derived intravenous AAT therapy (AAT cohort).[21]

Dr Turner explained that inclusion criteria included evidence of lung disease, *PiZZ* genotype (a homozygous substitution of lysine for glutamic acid at position 342) or worse AATD genotype, and age >18 years.[21] Patients were matched by age, sex, baseline year, and smoking status.[21] After matching, each cohort consisted of 655 patients, with a mean age of 52 years and a male predominance of approximately 60% in each group.[21] Median follow-up time was 7 years in the control group, and 9 years in the AAT group.[21] Approximately 6% of patients in each cohort received a lung transplant during the study period, and 193 of the control group died versus 167 of the AAT group (p=0.122).[21]

Kaplan–Meier analysis showed a statistically significant difference in overall survival between the two cohorts, with a 10-year survival probability of 68.5% in the control group and 80.0% in the AAT group (p<0.001).[21] Among patients who received a lung transplant during the study period, those in the control group were likely to undergo surgery sooner, with a median time to lung transplant of 5 years, compared with 13 years in the AAT group (p<0.001).[21] Because lung transplant is an important life event, Dr Turner stressed that delaying the need for surgery is a potential indicator of delayed disease progression.

Observational data has inherent limitations, such as confounding comorbidity and immortal time bias. For example, patients could have started AAT therapy many years before the AATD registry existed, and this treatment period would not be represented in the data. Respective analyses are being conducted on the data gathered for this study to address some of these issues.

One post hoc analysis that has already been performed is the assessment of QoL. Prof Sandhaus explained that any truly disease-modifying therapy might influence this outcome. By looking at QoL measured by the St. George's Respiratory Questionnaire (SGRQ) over a specific time frame, immortal time bias can be eliminated, and to a large extent, one can control for the impact of factors like baseline forced expiratory volume in 1 second (FEV_1) and comorbidities on this outcome. Upcoming data from this analysis indicate that QoL in patients who received AAT therapy declined more slowly than in controls.

Despite this study not fulfilling the criteria of a randomised clinical trial, it provides encouraging data on the positive impact of AAT therapy in patients with AATD. When the findings are translated to median life-years gained, an outcome commonly measured in clinical trials, patients receiving AAT therapy were found to gain around 6 life-years compared with controls. This is similar to data from a post hoc analysis of the RAPID trial, which indicate that AAT therapy may result in a gain of about 5.5 life-years, as measured by time to terminal respiratory failure estimated from the average group lung tissue atrophy.[19]

Questions and Answers

Q: What other investigations are planned to further investigate the impact of AATD treatment on mortality in the real world?

Prof Greulich described the European Alpha-1 Research Collaboration (EARCO),[22,23] a new European Respiratory Society (ERS) Clinical Research Collaboration, which aims to collect international data from approximately 3,000 patients with AATD over the next few years. He explained that baseline data should be available in the near future, and longitudinal data will be available after 3–5 years, depending on funding. EARCO will provide the opportunity for researchers to match patients using a variety of baseline characteristics to minimise bias.

Development of Specialised Treatments for Severe Respiratory Conditions

Professor Marco Idzko, Professor Dave Singh, and Professor James Chalmers

While AAT therapy is effective at treating lung disease in patients with AATD, Prof Idzko emphasised that there remains an unmet need in other respiratory conditions, such as severe asthma and NCFB.

Targeting the Different Immunological Phenotypes of Severe Asthma

In the vast majority of patients with asthma, symptoms can be controlled with combination therapy of inhaled steroids and either long-acting muscarinic antagonists or long-acting β agonists.[24] However, around 5–10% of patients have a severe form of asthma that cannot be controlled without maximal inhalation therapy.[24] These patients experience considerable morbidity and account for approximately 50% of the total healthcare cost associated with asthma.[25]

Prof Idzko explained that progress has been made in identifying the immunological phenotypes of severe asthma over the past year. It is now possible to discriminate between allergic/nonallergic Th2 cell high (Th2-high) eosinophilic asthma, which is characterised by increased levels of eosinophils in the blood and sputum, but normal neutrophil counts, and Th2-low neutrophilic asthma, which is characterised by elevated levels of neutrophils.[26]

The improved understanding of immunological phenotypes has led to the development of new, targeted therapies for both allergic and nonallergic Th2-high eosinophilic asthma, with a particular focus on IL-5 pathways.[26] However, Prof Idzko highlighted that these therapies are not always effective, and treatments for patients with Th2-low neutrophilic asthma have yet to be developed.

Prof Singh highlighted that granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5 all play an important role in the maturation of a broad range of inflammatory cells, including eosinophils and neutrophils.[27] All three cytokines are expressed at higher levels in the lungs of patients with asthma compared with controls. The fully human IgG4-κ monoclonal antibody (CSL311) is currently in drug development, which specifically targets the β common chain in the receptors for GM-CSF, IL-3, and IL-5, and could result in a broad range of anti-inflammatory activity.[27,28] Compared with treatments currently used in clinical practice, CSL311 may be better placed to treat the broader severe asthma population, and a Phase I trial of CSL311 in patients with mild asthma is now underway, with results expected in 2021.[28,29]

Questions and Answers

Q: If we develop drugs that act on the broad range of severe asthma, will we still need to phenotype our patients?

Prof Idzko emphasised that although CSL311 could be effective in a broad severe asthma population, it is still important to look for phenotypic biomarkers such as eosinophils, IgE levels, and exhaled nitric oxide levels. Asthma therapy, both now and in the future, should always be personalised to the characteristics and phenotype of each patient.

Q: Some patients with severe asthma experience considerable limitations in their daily life. Could new treatments such as CSL311 improve QoL as well as exacerbation rates?

Prof Idzko explained that any treatment that reduces asthma exacerbations would be expected to improve QoL. However, measuring this outcome in clinical trial conditions will require long study periods with detailed questionnaires.

Reducing the Frequency of Exacerbations in Non-cystic Fibrosis Bronchiectasis

Prof Idzko highlighted that NCFB is another respiratory disorder that is challenging to treat. NCFB is defined as the irreversible, pathological dilation of the bronchi, and is characterised by recurrent infection, inflammation, persistent cough, and sputum production.[30]

Prof Chalmers explained that the therapeutic goal in NCFB is to prevent exacerbations, or to treat them early when they do occur to prevent further lung damage. Exacerbations are driven by bacterial infection, which also promotes neutrophilic inflammation that can lead to structural lung damage.[30,31]

In patients who experience frequent exacerbations, the ERS guidelines provide a conditional recommendation for the long-term use of antibiotics.[32] However, there is limited evidence to support this approach,[32] and the development of antibiotic resistance is a major problem. Prof Chalmers emphasised that there is a need for additional therapies, and one

drug under investigation for NCFB is nebulised IgG (CSL787).

The proposed primary mode of action for CSL787 is prevention of exacerbations by reducing bacterial burden in the lungs. CSL787 may also enhance local immunity, with the potential to protect the lung from infection. Phase I studies are now being prepared to investigate the use of nebulised IgG to prevent chronic respiratory tract infection and the progression of lung disease.

Summary

Despite the challenges of providing routine healthcare and conducting clinical trials during the current COVID-19 pandemic, advances continue to be made in the development of drugs to treat severe respiratory conditions.

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Successful Inhalation Therapy in 2020: Patients and Inhalers in Focus

This symposium took place on 7th and 8th of September 2020, as part of the virtual European Respiratory Society (ERS) International Congress

Chairpeople: Eric Bateman[1]

Speakers: Eric Bateman,[1] Klaus Rabe,[2,3] Lauri Lehtimäki,[4,5] Omar Usmani[6,7]

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Meeting Summary

Currently, there are many different inhaler options for the treatment of airway diseases. While having options can be of benefit, it also presents a challenge for physicians and other healthcare providers (HCP). Selecting the correct drug and dose is only one-half of their role; they also need to be sufficiently familiar with each device to be able to select the best option for each patient, as well as correctly advising patients on their use, as errors with inhaler use adversely affect the success of treatment. Understanding the key principles in device technology will help clinicians to navigate this field.

In the first presentation, Prof Rabe considered the selection of treatment in patients with chronic obstructive pulmonary disease (COPD) and discussed which patients are most likely to benefit

from the use of inhaled corticosteroid (ICS). He noted that the largest effect size in exacerbation reduction was achieved in patients with higher levels of blood eosinophilic component and/or a past history of asthma.

Prof Lehtimäki then provided an overview of inhaler device technology, environmental factors relating to their manufacture and disposal, and the application of digital technology to improve inhaler use and patient adherence. Because of the high greenhouse gas potential of propellants in pressurised metered-dose inhalers (pMDI), their carbon footprint is estimated to be 10–37 times higher than that of dry powder inhalers (DPI). Digital solutions will help to assess patient adherence and inhalation quality in the future.

Next, Dr Usmani discussed inhaler device handling errors and how to avoid them. During the last 40 years, handling errors have not decreased, and many HCP are thought to be overwhelmed by the plethora of devices and drugs on offer. Education in the correct use of devices for both trainers and users is paramount to the success of inhalation therapy. Important advice includes avoiding the prescription of different devices to the same patient, and to favour combination products to avoid multiple inhalers.

Finally, Prof Bateman reviewed the rationale and evidence for maintenance and reliever therapy, and in particular the value of the anti-inflammatory effect of ICS doses taken when symptoms occur. This approach, when compared with similar or even higher maintenance doses of ICS with a short-acting β-agonist (SABA) reliever, has been consistently associated with lower exacerbations rates.

Why Do Some Patients with Chronic Obstructive Pulmonary Disease Benefit from Inhaled Corticosteroid Treatment?

Professor Klaus Rabe

Prof Rabe first showed the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) initial treatment guidelines and explained the reasoning behind the recommendation to consider ICS treatment for patients with a blood eosinophil count >300 cells/µL. An analysis by Harries et al.[1] summarised the effect of ICS on COPD in 12 clinical studies. While the overall effect size was positive, there were a few outliers. It transpired that the higher the eosinophil threshold selected in each trial, the larger the effect size; this explained the difference between the studies. The conclusion was also supported by clinical trials on triple combinations, in which patients with a blood eosinophil count of >300 cells/µL were most likely to benefit from the addition of ICS.[2-6] Prof Rabe concluded that ICS treatment must be personalised and based on clinical and biological markers. Markers strongly supporting inclusion of ICS in treatment are two or more hospitalisations for exacerbations per year despite appropriate long-acting bronchodilator therapy, a blood eosinophil count >300 cells/µL, and history or current diagnosis of asthma. ICS treatment may also be considered in patients with only one moderate exacerbation per year and a blood eosinophil count of 100–200 cells/µL. However, it should be avoided in patients experiencing repeated pneumonia events, those with a blood eosinophil count <100 cells/µL, and those with a history of mycobacterial infections.[7]

Key Features of Inhaler Device Technology

Professor Lauri Lehtimäki

Prof Lehtimäki then led the discussion on the relevance of inhaler technology for patients. Particle size and inhalation flow are the two factors that affect particle deposition within the respiratory system. Smaller particles are more likely to travel deeper into the lungs as they more easily follow the streamlines of the inhalation flow. However, particles that are too small are ineffective as they are not deposited within the time of inhalation and are exhaled. With fixed particle size, a higher flow rate leads to more central deposition than lower flow rates.[8] In real life, all device-formulation

combinations are optimised for specific inhalation manoeuvres and patients should follow the manufacturer's instructions.

There are three main types of portable inhaler devices. DPI come in prefilled and capsule-based variants and rely on the patient's inspiratory effort to disaggregate the drug particles from large lactose carriers. In general, the higher the resistance of the inhaler's flow channel, the lower the required inhalation flow is. With the medium-high and high-resistance inhalers, the required inhalation flow is generally only 30 L/min.[9] The benefit of using inhalation flow for drug dispersion is that the patient can prepare the inhaler for actuation and then inhale when they are ready, without the need to co-ordinate these events. In pMDI, propellant gas is utilised to aerosolise the drug solution or suspension. They require the patient to co-ordinate the actuation and inhalation for successful drug delivery. Spacers are often needed for optimal dosing, but different brands have been shown to affect dosing differently.[10] There are also some models that are breath actuated. Soft mist inhalers create small droplets from solution via a mechanical apparatus rather than pressurised gas. There are many factors to consider when designing an inhaler, but the ideal inhaler device should be:

- effective
- efficient
- engaging
- error-tolerant
- easy-to-teach
- easy-to-switch-to
- environmentally friendly.

Prof Lehtimäki provided some practical tips on how to choose inhaled medication for the patient. The first was to define the pharmacological interventions required and to choose the drug class accordingly. Next was to discuss, try, and confirm with the patients the inhaler they are able to use and most comfortable with. Using more than one different type of inhaler increases the risk of inhaler errors;[11,12] therefore, it is best to select a device type that can offer as many of the drugs needed as possible. It is paramount to always teach and check inhaler technique.

Novel devices with digital integration or add-ons are now entering the market. In the future, they will help clinicians to assess whether poor treatment results are attributable to poor adherence or lack of efficacy, as well as help the patient to play a more active role in their own treatment. The ideal digital aide should remind the patient to take their medication, monitor inhalations, and check the patient's inhalation technique. As an example, Figure 1 shows the components of the Easyhaler® (Orion Pharma, Espoo, Finland) DPI connected to the Propeller sensor and platform. The sensor attaches to all Easyhaler products and pairs with the Propeller mobile app.

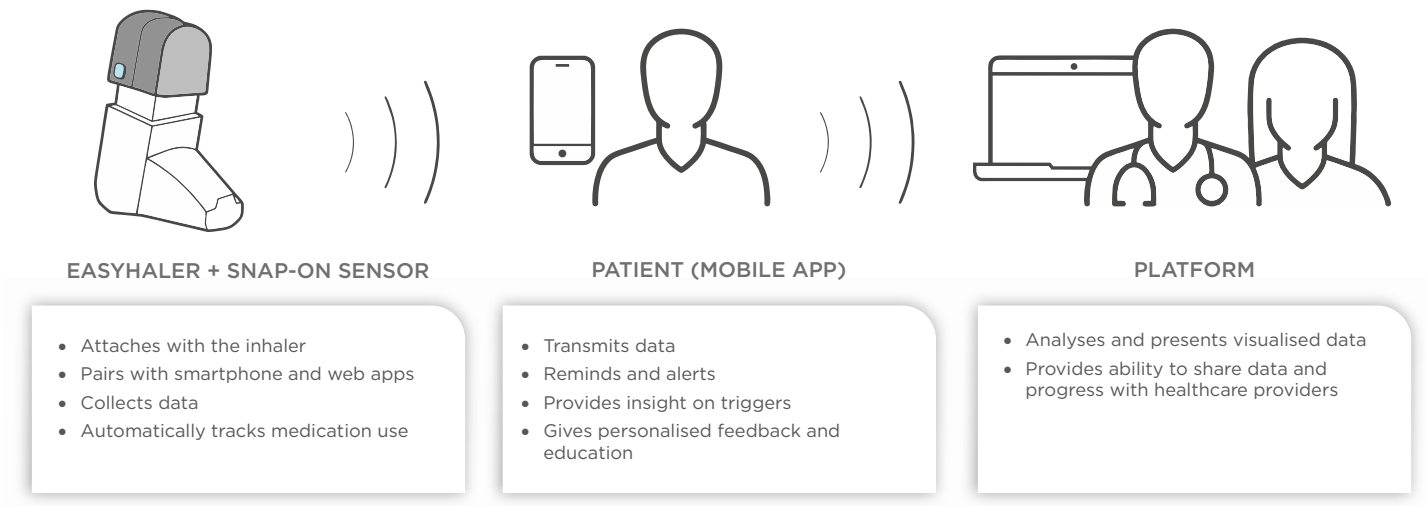

Figure 1: Schematic presentation of digital aide integration to mobile platform.

The platform provides the patients and caregivers with an opportunity to monitor adherence and to receive reminders when it is time to take a dose. The platform also provides personalised feedback and insight on triggers. Finally, HCP can access a portal to view patient data and ultimately make better informed therapeutic decisions. The use of such digital platforms has been shown to improve both patient adherence and asthma control.[13,14]

Patients, prescribers, and manufacturers are increasingly aware of the environmental impact of inhalation therapies. There are large variations between different inhaler devices in this respect. According to Montreal Protocol Medical and Chemicals Technical Options Committee (MCTOC) 2018 Assessment Report,[15] pMDI have a 10–37 times higher carbon footprint compared to DPI. This conclusion was supported by an analysis by Janson et al.[16] for selected marketed inhalers.[15] Changing from a pMDI to DPI has almost the same impact on personal carbon footprint as changing to a plant-based diet or switching from gasoline to a hybrid car. As an example, breakdown of carbon footprint of Easyhaler DPI is provided in Figure 2.[17] The difference between DPI and pMDI arises largely from the propellants used in pMDI devices. While original ozone-depleting chlorofluorocarbons have been phased out, modern hydrofluoroalkane propellants are still extremely powerful greenhouse gases.[8] The patient's ability to use the inhaler, their preferences, and efficacy of the medication are the most important factors in selecting inhaled medication, but environmental aspects of the device are emerging as a factor in treatment selection.

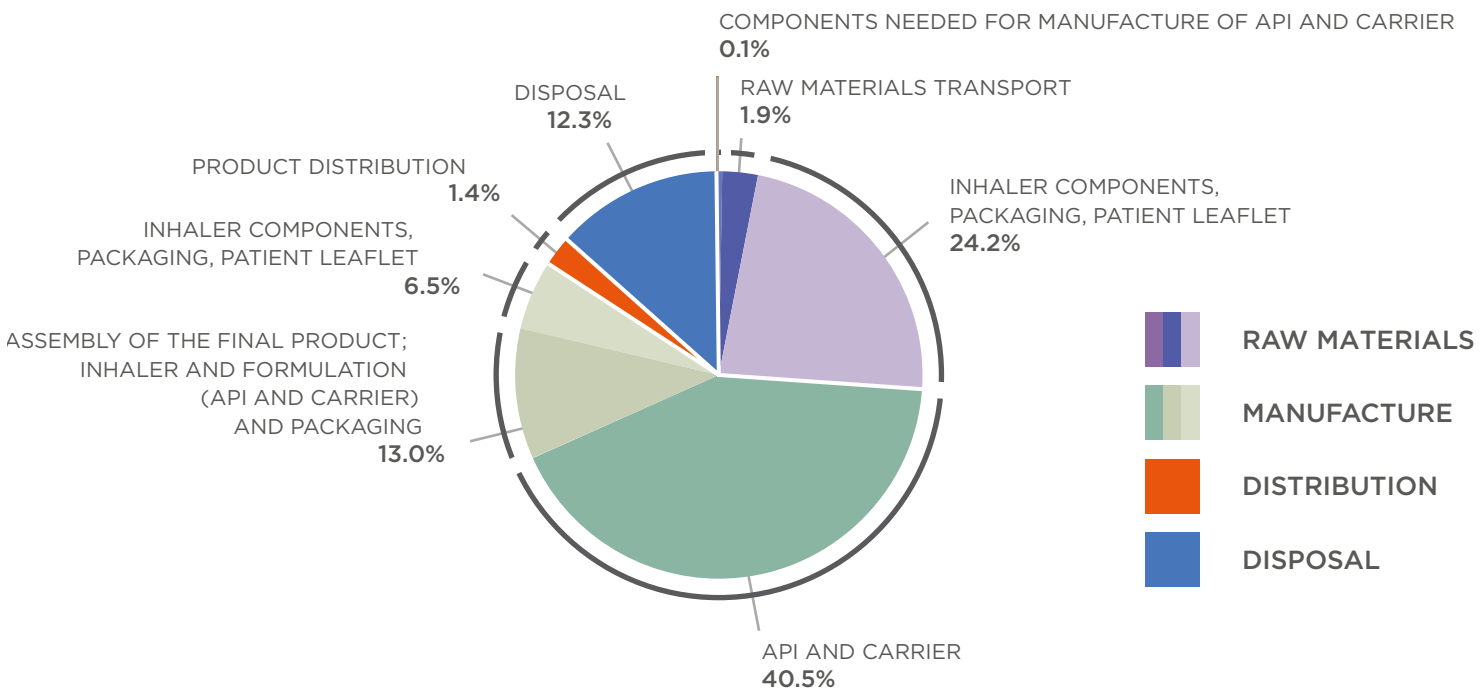

Figure 2: Breakdown of Easyhaler® (Orion Pharma, Espoo, Finland) carbon footprint according to raw materials, manufacture, distribution, and disposal.

Total cradle-to-grave life cycle emissions for one Easyhaler (average) is 0.588 kg CO_2e.

Average of the four Easyhaler products (salbutamol, formoterol, salmeterol-fluticasone, and budesonide-formoterol Easyhaler). For each, the most used strength and number of doses per product was used for this analysis. Analyses were performed in accordance with ISO 14040 and ISO 14044 and verified by external carbon footprinting company (Carbon Footprint Ltd., Basingstoke, UK).

API: active pharmaceutical ingredient.

Adapted from Orion.[17]

Trainers and Trainees: How to Ensure Successful Inhalation Treatment for Patients?

Doctor Omar Usmani

Dr Usmani began his talk with an overview on inhaler development. However, the technological advances have not translated to more proficient use. A systematic review by Sanchis et al.[18] showed that despite the advances in technology, the correct inhaler technique by the patient has been stagnated at approximately 30% for the past 40 years. However, the lack of inhaler knowledge is not only limited to the patients, but is also evident in HCP.[19] Plaza et al.[20] studied the inhaler technique of physicians, respiratory therapists, and pharmacists and found the success rate of HCP to be only 12%. Even though the inhaler device is essential to the treatment of pulmonary patients, respiratory doctors get very little or no training in the devices. Still, both the Global Initiative for Asthma (GINA) and GOLD treatment guidelines stress the importance of inhaler technique and adherence in the assessment of the patient.[21,22] While it is generally agreed that inhaler errors are a problem, there is no consensus on the definition, which has been illustrated in a systematic review by Usmani et al.[23] that found 299 descriptions of inhaler errors.

Different types of inhalers vary in how challenging the required inhalation manoeuvre is. Figure 3 shows results of a study conducted in the UK on patients with asthma in a primary care setting.[24] Over 90% of the patients were able to achieve sufficient flow rates even for high-resistance inhalers, but >30% of the patients who used a pMDI were inhaling too forcefully. In conclusion, almost everyone was able to use a high-resistance DPI, but a significant portion of the patients using pMDI were not able to use their inhaler correctly, even after teaching and coaching by HCP.[24]

British inhaler treatment guidelines promote the 'ACT'-method for device selection.[25] Firstly, when prescribing inhaled medications, the HCP should **A**ssess whether the patient is able to inhale quickly, deeply, and forcefully (DPI) or slowly and steadily (pMDI, soft mist inhalers, or breath-actuated inhaler). The inhaler type that is better suited for the patient is then **C**hosen. Inhalers have considerable environmental impact and when it does not compromise the treatment, it should be considered when choosing the device for the patient. Lastly, the patient should be **T**rained to use their device with placebo inhalers and materials should be given so the patient can revise the technique. It is also essential to check and correct the patient's inhalation technique at every opportunity.

A patient's inhalation technique can be estimated using seven steps:

1. Preparation

- Check dose counter
- Shake inhaler if instructed

2. Priming

- Prime the device ready for use

3. Exhaling

- Exhale gently away from the mouthpiece

4. Mouth

- Place the mouthpiece in mouth, tilt the chin, and close lips tightly around the mouthpiece

5. Inhalation

- DPI: quick and deep
- pMDI: slow and steady

6. Breath holding

- Remove inhaler from mouth and hold breath for up to 5 seconds

7. Closing and repeating

- Close the inhaler/cap
- Repeat if necessary

Finally, Dr Usmani gave some practical tips for the clinicians. Firstly, the inhaler device should not be changed without talking to the patient. Doyle et al.[26] showed that switching without consent may diminish self-control, which is associated with better asthma management. Secondly, inhaler devices should not be mixed.

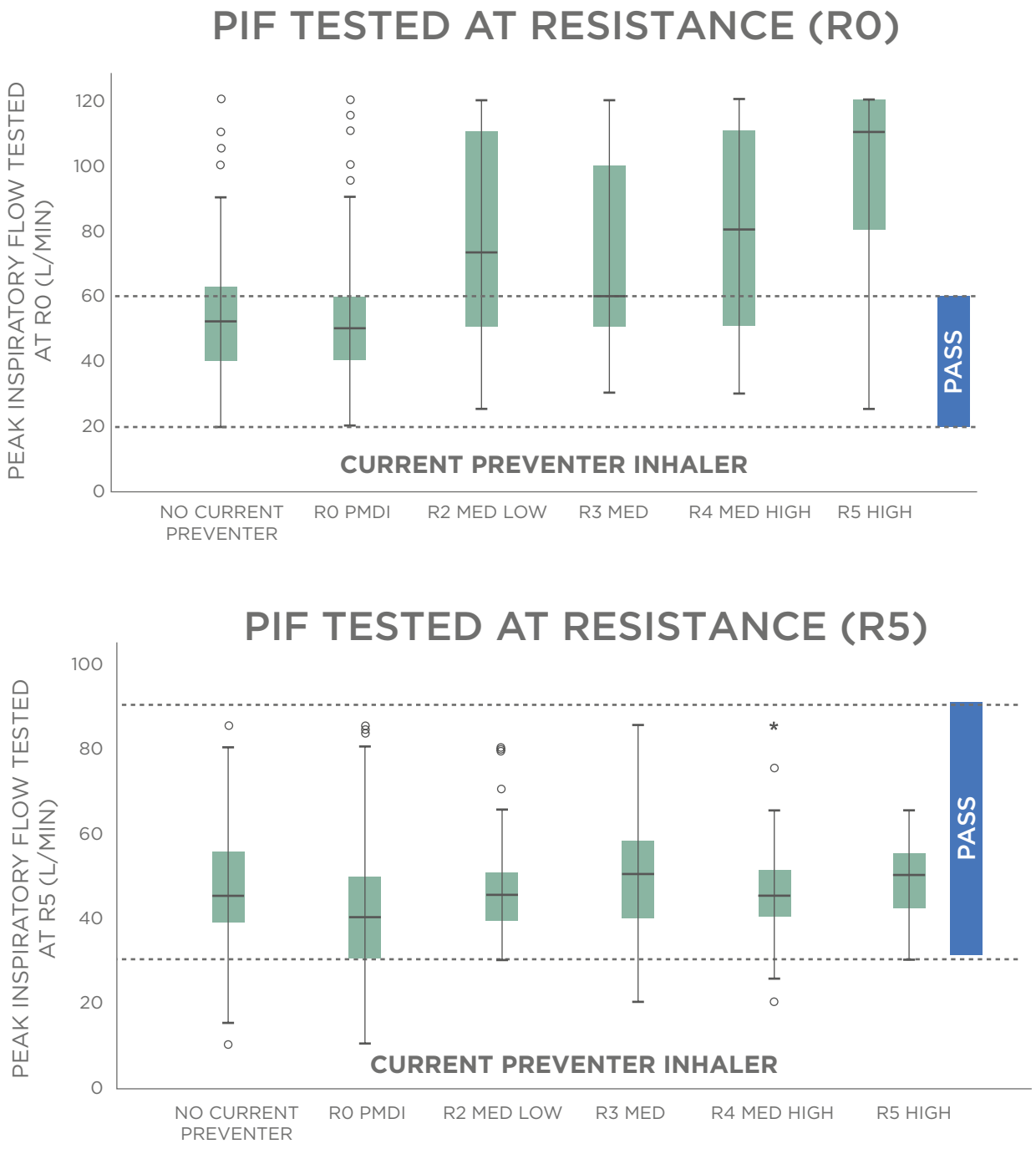

Figure 3: Measured inspiratory flows with pressurised metered dose inhalers and high dry powder inhaler resistances.

MED: medium; PIF: peak inspiratory flow; pMDI: pressurised metred dose inhalers.

Adapted from Haughney et al.[24]

For patients with asthma or COPD it has been shown that the disease control worsens and exacerbations are more common in patients with inhalers needing different inhalation techniques.[11,12] At least, the inhaler selection should be stratified to the same type of device. Thirdly, patients' inhaler technique should be checked at every opportunity and fourthly, HCP need to train themselves. The most expensive inhaler is the one not used, or taught, correctly.

Changing Perceptions and Improving Asthma Outcomes: Spotlight on Maintenance and Reliever Therapy

Professor Eric Bateman

Prof Bateman described patient factors that influence adherence to ICS treatment in asthma.[27] Paramount among these were the patient's beliefs about the necessity for treatment and concerns about the safety of the treatment. Acceptance of the necessity for treatment with low concern about safety was associated with the highest adherence rates, whereas indifference or scepticism with or without concerns about safety led to low adherence. Additional factors for some patients are perceived social stigma or embarrassment about inhaler use, and fear of addiction.[28] In a large European survey of patient attitudes to asthma treatment, fewer than one-half of the patients reported taking their inhaler every day, and most reported taking it on some days and not on others, or only when symptoms occurred.[29] The problem of nonadherence with controller treatment results in many patients relying entirely on SABA taken as-needed, living with high levels of symptoms, and at risk of asthma attacks.[30] In addition, regular (four times daily) SABA use has been shown to increase airway hyperresponsiveness and worsen eosinophilic inflammation compared to regimens that include an ICS.[31] In national surveys, the prescription of three or more canisters of SABA per year has been associated with increased risk of exacerbations and even of asthma deaths.[32] This is explained in part by reliance and escalating use of SABA and an associated delay in seeking medical care.[33] Remote detection of excessive SABA use as a trigger to timely medical interventions is a potential application for novel digital platforms currently under development.

An alternative approach to reliever use, now recommended as the preferred option in the 2019 and 2020 GINA guide, is the use of an ICS/formoterol combination inhaler. The basis for this is that increasing symptoms in asthma usually reflects worsening airway inflammation, indicated, for example, by an increased level of exhaled nitric oxide.[34] In experimental rhinovirus infection in patients with moderate asthma, symptoms of the common cold peak at Day 5, and asthma symptoms at Day 7.[35] The latter are associated with large increases in cytokines, reflecting Type 2 inflammation: IL-4, IL-5, and IL-13. The prompt administration of the ICS-containing reliever (effectively an 'anti-inflammatory reliever') ensures that both symptoms and the cause of symptoms are addressed, as well as preventing severe exacerbations.[36] This effect is evident in analyses of exacerbation risk in the days following reliever use: high symptom-prompted reliever use is an indicator of high exacerbation risk. This is considerably reduced if the reliever contains an ICS.[37] The level of day-to-day asthma symptom control with this regimen is similar to that of the fixed maintenance dose plus SABA regimens.[37] On the basis of four recent clinical trials on the use of as-needed ICS/formoterol without daily controller, this treatment is now recommended by GINA as the preferred approach in mild asthma. In the 'real-life' NOVEL START study, patients using an anti-inflammatory reliever required fewer courses of oral glucocorticoids, and had a lesser need of urgent medical care than both those taking SABA as-needed alone, and patients who received low-dose maintenance budesonide plus SABA as-needed.[36] Prof Bateman concluded with the reminder that exacerbations occur in all severities of asthma and that maintenance and reliever treatment leverages normal patient behaviour when faced with symptoms. Use of an anti-inflammatory reliever titrated in this way provides a safer option, a 'safety net', preventing a large proportion of severe attacks across the range of asthma treatment steps.

Summary

Professor Eric Bateman

Many factors should affect the selection of inhaler devices. The patient's mastery of the device and preference must be taken into account, but prescribers should consider selecting devices that have the lowest impact on the environment. By selecting devices with a high resistance, inspiratory flow is rarely a limiting factor because a low flow is sufficient for optimal results. There is an urgent need to formalise, and make mandatory, training in the use of inhaler

devices for HCP. Proficiency of both HCP and patients is essential for successful therapy. Finally, maintenance and reliever therapy, which simplifies treatment by requiring a single inhaler for both maintenance and relief of symptoms, and leverages patients' normal tendency to self-medicate when symptomatic, has been shown to improve ICS coverage, especially in patients who have faltering adherence.

THE FULL SYMPOSIUM IS AVAILABLE TO VIEW AT WEHALE.LIFE/EVENTS, IN ORION PHARMA'S NEW ONLINE EXHIBITION & VIDEOS GALLERY ←

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Importance of Detecting Wheezing in Young Children to Minimise Asthma Exacerbation

This symposium took place on 7th September 2020, as part of the virtual European Respiratory Society (ERS) International Congress

Chairperson: Kostas Priftis[1]

Speakers: Kostas Priftis,[1] Bülent Karadag,[2] Wim van Aalderen[3]

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Meeting Summary

Breath sounds, such as wheeze, may be one of the oldest clinical signs described in the medical dictionary, but their definition and interpretation among clinicians varies widely. Efforts to classify breath sounds have often created further confusion over what does and does not constitute wheeze, a breath sound that can be indicative of asthma, bronchiolitis, and various other air trapping lung diseases in preschool children. There is also a disconnect between parental and physician understanding of wheeze, with high levels of disagreement between the two groups. The result is a failure to recognise or to hyperdiagnose wheeze. This can lead to inappropriate medication use, including over- and underuse, and children undergoing unnecessary testing and procedures, as well as increased levels of anxiety for parents and carers. Crucially, failing to recognise wheeze can delay the detection of asthmatic disorders, blocking access to preventative treatments, and make exacerbation more likely.

During this symposium, Assoc Prof Priftis, Prof Karadag, and Prof van Aalderen discussed the definition of wheeze, what it might mean in preschool children, and the implications of not recognising it. They also talked about the importance of a patient-centred approach to diagnosis, how to 'close the gap' between patient and physician understanding, and suggested that new technologies, such as artificial intelligence (AI), may play a role in detecting wheeze.

What Is a Wheeze and Why Is It Important to Confirm It Is a Wheezing Sound?

Associate Professor
Doctor Kostas Priftis

In 1819, René Laënnec, inventor of the stethoscope, said that breath sounds were "much more difficult to describe than to distinguish." Just over 200 years later, the same is still true, said Assoc Prof Priftis.

"Noisy breathing is a very well-known clinical sign used by all physicians, especially paediatricians," he said. Yet, despite its wide and long-term usage as a clinical sign, interpreting the meaning behind noisy breathing is far from straightforward. Various papers have attempted to assist by classifying and defining breathing sounds in recent years, but there remains much confusion and little standardisation among physicians, Assoc Prof Priftis told the symposium attendees.

Classifications

Bohadana et al.'s[1] 'Fundamentals of Lung Auscultation', published in 2014, attempted to define and classify breathing sounds in a bid to help clinicians better recognise signs of respiratory disease. It grouped tracheal sound, lung or vesicular sounds, and bronchial breathing together as normal respiratory sounds. The abnormal respiratory sounds were split into subcategories: musical (m), nonmusical (nm), and mixed. Stridor, wheeze, and rhonchus fell into the 'm' group, whereas fine crackle, coarse crackle, and pleural friction rub were considered 'nm'. The authors classified squawk as mixed.

Two years later, Assoc Prof Priftis explained, a European Respiratory Society (ERS) taskforce published a statement that classed a wheeze as an adventitious sound, originating from the chest wall, trachea, or mouth. The authors described it as a continuous, high-pitched respiratory sound. Rhonchus was also defined as being continuous, but low-pitched.[2]

"A wheeze [...] can be heard with or without a stethoscope, especially during expiration, and is produced by the obstruction of airflow within intrathoracic airways," said Assoc Prof Priftis. "In this way, we can detect asthma, as it is an asthma sign, but it can also be produced by other causes such as bronchiolitis, bronchomalacia, or a foreign body."

Clinical Importance

Recognising breath sounds is essential to the early diagnosis and appropriate treatment of respiratory health conditions.

However, a 2016 study by ERS taskforce members on lung sounds found that even the experts were unable to agree on the correct classification of prerecorded respiratory noises.[3] When the study participants were asked to choose between 10 predefined breath sounds according to the recommended English language nomenclature, there was little agreement between them. When the field was reduced to four breathing sounds, namely expiratory crackle, inspiratory crackle, expiratory wheeze, and inspiratory wheeze, the specialists were slightly more in agreement. However, it was only when the experts were asked to classify the sounds as simply either a crackle or a wheeze that they achieved a 'good' or 'excellent' level of agreement. Simplifying the description of lung sounds would, Assoc Prof Priftis argued, help to increase agreement on their use. "It seems the essence of our clinical practice is to confirm a breath sound as a crackle or a wheeze," said Assoc Prof Priftis, highlighting a 1979 paper that described just two types of breath sounds, discontinuous and continuous, with wheeze falling into the latter.[4]

The ERS taskforce also sought to understand if there were common terms for the different breathing sounds. They found huge variation across countries and, in some cases, within countries regarding the word they used to describe 'wheezing'.[3] "Again, it was a mess, because even in the same country we had different names for the same sound," said Assoc Prof Priftis. If doctors have difficulty naming and recognising breath sounds, how could they explain how to interpret them to patients and their parents, he questioned.

Objective Recognition and Description

An objective description of wheeze would inform more universal recognition of the breath sound that can be indicative of health conditions

such as asthma and bronchiolitis, both of which benefit from early detection and treatment, considered Assoc Prof Priftis. Crackles and wheezes, he argued, are well recognised and routinely used in daily practice, meaning that no further classification is required. Further descriptions would serve to introduce confusion and nonstandardisation. "Enough is enough, we need no more," he said.

Assoc Prof Priftis concluded: "After 200 years of stethoscope usage, it is still more difficult to describe than to distinguish breath sounds."

The Struggle of Paediatricians and Parents with a Wheezing Child

Professor Doctor Bülent Karadag

For all the reasons highlighted by Assoc Prof Priftis, said Prof Karadag, recognising wheezing in a child can be challenging. In addition, this is often compounded by a lack of agreement between healthcare professionals and families on whether the symptom is present and, if it is, what it means. It is important to remember that not every wheeze a parent reports will match the clinical description, and that not every confirmed wheeze is caused by asthma, clarified Prof Karadag.

Prof Karadag started his presentation with a list of reasons why it was important to recognise wheeze. "Now we are moving into autumn and winter, our emergency rooms will be full of wheezing children with bronchiolitis and asthma," he said, explaining that wheeze was the "most important tool" for diagnosing asthma. "In order to get appropriate medical treatment, you should diagnose wheezing. Otherwise, you will not be giving inhaled steroids or leukotriene receptor antagonists to treat and to control asthma," he warned. Recognising wheeze and its causes, he explained, also helps clinicians to avoid inappropriate antibiotics and unnecessary laboratory testing.

Crucially, recognising wheeze is an integral part of patient-centred care, he continued. Clinicians can decrease children's and parents' anxiety levels by identifying and explaining the breathing sound, he said. To demonstrate his point, Prof Karadag highlighted a UK study of parents of preschool children with recurrent wheeze. It found a mix of positive and negative feelings about healthcare services among those whose wheezing toddlers were being cared for in primary care, emergency departments, paediatric wards, and paediatric specialist clinics. Following discharge, however, parents only reported feelings of stress, fear, or anger relating to their child's care.[5] Prof Karadag explained: "When they are at home there are no happy moments because there is uncertainty. Is it wheeze? Is there any severe disease? Should I take my child to the emergency room? But even in the emergency room and paediatric ward, if the diagnosis is not clear, if the physician cannot say it is wheezing, this fear and anger continues."

Discrepancy in Understanding

Prof Karadag said that there was a significant discrepancy between parental and physician understanding of wheeze.

One of the first papers to demonstrate this was published 20 years ago and showed that parents and doctors only agreed in 45% of cases.[6] In 39% of cases, doctors defined a child's breathing sound as wheezing, though it had not been described as such by the parents. Additionally, in 14% of cases the parents said it was a wheeze, but the doctor disagreed. A key point here is the differing terminology for wheeze, as outlined by Assoc Prof Priftis, Prof Karadag said. When parents were asked to describe their child's breathing sound, they used a multitude of words, including hissing, squeaking, whistle, and rasp.[6] "Doctors do not know what to label it, but from the patient/parent side, it is terrible. In Turkey, I can never be sure of what they will call it, so I always ask them to mimic the sound, but it is not accurate."

Another study, from 1996, showed that the easier it is to hear the wheezing, the higher the level of agreement between parent and doctor.[7] "When you look at the peak expiratory flow rates, if you hear the wheezing easily, flow rate is something around 55%, and if there is no sound, it is about 90%. So, if the parents are hearing wheezing at home easily, you should ask them to rush directly to the emergency room because there may be a risk of hypoxia."

Other factors that might affect parental understanding, interpretation, and terminology surrounding wheeze are ethnicity and socioeconomic background. A UK study of 4,000 patients showed that parents from a South Asian background and those who did not speak English as a first language were less likely to correctly define wheeze compared to Caucasian, native speakers, for example.[8]

Agreement matters because there is a link between parent-reported wheezing and general practitioner-recorded asthma diagnosis, according to a 2018 study from Wales, UK.[9] "If the parents report true wheeze, true positive wheeze, asthma prevalence is nearly 20%. But if there is a false positive wheeze it is 4%.[10] So, if there is an agreement between the physician and the parents, you can say that the risk of asthma is much higher than in the normal population," stated Prof Karadag.

Summarising the problem, he said: "Identifying wheezing is challenging for parents. Children may not be able to, and of course we don't expect them to, articulate their breathing trouble." Wheeze does not always sound the same, and it can be confused with noisy breathing, congestion, a blocked nose, or even a throat infection.

Not Every Wheeze Is Asthma

Recognising wheeze is the first step on a diagnostic journey, but the destination is not always asthma. Clinicians need to ask if the sound is a wheeze or a rattle, and consider any additional findings, including whether the noise is localised. They should also be aware of the risk of bronchial disease, said Prof Karadag. "There are two parts to this: is it really wheezing and is there any underlying disease?" he asked. In acute bronchiolitis, which is more common than asthma, clinicians will hear polyphonic wheeze and inspiratory crackles. Children with acute bronchitis may present with an audible rattle, caused by secretions, which it is also a symptom of acute viral bronchiolitis. Detecting asthma, therefore, is not as straightforward as recognising wheeze. Wheeze at rest and nocturnal cough are indicators of asthma, said Prof Karadag.

He continued: "In conclusion, many cultures do not have a word for wheeze, and nearly half of parents struggle to identify wheezing sounds. Doctors fear patients will be undertreated due to the lack of awareness around wheezing. The 'wait-and-see' approach may cause delayed interventions to prevent attacks, and if physicians hesitate, they will miss any underlying diagnosis, mainly pneumonia. My take-home message is that it is important to clarify the sound heard by the parents, and even the sound heard by doctors. We need to standardise it and AI may help us to overcome this barrier."

New Tool to Help Parents Confirm Wheeze

Professor Doctor Wim van Aalderen

AI may play a role in helping parents and physicians detect wheeze in children. Devices such as the OMRON WheezeScan (HWZ-1000T-E; OMRON Healthcare, Kyoto, Japan), which has been recently been launched as an aid for parents in the UK and Germany, use a validated algorithm to listen to auscultation and return a 'wheeze' or 'no wheeze' result. The value of such tools, which currently allow parents to confirm their suspicions of wheeze in children aged between 4 months and 7 years old, lies in their potential to assist in the early diagnosis of asthma and other respiratory conditions, said Prof van Aalderen, highlighting that preschool wheeze costs the UK £53 million a year, or 0.15% of country's overall health budget.[11]

Prevalence and Interpretation

Discussing the impact of wheeze, he said that one in three children experience it before their 3rd birthday, adding that the cumulative prevalence is 50% by the age of 6 years. A well-known study from 1995 found that 40% of those who had a wheezing episode before the age of 3 years, and most of those who persistently wheezed before turning 6 years of age, went on to be diagnosed with asthma.[12] "This is a very important study, but [...] it doesn't help you if you are in your office with a wheezing child in front of you. It doesn't give a clue about the future of the wheeze of this child," remarked Prof van Aalderen.

Of course, asthma is not the only cause of wheeze. Recurrent viral upper airway infections and cigarette smoke exposure can cause the

breathing sound, and postviral wheeze is common in young children, especially in those recovering from respiratory syncytial virus. Prof van Aalderen also listed several rare diseases as possible differential diagnoses of preschool wheezing. These included cystic fibrosis, congenital heart disease, and anatomic malformation, such as tracheomalacia.

He reiterated the point made by both Assoc Prof Priftis and Prof Karadag, that wheeze can be interpreted differently between parent/carer and healthcare provider and is dependent upon whether it is reported retrospectively or in real time. "For us, what is important is the agreement between parents and healthcare providers," he said, pointing to a 2000 study showing these two groups disagreed on their assessment of wheezing in 55% of cases.[6] The importance of this was highlighted in a paper published in 2004, which found the lung function in children with physician-confirmed wheeze was significantly lower than that in children with parental-only reported wheeze.[13]

Predictors of Asthma

Detecting wheeze is an important first step in the diagnostic journey, but it is not the only predictor of asthma. Clinicians with a confirmed incidence of wheeze will carry out a physical examination and take a thorough history, paying particular attention to any family history of asthma or allergies. Noninvasive measurements such as exhaled nitric oxide and serum markers, especially IgE if there is a history of allergic disease, may also be useful, explained Prof van Aalderen. "History, a positive family history for allergic disease in the first-line, and a positive specific IgE all increase the chance of developing asthma, but there is overlap between groups and there is no diagnostic available for daily practice," he said.

Artificially Detecting Wheeze

New technologies may help parents to identify wheeze, and lead to greater agreement between them and physicians. WheezeScan, for example, connects to an app that allows parents to share information with doctors. They do not, however, change the role of the clinician: "If a parent reports to you that their child has wheeze, you still have to do a full follow-up in your own office. It helps with diagnosis, but your job as a doctor remains the same as it was yesterday," explained Prof van Aalderen.

Questions and Answers

Following the presentations, the panel answered questions from delegates and from each other.

Q: Should We Teach Parents What Wheeze Is?

Assoc Prof Priftis said parents would simply need to know if a child were wheezing or not so they could relay that information to their doctor. It is then the clinician's role to differentiate what the wheeze means through the history and examination.

Q: How Can We Close the Gap Between Parent and Physician Understanding of Wheeze?

Prof Karadag said we were "at the start of a new era in terms of closing the gap." This is being driven in part by new technologies, such as AI, but also by a new emphasis on personalised care. "Being a good physician and making the right decisions depends on the time you are spending with your patient," he said. Factors such as the parent's education and occupation, whether the child is their first, and how old they were when they became a parent, for example, all have a bearing on their interpretation of a wheeze and its severity, he observed. "I think giving enough time to each patient and taking a detailed history will help physicians to close this gap."

The essential point, said Assoc Prof Priftis, is to educate doctors so they can educate their patients.

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Dupilumab in Moderate-to-Severe Asthma: Updates from the ERS International Congress 2020

These narrated poster presentations took place from 7th to 9th September 2020, as part of the virtual European Respiratory Society (ERS) International Congress 2020

Presenters: Michael E. Wechsler,[1] Nicola A. Hanania,[2] Jorge F. Maspero[3]

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Meeting Summary

Dupilumab (Dupixent®) is a fully human monoclonal antibody[1] that inhibits IL signalling of both IL-4 and IL-13, which are drivers of type 2 inflammation in multiple atopic diseases, including asthma.[2] Dupilumab has been developed as an add-on maintenance treatment for asthma in adult and adolescent patients. There are some differences in specific indications of disease severity and clinical characteristics on the USA and European Union (EU) labels,[3,4] and in the EU the approved indication for dupilumab in asthma is specifically for patients exhibiting type 2 inflammation, characterised by elevated blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO).[4] The clinical development programme for dupilumab in asthma (LIBERTY ASTHMA) includes the pivotal Phase III trials QUEST[5,6] and VENTURE,[7,8] and an open-label extension study (OLE), TRAVERSE,[9] which recruited patients from QUEST, VENTURE, and two Phase II studies.

Dr Wechsler presented the first long-term efficacy and safety data to emerge from TRAVERSE at the European Respiratory Society (ERS) International Congress 2020. He showed that the long-term safety profile of dupilumab was consistent with that observed in the parent studies and that efficacy was maintained, including a persistently low exacerbation rate and improvements in lung function sustained for up to 96 weeks. Dr Hanania presented a poster reporting a post hoc analysis of QUEST, which explored exacerbation rates in patient subgroups defined according to degree of lung function

improvement. Dr Maspero presented a similar post hoc analysis of VENTURE, which was a study in patients who were glucocorticoid-dependent, exploring relationships between oral corticosteroid (OCS) use and lung function improvement. Both analyses showed that dupilumab improved outcomes (exacerbation rates and OCS use, respectively) across patient subgroups with varying degrees of improvement in lung function.

Dupilumab Long-Term Safety and Efficacy in Patients with Asthma: LIBERTY ASTHMA TRAVERSE

Doctor Michael E. Wechsler

LIBERTY ASTHMA TRAVERSE,[9] the first long-term study of the safety and efficacy of dupilumab in asthma, was an OLE study in patients with asthma who had participated in any of four Phase II or III clinical trials of dupilumab: a Phase IIa proof-of-concept study (EXPEDITION),[10] a Phase IIb dose-ranging investigation,[11] and the Phase III QUEST[6] and VENTURE[8] studies. Patients entering TRAVERSE received open-label treatment with dupilumab 300 mg every 2 weeks (q2w) for 48–96 weeks. The study population comprised 2,282 adult and adolescent patients (aged ≥12 years) with moderate-to-severe asthma, including some patients with OCS-dependent asthma.

Dr Wechsler presented the headline safety and efficacy results from TRAVERSE. The safety profile was consistent with that seen in the parent studies, and no new safety signals were observed. Treatment-emergent adverse events were experienced by 76–88% of patients at any time during TRAVERSE, across study groups based on parent study and randomised treatment group in the parent study. The most common treatment-emergent adverse events were nasopharyngitis and injection site erythema. The rate of serious adverse events was 9–13%.

Efficacy results were presented for the non-OCS-dependent patient population, which included patients recruited from the Phase IIb study and the Phase III QUEST study (n=2,062). The primary efficacy endpoint was annualised exacerbation rate (AER). Low exacerbation rates observed in the parent studies were sustained in the OLE and ranged from 0.31 to 0.35 across study groups in the overall exposed population (Figure 1). This compares with baseline AER of 1.85–2.37 across treatment groups at the start of the Phase IIb and QUEST studies. A subgroup of patients with type 2 asthma phenotype (defined as eosinophils ≥150 cells/µl or FeNO ≥25 parts per billion at parent study baseline; n=1,679) had similar results, with AER during the TRAVERSE study ranging from 0.29 to 0.33 (Figure 1).

An analysis of lung function based on forced expiratory volume in 1 second (FEV_1) showed that for patients who were randomised to dupilumab in the parent studies (Phase IIb or QUEST), improvements in FEV_1 were sustained throughout the OLE, while patients who received placebo in the parent studies had rapid improvements in FEV_1 on commencing dupilumab in the OLE. Baseline FEV_1 was 1.75–1.86 L across treatment groups at baseline in the Phase IIb and QUEST parent studies, increasing to 2.02–2.12 L by Week 96 of TRAVERSE, representing a 13–22% improvement in the non-OCS-dependent population. Similar improvements in lung function, by 13–25%, were seen in the subgroup of patients with type 2 phenotype asthma.

Transient increases in eosinophils have been observed in dupilumab clinical studies, including parent studies feeding into TRAVERSE, and are consistent with the mechanism of action of dupilumab.[5,7,12] In the parent studies, mean eosinophil counts returned to baseline or close to baseline by the end of the study.[5,7,12] Monitoring of eosinophil counts continued in the OLE for patients in the non-OCS-dependent population (patients recruited from the Phase IIb and QUEST studies). Transient increases were observed during the first few weeks of TRAVERSE in patients who had received placebo in QUEST and commenced dupilumab treatment on entering TRAVERSE, and in patients entering TRAVERSE from the Phase IIb study, who had a 16-week treatment-free follow-up period between completing the double-blind treatment period in the parent study and entering the OLE; these increases resolved by Weeks 12–24. Longer-term follow up showed that, by Week 96 of the OLE, mean eosinophil counts had decreased to below parent study baseline levels.

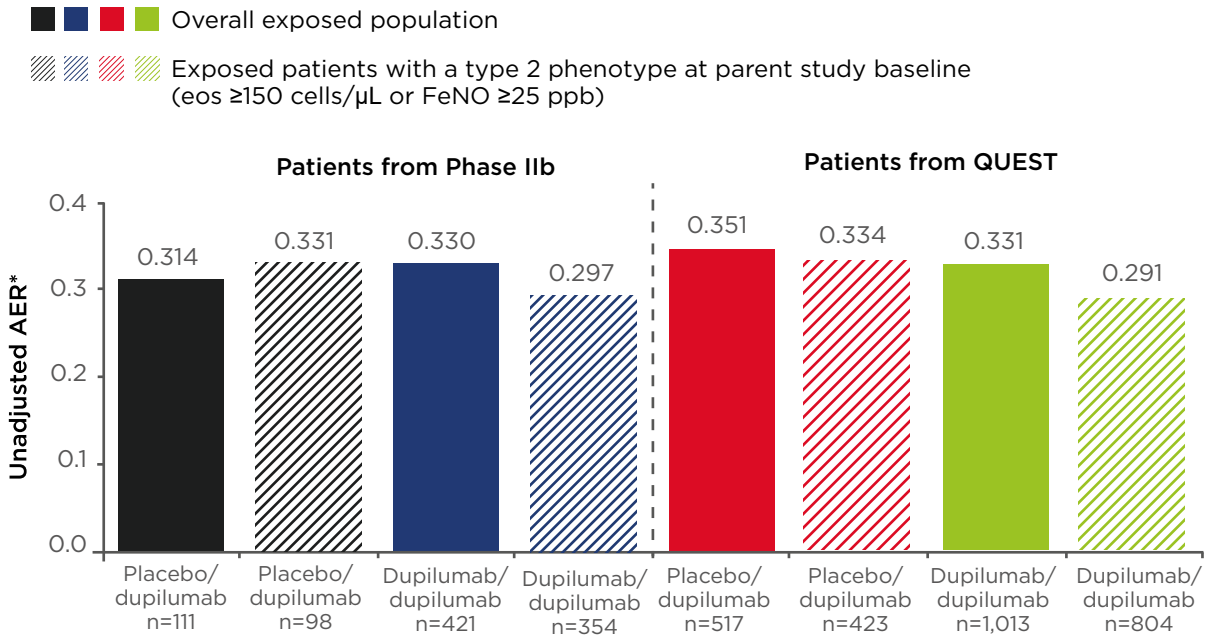

Figure 1: Annualised exacerbation rate in the non-oral-corticosteroid-dependent population in LIBERTY ASTHMA TRAVERSE.

AER was assessed in the exposed population (observed cases).

*The total number of events that occurred during the treatment period divided by the total number of patient years in the treatment period.

AER: annualised exacerbation rate; eos: eosinophils; FeNO: fractional exhaled nitric oxide; ppb: parts per billion.

Eosinophils are a key marker of type 2 asthma. Serum IgE is an additional marker, specifically of allergic asthma, which is characterised by IgE-mediated type 2 inflammation.[13] Serum IgE has been measured as an exploratory biomarker in dupilumab asthma studies. Data on serum IgE were available for patients who participated in the Phase IIb study, and serum IgE measurements were repeated in these patients (n=532) during the OLE. At the start of the OLE, mean serum IgE was lower in patients from the dupilumab treatment group compared with those from the placebo group in the Phase IIb feeder study. By Week 96 of the OLE, mean IgE levels dropped markedly in both groups, decreasing by 82% from parent study baseline in the overall Phase IIb study population.

Dr Wechsler concluded that long-term treatment with dupilumab was generally well tolerated, and that the clinical efficacy observed in the parent studies was maintained, including a persistently low exacerbation rate and sustained improvements in lung function. Markers of type 2 inflammation also decreased during long-term dupilumab treatment.

Effect of Dupilumab on Severe Exacerbations in Asthma Patients With and Without Lung Function Improvements

Doctor Nicola A. Hanania

LIBERTY ASTHMA QUEST study is the largest randomised controlled trial of dupilumab in patients with asthma, contributing >50% of the patients who enrolled in the TRAVERSE study described above. In the QUEST study, a total of 1,902 adult or adolescent patients (aged ≥12 years) with uncontrolled moderate-to-severe asthma were randomised to treatment with dupilumab 200 mg or 300 mg q2w, or matched placebo, for 52 weeks. The primary endpoints were annualised rate of severe exacerbations over 52 weeks and change from baseline to Week 12 in prebronchodilator FEV_1.[5] Significantly lower annualised rates of severe exacerbations were recorded in both dupilumab groups compared with matched placebo (46–48% relative reductions), while mean increases in

FEV_1 were significantly greater in dupilumab groups (320–340 mL) compared with placebo (180–210 mL).[5]

Dr Hanania presented a post hoc analysis exploring the relationship between these two outcomes. The objective of the analysis was to assess the efficacy of dupilumab in reducing severe exacerbations in subgroups of patients who did and did not achieve clinically meaningful improvements in lung function. This is of interest because poor lung function (low FEV_1) is associated with difficult-to-treat disease and worse outcomes.[14]

Two definitions of clinically meaningful improvement in lung function were applied, with thresholds of ≥100 mL or ≥200 mL increase in pre-bronchodilator FEV_1 from baseline to Week 12 constituting a clinically meaningful improvement. Using the 100 mL threshold, 62% of patients in dupilumab groups (combined dose groups) and 49% of patients in combined matched placebo groups achieved clinically meaningful improvement. In total, 49% and 37% of patients, respectively, achieved clinically meaningful improvement using the more stringent definition of ≥200 mL increase in prebronchodilator FEV_1. Annualised rates of severe exacerbations were lower among patients with clinically meaningful improvements in lung function (either definition) than among their counterparts without clinically meaningful improvements, both in dupilumab treatment groups and in placebo groups (Figure 2). Significant treatment effects of dupilumab on reducing annualised severe exacerbation rates were apparent in all patient subgroups, with and without clinically meaningful improvements in lung function based on either definition (Figure 2). There was a trend for a greater magnitude of reduction in severe exacerbations, with dupilumab versus placebo, in the patient subgroups with clinically meaningful improvements in lung function. There was a 37–54% reduction among patients with improved lung function (either definition) compared with 35–38% reduction in patients without clinically meaningful improvements in lung function (Figure 2), but the interactions between treatment effect and subgroups were not statistically significant.

In the primary efficacy analyses in QUEST, treatment effects on severe exacerbation rates were greater in patients with elevated type 2 biomarkers than in the overall intent-to-treat population.[5] This post hoc analysis was repeated in the subgroup of patients with blood eosinophils ≥150 cells/µL and/or FeNO ≥25 parts per billion (which represented most of the overall analysis population: 1,469 of 1,841 patients included in the analysis). Results were similar to the analysis in the overall study population, with significant effects of dupilumab on annualised rates of severe exacerbations seen both in patients with and without clinically meaningful improvements in lung function.

In conclusion, this post hoc analysis showed that higher proportions of patients achieved clinically meaningful improvements in lung function when treated with dupilumab compared with placebo, but the effect of dupilumab on reducing annualised severe exacerbation rate was not dependent on achieving improvement in lung function.

Effect of Dupilumab on Oral Corticosteroid Use in Severe Asthma Patients With Improving Lung Function

Doctor Jorge F. Maspero

Dr Maspero presented a post hoc analysis of the VENTURE trial, exploring the impact of dupilumab on the need for OCS in patients with differing degrees of response in terms of improvement in lung function. Inclusion criteria for VENTURE included regular use of systemic (oral) glucocorticoids (5–35 mg/day prednisone, prednisolone, or equivalent) in the 6 months prior to enrolment, and the study population was therefore a glucocorticoid-dependent population with severe asthma (n=210).[7] Patients aged ≥12 years were randomised to receive dupilumab 300 mg q2w or placebo, as add-on treatment to their existing treatment regimen (including bronchodilators, inhaled corticosteroids, and OCS), for 24 weeks. During the study period, patients' OCS doses were reviewed every 4 weeks and reduced in accordance with a predetermined schedule, dependent on the patient's optimised baseline OCS dose, until the patient met prespecified criteria indicating that further dose reduction was not acceptable.

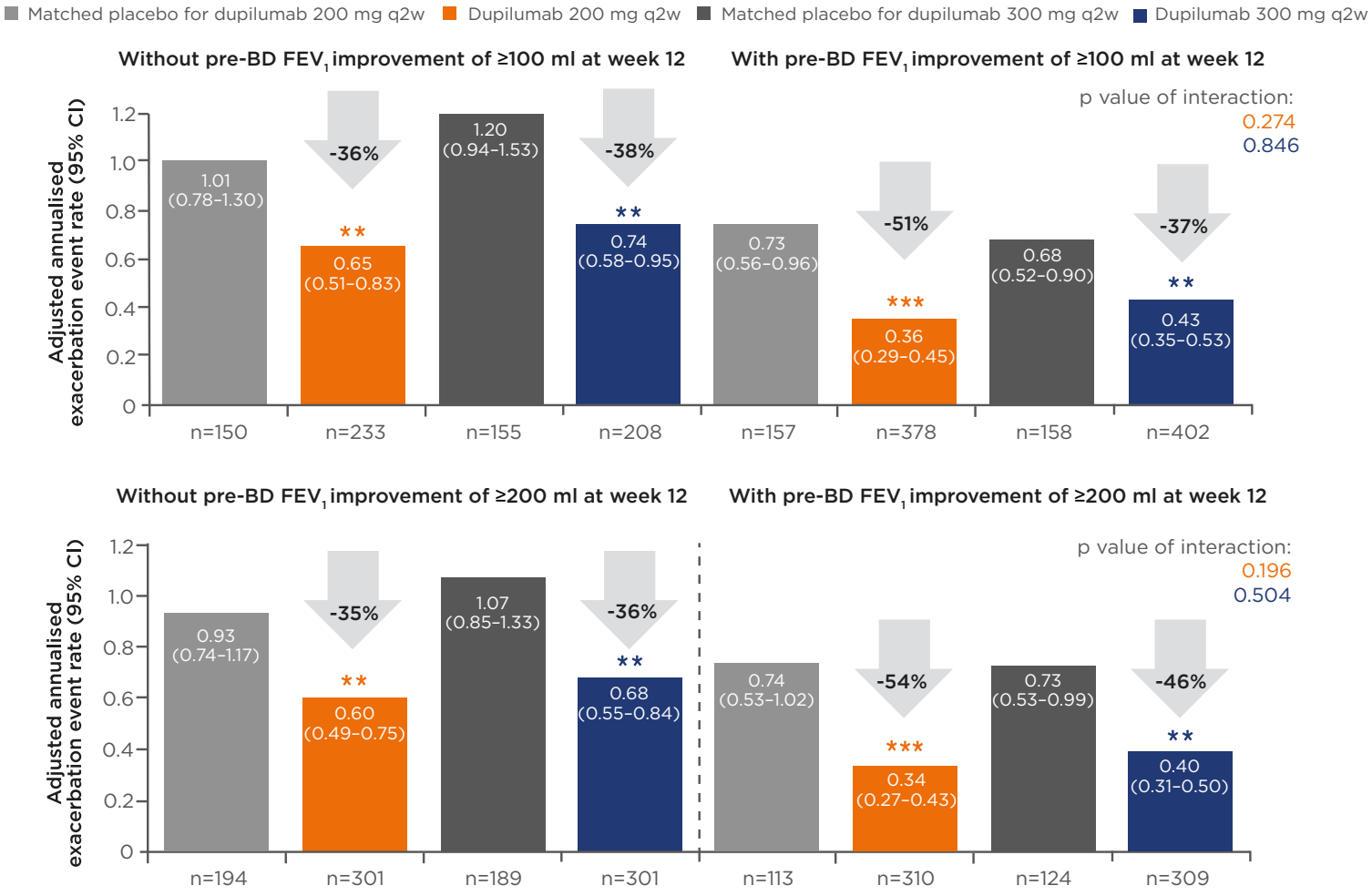

Figure 2: Annualised rate of severe exacerbations during the 52-week treatment period in QUEST in patients with/without clinically meaningful improvements of ≥100 mL and ≥200 mL increases in prebronchodilator forced expiratory volume in 1 second at Week 12 (overall intent-to-treat population).

**p<0.01 versus matched placebo.

***p<0.001 versus matched placebo.

CI: confidence interval; pre-BD FEV_1: pre-bronchodilator forced expiratory volume in 1 second; q2w: every 2 weeks.

The primary study endpoint was percentage reduction in OCS dose from baseline to Week 24; key secondary endpoints were proportion of patients with at least 50% reduction in OCS dose at Week 24, and proportion of patients with reduction in OCS dose to <5 mg/day.[7]

In the overall study population, OCS doses decreased by 70% (least-squares mean percentage change) from baseline to Week 24 in the dupilumab group, compared with a 42% reduction in the placebo group (p<0.001).

In addition, significantly higher proportions of patients in the dupilumab group compared with the placebo group met the secondary endpoints of ≥50% reduction in OCS dose (80% versus 50%, respectively) and reduction in OCS dose to <5 mg/day (69% versus 33%, respectively). Despite greater reductions in OCS use in the dupilumab group, the rate of severe exacerbations was significantly lower and there was a greater increase in mean prebronchodilator FEV_1 in the dupilumab group compared with the placebo group.[7]

In the post hoc analysis that Dr Maspero presented, similar to the analysis of QUEST presented by Dr Hanania and described above, patients were stratified according to their degree of lung function improvement, using thresholds of </≥100 mL and </≥200 mL increases in prebronchodilator FEV_1 from baseline to Week 24.

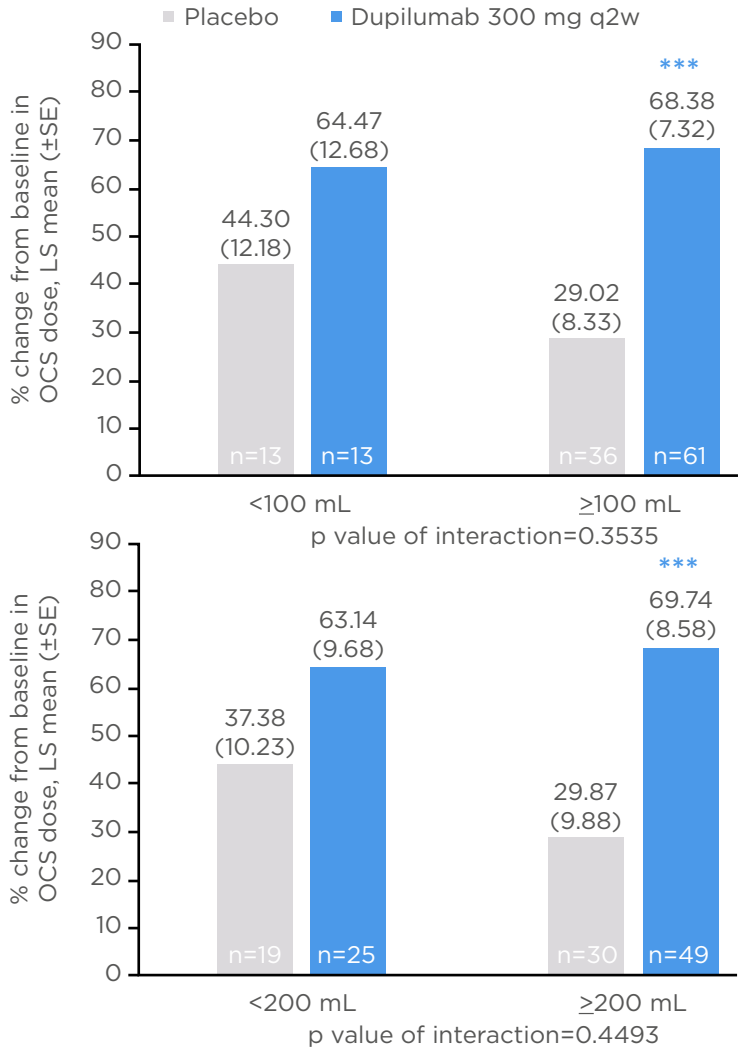

Figure 3: Oral corticosteroid dose reduction (%) from baseline at Week 24 in patients with improvement from baseline in prebronchodilator forced expiratory volume in 1 second of <100, <200, ≥100, or ≥200 mL at Week 24.

***p<0.001 versus matched placebo.

LS: least squares; OCS: oral corticosteroid; q2w: every 2 weeks; SE: standard error.

Among patients with ≥100 mL or ≥200 mL increase in FEV_1, those in the dupilumab group had 68–70% reductions in OCS dose (similar magnitude of reduction regardless of which FEV_1 threshold was used), while patients in the placebo group reduced their OCS doses by only 29–30% (p<0.001 for dupilumab versus placebo; Figure 3).

Among patients with lesser degrees of lung function improvement (<100 mL or <200 mL), reductions in OCS dose in the dupilumab group were similar to those in the improved lung function subgroups (63–64%), but did not reach statistical significance versus placebo.

Similar patterns were observed for other measures of OCS use. In patient subgroups with ≥100 mL or ≥200 mL increase in FEV_1, 85–88% of patients in the dupilumab group achieved ≥50% reduction in OCS dose, compared with 49–53% in the placebo group; 79–82% and 40–43% of patients, respectively, reduced their OCS dose to <5 mg/day; and 57–59% and 31–33%, respectively, achieved the maximum OCS dose reduction possible according to their individual dose-reduction schedules (all p<0.05 for dupilumab versus placebo). In the patient subgroups with lower degrees of lung function improvement (<100 mL and <200 mL increase in FEV_1), the magnitudes of effect of dupilumab on each of these endpoints were broadly similar, but did not reach statistical significance versus placebo in most cases. This

may reflect factors such as different sizes of subgroups (subgroups of patients with <100 mL and <200 mL increase in FEV_1 were relatively small compared to the corresponding subgroups with ≥100 mL and ≥200 mL increases in FEV_1) because there was no statistically significant interaction between treatment effect and subgroup.

Dr Maspero noted that the findings may be limited by the post hoc nature of the analysis and the low sample sizes in some subgroups. Nonetheless, this analysis indicated that OCS-dependent severe asthma patients, with various levels of improvement in lung function, were able to reduce OCS use during treatment with dupilumab to a greater extent than patients receiving placebo, based on multiple measures of OCS use.

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Dupilumab Improves Outcomes for Patients with Severe Chronic Rhinosinusitis with Nasal Polyps Irrespective of the Number of Surgeries and the Time Since Surgery or Diagnosis

These poster presentations took place from 10th to 12th September 2020, as part of the virtual American Rhinologic Society (ARS) 66th Annual Meeting

Presenters: Claire Hopkins,[1] Joaquim Mullol[2]

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Meeting Summary

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a persistent, chronic inflammatory condition of the nasal passages and paranasal sinuses.[1] Patients with CRSwNP experience a range of symptoms, including smell impairment, nasal obstruction, nasal congestion, headaches, and postnasal drip.[2] The high symptom burden experienced by patients with CRSwNP negatively impacts their health-related quality of life (HRQoL).[1-3] Most patients with CRSwNP have a type 2 pattern of inflammation characterised by elevated levels of IL-4, IL-5, and IL-13 and tissue infiltration by eosinophils, lymphocytes, basophils, and mast cells.[4-6] First-line management options are limited and endoscopic sinus surgery is used when pharmacological interventions are unsuccessful; however, a considerable proportion of patients experience symptom recurrence following surgery.[3,6-9] Dupilumab is a human monoclonal antibody that binds to the IL-4 receptor α subunit and inhibits signalling of IL-4 and IL-13, both of which act as key drivers of type 2 inflammation.[10-13] Dupilumab has been approved in the USA and the European Union (EU) as an add-on maintenance treatment in adult patients with inadequately-controlled CRSwNP.[14,15]

Dupilumab Efficacy in Patients with Chronic Rhinosinusitis with Nasal Polyps by History of Prior Sinonasal Surgery: Pooled Results From the SINUS-24 and SINUS-52 Phase III Studies

Professor Claire Hopkins

Patients with serious CRSwNP or who experience disease relapse following pharmacological interventions may undergo endoscopic sinus surgery. However, symptom reappearance following surgery is common, occurring in 50–80% of patients within 3–5 years.[3,6-9,16-18] Moreover, patients may not experience an improvement in smell following multiple surgeries. This study investigated dupilumab efficacy by quantifying prior sinonasal surgeries and the time since last surgery in patients with severe CRSwNP refractory to the standard of care. Pooled efficacy and safety datasets up to Week 24 from the Phase III SINUS-24 and SINUS-52 studies were used for the analysis. SINUS-24 and SINUS-52 evaluated dupilumab on a background of mometasone furoate nasal spray compared with mometasone furoate nasal spray alone (placebo).[19] Participants enrolled in SINUS-24 were randomly assigned (1:1) to receive either subcutaneous dupilumab 300 mg (n=143) or placebo (n=133) every 2 weeks (q2w) for 24 weeks.[19] Patients in SINUS-52 were randomly assigned (1:1:1) to dupilumab 300 mg q2w for 52 weeks (n=150), dupilumab q2w for 24 weeks and then every 4 weeks for the remaining 28 weeks (n=145), or placebo q2w for 52 weeks (n=153). Rescue treatment with either systemic corticosteroids and/or surgery was permitted for study participants.[19] Patients were categorised according to the number of prior surgeries and time since last surgery. At baseline, the proportion of patients in these categories was well balanced between the study arms. Efficacy was measured using several scores:[20] nasal polyp score (NPS), scale: 0–4 in each nostril, 0: no nasal polyps, 8: large nasal polyps causing complete obstruction of the inferior nasal cavity; nasal congestion (NC) score, scale: 0–3, 0: no symptoms, 3: severe symptoms that are hard to tolerate and cause interference with daily activities; Lund–Mackay (LMK) score, scale: 0–24 (0–12 for each nostril), 0: healthy, 2: total opacification; loss of smell symptom score, scale: 0–3, 0: no symptoms, 3: severe symptoms; University of Pennsylvania Smell Identification Test (UPSIT), scale: 0–40, <19: anosmia; the 22-item Sino-Nasal Outcome Test (SNOT-22), range: 0–110, item score: 0–5, 0: no problem, 5: problem as bad as it can be.

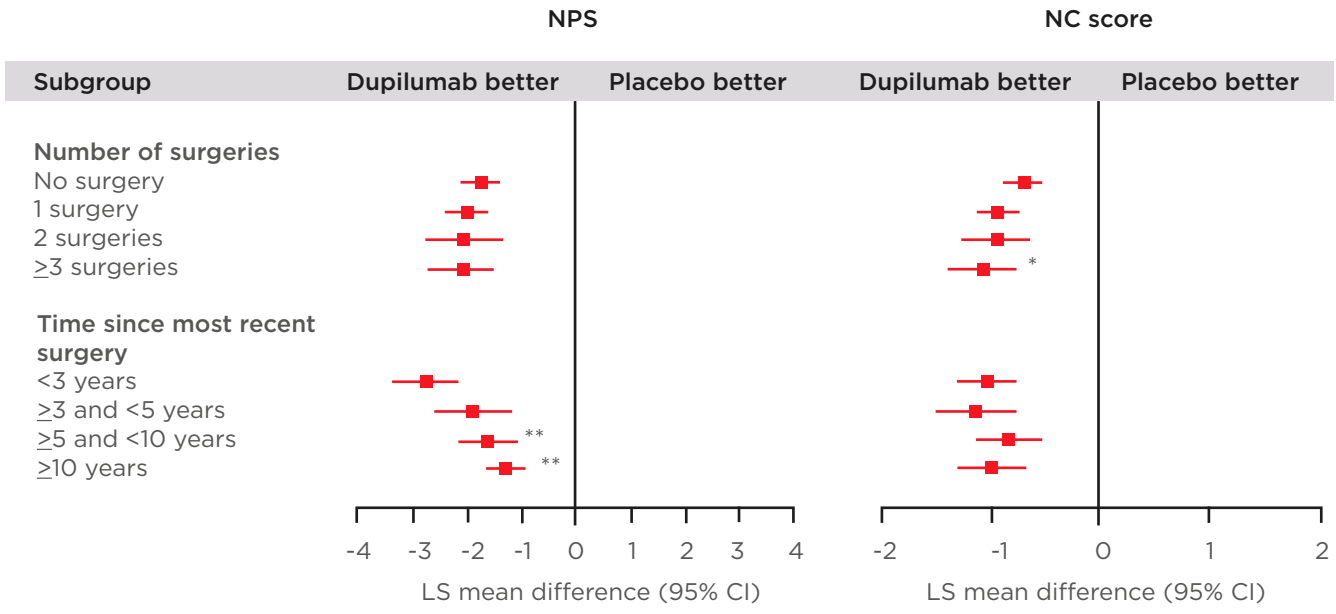

Figure 1: Efficacy outcomes using multiple measures assessing chronic rhinosinusitis with nasal polyp disease severity at Week 24 in patients receiving either dupilumab or placebo.

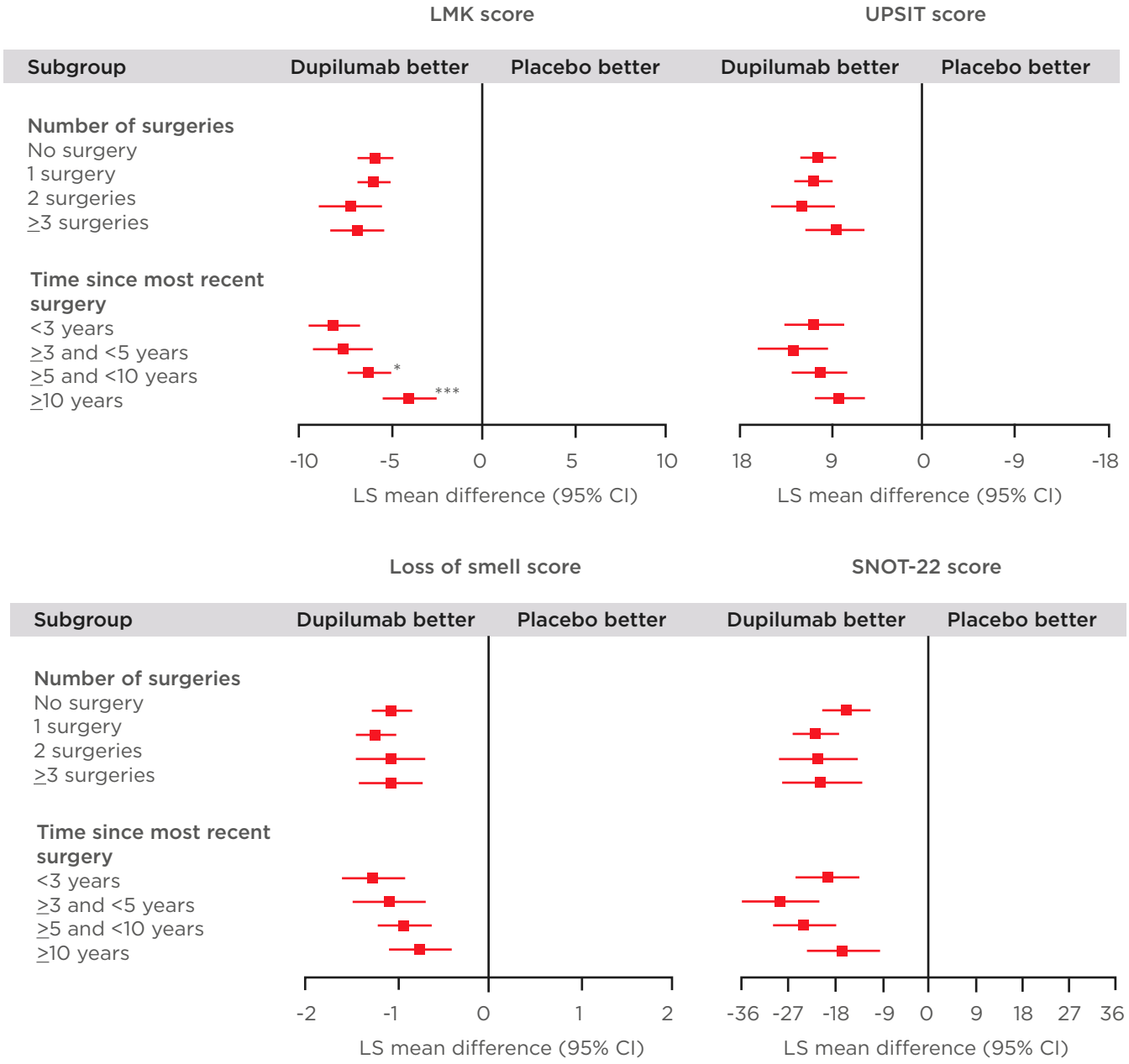

Figure 1 continued.

Subgroup-by-treatment interaction (comparing number of surgeries versus no surgery and time since more recent surgery versus <3 years).

*p<0.05

**p<0.01

***p<0.001

CI: confidence interval; LMK: Lund-Mackay; LS: least squares; NC: nasal congestion; NPS: nasal polyp score; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test.

A total of 458 individuals were included in this study. Baseline sinus disease, measured by NPS (p=0.0047), NC score (p=0.0151), and LMK score (p<0.0001), was significantly worse for those patients who had not received surgery compared with individuals who had undergone surgery.

This was also true for olfactory dysfunction measured by the UPSIT and loss of smell scores (both p<0.0001). At baseline, patients who had surgery <3 years previously were younger (mean age: 46.4 years), had a higher LMK score (19.96), and lower mean bilateral endoscopic NPS (5.41;

all p<0.0001) compared with participants in the ≥3 to <5 years, ≥5 to 10 years, and ≥10 year groups.

The study found that dupilumab improved all outcome measures irrespective of the number of prior surgeries or time since last surgery (Figure 1). Significantly greater improvements in the NPS were observed in patients who had a shorter time since last surgery (time since more recent surgery versus <3 years; p<0.05). Patients who received dupilumab with ≥3 surgeries had significantly higher NC scores compared with those individuals who did not have prior surgery (p<0.01; Figure 1). Dupilumab was also associated with greater improvements in both the LMK and UPSIT scores compared with placebo regardless of the time since last surgery or the number of prior surgeries (Figure 1). Significant improvements in LMK scores were seen in patients with a shorter time since last surgery compared to those with longer time since last surgery (<3 years versus >5 and <10 years; p<0.05, <3 years versus ≥10 years; p<0.001). Dupilumab also resulted in improvements in smell and SNOT-22 scores compared with placebo regardless of number of prior surgeries and time since last surgery.

The efficacy of dupilumab was demonstrated over 24 weeks with a shorter time (<3 years) since last surgery associated with improved NPS and LMK scores, which may be indicative of high type 2 inflammation burden in these patients. Dupilumab reduced the need for rescue treatment with systemic corticosteroid and/or NP surgeries versus placebo, regardless of the number of prior surgeries or the time since last surgery within 10 years (Figure 2). Dupilumab had a favourable tolerability profile in individuals with and without prior surgery. The most common treatment emergent adverse events occurring in ≥5% of patients were nasopharyngitis (dupilumab 12.5% versus placebo 14.5%), nasal polyps (dupilumab 2.7% versus placebo 11.7%), and injection-site erythema (dupilumab 6.3% versus placebo 7.8%). This study demonstrated that over 24 weeks dupilumab consistently improved multiple measures of CRSwNP disease severity regardless of the number of prior sinonasal surgeries or time to last surgery.

Dupilumab Improved Smell Outcomes in Patients Irrespective of Years Since Chronic Rhinosinusitis with Nasal Polyps Diagnosis: Pooled Results From the SINUS-24 and SINUS-52 Phase III Studies

Professor Joaquim Mullol

Of all the symptoms experienced by patients with CRSwNP, the loss of smell is particularly troublesome and refractory to existing therapies.[21,22] Loss of smell can be correlated with disease severity and has a considerable negative impact on an individual's HRQoL.[21-23]

The objective of this study was to evaluate the effect of dupilumab on the individuals' sense of smell in patients with severe CRSwNP using pooled data from SINUS-24 and SINUS-52 and to categorise these data according to the time since CRSwNP diagnosis. The study design of SINUS-24 and SINUS-52 was described in a previous review. Pooled data from SINUS-24 and SINUS-52 were analysed post hoc and the time since first diagnosis of CRSwNP was categorised into four groups: <5 years, 5 to <10 years, 10 to <15 years, and ≥15 years. Sense of smell outcomes at 24 weeks were determined by the loss of smell symptom score, UPSIT, and the smell/taste item of the SNOT-22 test.

Pooled data for each study arm and the time from diagnosis groups were analysed by the least square mean difference and 95% confidence interval (CI) of the change from baseline to Week 24. Furthermore, the odds ratio (95% CI) and risk difference (95% CI) were calculated for the absence of anosmia (UPSIT ≥19) for dupilumab versus placebo at Week 24. Findings from different subgroups were compared using the treatment-by-subgroup interaction p value.

A total of 719 patients were included in this analysis: <5 years, n=236; 5 to <10 years, n=157; 10 to <15 years, n=118; ≥15 years, n=208.

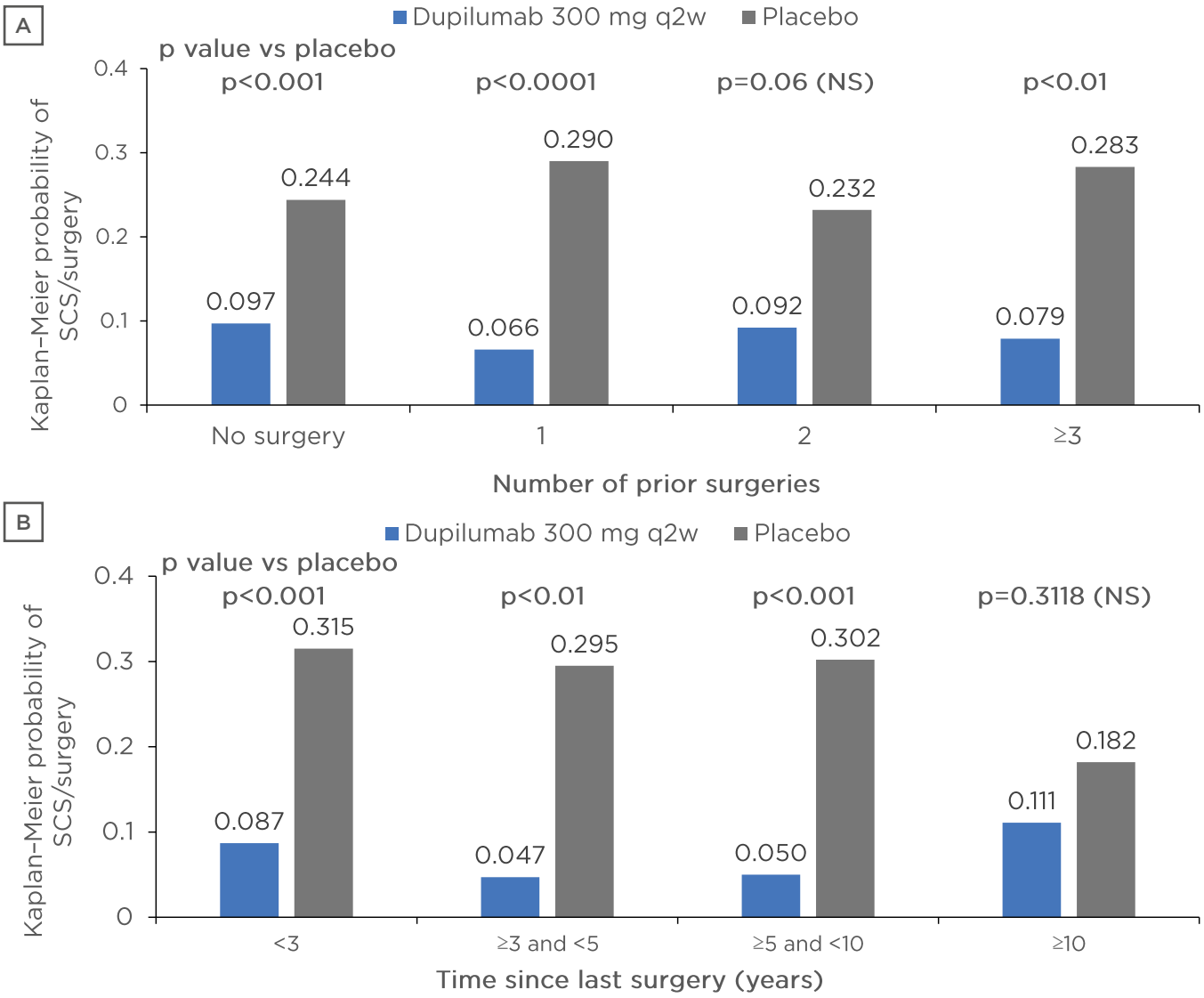

Figure 2: Probability of the need for rescue treatment and/or surgery according to A) number of prior surgeries and B) time since surgery in patients receiving either dupilumab or placebo.

p values derived from Cox proportional hazard models with the event of first systemic corticosteroid use and/or nasal polyp surgery (actual or planned, whichever is earlier) as the response variable, and study identifier, treatment, asthma/nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease status, prior surgery history, and region (pooled countries) as covariates. No significant subgroup-by-treatment interaction.

NS: not significant; SCS: systemic corticosteroid; q2w: every 2 weeks.

Most study participants were male (n=435; 60.5%) and at baseline there were significantly more patients in the ≥15 years subgroup who had ≥1 prior surgery (n=187; 89.9%; p<0.0001) compared with other time from diagnosis groups. Baseline data found that in severe, inadequately-controlled CRSwNP, a longer duration of CRSwNP was associated with greater impairment in the sense of smell.

This study found that in multiple measures of smell loss, dupilumab improved the sense of smell compared with placebo irrespective of the time from diagnosis (Figure 3). Significant differences were reported for all time from diagnosis groups (p<0.0001) except the <5 years subgroup. Furthermore, the investigation found that the proportion of patients in each subgroup without anosmia at Week 24 was significantly higher in all time from diagnosis groups for those receiving dupilumab than patients receiving placebo (nominal p<0.0001 derived using a linear probability model with treatment group,

study, asthma/nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease status, prior surgery history, and region as covariates). The study concluded that dupilumab improved smell outcomes from baseline to Week 24 in all patient subgroups regardless of the time from diagnosis. These results highlight the sense of smell improvements associated with dupilumab for patients with severe CRSwNP who otherwise have few therapeutic options and poor HRQoL.[21-23]

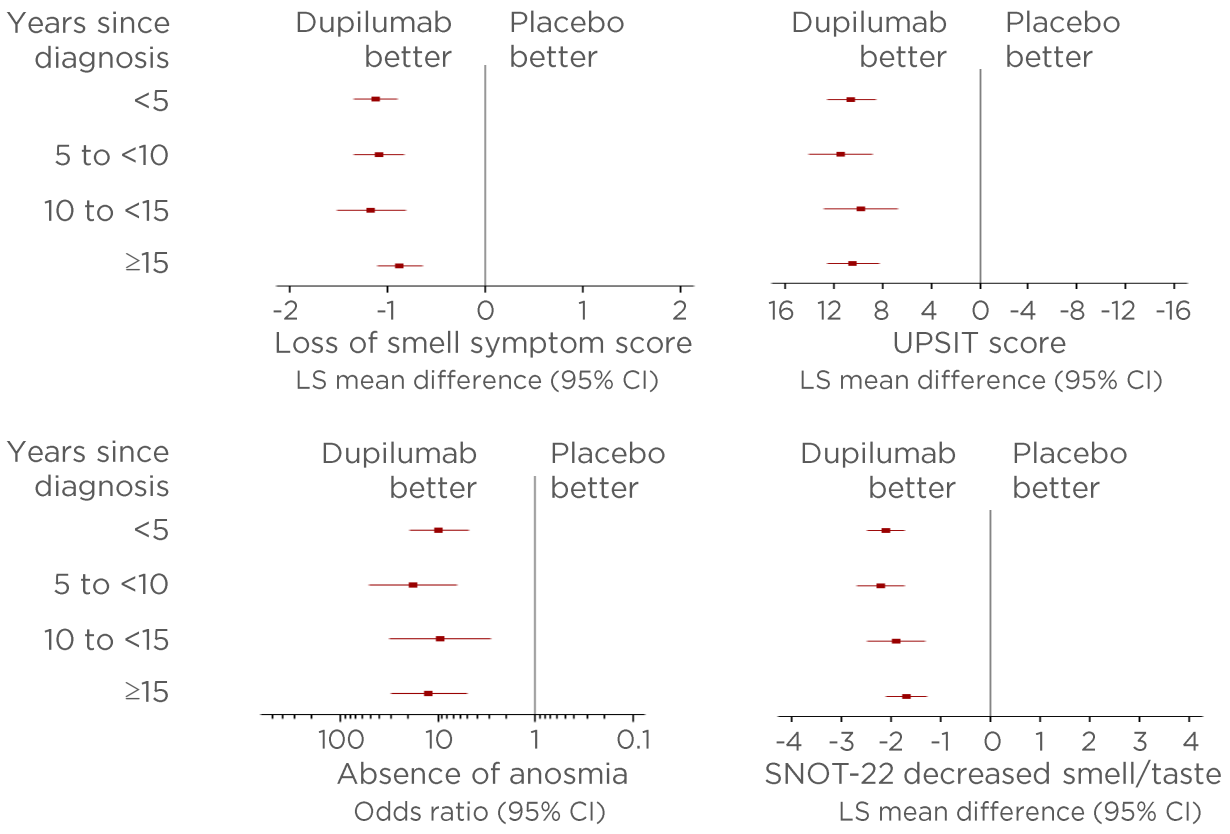

Figure 3: Outcomes in measures of sense of smell from baseline to Week 24 according to years since chronic rhinosinusitis with nasal polyp diagnosis.

Absence of anosmia: UPSIT ≥19. In each subgroup, each of the imputed complete data was analysed by fitting an ANCOVA model for quantitative parameters with the corresponding baseline value, treatment group, asthma/nonsteroidal anti-inflammatory drugs-exacerbated respiratory disease status, prior surgery history, and regions as covariates. The interaction p value was computed by fitting a similar ANCOVA model plus the time since diagnosis and the time since diagnosis-by-treatment interaction, using the <5 years subgroup as a reference. There was no significant difference versus the <5 years subgroup ($p<0.05$).

ANCOVA: analysis of covariance; CI: confidence interval; LS: least squares; SNOT-22: 22-item Sino-Nasal Outcomes Test; UPSIT: University of Pennsylvania Smell Identification Test.

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MAT-EU-2000369 October 2020

Abstract Reviews

The following abstract review articles provide unique insights from posters presented at ERS International Congress 2020, written by the poster authors themselves.

A Randomised Controlled Trial of Acute Health Effects in Patients with Chronic Obstructive Pulmonary Disease After Passive Vape Exposure from e-cigarettes

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Keywords: Chronic obstructive pulmonary disease (COPD), electronic cigarettes (e-cigarettes), electronic nicotine delivery systems, human exposure, particulate matter (PM), spirometry.

Citation: EMJ Respir. 2020;8[1]:65-66. Abstract Review No. AR1.

BACKGROUND AND AIM

Since their introduction to the European and USA markets in 2006–2007, electronic cigarettes (e-cigarettes) have become popular nicotine-

delivery devices.[1] They have been rapidly adopted by millions of users worldwide and are steadily spreading among younger people, especially in high-income and urban populations.[2] As the number of e-cigarette users is increasing, so is exposure to passive vape. Passive vape exposure remains a concern as previous studies have demonstrated that vape from e-cigarettes can contain toxic chemicals that are harmful to health.[3] A World Health Organization (WHO)-commissioned review found that while there are a limited number of studies in this area, it can be concluded that e-cigarette vapour is a new air contamination source for particulate matter (PM), which includes fine and ultrafine particles, as well as 1,2-propanediol, volatile organic compounds, heavy metals, and nicotine.[4] More research is needed to better understand potential health effects to passive bystanders, especially among vulnerable populations, including individuals with existing respiratory disease, known to be frail to environmental exposure.[5]

The aim of this study was to investigate acute local and systemic effects of short-term passive exposure to vape from e-cigarettes among individuals with mild or moderate chronic obstructive pulmonary disease (COPD).

MATERIALS AND METHODS

The study was conducted at the Climate Chamber facilities at the Department of Public Health, Aarhus University, Aarhus, Denmark. Exposure sessions took place under controlled conditions in a 79 m^3 climate chamber made of welded stainless steel, while exposure generation took place in a similar 29 m^3 adjacent chamber. In a double-blinded crossover study, non-smoking patients with COPD were randomly exposed for 4 hours to passive vape (median $PM_{2.5}$: 18 $\mu g/m^3$; range: 8–333) and clean air ($PM_{2.5}$<6 $\mu g/m^3$) separated by 14 days. In order to blind the exposure, e-cigarette users in an adjacent chamber were either vaping or chewing gum, and the (vape-polluted) air was passed to the exposure chamber. Particles were measured using an ultrafine particle counter (P-TRAK®, TSI Incorporated, Shoreview, Minnesota, USA) and a scanning mobility particle sizer. Health effects, including surfactant protein-A (SP-A) and albumin in exhaled air, spirometry, fractional exhaled nitric oxide, and plasma proteins, were evaluated before, right after, and 24 hours after exposure. Participants reported symptoms every 30 minutes throughout exposure sessions. Data were analysed using mixed models.

RESULTS

Sixteen patients (six female, 10 male) with moderately severe COPD and a mean age of 67.6 years participated. The primary outcome, SP-A in exhaled air, was affected by time and exposure to vape, indicating a negative effect of passive vape on SP-A the morning after exposure (-1.78 [-3.35 to -0.20]; p=0.03). Furthermore, several plasma proteins increased significantly, indicating inflammation caused by vape exposure. Throat irritation was more pronounced during passive vape exposure, while forced vital capacity and forced expiratory volume in 1 second decreased. However, estimates were only borderline significant (forced vital capacity: -0.07 [-0.15 to 0.00]; p=0.07) (forced expiratory volume in 1 second: -0.05 [-0.10 to 0.00]; p=0.07). No effect on fractional exhaled nitric oxide was observed among the 16 patients with COPD exposed to passive vape.

CONCLUSION

This study shows that passive vaping is capable of exerting acute inflammatory responses in lungs and blood as well as throat irritation among patients with COPD. Although more research is required, it is clear that e-cigarette emissions are not merely harmless vapour. In the future, more studies on passive vape exposure in sensitive subgroups are recommended, as such studies are virtually nonexistent.

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Altered Iron Metabolism and Elevated Cellular Senescence in Chronic Obstructive Pulmonary Disease Small Airway Epithelial Cells

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Ageing, chronic obstructive pulmonary disease (COPD), iron, senescence.

Citation: EMJ Respir. 2020;8[1]:67-68. Abstract Review No. AR2.

BACKGROUND AND AIMS

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that affects nearly 10% of people over the age of 40 years.[1] COPD is a disease of accelerated ageing,[2] associated with accumulation of senescent cells in the lung.[3,4] Senescent cells are in cell-cycle arrest and therefore do not proliferate. However, they remain metabolically active and secrete a milieu of proinflammatory mediators, known as the senescence-associated secretory phenotype,[5] which is the same inflammatory profile seen in the lungs of COPD patients.[6] These cells may, therefore, play a role in COPD pathogenesis through the loss of lung repair mechanisms and release of inflammatory mediators. Altered iron metabolism is important in the pathogenesis of COPD, with iron chelation therapy being shown to be protective at early time points *in vivo*.[7] Elevated levels of iron are found within bronchoalveolar lavage fluid of COPD patients,[8] but the consequences of this are not fully elucidated. Recently, data have suggested elevated levels of intracellular iron are found in senescent cells, with this potentially driving cellular senescence.[9] However, this has not been studied in the context of COPD. The aim of this study was to assess the relationship between excess intracellular iron and cellular senescence in COPD small airway epithelial cells (SAEC).

METHODS

Total intracellular iron was detected in SAEC from non-smokers (NS) and COPD patients by graphite furnace atomic absorbance spectrometry. SAEC were treated with ammonia iron (Fe^{3+}) citrate (FAC), the iron chelator deferoxamine, or doxorubicin to induce senescence. Iron and senescence markers were detected by Western blot and quantitative reverse transcription PCR in lung homogenate samples and SAEC.

RESULTS

Both intracellular and haem iron were significantly increased in COPD SAEC compared to NS. Treatment of NS and COPD SAEC with FAC caused a significant increase in total iron, with COPD SAEC taking up significantly more iron than NS cells. Chelation of iron significantly reduced intracellular iron levels in COPD SAEC, but not NS. Significant increases in the gene expression of senescence markers $p21^{Cip1}$ and BCL-2 were detected in lung homogenate samples of COPD patients compared to NS, with significantly increased expression of the transferrin receptor and decreased expression of ferroportin also observed. Elevated protein levels of the transferrin heavy chain and transferrin receptor were detected in COPD SAEC compared to NS, and these correlated with changes in the expression of p21 and the anti-ageing molecules sirtuin-1 and -6. Induction of cellular senescence using doxorubicin led to elevated gene expression of both p21 and the transferrin receptor, suggesting a link between senescence and elevated iron uptake.

CONCLUSIONS

Elevated levels of intracellular iron were observed in COPD SAEC compared to NS. COPD SAEC had increased capacity to uptake extracellular iron, which could be chelated. COPD SAEC and lung homogenate samples had increased

senescence markers, as well as altered iron metabolism proteins. Senescence induction led to increased expression of the iron import protein, the transferrin receptor. Overall, these data suggest both elevated intracellular iron levels and senescence in COPD SAEC. Further work is needed to elucidate how these two processes are linked.

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The Impact of a Stewardship Programme on Outcomes in Patients Admitted with Community-Acquired Pneumonia

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Keywords: Community-acquired pneumonia (CAP), healthcare quality, outcomes, quality improvement, stewardship programme

Citation: EMJ Respir. 2020;8[1]:68-69. Abstract Review No. AR3.

BACKGROUND AND AIMS

Community-acquired pneumonia (CAP) is a common cause of antibiotic prescription, hospital admission, and mortality.[1] Treatment according to guidelines has shown to be beneficial in CAP.[2] However, adherence to the recommendations given in guidelines is highly variable.[3] The authors have previously conducted a quality improvement project to increase guideline adherence;[4] the project itself was a success, but the impact on key outcomes had not yet been assessed.

The aim of this study was to estimate the impact of a stewardship programme on patient management and outcomes in patients admitted with CAP.

MATERIALS AND METHODS

The authors conducted a before-after study comparing the odds for key outcomes in CAP before and after the implementation of an 8-month stewardship programme at three

Danish hospitals. Comparisons were made using logistic regression models. The outcomes considered were antibiotics for ≤7 days, intravenous antibiotics for ≤3 days, antibiotics according to the guideline, length of stay ≤5 days, in-hospital mortality, and 30-day mortality. As stability within 72 hours of admission is a strong confounder, all analyses were performed on the overall cohort as well as a subset of patients stable within 72 hours. Univariable and multivariable analyses were performed, as well as a sensitivity analysis on a propensity score-matched cohort. The variables used for adjustment and matching were age, sex, comorbidities, pneumonia severity, antibiotics before admission, multilobular infiltrates, low oxygen saturation at admission, and a positive smoking history.

RESULTS

In total, 771 patients were eligible for participation in the present study. Of these, 423 were admitted in the baseline period and 348 in the follow-up period. The study cohort was a classic CAP cohort; the mean age was 72 years, and the sex ratio was balanced. Severe CAP with a CURB-65 score of 3–5 was observed in 17% of cases. Median durations of intravenous antibiotic treatment, total antibiotic treatment, and length of hospital stay were 2.6, 10.0, and 4.0 days at baseline, respectively.

The adjusted odds ratios (OR; 95% confidence interval [CI]) for antibiotics for ≤7 days were 1.85 (1.34–2.55) for the overall cohort and 2.14 (1.43–3.22) for the stable subgroup. The adjusted OR (95% CI) for correct empiric antibiotics were 1.94 (1.42–2.65) in the overall cohort and 1.78 (1.19–2.66) in stable patients. For all other outcomes, the effect sizes indicated no significant changes. Results for the propensity score-matched cohort were comparable to the results from the multivariable analyses.

CONCLUSION

The stewardship programme led to an increase in patients treated with the correct antibiotics according to the guideline, as well as a higher number of patients treated for 7 days or less. Significant changes were not observed for intravenous antibiotic treatment for 3 days or less, nor length of hospital stay of 5 days or less. However, the median durations of intravenous antibiotics and hospital stay were already satisfactory at baseline and noticeably better than reported in previously conducted studies. Hence, the improvement potential was not great. Significant changes regarding in-hospital or 30-day mortality were not detected. This was unsurprising, as the study was not powered to detect significant changes in mortality.

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Treatment Complication Rates in Ongoing Smokers Versus Quitters After a Diagnosis of Lung Cancer: A Cohort Study

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Keywords: Complications, lung cancer, smoking.

Citation: EMJ Respir. 2020;8[1]:70-71. Abstract Review No. AR4.

BACKGROUND AND AIMS

Despite technical advances in investigations and treatment, the 5-year survival for lung cancer (LC) remains poor. Studies suggest that continued smoking after a diagnosis of LC independently worsens quality of life and shortens life expectancy; however, these were small, retrospective cohorts where smoking was usually only self-reported and only recorded at baseline. The authors have recently shown that quitting smoking following a diagnosis of non-small cell lung cancer (NSCLC) may lead to a reduction in mortality by 17% at 1 year.[1]

Smoking can adversely affect outcome by causing and accelerating other illnesses in people with LC. Smokers are more likely to be diagnosed with chronic obstructive pulmonary disease, heart disease, cerebrovascular disease, high blood pressure, diabetes, thrombosis, and many other conditions.[2,3] Continued smoking worsens any comorbid condition, which can lead to increased risk of infections, resulting in delays or interruptions to LC treatment.

In patients with head and neck cancer, those who stopped smoking following diagnosis survived twice as long as those who continued to smoke. Those who continued to smoke had a four-times greater rate of recurrence.[4] In patients with breast cancer, recurrence in smokers was 15% higher (p=0.039) compared to those who quit.[5] This is further replicated in patients with prostate cancer.[6]

The aim of the study was to determine if quitting smoking after a diagnosis of LC reduces complication rates, including treatment interruptions and hospital admission.

MATERIALS AND METHODS

As part of a UK multicentre, prospective, observational cohort study of 1,134 patients with newly diagnosed NSCLC, the authors recorded self-reported smoking status, validated with exhaled carbon monoxide readings, at baseline and each follow-up visit until death for up to 2 years. Treatment complications were noted by free text if reported by the patient (e.g., diarrhoea, vomiting), or by the clinical team (e.g., post-operative wound infection, chemotherapy-induced neutropenia, radiation pneumonitis). They were reviewed by a study clinician blinded to smoking status but were not graded according to severity.

Smoking cessation treatments were offered according to local services. Data were recorded on study case report forms and confirmed from hospital records and cancer databases; data were analysed with Stata.

RESULTS

Of the 1,134 patients recruited, 290 (25.6%) were smokers at baseline and 84 (29%) of these quit within 3 months of diagnosis. Continued smokers (66.5 years; standard deviation: 9.4) were of similar age to quitters (66.1 years; standard deviation: 9.6; p=0.232), but 34.7% of quitters had Stage I and II NSCLC, compared to 19.2% of smokers (p<0.001). 28.6% underwent surgery compared to 8.1% in those who continued to smoke (p<0.001). At 12 months, 55.6% of quitters were deceased compared to 68.1% of continued smokers (p<0.01).

At 1 month, quitters had fewer treatment complications than those who continued to smoke (p=0.03). At 6 months (p=0.76) and 12 months (p=1.00), there were no differences in complication rates between quitters and continued smokers (Figure 1).

CONCLUSION

Quitting smoking after a diagnosis of NSCLC is associated with fewer treatment complications at Month 1. This may be due to the confounding effects of increased Stage I and II tumours and higher number of surgical resections in quitters. The authors have continued to follow outcomes with larger numbers, grouping treatment-related complications into 'mild', 'moderate', or 'severe' according to standard definitions, as well as noting whether these complications necessitated treatment delays or treatment changes.

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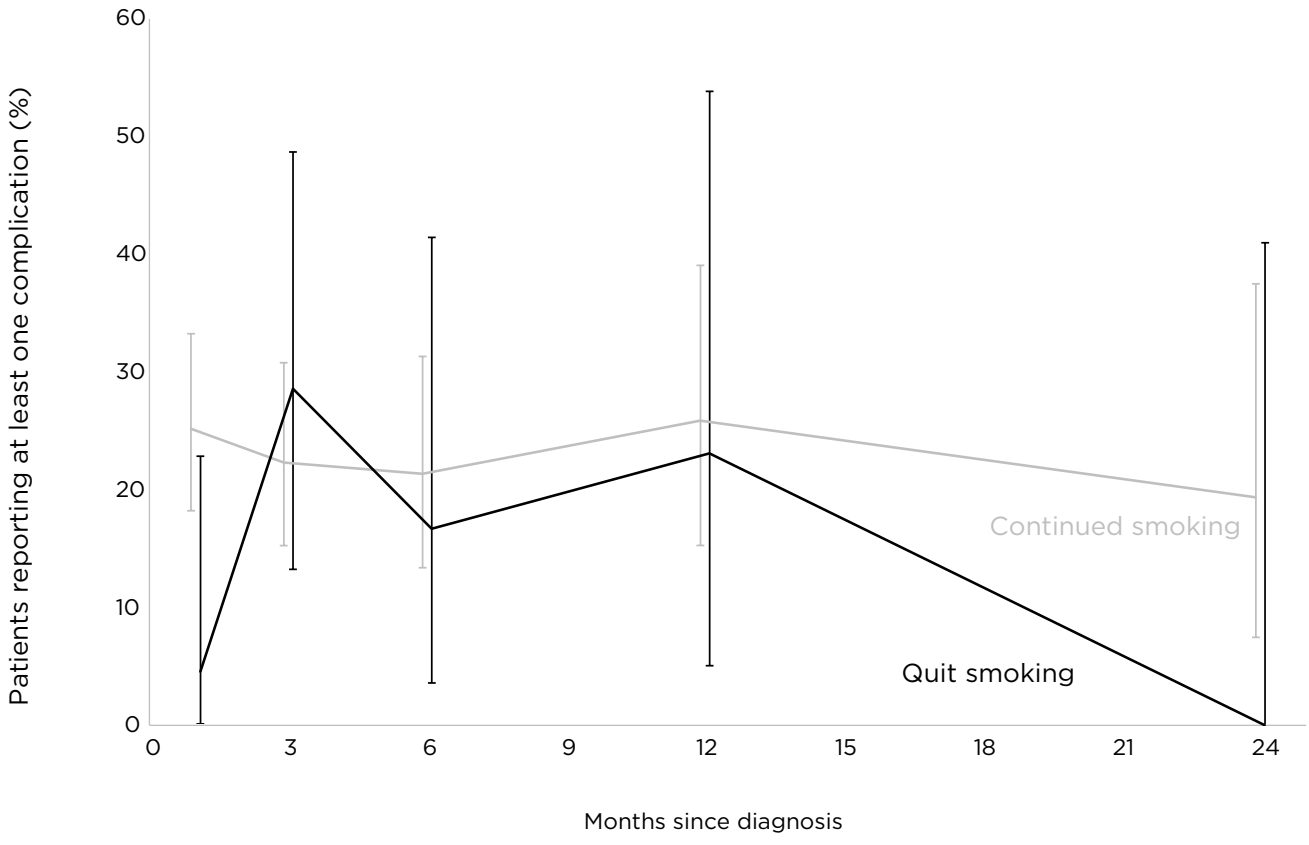

Figure 1: Non-small cell lung cancer treatment complication rates comparison by smoking status.

Liquid Biopsy in Patients With Adenocarcinoma – Comparison Between Bronchoalveolar Lavage and Blood Samples

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Keywords: Adenocarcinoma, bronchoalveolar lavage (BAL), liquid biopsy.

Citation: EMJ Respir. 2020;8[1]:72-73. Abstract Review No. AR5.

BACKGROUND AND AIMS

In recent years, there has been a revolution in genomic profiling and molecular typing of lung cancer. *EGFR* is a key oncogene, and a gold standard for determining *EGFR* mutation status is a histological specimen taken by a bronchoscopic method or surgical material, but it is often difficult to obtain enough tumour tissue for morphological and molecular verification. Isolation of free circulating peripheral blood tumour DNA (ctDNA), known as 'liquid biopsy', is a noninvasive alternative method to tissue biopsy for performing molecular screening in patients suitable for targeted therapy. This study aimed to compare the prevalence of *EGFR* mutation status in bronchoalveolar lavage (BAL) and peripheral blood according to the gold standard tissue biopsy in patients with primary lung adenocarcinoma.

MATERIALS AND METHODS

All patients scheduled for bronchoscopy in the authors' hospital between October 2018 and August 2019 were assessed. The exclusion criteria did not differ to those for standard contraindications for a bronchoscopy. Flexible bronchoscopy was performed in all patients under local anaesthesia. The biopsy techniques were forceps biopsy, transbronchial biopsy with or without fluorographic control (based on preliminary CT data), and BAL.

RESULTS

In the period of the study, 140 bronchoscopies were performed. In 112 patients (80%), a tumour was verified. Adenocarcinoma was present in 23.2% (26/112) of the patients with lung cancer, which was verified with immunohistochemistry. The groups did not differ regarding age and tumour maximum diameter. However, there were significantly more females with *EGFR* mutation (77%; 10/13) as opposed to males (23%; 3/13; p=0.017).

Thirteen patients had wild-type *EGFR* and the other 13 had *EGFR* mutation. *EGFR* mutation from a peripheral blood sample was identified in 38.5% (5/13) of patients, whereas *EGFR* mutation obtained from BAL was identified in 92.3% (12/13) (Table 1). In one case, in both liquid biopsy samples (BAL and plasma) additional T790M mutation along with deletion in exon 19 were found, which was not established in the corresponding formalin-fixed paraffin-embedded tissue sample (Patient 8). Neither BAL nor blood sample confirmed *EGFR* mutation in one patient, which was defined as positive only in the tissue sample.

CONCLUSION

The current standard for detection of mutation in patients with unknown status after negative tissue sampling is rebiopsy. Unfortunately, rebiopsy is not always feasible due to many reasons. In this context, liquid biopsy could be an effective solution.

Table 1: Confirmation of *EGFR* mutation in bronchoalveolar lavage and blood samples.

	Confirmed *EGFR* mutation
BAL sample	12 (92.3%)
Blood sample	5 (38.5%)
Total patients	13 (100.0%)

BAL: bronchoalveolar lavage.

However, results from individual studies are variable,[1-3] with many indicating that detection of *EGFR* mutations in ctDNA is more difficult in plasma samples than in tumour tissue, with an average sensitivity of 65–70%. On the other hand, establishing *EGFR* status from BAL is a viable and safe procedure, especially in impaired patients with promising results.

In this study, the authors demonstrated the superiority of BAL to venous blood liquid biopsy in establishing an *EGFR* mutation. This could facilitate a diagnosis with a minimally invasive method and lower risk for the patient with comparable results to formalin-fixed paraffin-embedded tissue.

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Lung Function in Extremely Preterm Born Adults Over Three Decades

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Keywords: Chronic obstructive pulmonary disease (COPD)-mechanism, lung-growth, neonatal, paediatrics, premature, spirometry.

Citation: EMJ Respir. 2020;8[1]:73-75. Abstract Review No. AR6.

BACKGROUND AND AIMS

Perinatal medicine has improved considerably since the 1980s, with the arrival of innovative treatments such as antenatal steroids, exogenous surfactant, and better ventilatory techniques. This has improved survival rates for infants born extremely preterm (EP), particularly among the most immature and vulnerable infants.[1] Conceivably, these trends might have influenced long-term health outcomes for this group of individuals in opposite directions, with the overall development difficult to predict. Bronchopulmonary dysplasia (BPD), a chronic lung-disease of prematurity, is one of the most common complications of preterm birth,[2] leading to varying degrees of compromised lung function in early adulthood.[3] The aim of this study was to assess pulmonary outcome at 18 years of age in EP-born and matched term-born control cohorts, born in three different decades and characterised by improvements in neonatal care.

METHODS

Three population-based birth-cohorts of subjects born at gestational age ≤28 weeks or with birth weight ≤1,000 g in 1982–1985 (82–85 cohort), 1991–1992 (91–92 cohort), and 1999–2000 (99–00 cohort) and individually matched term-born control subjects performed spirometry at approximately 18 years of age. Independent sample t-tests were used to compare 'within-decade' differences between the EP and term-born groups, whereas one-way ANOVA analyses were performed to compare lung function deficits for the EP-born over three decades.

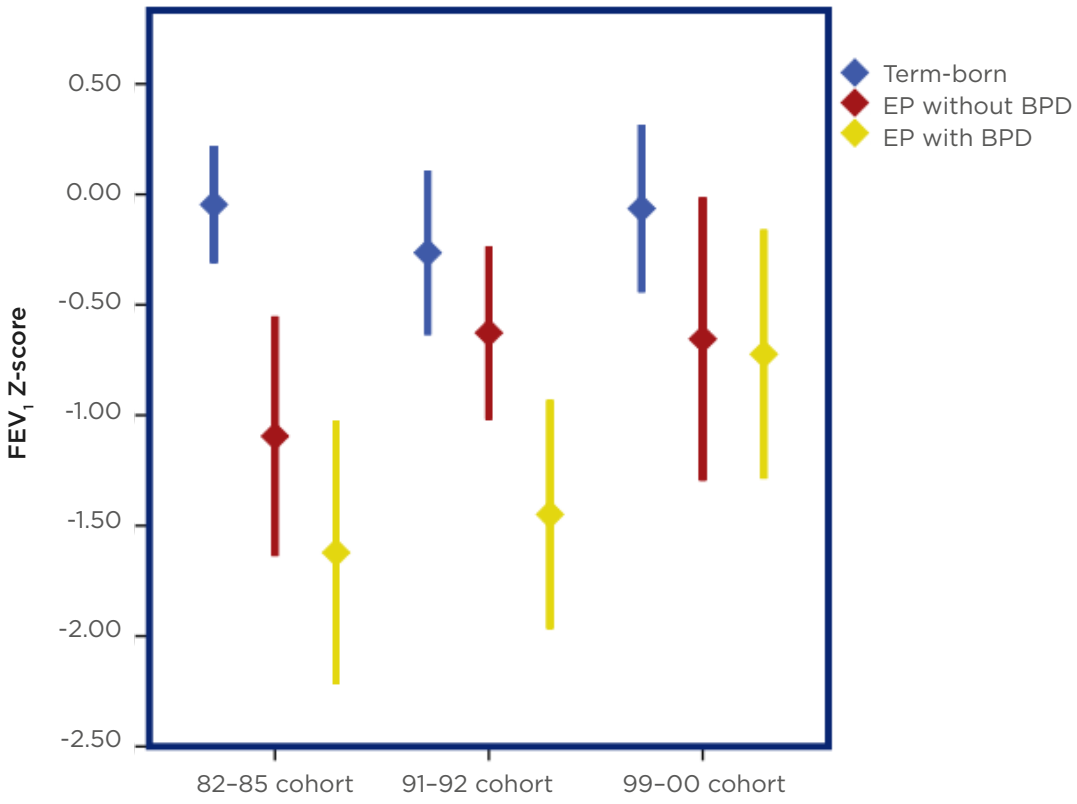

Figure 1: Forced expiratory volume in 1 second (FEV_1) Z-score group means with 95% confidence intervals.

BPD: bronchopulmonary dysplasia; EP: extremely preterm.

RESULTS

In total, 118 EP and 111 term-born participants (68% and 80% of eligible subjects, respectively) performed spirometry at approximately 18 years of age. Forced expiratory volume in 1 second (FEV_1) Z-scores were lower in EP-born compared to term-born in all three cohorts, deficits being -1.23, -0.68, -0.45 for the 82–85, 91–92, and 99–00 cohorts, respectively ($p<0.01$; $p<0.01$; $p=0.04$). Mean FEV_1 Z-scores improved significantly from the 82–85 to the 99–00 EP-born cohort, but not for the corresponding term-born controls (mean differences: 0.67 [$p=0.02$] and 0.11 [$p=1.0$], respectively). When splitting the EP-born by BPD, mean FEV_1 Z-scores improved significantly from the 82–85 to the 99–00 cohort for subjects with BPD, but not for those without BPD (mean differences: 1.12 [$p=0.02$] and 0.46 [$p=0.59$], respectively; Figure 1).

CONCLUSION

At 18 years of age, survivors of EP birth from all three cohorts had lower lung function than their term-born peers. Pulmonary outcome had improved over the three decades, mainly explained by those with BPD.

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Engaging Younger People in Their Asthma Management – Findings From a Pilot Telemedicine Asthma Nurse Service

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Keywords: Asthma, digital care, e-health, health advice, remote care, young people.

Citation: EMJ Respir. 2020;8[1]:75-76. Abstract Review No. AR7.

BACKGROUND AND AIM

Asthma UK has a well-established, free asthma telephone helpline, for which people with asthma can receive individual advice on managing their condition from a nurse during the working day (weekdays 9 am–5 pm [BST]). However, not all people with asthma are receiving the care they need. The Asthma UK 2018 Annual Asthma Survey found that only 33% of people aged 18–29 received three elements of basic care: an annual review, an inhaler technique check, and a written asthma action plan.[1] Provision of a telephone helpline requires significant investment of manpower and the supply and demand is often difficult to predict and manage. Additionally, given that people with asthma looking for help are often adolescents and young adults, of whom most extensively use a mobile phone on a daily basis, a telephone service is increasingly not the medium they would choose and may indeed put them off seeking help. The team at Asthma UK developed a WhatsApp service that aimed to help capitalise on this groups' high level of digital literacy and engagement, and address this unmet care need. The service allows people with asthma to message a nurse directly and

receive advice via a text message, a useful link, infographic, or video.

METHOD

Early popularity of the service necessitated a plan to scale it up. To understand the feasibility of this, user research was conducted via a post-chat survey and in-depth interviews were conducted with users. Key objectives of this research were to find out if the service helped improve a user's management of their asthma; how to improve the user experience; enable a better understanding of service users; and to develop a service taxonomy to tag and analyse the conversations. This created improved service intelligence, which helped to scale up the service. To scale it up, a rapid procurement process was necessary in order to cope with an expected peak in use during winter, and an off-the-shelf platform best met these requirements. Staff were trained on how to use the new platform, and Asthma UK and the British Lung Foundation partnership (AUK–BLF) worked with the company procured to ensure a smooth launch of the expanded platform.

RESULTS

This service proved popular with service users, with 91.5% 'very satisfied' with the service. The content was apparently pitched at the correct health literacy level, with 98.4% finding the advice easy to understand. The survey results indicated that 63.5% of service users felt more confident in managing their asthma. Those aged 18–33 comprised 37.6% of the survey respondents, suggesting success in attracting a younger demographic to use this service.

CONCLUSIONS

This research has positive implications for future models of care. It shows that remote health advice can be delivered in a manner tailored to new audiences and can help people manage their asthma with more confidence and be better informed about their condition. The future challenge will be to ensure that these improvements are sustained, and to scale up this project to help more people with asthma, and potentially other conditions.

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Interaction Between Occupational Exposures and Antioxidant Genes on Chronic Obstructive Pulmonary Disease in UK Biobank

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Keywords: Antioxidants, chronic obstructive pulmonary disease (COPD), gene–environment interaction, occupational exposures.

Citation: EMJ Respir. 2020;8[1]:77-78. Abstract Review No. AR8.

BACKGROUND AND AIM

Occupational exposure to vapours, gases, dusts, and fumes (VGDF) has been associated with lower lung function[1] and a higher risk of chronic obstructive pulmonary disease (COPD).[2] The proportion of COPD attributable to occupational exposures has been estimated at 14%.[3] A proposed mechanism underlying the effect of VGDF on COPD is through oxidative stress. A reduced antioxidant capacity has been found in COPD patients[4] and higher levels of oxidative stress biomarkers have been associated with exposure to VGDF.[5] The effect of VGDF on the lung might be apparent (or might be substantial) only in the presence of genetic variation (e.g., single nucleotide polymorphisms [SNP]) in antioxidant genes, indicating a gene–environment interaction. The study aimed to identify interactions between variants in well-known antioxidant genes and VGDF exposure on COPD risk.

METHODS

To assess antioxidant gene–VGDF interactions, the authors included 199,607 working individuals from the large UK Biobank (UKB; aged 39–71; 49% male; 44% never-smoker). Of these, 16,389 individuals had COPD spirometrically defined as forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC)< lower limit of normal (GLI-2012) and 34% were exposed to VGDF estimated using the airborne chemical (ACE) job exposure matrix.[6] All independent SNP within 15 antioxidant genes selected based on a recent review were analysed.[7] Gene–VGDF interactions were invested using a case-only approach using BOLT-LMM adjusted for sex, age, height, smoking status, genotyping batch, and centre, and accounting for population stratification/relatedness. Analyses were stratified according to smoking status. For significant interacting SNP, the authors assessed effects on gene-expression and DNA methylation levels using the online tool PhenoScanner.[8]

RESULTS

Overall, subjects exposed to VGDF had a 7% increased risk of COPD (Table 1a). However, this increase in risk was only seen in ever-smokers and was significantly different to never-smokers (interaction $p=8.79x10^{-5}$).

In the SNP–VGDF interaction analyses, the authors identified nine nominally significant interactions ($p<0.05$) for the antioxidant genes *CAT* (two SNP), *GC* (two SNP), *GSTP1*, *GSTT1*, *NOS1*, *SOD1,* and *SOD2*. Except for a SNP in *GC*, none of the SNP had a marginal effect on COPD and would therefore not be found if ignoring the effect modification by VGDF. Of the nine SNP, only two rare SNP with minor allele frequencies <3% in *GSTP1* (rs8191445) and *NOS1* (rs145671209) survived correction for multiple testing (false discovery rate <5%). Subjects exposed to VGDF and carrying a copy of the minor allele of the *GSTP1* and *NOS1* SNP had a respective 19% and

30% higher risk of COPD compared to subject not exposed to VGDF and not carrying a copy of the minor allele (Table 1b). Although the interactions were only significant in never-smokers, the three-way SNP–VGDF–smoking interactions were not significant (p=0.338 for *GSTP1* and p=0.460 for *NOS1*). The *GSTP1* SNP was associated with expression of two nearby genes (*DOC2GP/NDUFS8*) in whole blood. No association was found with DNA methylation for either SNP.

CONCLUSION

These results suggest that VGDF exposure is associated with a higher risk of COPD, but that this risk may be confined to smokers. Those with rare variations in the antioxidant genes *GSTP1* and *NOS1* may be more susceptible to the effects of VGDF on COPD, and this effect might be more apparent in never-smokers. Further work is needed to replicate these results in independent samples and to investigate the possibility of three-way SNP–VGDF–smoking interactions.

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Table 1: Results of the association analysis of A) VGDF with COPD (marginal effect of VGDF); and B) of the SNP-VGDF interaction analyses for both the *GSTP1* and the *NOS1* SNP, stratified by smoking.

	All (N=199,607)			Never-smokers (n=112,476)			Ever-smokers (n=87,180)		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
a) Marginal effect of VGDF									
VGDF	1.07	1.03–1.11	**$2.59x10^{-4}$**	1.01	0.95–1.06	0.851	1.12	1.07–1.18	**$1.45x10^{-6}$**
b) Results from the interaction analysis									
VGDF	1.06	1.02–1.10	**$3.20x10^{-3}$**	0.99	0.94–1.04	0.695	1.12	1.06–1.17	**$1.32x10^{-5}$**
GSTP1 (rs8191445)	0.90	0.82–0.98	**0.020**	0.90	0.79–1.03	0.121	0.89	0.78–1.01	0.074
VGDF**GSTP1*	1.19	1.03–1.37	**0.019**	1.27	1.03–1.57	**0.024**	1.13	0.93–1.38	0.212
VGDF	1.06	1.02–1.10	**$1.44x10^{-3}$**	0.99	0.94–1.05	0.846	1.12	1.07–1.17	**$5.73x10^{-6}$**
NOS1 (rs145671209)	0.89	0.78–1.01	0.069	0.86	0.71–1.03	0.094	0.93	0.77–1.11	0.408
VGDF**NOS1*	1.30	1.07–1.59	**0.010**	1.42	1.05–1.91	**0.021**	1.21	0.92–1.60	0.171

Significant results are presented in bold.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; OR: odds ratio; SNP: single nucleotide polymorphism; VGDF: vapours, gases, dusts, and fumes.

A Qualitative Study of Patients' and Healthcare Professionals' Views on Self-Management in Bronchiectasis

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Keywords: Bronchiectasis, chronic diseases, education, self-management (SM).

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BACKGROUND

Bronchiectasis is a chronic respiratory condition that has a significant impact on morbidity, quality of life, mortality, and healthcare services.[1] The current aims of therapeutic management are preservation of lung function, reduction of exacerbations, minimising complications, and improving quality of life.[2,3] The British Thoracic Society (BTS) guidelines suggest a five-step plan to treat patients with bronchiectasis, ranging from Step 1, which includes all patients, to Step 5, which is specific to those with worse symptoms.[3] Therapeutic strategies and interventions common to most international guidelines include antibiotics, airway clearance techniques, and pulmonary rehabilitation.[2,3] The aim is to break the vicious recurrent cycle of infection, inflammation, impaired mucociliary clearance, and structural lung damage. Self-management (SM) has been recommended in clinical guidelines as an important intervention that could potentially empower patients to manage their condition, reduce exacerbations and therefore disease burden, and improve quality of life.[3] Yet, to date, there is very little evidence to support SM programmes for patients with bronchiectasis, despite being a recommendation in Step 1 of the BTS guidelines. A previous Cochrane systematic review found insufficient evidence to determine whether SM interventions benefit patients with bronchiectasis,[4] which has since been confirmed by a broader review.[5]

METHODS

Three focus groups of 17 adults with bronchiectasis were conducted at three National Health Service (NHS) sites in North West England, UK. Additionally, semi-structured interviews were undertaken with 11 healthcare professionals (HCP), including doctors, nurses, and physiotherapists. Thematic analysis identified key findings which were verified by independent audit. This study was approved by NHS London Harrow Research Ethics committee (ref 18/LO/1671).

RESULTS

Four key and common themes were identified from both HCP and patients: what is SM?; influencers of SM; benefits of SM; and barriers to SM (Table 1). When considering what SM is, both groups recognised similar components of SM. Sub-themes varied among the groups, with patients highlighting that SM was about learning what works for you, and how it can be used to moderate behaviour. HCP focussed on delivery and structure of SM and resources. Influencers for engaging in SM were recognised by HCP as individual patient attributes in addition to the knowledge and skills of HCP. Both groups saw distinct benefits to SM, namely treating and preventing exacerbations and controlling anxiety, and, from the patients' perspective, as a proxy for HCP; HCP focussed on clinical outcomes, empowering patients and improving economic benefits to healthcare delivery. Patients and HCP recognised common barriers, but only patients referred to SM as time-consuming. Both groups recognised the importance of access (or lack of) to resources including HCP's knowledge of the condition.

Patients did not refer to distinct traits in themselves that may influence engagement in SM, but demographics gave insight into activity levels relating to SM.

Table 1: Key themes and subthemes for patients and healthcare professionals.

What is self-management?					
Patients			**HCP**		
Components	Learning what works for you	Moderating behaviour	Components	Delivery and structure	Resources
Influencers on self-management					
Patients			**HCP**		
Peer, carer, and social support	HCP knowledge	Easy access	The patient	The HCP	
Benefits of self-management					
Patients			**HCP**		
Treat and prevent exacerbations	Proxy for HCP	Control anxiety	Empowering patients	Clinical outcomes	Economic benefits
Barriers to self-management					
Patients			**HCP**		
Time-consuming	Lack of access to HCP	Outlook on life	Patient factors	Lack of tools/resources resentment	

HCP: healthcare professionals.

Patients valued peer learning whilst HCP acknowledged individuals' need for different approaches and it's not one size fits all.

SUMMARY

Both patients and HCP had common insights about SM for patients with bronchiectasis. All participants were positive about SM, but barriers were identified that provided a vital insight necessary to the design of future programmes. Findings from this study suggest that patients' psychosocial and socioeconomic circumstances may affect adoption and activation of SM behaviours.

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Promising Integrated Care Platform Developed with and Tested by Respiratory Patients: Lessons Learned From the European H2020 CONNECARE Study

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Keywords: Asthma, chronic obstructive pulmonary disease (COPD), eHealth, physical activity, telemonitoring, usability, wearables.

Citation: EMJ Respir. 2020;8[1]:81-82. Abstract Review No. AR10.

BACKGROUND AND AIMS

In 2014, the European Union (EU) H2020 CONNECARE project was initiated in the Netherlands, Spain, Italy, Germany, Israel, and the UK. In this project, clinicians, information technology (IT) professionals, IT companies, and researchers work together to develop an online integrated care platform for complex chronic patients. The European population is ageing and thereby the proportion of people with one or more chronic diseases is increasing. At this moment, many healthcare systems are fragmented into medical specialisations, whereas a large proportion of chronic patients have more than one chronic illness. The aim of the CONNECARE platform is to develop an integrated care system that facilitates co-operation between healthcare professionals and supporting patients in self-management thereby enhancing personalised healthcare. The aim of this study was to evaluate the feasibility and usability of the CONNECARE platform by patients and case managers.

METHODS

The first prototype consists of a dashboard for case managers and a self-management app for patients, a chat function, symptom questionnaires, and the integration of an activity tracker. The system was evaluated for 6 months in Dutch patients with chronic obstructive pulmonary disease (COPD). A group of COPD patients were randomly assigned to the app with or without weekly messages regarding physical activity. The feasibility was evaluated via questionnaires and focus groups with COPD patients, tracking of step counts, and a comparison between patients who received weekly messages. These messages contained information about the benefits of physical activity, for example "Making a phone call? Good moment for a little walk." Usability was evaluated by using the system usability scale (SUS), a logbook for technical issues, and an evaluation of case managers' opinions.

RESULTS

Of the 46 patients with COPD who participated in the study (mean age: 60±13 years; range: 31–82 years; 52% male; 30% had asthma; 65% had COPD; 4% had asthma–COPD overlap), 21 received the weekly messages. The authors found no statistically significant difference in step count between the groups. Patients were able to use the app and to communicate with the case manager via the messaging function in the app. Regular evaluations with patients and stakeholders led to constant optimisation of the application. However, three patients felt uncomfortable when using the activity tracker: "Others can see my data if I use Bluetooth." The SUS in patients after 3 months was 81% ('excellent'; n=30) and dropped to 74% after 6 months ('good'). There was no difference in SUS between patients with low or high social economic status. The chat function was considered to be easy to use.

CONCLUSION

The initial version of the CONNECARE system was easy to use by patients and feasible to

implement even in this COPD population. The ongoing evaluation in patients and case managers and regular communication with IT specialist led to constant optimisation of the system and the communication between all different stakeholders appeared to be essential in the development of this system. There are no significant effects of messages on the effort step count, possibly because of the low number of participants. Future studies should look into the effect of regular stimulating messages on physical activity in a larger group possibly also including individualised messages. The next step for the CONNECARE system is to prepare it for the technical and process integration in existing healthcare systems.

Induction of the Transcriptional Repressor B Lymphocytes-Induced Maturation Protein-1 (Blimp-1) in Lung Cancer

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Keywords: B lymphocytes-induced maturation protein-1 (Blimp-1), immunotherapy, non-small cell lung cancer (NSCLC), tumor infiltrating lymphocytes, T-box-expressed in T cells (T-bet).

Citation: EMJ Respir. 2020;8[1]:82-83. Abstract Review No. AR11.

BACKGROUND AND AIM

Lung cancer immunotherapy has improved the survival for patients with advanced non-small cell lung cancer (NSCLC). Immunotherapy could improve the prognosis for lung cancer by activation of tumour-infiltrating lymphocytes, which are silenced by the expression of T-cell receptor inhibitor molecules such as programmed cell death protein 1. Immunotherapy, such as antiprogrammed death-ligand 1 antibody therapy, results in the activation of tumour-infiltrating lymphocytes into cytotoxic CD4+ and CD8+ T cells in the tumour microenvironment and suppression of immune-repressing regulatory T cells (Treg).[1] The authors previously demonstrated that the recognition and elimination of lung tumour cells by T lymphocytes requires the presence of T-box-expressed in T cells (T-bet), a transcriptional regulator that induces Th1 differentiation, which promotes cytolytic $CD8^+$ T cells, natural killer, and natural killer T cells and inhibits Treg cells.[2] Moreover, recent studies showed that IL-2 in the tumour microenvironment supports acquisition of cytotoxic activity by Th cells orchestrated by the transcriptional repressor B lymphocytes-induced maturation protein-1 (Blimp-1).[3] As Blimp-1 also affects the homeostasis and function of CD4 and CD8+ T cells as well as Treg cells, the authors hypothesised that this transcription factor might play an important role in lung cancer.

METHODS

The authors have recently described their biobank obtained from a cohort of patients with NSCLC.[6] Specifically, after lung resection, the authors immediately transported on ice the lung samples in cell culture medium to their department and froze samples immediately for further analysis. Next, proteins from these lung sections were extracted and the Blimp-1 protein expression was analysed by Western blot analysis using proteins isolated from the different region of the lung of a cohort of patients that

underwent surgery because of NSCLC and subsequent histological classification as lung adenocarcinoma (ADC).

RESULTS

The authors found that patients with lung ADC had a significant induction of Blimp-1 protein expression in the tumoural region of ADC (solid tumour) as compared control lung region (tumour-free control area). The expression of T-bet in these patients was further analysed and it was found that T-bet, as opposed to Blimp-1, was mainly expressed in the control region of the lung of these patients and downregulated in the tumoral region. Next, the localisation of Blimp1 positive cells in the tumour microenvironment was analysed by immunostaining lung sections from the cohort of patients using anti-Blimp 1 antibodies followed by DAPI staining. Here, the accumulation of Blimp1-positive cells surrounding the tumour was observed, as compared to the control region.

CONCLUSION

In conclusion, these data suggest that Blimp-1 might represent an additional new marker to be considered in the absence of T-bet as regulator of antitumour immune responses in lung cancer.

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Congress Interviews

We spoke with two European Respiratory Society (ERS) 2020 Award Winners about their area of expertise and the coronavirus disease (COVID-19) pandemic.

Dr Dina Brooks

ERS Assembly Lifetime Achievement Award Winner
School of Rehabilitation Sciences, McMaster University, Hamilton, Canada

Q1 What led you to pursue a career in cardiopulmonary rehabilitation?

When I was doing my physiotherapy degree, I had a very inspiring instructor who taught cardiopulmonary physiotherapy. Her passion was contagious. In addition, I loved being in acute care and I enjoyed the hospital environment. I felt that we could make such a difference to people's lives. I then enrolled in a MSc degree in respiratory physiology and very much enjoyed the scientific enquiry.

Q2 This year, you received the ERS Assembly Lifetime Achievement Award. Which contributions to respiratory medicine are you most proud of?

I am most proud of the studies we have done to figure out how to maintain the effects of pulmonary rehabilitation longer. We have created different models of follow-up after completion of rehabilitation. One example is to use community centres and fitness instructors in maintenance programmes. I do not think we have the perfect answer yet, but we know that some contact with a healthcare professional is important. We also know that we can create safe community-based follow-up programmes. One study where we used dance to keep people with chronic obstructive pulmonary disease active after pulmonary rehabilitation showed us that the activities need to be enjoyable for the individuals.

Q3 Could you please tell us about your current research and the outcomes you hope for?

My most challenging study at this time is an international randomised controlled trial

"The virtual rehabilitation will be great long-term, especially for those who live far from pulmonary rehabilitation centres."

examining the effect of balance training on falls in individuals with chronic obstructive pulmonary disease. We have partners in Australia, Europe, and Canada and we are trying to recruit over 300 patients. Managing such a large trial has been challenging but exciting.

Q4 What impact is the COVID-19 pandemic having on pulmonary rehabilitation, and how do you think it will shape the future of the field?

Pulmonary rehabilitation has had to pivot to be virtual to some degree or another. Virtual pulmonary rehabilitation is a challenge as it is difficult to assess physical function and prescribe specific exercises. However, there are many advantages as it minimises the barriers related to access. The virtual rehabilitation will be great long-term, especially for those who live far from pulmonary rehabilitation centres.

Q5 What is the biggest challenge facing cardiopulmonary rehabilitation currently?

The biggest challenge is the stigma against people with lung disease. The stigma impacts funding and services that people with pulmonary disease can access.

Q6 Which ongoing developments in cardiopulmonary rehabilitation do you consider to be promising and exciting?

Exciting developments include the role of non-traditional approaches in rehabilitation. For example, I am excited about the potential of dance as a way to maintain physical activity.

Q7 Mobile and digital health are being utilised in many areas of medicine. What is your opinion on their potential in cardiopulmonary rehabilitation?

It is an area that we are studying. We are interested in the perspectives of patients and healthcare professional. Mobile and digital health will resonate with some patients but not others. The key is how to choose wisely which patients would benefit from mobile and digital health.

Prof Greet Van den Berghe

ERS Gold Medal in ARDS Winner
Chair Intensive Care Medicine, UZ Leuven, and Head Laboratory of Intensive Care Medicine, KU Leuven, Leuven, Belgium

Q1 What attracted you to specialise in the endocrinology of critical illness?

When I was a junior attending physician in the intensive care unit (ICU), quite some time ago, I noticed that long-stay ICU patients, adults and children alike, quickly started to look much older than their chronological age and at the same time showed endocrine and metabolic abnormalities that mimicked certain alterations characteristic of 'ageing'. I hypothesised that maybe this 'accelerated ageing' phenotype of ICU patients could in part be iatrogenic and, if so, could perhaps be preventable. These thoughts were the trigger for my PhD research, in which I could show that the infusion of dopamine, a drug at that time used in virtually every ICU patient, was causing a suppression of the anterior pituitary, which could be reversed by omitting its use. In my postdoctoral research, we went a step further and identified the biphasic neuroendocrine and metabolic responses to acute and prolonged critical illness both in patients and in animal models. This research clarified many earlier apparent paradoxes and provided the basis for the subsequent large scale randomised controlled trials (RCT) that we have performed with our team.

Q2 One of your main research areas regards parenteral nutrition in the critically ill. What have been your most interesting results?

As ICU patients cannot eat normally by mouth and often do not tolerate gastric tube feeding, a finding that was associated with poor outcome, for decades ICU physicians advocated the early use of supplemental parenteral nutrition, which was assumed to prevent the loss of lean body mass in critically ill patients and hereby to improve outcome. However, the causality of this association was never tested by well-designed RCT. After we had shown that hyperglycaemia, which is substantially aggravated by the infusion of parenteral nutrition, was causally related to poor outcome, we started to have doubts about the assumed benefit of the early use of parenteral nutrition for ICU patients. In fact, we hypothesised that fasting responses during severe illnesses may have evolutionary conserved benefits by helping the body to clear cellular damage, which is essential for recovery from critical illness. After further consolidation of this hypothesis through research in our animal models, we performed two large, multicentre RCT comparing the use of early parenteral nutrition with not using it and instead accepting virtual fasting up to 1 week in the ICU. The results were striking. Omitting the use of early parenteral nutrition and hereby allowing the fasting responses, such as the activation of autophagy, to play their cellular housekeeping roles during the first week of critical illness, accelerated recovery from critical illness both in adults and even more so in young children. We also could show that this simple metabolic intervention, the omission of the early use of parenteral nutrition, also had long-term benefits, years after critical illness and treatment in the ICU. In particular in critically ill children, this long-term benefit meant prevention of neurocognitive impairment of which the importance cannot be neglected. Very recently, we could show that epigenetic alterations, more specifically aberrant alterations in DNA methylation, provided a biological basis for this long-term harm induced by the early use of parenteral nutrition during critical illness.

Q3 This year, you were awarded the ERS Gold Medal in ARDS. Please could you tell about the key research that contributed to this?

I have no idea, as the nomination really came as a total surprise to me. I can only speculate

on what exactly contributed to being awarded this prestigious Gold Medal. Perhaps because my translational research - from the bed to the bench and back - spans from basic research on pathophysiology and on the discovery of novel preventive and therapeutic targets all the way to clinical research with large RCT with patient-centred hard clinical endpoints, including long-term physical and neurocognitive outcomes.

Q4 Over the years that you have been practising in intensive care, how have you seen the field change in terms of advancements to the technology or approaches used?

Intensive care medicine is a rather young discipline which took a start in the 1950s with the polio epidemic and the introduction of mechanical ventilation. Since then, there has been a truly revolutionising phase with new technologies being developed and introduced in the clinic, which allowed to prevent death from previously lethal conditions. Those early years were characterised by progressively introducing more and more treatments that were assumed to improve outcome, or if not were probably harmless, although solid evidence from good quality research was often lacking. The recent years have been characterised by a shift towards critically questioning and investigating a lot of what we were used to do in the ICU and the main lesson, in my view, is that also in intensive care medicine, "less may be more". The assumption "if not beneficial, likely harmless" has proven wrong more often than occasionally. I am a strong advocate of further prioritising excellence in basic and clinical research in intensive care, and of not rushing into conclusions based on results from too small or poorly designed studies, in order to improve patient outcomes. No less so in the context of the COVID-19 pandemic.

"I hope that all three programmes will reveal insights that will be important to pave the way towards improved outcome for critically ill adults and children."

Q5 In your opinion, what do you believe to be a particularly promising area in the field of intensive care medicine?

I can only answer this question from my own focus and research interests, which inevitably is biased, I am afraid. Currently, my group is focussing on three large areas. First, we are performing exciting research on how metabolic interventions, such as blood glucose control or feeding strategies,affecttheepigenome as a potential mediator of ICU-acquired weakness and its long-term legacy. Second, the team is investigating whether the evolutionary conserved catabolic pathways, such as lipolysis and ketogenesis, can be exploited in the search for prevention of brain dysfunction and of ICU-acquired weakness in critically ill patients. In that context, the team is also exploring the role of fasting-mimicking diets in the ICU. A third large programme is on further understanding the hypothalamic–pituitary–adrenal stress responses to acute and prolonged critical illness. The latter is also one of the main research questions that are being addressed by the team in relation to COVID-19-induced respiratory and multiple organ failure. I hope that all three programmes will reveal insights that will be important to pave the way towards improved outcome for critically ill adults and children. More generally in intensive care medicine, I think that the fascinating link between metabolism, coagulation, and immunology is one to further explore in detail.

"Everybody now understands the importance of our medical discipline and hopefully this will result in the allocation of more governmental budgets to clinical intensive care and to research in the field."

Q6 What impact is the COVID-19 pandemic having on intensive care medicine, and how do you think it will shape the future of the field?

The COVID-19 pandemic has already had an enormous impact on intensive care medicine and on the medical and paramedical staff all around the globe. It has been a very stressful time for all of us and some have paid a too high price while helping patients and trying to cope. Again, I can only speculate about the future, but one good thing that may result from the COVID-19 disaster is that intensive care medicine now no longer is something obscure and unknown to the lay public and to policy makers. Everybody now understands the importance of our medical discipline and hopefully this will result in the allocation of more governmental budgets to clinical intensive care and to research in the field.

Q7 In intensive care medicine, what have been the most important learnings from the COVID-19 pandemic so far?

If you are referring to the most important new insights about the disease pathophysiology and possible treatments, I think it is too early to know for sure. As I said earlier, we should not rush into conclusions. We should continue to focus on high-quality research so that we understand better before we introduce treatments that may not only be beneficial but could also carry risk of harm.

While being cautious and advising not to overinterpret any of the available data, I think that the severe form of COVID-19 respiratory failure and acute respiratory distress syndrome, that we have seen in our ICU worldwide, is quite different from the typical bacterial sepsis-induced acute respiratory distress syndrome. There is reason to believe that severe COVID-19 may start as a local 'endotheliitis' in the lungs rather than as a particularly destructive form of 'alveolitis' and that the early activation of coagulation may be a key trigger upstream in the cascade of inflammation and organ failure. In my personal opinion, protecting the endothelium, by omitting early use of parenteral nutrition and preventing hyperglycaemia and by a cautious use of corticosteroids for selected patients, to name but a few strategies that may work, while putting a brake on the coagulation cascade very early on in the disease course could be quite important in preventing poor outcome. This has been the strategy that we have followed during the first COVID-19 wave in our centre, where the very low mortality rate may have been a consequence hereof. But again, high-quality research via RCT is the only way to investigate properly whether that statement is true or false.

Sore Throat Treatment Guidelines are Fanning the Flames of Antimicrobial Resistance

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Interview Summary

Sore throat represents a significant yet under-recognised battle in the war against antimicrobial resistance (AMR). It is one of the most common reasons people visit a doctor and approximately 60% walk away with a prescription for antibiotics.[1] However, studies have indicated that 70–95% of all cases are viral[2] and most patients would be better served with symptom relief.

A systematic review of global sore throat management guidelines by members of the Global Respiratory Infection Partnership (GRIP) suggested the problem could be rooted in a focus on serious, yet increasingly rare, conditions, such as quinsy and acute rheumatic fever (ARF). While ARF can be a dangerous complication of Group A streptococci (GAS), which are identified in 15–30% of sore throat cases, the incidence of ARF is exceedingly rare in most parts of the world.[3] All but one of the 36 identified guideline documents discussed antibiotic therapy and less than two-thirds advocated the use of laboratory tests to confirm GAS. Just 50% gave advice on symptom relief, which evidence suggests is the most appropriate approach in most cases.[4]

Dr Martin Duerden, lecturer in therapeutics and prescribing at Cardiff University, Cardiff, UK, member of the GRIP, recently retired general practitioner, and co-author of the review, believes countries should re-evaluate their guidelines.

In this interview, Dr Duerden talks about the role of fit-for-purpose sore throat guidelines in antimicrobial stewardship, the importance of appropriate symptom relief, and how coronavirus disease (COVID-19) could represent an opportunity for change.

ANTIMICROBIAL STEWARDSHIP AND SORE THROATS

More than one-half of the people who visit a healthcare professional with sore throat, one of the most common health complaints globally, are prescribed antibiotics.[1] Historically this approach was employed, among other reasons, to avoid ARF, which was much more common in the 1950s and 1960s. This is a complication of GAS infection that can lead to rheumatic heart disease, mortality, and morbidity. While it is still

seen in some low-to-middle-income countries in Africa, Southeast Asia, and the Western Pacific, ARF is actually exceedingly rare elsewhere.[4] The overwhelming majority of sore throats are viral in origin, said Dr Duerden, adding that antibiotics are often not even required in the 15–30% of cases in which GAS is identified. The over-prescription of antibiotics for sore throat, which is better treated with symptom relief such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAID), lozenges, and sprays, is "really quite concerning," commented Dr Duerden.

"We are seeing increasing resistance to antibiotics and are finding severe infections, such as septicaemia, difficult to treat. We now know there's really a large number of deaths associated with resistant bacteria that don't respond to standard therapy."[5] Continuing, Dr Duerden emphasised that: "We have not had a new class of antibiotics for about 40 years and we are running out of them, the use of antibiotics for sore throat is actually stoking up the problem."

GUIDELINE REVIEW

To check the consistency of diagnostic and treatment criteria for sore throat, Coutinho et al.[3] carried out a multilingual, multi-region, systematic literature search that identified 36 treatment guidelines for sore throat from 26 countries.[3] All but one provided criteria for starting antibiotic therapy as a first-line treatment, but fewer than two-thirds advocated the use of laboratory tests to diagnose GAS prior to initiating therapy. Importantly, only one-half discussed symptom relief, which Dr Duerden described as the mainstay of treatment in most cases.[3]

Combined with the right diagnostic tests, antibiotics may be an important part of ARF containment strategies in high-risk areas. However, the approach is irrelevant in the many countries where ARF is exceedingly rare, Dr Duerden explained.

The study also highlighted worrying regional differences between the guidelines. Discrepancies were explained by historical, rather than current, incidences of ARF for example, or by guidelines being adopted from neighbouring countries with no adaptation for local circumstances. Guidelines may be bypassed altogether in countries where antibiotics can be purchased without a prescription, such as in Southeast Asia, and are unavailable in some regions, such as parts of Africa. The absence of guidance in Nigeria, for example, means most people presenting with sore throat are prescribed antibiotics as a matter of course.

All of these factors result in a significant volume of antibiotics being inappropriately prescribed and taken. "We're in a situation where we must reduce unnecessary antibiotic use. It is critical to make sure that we have clear ideas and structures around the processes of care, and that's particularly so for sore throats," emphasised Dr Duerden.

Rather than promoting the use of antibiotics, sore throat guidelines should ensure people are recommended symptom relief, Dr Duerden explained, adding that the review found extremely limited advice in this regard. Just 20 of the 36 guidelines recommended symptom relief such as paracetamol or NSAID, and only four of these mentioned topical treatments such as lozenges, gargles, or sprays, which evidence has suggested can treat symptoms much more effectively than antibiotics. "The most effective way of treating sore throat in nearly all parts of the world is providing symptom relief. Antibiotics have a very small part to play in terms of affecting the outcome of the infection," highlighted Dr Duerden.

Global approaches to the treatment of sore throat represent an international threat to antimicrobial stewardship, yet Dr Duerden fears the issue is not taken seriously. "Sore throats have been treated this way for 30 or 40 years and people don't think it's particularly important. They don't see it as being part of the problem," he said.

DEVELOPING THE GUIDELINES OF THE FUTURE

AMR is an issue receiving international oversight from bodies such as the World Health Organization (WHO). Focussing on the appropriate treatment of sore throat, Dr Duerden suggested, could represent a significant opportunity to make a difference. To this end, the GRIP has been encouraging countries to re-evaluate their guidelines.

"If complications of GAS are a particular problem in your area, you will want to reduce infection and transmission. For most parts of the world, complications from sore throat are astonishingly rare and really what we're talking about is reducing symptoms," said Dr Duerden. "One possibility is developing or emulating high-quality guidelines which cover the essentials but are configured to local needs."

Guidelines should include a clear description of the disease, the diagnosis pathway, and necessary tests, as well as instructions on using symptom scores, which may indicate a more severe infection, he noted. Throat swab cultures are the gold standard for diagnosis of GAS and some countries advocate near-patient 'rapid antigen' testing. Where antibiotics are indicated, the guideline should explain the reasons, and set out the medication class and duration of treatment. "We also need to make sure people know the 'red flags', or the things likely to indicate severe infection, such as impaired swallowing, and when people should return if their symptoms persist," said Dr Duerden.

Critically, guidelines should advise on symptom relief, including paracetamol, NSAID, and topical treatments, such as lozenges, sprays, or gargles. Not only are these much more effective than antibiotics, they do not contribute to AMR, Dr Duerden explained.

Patient education is another consideration. Past experience often leads people with sore throat to ask their healthcare professional for antibiotics. Dr Duerden remarked: "We can educate around how sore throats are generally self-limiting, that you don't need to see a doctor, and that you can go to your pharmacist and take simple, symptomatic treatment."

THE COVID-19 OPPORTUNITY

The emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could represent an opportunity to correct guideline omissions, avoid antibiotic overuse, and ensure people have access to evidence-based symptomatic treatment, said Dr Duerden. "I think COVID-19 is going to change things," he said. "Obviously, sore throat is a symptom of COVID-19. In the future, it's possible that when we see people with sore throat, we may need to do swabs or tests for coronavirus, and we need to think about how that gets built into guidelines."

"It's early days and we're not entirely sure how COVID-19 will pan out, but we need to be thinking about how we incorporate it into assessment for sore throat," he concluded.

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Loose ENDs: Electronic Nicotine Delivery Systems and the FDA's Recent Enforcement Policy

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INTRODUCTION

Electronic nicotine delivery systems (ENDS), including electronic cigarettes (e-cigarettes), have been commercially available since the early 2000s. Since then, their use has increased both among adults and adolescents.[1] E-cigarettes consist of an electric heater that aerosolises a liquid (e-liquid), which usually contains nicotine dissolved in a liquid vehicle (propylene glycol [PG] and vegetable glycerin [VG]) and chemical flavours.[2] These flavours served to mask the bitter taste of nicotine, and they also facilitate the initiation and uptake of e-cigarettes by attracting youth and young adults.[3] In the USA alone, there are over 1,200 different vendors and over 8,000 flavors.[4] E-cigarettes have undergone a series of design evolutions and are currently sold both as tank-based devices (e.g., 'mods', so called because of their customisability) and as cartridge-based (JUUL-type) devices, with cartridge-based e-cigarette products currently being the most popular form of e-cigarette in the USA.[5,6] These products are especially popular among young adults and adolescents,[7] and may facilitate nicotine addiction and dependence.[8]

The long-term impact of vaping on the cardiovascular system, and the cancer risk, remain to be determined. However, increasing evidence shows that exposure to e-cigarette vapor in human models affects pulmonary and vascular functions,[9,10] although the impact of individual flavours to these effects remain to be fully determined. More recently, e-cigarette or vaping product use associated lung injury (EVALI) has been described, which was particularly prevalent in youth, and has further raised concern over e-cigarette safety.[11] In many cases, EVALI was most likely caused by the inclusion of vitamin E acetate, which was present to solubilise tetrahydrocannabinol,[12] although not all EVALI patients used tetrahydrocannabinol, suggesting that other, as-yet-unknown, e-cigarette components may have been responsible.[11] The EVALI outbreak of 2019 reconfirms the need for appropriate e-liquid regulation. As a case in point, the European Union's (EU) Tobacco Product Directive banned both the use of refillable cartridges and the inclusion of vitamins in e-liquids,[13] and to date, EVALI has essentially been absent from the EU,[14] suggesting that appropriate e-cigarette legislation can influence health outcomes.

The Family Smoking Prevention and Tobacco Control Act of 2009 banned the use of all natural and artificial flavour compounds (except for menthol) in combustible cigarettes and any of their component parts to eliminate flavoured

tobacco products that held special appeal in the youth market. However, this ruling did not apply to other tobacco products, such as 'little cigars', and also did not apply to e-cigarettes. In 2020, the U.S. Food and Drug Administration (FDA) finalised their enforcement policy on flavoured cartridge-based e-cigarette products, including fruit and mint flavors.[15] In this commentary, the authors discuss the potential impact of flavours on human health and addiction, and the implications on regulation.

TYPES OF FLAVOURS

Flavour is most commonly sensed by taste receptors in the mouth and the five flavours bitter, salty, sour, sweet, and umami (savoury), can be sensed. These receptors are typically either G-protein coupled receptors (e.g., taste receptor TAS1R2, sweet) or ion channels (e.g., the epithelial Na^+ channel, salty).[16,17] Flavour, and activation of taste receptors, is an important part of the smoking/vaping experience. For example, the inclusion of sweet flavours is reinforcing and has been shown to potentiate the effect of nicotine on the brain.[18]

E-liquids contain many different flavours, including aldehydes (vanillin, benzaldehyde, cinnamaldehyde, damascenone), benzyl alcohol, terpenes (linalool, limonene, farnesol), pyrazines, menthol, and sweet flavours including ethyl maltol. These flavours are mixed to produce the thousands of commercially available e-liquids. Many of these flavours have also been used in the food and perfumes/cosmetics industries. However, their safety in the lung, at levels inhaled by e-cigarette users, is uncertain because the majority of toxicology studies for these flavours were carried out following oral ingestion only.[19] For example, high doses of inhaled diacetyl (2,3 butanedione, used for buttery flavour in popcorn) can lead to severe lung disease, in the form of bronchiolitis obliterans (aka 'popcorn lung').[20] Despite the danger, diacetyl has been detected in some e-liquids.[21,22]

Flavoured e-liquids and individual flavours have been shown to induce toxicity and/or exert biological effects, which has been reviewed elsewhere.[23] The number of flavours used in an e-liquid varies from product to product; previously, the authors identified 100 different flavours in 148 e-liquids, and found that vanillin was the most common flavour.[22] Interestingly, the number of flavours contained within an e-liquid directly correlated with degree of toxicity.[22] Flavour concentrations in most e-liquids have not yet been determined; however, both vanillin and cinnamaldehyde were typically in the mmol/L range, and in some cases, cinnamaldehyde levels exceeded 1 mol/L.[22,24] Flavourings such as vanillin and cinnamaldehyde are aldehydes that have the potential to form adducts with proteins and DNA. This adduct binding can alter protein function and possibly cause DNA mutations as DNA adduct levels have been considered to serve as biomarkers for carcinogen exposure.[23,25,26]

ROLE OF FLAVOURS IN UPTAKE/ APPEAL TO YOUTH

Most people who start using nicotine do so as a teenager.[27,28] For cigarettes, the use of flavours to mask the unpleasant taste (bitter) and irritation of the combusted cigarette has been well described.[29-31] Moreover, menthol directly activates transient receptor potential channels in pulmonary neurons to suppress cough and irritation, thus making it easier to overcome the initially unpleasant effects of tobacco smoke inhalation.[32] The 2019 National Youth Tobacco Survey (NYTS) found that over 5 million middle and high school students in the USA (10.5% and 27.5%, respectively) were e-cigarette users, defined as having used e-cigarettes within the last 30 days,[33] the majority of whom used cartridge-based products. In addition to masking the unpleasant sensations of nicotine, e-cigarettes can be made in appealing 'candy', 'dessert', and 'fruit' flavours, among several others, which also aids with marketing and appeal to teenagers.[34-36]

UPDATE ON RECENT LEGISLATION

Having a broad range of commercially-available flavours is a common marketing practice used by e-liquid vendors.[37] The FDA has taken steps to regulate e-cigarette sales in order to prevent sales to youth. First, they deemed e-cigarettes to be tobacco products and included them in the 2009's Family Smoking Prevention and Tobacco Control Act.[38] They subsequently issued an "Advanced Notice of Proposed Rulemaking" that gives importance to the regulation of flavours in

tobacco products.[39] This year, the FDA finalised their rules on flavours and have banned flavoured, cartridge-based e-cigarettes.[40] Given that JUUL-type cartridges have the largest market share, this is certainly a step in the right direction. More specifically, the FDA has banned: a) any flavoured, cartridge-based ENDS product (other than a tobacco- or menthol-flavoured ENDS product); b) all other ENDS products for which the manufacturer has failed to take (or is failing to take) adequate measures to prevent minors' access; and c) any ENDS product that is targeted to minors or likely to promote use of ENDS by minors.[40]

This legislation is certainly a step in the right direction. For example, JUUL previously sold eight different flavours, including Crème brûlée, mint, fruit medley, and mango, with mint, mango, and fruit medley being the most popular amongst school-age vapers.[41] However, now they only sell 'Classic Tobacco', 'Virginia Tobacco', and 'Menthol', which will likely limit appeal to youth, as intended by the FDA. Unfortunately, this legislation has some loopholes. For example, while sales of e-cigarette cartridges containing flavoured e-liquids have been banned, individual containers of flavoured e-liquids, including those with fruit, candy, and other enigmatic names are still commercially available via a number of websites. Moreover, it is now possible to purchase off-market, empty/refillable cartridges for cartridges-type devices. Therefore, at the moment it is relatively easy to circumvent the flavour ban by purchasing flavoured e-liquids, and putting these into either second- or third-generation e-cigarette devices which are refillable, or by using refillable cartridges for JUUL-type e-cigarettes. One might argue that these attractively-named, flavoured e-liquids are targeted at minors, in which case, the FDA needs to enforce the sale of flavoured non-cartridge e-liquids in order to fully enforce the flavour ban for cartridge-based e-cigarettes.

Another important omission from the FDA's rule is the continued sale of menthol. As mentioned above, menthol directly stimulates neuronal transient receptor potential channels to suppress cough after smoke inhalation and is arguably the most biologically active of the available flavours.[32] There is strong evidence that menthol initiates smoking, and menthol is popular among young smokers. Indeed, cigarette and e-cigarette company marketing strategies have been based around this information. Thus, given its impact on smoking initiation, it is hard to explain why menthol continues to be available despite the flavour ban. The tobacco industry continues to lobby for the promotion of their products and USA states with more active tobacco lobbies are less likely to legislate for tobacco control.[42] However, the degree to which lobbying has influenced the continued availability of menthol remains to be determined.

CONCLUSIONS

In conclusion, the FDA's recent ban on flavoured e-cigarette cartridges is an important milestone in the regulation of this relatively new product. Given that it took many individuals, several decades, and innumerable lawsuits before conventional tobacco was regulated, by comparison the FDA has moved at "light speed" with their deeming rules and their flavour ban. However, loose ends need to be addressed, including the availability of e-liquid flavours in other forms, the availability of refillable cartridges, and the lack of regulation surrounding menthol.

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Improving Antenatal Asthma Management: A Complex Journey

EDITOR'S PICK

Worsening of asthma during pregnancy is of major concern due to the potential impacts on the mother and fetus. Therefore, the Editor's Pick for this issue is the article is by Chen et al., which delineates the current pharmacological and non-pharmacological interventions that can be utilised in patients with uncontrolled asthma during pregnancy.

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Abstract

Asthma is a highly prevalent comorbidity during pregnancy, which can worsen as gestation progresses and is associated with several adverse perinatal outcomes. The adverse outcomes associated with maternal asthma are preventable with appropriate asthma management in pregnancy. However, the prevalence of adverse outcomes has not changed significantly over the last 20 years, even though knowledge and treatments for managing the disease in pregnancy has improved significantly. This is of concern now in the current climate with the coronavirus disease (COVID-19) pandemic and its potential impact on pregnant individuals with asthma. This article will discuss the treatments available for the management of asthma in pregnancy, the barriers for the translation of current knowledge into obstetric practice, and the importance of asthma education and self-management skills.

INTRODUCTION

Worldwide, asthma is one of the most prevalent chronic conditions to potentially have adverse effects in pregnancy and subsequent perinatal outcomes. It affects up to 16% of females of reproductive age, resulting in asthma being one of the most common morbidities to affect pregnancy.[1] Limited progress has been made towards optimising maternal asthma management, particularly in relation to improving adverse outcomes associated with uncontrolled

asthma during pregnancy. With rapid global impacts such as the coronavirus disease (COVID-19) pandemic, this emphasises the need to reassess current strategies and evidence to facilitate more productive approaches. Therefore, this commentary serves to highlight the consequences of uncontrolled asthma during pregnancy and provide insight into existing implications impeding effective management. Additionally, it also aims to evaluate the current literature to understand knowledge gaps and promote future areas of research towards enhancing asthma management during pregnancy.

CONSEQUENCES OF UNCONTROLLED MATERNAL ASTHMA

Pregnant individuals with asthma often experience unpredictable changes in their asthma symptoms, with 50% experiencing a loss of asthma control and 20% experiencing moderate to severe exacerbations.[2] The reasons for these changes are largely unknown, but can be attributed to the complexity and heterogeneity of the disease itself.[3,4] Patients with asthma are likely to undergo mechanical, immunological, hormonal, and metabolic changes during pregnancy, ultimately experiencing varying degrees of dyspnoea and changes in pulmonary function.[2,4-8] However, the evidence quantifying the extent and significance of such influences are frequently inconsistent and inconclusive.[2,4] More importantly, uncontrolled maternal asthma and subsequent exacerbations are significant risk factors for adverse maternal and perinatal outcomes.[9] This includes an increased risk for pre-eclampsia, gestational hypertension, gestational diabetes, caesarean, preterm birth, neonatal hypoxia, and perinatal mortality.[9-12]

New findings have also acknowledged that adverse effects related to uncontrolled maternal asthma extend past birth. A study conducted by Abdullah et al.[12] was the first to longitudinally investigate the long-term intergenerational impact of maternal asthma exacerbations. Children younger than 5 years of age had a 23% increased risk of developing early childhood asthma and a 12% higher chance of developing pneumonia if their mother had experienced asthma exacerbations during their gestation. These findings support the outcomes of smaller cross-sectional studies,[13,14] which identified childhood bronchiolitis and allergic rhinitis as a potential long-term development risk. Additionally, a nationwide Swedish cohort study[15] found that the risk of developing childhood allergic rhinitis was higher in children born preterm or via caesarean delivery, which are known adverse outcomes of uncontrolled maternal asthma.[9] These findings suggest that maternal asthma in pregnancy may confer an inherited genetic risk for childhood asthma and allergies, while its lack of control may confer an epigenetic risk for both the fetus and the child.[12,15] Given these alarming outcomes, there is a need to re-evaluate and optimise evidence-based asthma management strategies during pregnancy to reduce adverse perinatal outcomes and early childhood diseases.

CURRENT ASTHMA MANAGEMENT STRATEGIES

According to international and national guidelines,[16,17] current maternal asthma therapy is the same as for non-pregnant people with asthma, with goals to optimise symptom control, preserve respiratory function, and provide medication with minimal adverse side effects. Another objective in pregnancy is to prevent maternal hypoxic episodes to maintain fetal oxygenation.[16,17] This is achieved through vigilant monitoring and clinical symptom assessment, self-management education that includes reviewing inhaler technique, medication adherence, and symptom management and application of pharmacotherapies advised by health professionals via a multidisciplinary approach.[16,17] Counselling for smoking cessation is also recommended as part of asthma education and management because it is a common problem in pregnant females with asthma[18,19] that contributes to severe exacerbations during pregnancy[20] and preterm delivery.[19] Clinical assessment of symptoms, including wheeze, shortness of breath, cough, and chest tightness, are typically measured using spirometry.[16,17] Guidelines also recommend a stepwise approach for pharmacological intervention, adjusted based on clinical assessment.[16,17] This primarily includes intermittent use of short-acting β-agonists as reliever medication with an appropriate dose of inhaled corticosteroids (ICS), combined with or without a long-acting β-agonist or other alternative treatments.[16,17] Active management

during pregnancy is also recommended, with regular monthly reviews, supply of a written asthma plan, and additional management of comorbid conditions.[16,17] Asthma exacerbations are serious events in pregnancy due to the risk of a hypoxic insult to the fetus and have been recommended to be managed aggressively with oral glucocorticoids as soon as possible.[16,17]

Recommendations for asthma management during labour and delivery advise asthma medications should be continued during labour.[21] Asthma symptoms can occur in 10% of females during labour[22] and intravenous hydrocortisone during labour for those with severe asthma is recommended to avoid the risk of an exacerbation during labour and/or adrenal insufficiency. Most patients (73%) return to prepregnancy asthma symptoms within 3 months postpartum and can be titrated back to prepregnancy asthma medications.[22] Overall, there is a need for improved guidelines for asthma management during pregnancy, birth, and the postpartum period, and this matter has been raised in several recent publications.[23,24]

LIFESTYLE MODIFICATION AND RISK FACTOR REDUCTION

There are a number of lifestyle factors and comorbidities that are known to affect asthma control and increase exacerbation risk in pregnancy, including smoking, dietary behaviour, rhinitis, gastric reflux, and mental health illnesses or disorders that could be modified with appropriate interventions to reduce the risk of a loss of asthma control or exacerbations during pregnancy. Cigarette use by pregnant individuals with asthma is a major health concern, affecting up to 30% of females.[18] From the authors' prospective cohort studies of pregnant individuals with asthma, 29% of smokers ceased smoking during early pregnancy through usual antenatal care support mechanisms.[25] In contrast, among those who received additional support through a nurse-led antenatal asthma management programme, 54% stopped smoking in early pregnancy, suggesting that lifestyle factors can be modified with an appropriate intervention.[25]

Another potentially modifiable behaviour in pregnancy is nutritional intake. In a socially disadvantaged population of pregnant females with asthma consuming a diet high in fat, sugar, and takeaway meals, there was an increased likelihood of uncontrolled asthma during pregnancy, whereas a diet high in protein, fruit, or vegetables was associated with controlled asthma.[26] Nutritional advice should be considered for individuals with asthma who are obese as there was an increased prevalence of asthma exacerbations among pregnant females who were overweight (51%) or obese (48%) compared with those with a healthy weight (25%).[8] However, pregnancy-related weight gain appeared to have no impact on exacerbation risk.[8] These findings provide important evidence that lifestyle modification is a consideration for the antenatal management of maternal asthma, but it remains to be determined whether they represent a key determinant for asthma control in pregnancy.

Comorbidities known to exacerbate asthma, including rhinitis, gastric reflux, and mental health illnesses and disorders, could be managed clinically with maternal antenatal asthma management. Rhinitis is the most common comorbidity, occurring in 65% of females with asthma during pregnancy, with 20% of females experiencing pregnancy rhinitis.[27] The presence of rhinitis was shown to be associated with poorer asthma control and lung function.[27] A history of depression or anxiety in patients with asthma during pregnancy increased the risk of uncontrolled asthma during pregnancy.[28-30] Furthermore, anxiety was an independent risk factor for poor asthma control and exacerbations.[29,30] A number of studies have also reported that gastric reflux exacerbates asthma in those who are not pregnant.[31] A prospective study reported that 80% of pregnant indiviuals experience some gastric reflux during pregnancy, with it being more severe in those with asthma;[32] therefore, it is possible asthma control in pregnancy may be influenced by the presence or absence of gastric reflux. These studies highlighted that lifestyle factors and comorbidities could be examined holistically with antenatal asthma management to develop preventive strategies for asthma control in pregnancy and ultimately improve pregnancy-related outcomes.

EFFECTIVENESS OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL INTERVENTIONS

Pharmacological Treatment

Pharmacological therapy is the current mainstay treatment for effective asthma control in pregnancy.[10,33,34] Uncontrolled maternal asthma poses a greater risk to the health of the mother and her baby than medication use.[33,34] Table 1 summarises asthma medication safety data with respect to reported doses and adverse events.[7,35-38]

The safety of ICS has been extensively investigated in pregnancy and there is growing evidence supporting ICS/long-acting β-agonists combinations.[10,33,34] This strengthens the argument and recommendation, by guidelines, that females entering pregnancy should continue medication/s they were taking prior to conception, if the treatment remains clinically appropriate. Other commonly used asthma medications with pregnancy safety data include systemic steroids, leukotriene receptor antagonists, omalizumab, and, rarely, theophylline.[10,33,34]

The cumulation of pharmacological safety data in pregnancy is progressive; however, may be limited by studies that have small sample sizes, insufficient control for cofounders, and missing data.[39] Thus, more research is required to improve evidence-based safety data of asthma pharmacological treatment during pregnancy.[39] Furthermore, asthma pharmacotherapy adjusted in response to lung function and symptom assessment does not always reflect airway inflammation, the target of ICS treatment.[40] This suggests that decisions in therapy based on clinical assessment alone may be inappropriate, with growing awareness of the heterogeneity of asthma and its differing phenotypes.[40] Therefore, the correct identification of phenotypic asthma unique to the individual proposes the potential for individualising asthma treatment.[41] Additionally, as mentioned before, the perceptions concerning the relative safety of medication use in pregnancy is a continuous impediment in optimising maternal asthma management.[34]

Fraction of Exhaled Nitric Oxide-Guided Diagnosis and Asthma Management

The pursuit for novel, individualising-type treatments is unsurprising, particularly as biomarker-guided therapies, such as the use of the noninvasive measure of fraction of exhaled nitric oxide (FeNO), have already shown to improve asthma control in those who are not pregnant.[42,43] In particular, as FeNO can be used to identify eosinophilic airway inflammation, it helps guide ICS dose titrations, thereby limiting ICS exposure and exacerbation rates.[42,43] In pregnancy, the efficacy of FeNO-based therapy has been established in one randomised controlled trial (RCT) study conducted by Powell et al.[44] The study involved 220 non-smoking females and reported that one-half of the exacerbations were reduced in the FeNO participants in comparison to the control group. It also reported that there was increased retention of asthma control in the FeNO participants, thereby allowing progressive ICS dose reductions, as well as minimised oral corticosteroid and short-acting β-agonist use.

Long-term benefits of FeNO treatment in pregnancy have also been investigated, with reports of reduced wheeze and childhood asthma prevalence in children of mothers who received FeNO treatment during pregnancy.[45,46] Additionally, a qualitative study by Mclaughlin et al.[42] determined that clinicians found FeNO-guided treatment implementation to be feasible within hospital-based antenatal care settings if resources and education are appropriately provided.

Despite these positive outcomes, limitations have been identified in this approach by Grzeskowiak and Clifton,[43] including its uncertain applicability in primary clinical care, accessibility, and cost-effectiveness. However, continuing studies such as The Breathing for Life Trial[40] will not only address these limitations to better comprehend the feasibility of FeNO-guided antenatal therapy, but will also include smokers within the pregnant females with asthma cohort. This allows the generalisability of this approach to be better understood, particularly because there is a high proportion of pregnant individuals with asthma who smoke (>20%).[19,43]

Table 1: Summary of the efficacy of asthma medications used in observational trials to maintain or strengthen asthma control in women with asthma.[7,35-38]

Medications and usual dose	Use	Associated risks, safety data, and other information on use
Short-acting inhaled β-agonists		
Salbutamol 100–200 µg when required	Rescue/reliever therapy	Salbutamol has more reassuring human data in pregnancy than terbutaline and is preferred in pregnancy.
Terbutaline 500–1,500 µg when required		
Long-acting inhaled β-agonists		
Salmeterol 25–50 µg twice daily	Rescue/reliever therapy; typically used as add-on therapy when asthma cannot be adequately controlled with inhaled corticosteroids alone, but should not be used without preventative/controller medication	Limited experience but reassuring data available for salmeterol or formoterol. Relationship with perinatal outcomes is conflicting but can assume that the pharmacologic and toxicologic profile is similar to short-acting inhaled β-agonists.
Formoterol 6–12 µg twice daily		
Vilanterol 25 µg once daily		
Inhaled corticosteroids		
Beclometasone dipropionate Low: 100–200 µg/day Medium: 250–400 µg/day High: >400 µg/day	Preferred preventative/controller medication; inhibits the number of and activity of inflammatory cells in airway	Reassuring human data available, but beclometasone, budesonide, or fluticasone propionate are preferred due to greater experience. No association with oral clefts, congenital malformations, caesarean delivery, or other offspring disease risk when used during pregnancy. Limited teratogenic risk data.
Budesonide Low: 200–400 µg/day Medium: 500–800 µg/day High: >800 µg/day		
Ciclesonide Low: 80–160 µg/day Medium: 240–320 µg/day High: >320 µg/day		
Fluticasone propionate Low: 100–200 µg/day Medium: 250–500 µg/day High: >500 µg/day		

Table 1 continued.

Medications and usual dose	Use	Associated risks, safety data, and other information on use
Systemic corticosteroids		
Prednisolone Exacerbation: 40–50 mg once daily for 5–10 days Maintenance: Variable dose according to response	Preventative medication and mainstay treatment of asthma exacerbations; used if asthma cannot be controlled with other preferred medications	Use of systemic corticosteroids associated with increased risk of oral cleft, especially if used in first trimester of pregnancy. Also associated with increased risk of adverse pregnancy outcomes (e.g., pre-eclampsia, preterm birth, small-for-gestational age), but likely confounded by maternal asthma severity.
Leukotriene receptor antagonist		
Montelukast 10 mg once daily	Inhaled corticosteroid alternative	Limited experience. Reassuring human data available as no risk for major congenital malformations has yet been found.
Zafirlukast 20 mg twice daily		
Other treatments		
Omalizumab Subcutaneous 75–375 mg every 2–4 weeks; dose according to weight and serum total IgE level	Anti-IgE monoclonal antibody; add-on therapy or inhaled corticosteroid alternative for allergic asthma	Limited experience but reassuring human data. No significant increased risk of major congenital malformations, small-for-gestational age, or prematurity was found for women taking it 8 weeks prior to conception or during pregnancy compared to pregnant asthmatics not taking it. Carries risk of anaphylaxis, so should not be started during pregnancy.
Theophylline 300–600 mg/day; dose according to theophylline level or use ideal weight to calculate dose for obese patients	Alternative therapy or alternative adjunctive long-acting bronchodilator therapy; rarely used in pregnancy.	Reassuring human data available but limited role in practice due to monitoring requirements and associated risk of toxicity (need to ensure serum levels remain between 5 and 12 µg/mL). Serum concentration can be increased with alcohol and concurrent use of formoterol.

Adapted from Grzeskowiak et al.[10]

It is also important to understand that FeNO cannot be applied as a stand-alone approach, nor does it replace the need for appropriate asthma self-management education.[42]

Asthma Self-Management Education: Optimal Models of Care

Antenatal asthma self-management education plays a key role in improving maternal asthma control and asthma-related outcomes in pregnancy. Many studies have established the benefits of asthma self-management education. A review by Williamson et al.[47] reported antenatal asthma self-management education implemented via two interventions, one nurse-led and the other pharmacist-led, showed significant improvements in asthma self-management and control. Patients had improved medication knowledge and inhaler technique, with more than 80% of the cohort retaining the skills they learnt for at least 6 months postpartum. This indicates that implementation of asthma self-management education could potentially reduce the perceived medication-related risks mothers might have.

The RCT conducted by Lim et al.[48] showed asthma self-management involving pharmacist-guided regular monitoring and education could improve maternal asthma outcomes. The study monitored asthma control in 60 pregnant females with asthma at less than 20 weeks' gestation via an Asthma Control Questionnaire (ACQ), where scores <1.5 indicated adequately controlled asthma. Patients who received guidance from the multidisciplinary intervention had significant reductions in their ACQ score, with adequately controlled asthma after 6 months compared to 69% of patients who received usual care. As this RCT was conducted at antenatal clinics in major maternity hospitals, this study also showed that the multidisciplinary intervention could easily be integrated into antenatal settings.

A recent RCT conducted by Zairina et al.[49] assessed the efficacy of a telehealth-based intervention in providing 72 pregnant patients asthma self-management education. The intervention group were supported by a smartphone application for advice on managing deteriorating asthma symptoms and allowed symptom monitoring via a handheld respiratory device. The study reported that they had superior asthma control and asthma-related quality of life at 6 months post intervention compared to usual care. This unique method alleviated the need to see health professionals in person, while also streamlined the process of communication between patient and health professionals as data were provided electronically. Across all these studies, appropriate implementation of asthma education, particularly via a multidisciplinary approach, had positive influences in improving maternal asthma control. However, more studies are required to see if these interventions actually lead to improved perinatal outcomes.[50]

OTHER LIMITATIONS AND RECOMMENDATIONS FOR IMPROVEMENT

A lack of uniformity and gaps for specific treatment recommendations exist within current maternal asthma guidelines. A systematic appraisal by McLaughlin et al.[23] identified that only respiratory guidelines included recommendations for managing maternal asthma, but antenatal guidelines did not. The specific recommendations are also unclear in certain categories; for instance, the need for regular asthma review in pregnancy is not well addressed in guidelines, but should be essential given the unforeseen physiological changes that can occur during pregnancy.[23] This also raises the concern that there are limited data available to determine which periods of pregnancy are critical for improving maternal asthma control to minimise the probability of an adverse outcome. Moreover, while guidelines have become increasingly more accessible to health professionals, the prevalence of poor outcomes for mothers with asthma and their neonates remain unchanged, indicating that there has been a lack of implementation of these guidelines.[31] Additionally, a review by Grzeskowiak et al.[10] found the evaluation of asthma exacerbations are not well defined, particularly as it often relies on the patient's own self-awareness and understanding of symptoms. This is unreliable, particularly as asthma exacerbations by self-help seeking behaviours generally leads to unnecessary emergency department presentations or unscheduled doctor visits.[10] These limitations and current gaps in knowledge in maternal asthma guidelines are future areas of research to improve current guidelines and limit short- and long-term risks of maternal asthma on mother and fetus.

BARRIERS PREVENTING EFFECTIVE MANAGEMENT

A discordance exists between current antenatal asthma management guidelines and clinical practice, which restricts health advances in optimising asthma management in pregnant females.[26] A contributing factor is that maternal asthma management appears to be reactive rather than proactive.[26,51] While current maternal asthma guidelines recommend a written asthma action plan, longitudinal and prospective studies showed only 10–20% of females had a written asthma action plan throughout their pregnancy. [26,35,51] These findings indicate that the majority of pregnant females self-manage their asthma, which may be problematic if they are unaware of how to appropriately respond to the changes in their asthma pathology.[51]

Another barrier limiting effective maternal asthma control is nonadherent medication use. For instance, a major reason for medication discontinuation relates to the perceived fear or lack of need to use asthma medications, particularly ICS.[50] Fear-related suboptimal use during pregnancy has been reported in multiple countries, reflecting the global scale of this problem.[35,52-55] Individuals were found to be unaware that their asthma symptoms could worsen during the course of their pregnancy, or considered medication use to be a greater concern than the potential risks associated with uncontrolled maternal asthma.[35,52-55] Other reasons also included inadequate support and guidance from health professionals and their desire to seek alternative therapies.[56]

Physician reluctance to prescribe and lack of confidence to endorse asthma medication use is another barrier towards effective maternal asthma control.[26] In a cross-sectional survey by Lim et al.,[57] >25% of pregnant patients with asthma were instructed by their family physician to cease and reduce asthma medication use despite having well-controlled asthma, while a French study by Beau et al.[58] showed guidelines were not followed by all physicians. In particular, one-half of pregnant patients with asthma were not prescribed asthma medication on a regular basis and medications prescribed differed to those used during preconception, which does not reflect guideline recommendations to continue the same preconception asthma medication/s during pregnancy.[58]

Clearly, based on the evidence, it can be inferred that asthma management largely differs depending on the healthcare specialist and views of the patient, highlighting the discrepancy between clinical practice and current maternal asthma guidelines. This emphasises the importance of asthma education for the patients and multidisciplinary teams managing their asthma. It also reinforces the idea that multifaceted approaches should work synergistically for optimal management of asthma during pregnancy.[50] A more current and pressing issue for pregnant individuals with asthma is the current outbreak of coronavirus disease (COVID-19) infection across the world and how it can be treated and managed in this vulnerable population.

MATERNAL ASTHMA MANAGEMENT AND COVID-19

In December 2019, an outbreak of pneumonia with unknown origins was identified in Wuhan, China. This was found to be caused by a novel coronavirus,[59] now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO).[60] This virus causes COVID-19, a disease characterised by a severe respiratory illness similar to severe acute respiratory syndrome (SARS).[61] The impact of the virus on pregnant females with asthma and their offspring is currently unknown, but we do know that the pregnant population has been at high risk of adverse outcomes in previous epidemics, with significantly higher rates of death during the 1918–1919 Spanish flu pandemic, 1957–1958 Asian flu pandemic,[36] 2002 SARS epidemic, and 2012 Middle East respiratory syndrome (MERS) epidemic. Case fatality rates for SARS and MERS were as high as 15% and 27%, respectively, for pregnant females, although this is based on only a small number of reported patients with disease.[37]

To date, preliminary reports from China indicated that pregnancy does not aggravate the course of symptoms of COVID-19[38] and, unlike SARS and MERS, there have been few maternal deaths associated with COVID-19 infection in pregnancy.[62] A systematic review of pregnancy outcomes from COVID-19 indicated that preterm birth and perinatal death were the most common outcomes in pregnancies complicated by the virus, with limited evidence of vertical transmission of the virus to the fetus.[63] In the USA, 15% of COVID-19 infections in pregnancy were severe and occurred in females who had comorbidities that included obesity and asthma.[64] Spanish data identified that 12.5% of pregnant patients with COVID-19 pneumonia have asthma.[65] One maternal death reported in the UK occurred in a 29-year-old Pakistani female who had multiple comorbidities, including asthma.[66] Brazilian data reporting COVID-19 maternal deaths associated with a comorbidity identified that 45% of deaths were pregnant females with asthma.[67] Personalised predictive modelling for mortality, ventilation, and need for intensive care unit admission developed from Mexican data reported that pregnancy and asthma were predictors of these outcomes.[68] These data suggest that severe COVID-19 infections arise in pregnant females with multiple comorbidities, including asthma, and that these females are at greater risk of intensive care unit admission and death. Furthermore, a prospective study examining viral infections in pregnant patients reported that those with asthma had a higher susceptibility to infection and more severe infections than those without asthma during pregnancy,[69] which suggests pregnant females with asthma are an at-risk population for COVID-19 infection. Centers for Disease Control and Protection (CDC) guidelines indicate people with asthma may be at greater risk of more severe disease if infected with COVID-19, and there are data emerging that supports this information.

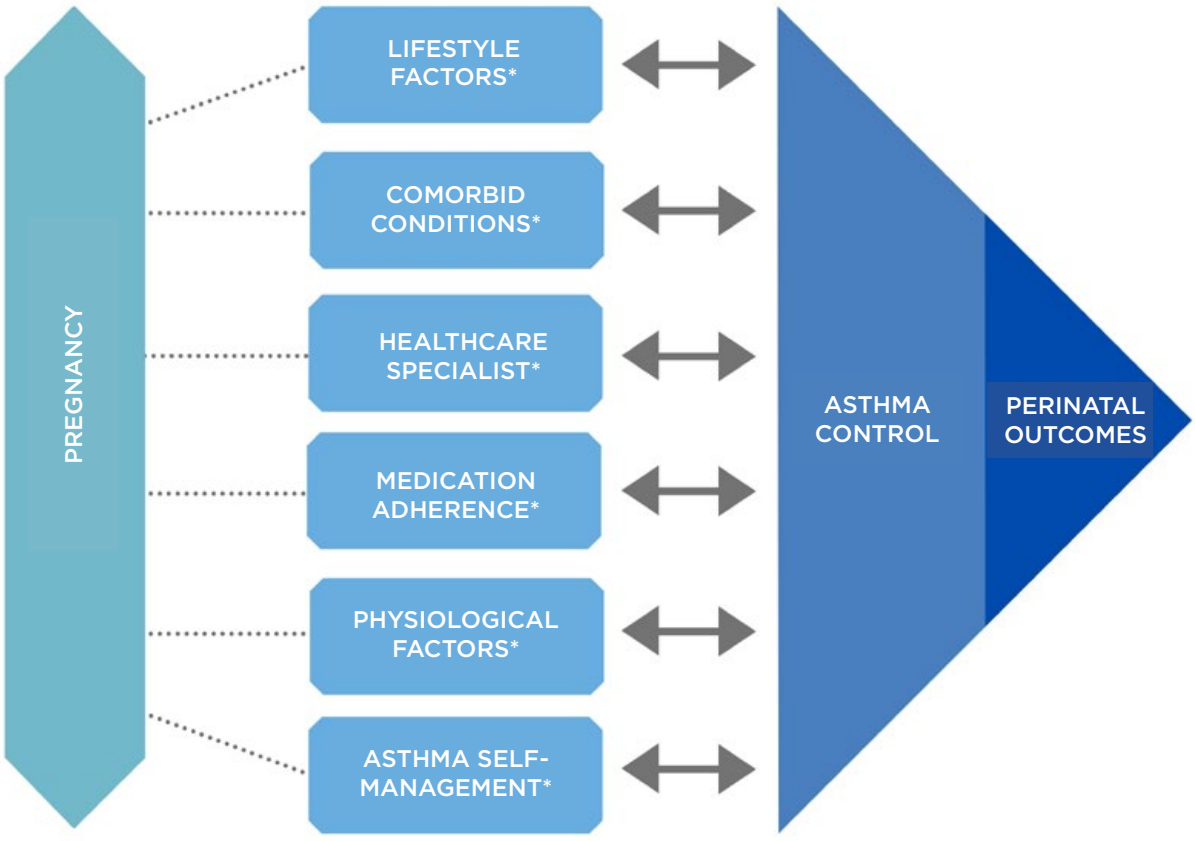

Figure 1: Variables that influence asthma control during pregnancy.

*Key interdependent factors known to affect asthma control and perinatal outcomes: factors may also influence each other.

Treatment recommendations for people with asthma and COVID-19 infection remain the same as noninfected people with asthma, but to avoid nebuliser treatments due to aerosolisation of the virus and potential risk of transmission to others.[70]

CONCLUSION

Maternal asthma is a substantial burden for both the mother and the health system. With the current paucity of the ability of evidence-based strategies to improve adverse outcomes, it is important to understand that uncontrolled maternal asthma and subsequent exacerbations in antenatal settings can contribute to increased risks of adverse pregnancy outcomes (Figure 1). More research evaluating the relationship between COVID-19 and its effect on the state of asthma control during pregnancy should be considered to determine if the development of treatment strategies is required. Ultimately, there is a need for evidence-based clinical practice guidelines that translate current research findings to clinical practice and optimise asthma control within antenatal settings to potentially improve health outcomes for the mother and baby.

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Spatiotemporal Cellular Networks Maintain Immune Homeostasis in the Lung

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Abstract

A dynamic and intricately connected tissue-resident immune cell network continuously monitors the lungs, which are incessantly subjected to external environmental insults. The lungs are protected by the respiratory epithelium, which not only serves as a physical barrier through mucociliary mechanisms, but also a reactive one that can release cytokines, chemokines, and other defence proteins in response to danger signals. In the maintenance of pulmonary homeostasis in health, the lung-resident immune cell network instructs tolerance to innocuous particulates and can rapidly and efficiently drive immunity and memory to pathogenic antigens. This review examines the spatiotemporal dynamics that underlie the exquisite network of highly specialised immune cells and their mediators in the support of pulmonary tissue homeostasis and effective lung immunity in health. In particular, this review examines the specialised immune cells that reside in distinct populations within the diverse compartments of the lung, and the molecular signals that retain and recruit lung-resident immune cells, to further our understanding of how these can be targeted therapeutically to return inflamed or diseased lungs to homeostasis.

INTRODUCTION

Lung homeostasis is maintained by an immune cell network of tissue-resident cells that constantly monitor the respiratory tract, which is exposed to inhaled matter containing aeroallergens and airborne pathogens that can cause infection, and noxious agents including dust, smoke, and other environmental pollutants known to induce lung tissue injury. Channelling air into the respiratory system are the conducting airways, comprised of a single layer of ciliated epithelium tissue interspersed with mucus-producing goblet cells that protects against particulates and infectious agents that adhere to the mucus, and through the actions of the cilia are cleared from the airways. This respiratory epithelial cell surface therefore represents a large and exquisitely delicate surface undergoing continuous challenge by immunogenic antigens. Maintenance of pulmonary immune

homeostasis, required to dynamically support efficient gas exchange between the epithelial cell surfaces and the vascular bed, is provided at this interface by constant immune surveillance differentiating between self and the environment, instructing tolerance mechanisms to innocuous inhaled particles, and through mounting rapid responses to pathogenic challenge.

Maintenance of immune homeostasis and the triggering of pathogenesis requires a sophisticated understanding of the dynamic interplay between the network of tissue-resident immune cells within the microanatomical organisation of the lung. This review will discuss the spatiotemporal cellular dynamics of the innate and adaptive immune cell networks during homeostasis, focussing on the participation of the individual lung-resident immune cell types and their intricate interplay to maintain the pulmonary microenvironment. How these immune cells then participate in wound healing and tissue repair, become dysregulated and contribute to chronic inflammation, and the treatment of subsequent respiratory complications will not be discussed in this review, but reference to topical studies on advancements in these fields will be highlighted.

SPATIOTEMPORAL ORGANISATION OF THE PULMONARY IMMUNE CELL NETWORK

The lung is populated by heterogenous tissue-resident innate and adaptive immune cells that function together to maintain tissue homeostasis and protect from recurrent pathogenic challenges. Dysregulation of the immune response can cause acute respiratory distress syndrome[1] and asthma,[2] or drive chronic inflammatory diseases[3] including chronic obstructive pulmonary disease (COPD),[4] bronchopulmonary dysplasia,[5] pulmonary fibrosis,[6] and lung cancer.[7] To appreciate the maintenance of homeostasis and development of immune responses within the lung, it is critically important to consider spatiotemporally how and where immune cells interact and function.

In the steady state, macrophages, the predominant innate leukocyte population, and dendritic cells (DC) continually sample and phagocytose the majority of inhaled innocuous and pathogenic particulate material that enters the airways, to protect local tissues from damage by suppressing induction of the adaptive immune response.[8] Cluster of differentiation (CD)4+ and CD8+ T cells are the prevalent adaptive immune cells that generate specific effector and memory responses to innocuous bacterial, viral, and fungal antigens.[9] Pathogenic antigen not cleared from the conducting airways within mucous secretions from goblet cells or digested by macrophages is sampled through the airway epithelium by DC and instead transported to the lung-draining lymph nodes for processing into the major histocompatibility complex Class I or II pathways for generation of a specific adaptive T-cell effector response (Figure 1).

Distinct leukocyte networks extend throughout the entirety of the lung, reflecting contrasting and variable levels of airborne antigen exposure experienced throughout the pulmonary system, which facilitate highly specific and directed immune responses to maintain tissue homeostasis. The lung is segregated into numerous anatomically distinct cellular compartments, including the conducting airway mucosa, the lung parenchyma, the draining lymph nodes, bronchoalveolar space, bronchus-associated lymphoid tissue (BALT), the intravascular cell pool, and periarterial space.[10]

Conducting Airway Mucosa

The conducting airway mucosa is composed of ciliated epithelial cells and mucus-secreting goblet cells that remove inhaled particulate through mucociliary clearance mechanisms. The bronchial epithelium contains a unique leukocyte network, enriched in DC, predominantly myeloid DC, as well as plasmacytoid DC (pDC) and pulmonary alveolar macrophages (AM). Lung-resident airway mucosal DC are reported to be strategically positioned with highly motile projections extended between epithelial cells to support direct antigen sampling from the airway luminal surface.[11-14] Interestingly, many of these studies are inferred from static imaging and flow cytometry studies[11,15,16] with recent work utilising elegant slice imaging, suggesting the conducting airways are rarely sites of transepithelial DC projections,[17] challenging current dogma and indicating antigenic sampling occurs upon escape of particulate from mucociliary actions and its exposure within the lung parenchyma.

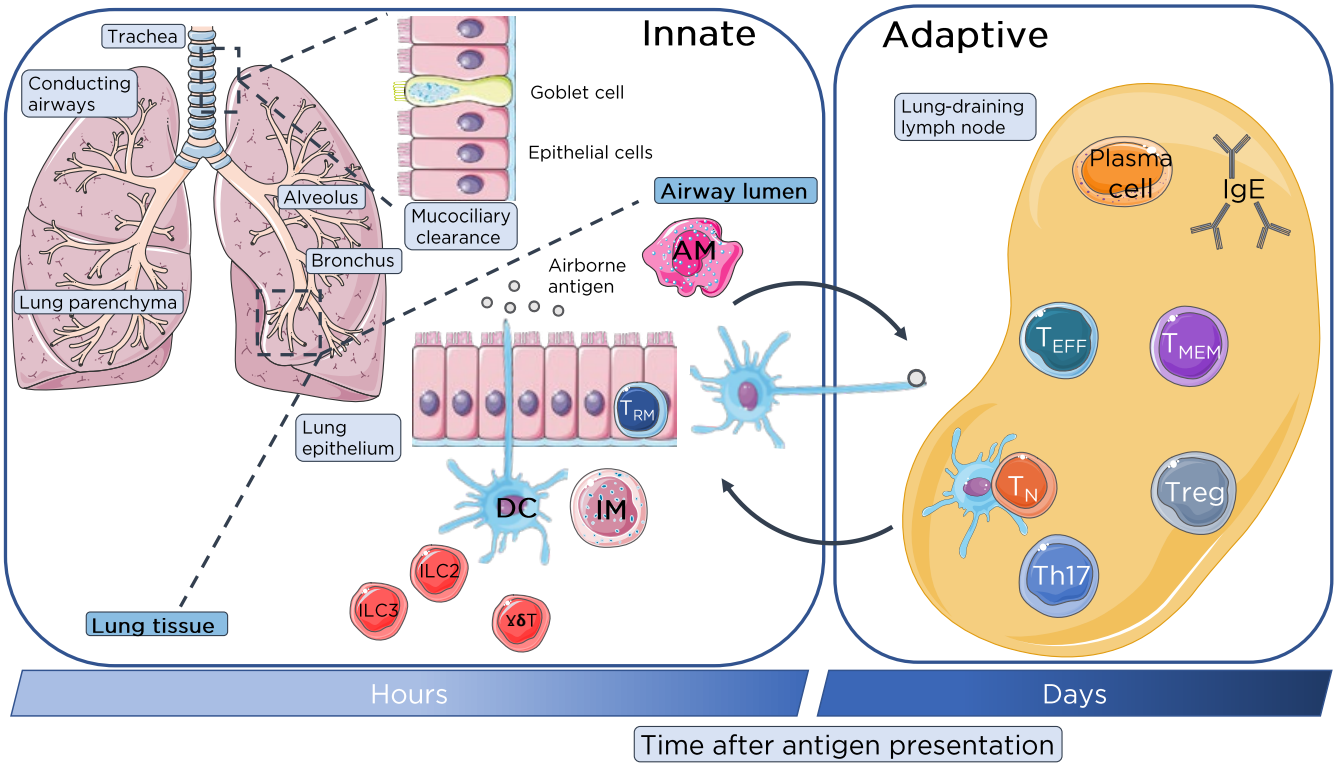

Figure 1: Lung-resident immune cell network.

Immune homeostasis is maintained in the numerous distinct compartments of the lung by specific populations of lung-resident immune cells beyond initial mucociliary clearance of inhaled innocuous and pathogenic antigens. Within the airways lung-resident AM and DC from the rapidly responding innate immune system phagocytose airborne antigen for clearance or processing and presentation respectively to T cells in the lung-draining lymph nodes. These innate cells, along with ILC and innate-like γδ-T cells provide a rapid first-line of defence to inhaled antigenic particulates. Antigens escaping mucociliary or phagocytic clearance are sampled by DC through the surface lung epithelium of the bronchial mucosa or alveoli of the conducting airways. Activated DC migrate to the lung-draining lymph nodes through the lymphatics which are recognised by T_N which become activated and differentiate into T_{EFF} including Treg and Th17 or generate memory. Antigen-specific activate T cells migrate through the lymphatics and pulmonary capillaries into the lung parenchyma and site of infection. B cells will also generate IgE antibody response through the differentiation and activation of plasma B cells.

AM: alveolar macrophages; DC: dendritic cells; IM: interstitial macrophages; ILC: innate lymphoid cells; T_{EFF}: effector T cells; T_{MEM}: memory T cells; T_N: naïve T cells; Treg: regulatory T cells.

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Intraepithelial lymphocytes (IEL), specialised lymphocytes that do not require antigen priming for their effector functions, are also found in relatively high numbers in the mucosal linings in the lung as well as gastrointestinal tract, where they are components of the gut-associated lymphoid tissue. Both CD8 and CD4+ intraepithelial T cells are found intraepithelially and in the lamina propria, and express an effector cell phenotype (CD45RO+). Indeed, in allergic inflammation and bronchial infections, intraepithelial lymphocytes participate in crosstalk with the bronchial epithelium in the regulation of inflammatory processes[18] and present with many functions.[19] The lamina propria also homes antibody-producing plasma cells (IgA+) and some B cells which may contribute to local antigen presentation, as demonstrated in the lymph nodes that drain the lungs.[20]

Lung Parenchyma

The lung parenchyma includes the respiratory bronchi, which branch into bronchioles and terminal bronchioles, which extend into alveolar

ducts and alveolar sacs. The pulmonary circulation, a dynamic network of capillaries that are in close contact with the alveolar space in the interstitium that separates the alveoli, localises a unique immune response within the parenchyma.

The alveolar space, and not the airways, appears to be the main site of particulate ingestion and movement to the airways. Intravital imaging has demonstrated that AM are the major phagocytes in the alveolar space and become immobile and phagocytic following antigen encounter, digesting all antigenic material that evades mucosal clearance. Lung-resident DC project dendrites into the alveoli to support antigen uptake, differentiating innocuous insults from dangerous ones, and trafficking to the airways to release antigen into the interstitium.[17] Having an abundant number of AM residing in the terminal alveoli suggests that particulate will be transported upward by DC to the branching airways to the lung-draining lymph nodes resulting in local or systemic activation of T cells.[21] Thus, DC uptake and presentation only appears to account for a fraction of antigen uptake at steady state, which is enhanced during immune responses.[17] This appears to be driven not by a change in the ability of DC to gain access to the alveoli, but by a rapid influx of monocyte-derived DC into the alveoli during antigenic challenge.

Another less commonly considered tissue-resident immune cell, the neutrophil, resides throughout the pulmonary vasculature of the parenchyma at steady state, sequestered at high numbers in both narrow and wide capillaries. In response to inflammatory challenge in models of lung injury, lung-resident neutrophils dramatically increase within the pulmonary capillaries, cluster, and extravasate rapidly.[17,22-24] Recent imaging has suggested that neutrophils may actually be sequestered following a leading monocyte population that transmigrates into the interstitium immediately after lung injury.[22] This suggests that in homeostasis, the lungs are primed to rapidly respond to insults due to the abundant number of neutrophils trapped throughout the microvasculature that are primed to enter the lung and immediately degranulate.

Lung-Draining Lymph Nodes

Lung-draining lymph nodes are an essential component of the pulmonary immune cell network, a critical site for the development of adaptive immunity in infection and allergy,[25] and the primary site for the induction of immunological memory. Migratory DC and AM, although participating in alternate transport pathways of antigen presentation, both migrate from the lung to the lung-draining lymph nodes to actively transfer antigen and activate effector T-cells responses.[26] Whether the lung-draining lymph nodes serve to functionally integrate with the overall immune system and exactly how this cross-communication is regulated is yet to be fully understood.

Intravascular Leukocyte Pool

The intravascular leukocyte pool is contained within the endothelium of capillaries and venules of the lung. Although the intravascular leukocyte pool is critical for the range of immune reactions in the lung, it remains unclear whether intravascular leukocytes are a prerequisite for efficient immune reactions in the lung[25,27,28] and how their numbers and migration into the lung parenchyma is regulated.[10]

Bronchus-Associated Lymphoid Tissue

Although only present during early childhood in healthy individuals, BALT is a potential inductive site contained with the greater airway mucosa.[29] BALT, comprising discrete lymphoid-cell aggregates underlying a specialised epithelium, is part of the integrated mucosal immune system, facilitating the migration of lymphocytes to other mucosal sites.[30] BALT can reappear in conditions of inflammation such as smoking.[31] Inducible BALT from mice that lack other organised lymphoid tissue can generate protective immunity against pathogens, such as influenza virus,[32] which suggests in early life that BALT may play a role in maintaining local immunological homeostasis when central lymphoid structures in the respiratory tract are functionally immature.

Periarterial Space

Periarterial space is located around the pulmonary arteries surrounded by lymphatic vessels and blood capillaries. The periarterial space was recently demonstrated to be involved in pulmonary host defense,[33] yet whether innate or adaptive immunity is dominant within the periarterial space and the mechanisms driving immune cell infiltrate from the alveoli to the periarterial space is yet to be understood.

CELLULAR DYNAMICS OF THE IMMUNE NETWORK IN THE LUNG

A dynamic dual phagocytic system involving AM and neutrophils is continually removing inhaled particulates, but activation and recruitment of adaptive immune cells to the site of infection is critical for elimination of innocuous micro-organisms from the alveolar space. Immune cell recruitment to the lungs is 'unique' in that it has two separate circulatory systems: the bronchial arteries from the systemic circulation that nourishes the bronchial wall and the low-pressure pulmonary system that circulates through the lung parenchyma.[34] The mucosal immune responses of the central airways are also integrated with those of distinct mucosal tissues through mucosal-associated lymphoid tissue. Lymphocytes in the lung have distinct imprinting of tissue-homing properties. Unlike naïve T cells that express adhesion molecules and chemokine receptors that restrict their migration to lymphoid tissue,[35] activated memory T cells downregulate these lymphoid-tissue-homing receptors and upregulate tissue-specific adhesion molecules and chemokine receptors that target their migration to non-lymphoid tissues.[36]

The regulation of T-cell migration in the lung is yet to be fully understood but it has been shown in viral infection that memory T cells mainly traffic and recirculate through the pulmonary capillaries and selectively accumulate in the lung parenchyma.[37] During homeostasis, endothelial cells in the pulmonary vasculature express intercellular adhesion molecule 1 (ICAM-1) and P-selectin. Lymphocyte function-associated antigen 1(LFA-1)–ICAM 1 interactions have been demonstrated as the requisite interaction to retain and support egress of effector CD8+ T cell from the pulmonary vasculature.[38] Further interactions with P-selectin, through P-selecting glycoprotein ligand 1 (PSGL-1) expression by CD8 T cells, further mediates the recruitment and retention of T cells in the alveoli and lung parenchyma. In addition, chemokine interactions, such as C-C chemokine receptor type 5 (CCR5) and chemokine ligand 5 (CCL5), was shown during viral challenge to recruit memory T cells to the parenchyma and also appear to play a role in tissue-specific lung homing.[37] Taken together with integrin mechanics, this suggests that specific combinations of integrin expression and chemokine gradients are an important mechanism for retention of T cells in the airways during homeostasis and pathogenesis.

To summarise the role of chemokine receptors expressed on immune cells in homeostasis in the lung is difficult, and largely inferred from studies on their role in the pathogenesis of lung diseases including COPD,[39,40] asthma and allergic airway diseases,[41-43] pulmonary fibrosis,[44,45] and pulmonary infections.[46,47] To determine the role of chemokine receptors, mice with a particular gene knockout, blocking antibodies, and specific inhibitors of chemokine receptors have been studied in different lung disease models which are comprehensively discussed in a review by Tomankova et al.[48]

TISSUE-RESIDENT IMMUNE CELLS CONTRIBUTING TO PULMONARY HOMEOSTASIS

Alveolar and Interstitial Macrophages

Alveolar and interstitial macrophages maintain pulmonary immune homeostasis via their intimate interactions with other lung-resident cells, specifically pulmonary epithelial cells. Expression of a broad range of surface receptors enables them to sense the environment and signal to local stromal cells in order to maintain immune homeostasis, but also to sense change within the inhaled environment. Macrophages sense change within the inhaled environment that can be activating (toll-like receptors [TLR] 2, 4, 6; IL-1 receptor; IFN-γ receptor; and TNF receptor) or suppressive (CD200 receptor, signal-regulatory protein α, mannose receptor, triggering receptor expressed on myeloid cells 2, IL-10 receptor, transforming growth factor [TGF] β receptor).[49] It is clear that close interaction and communication between airway epithelial cells and airway macrophages is vital for maintenance of immune homeostasis within the respiratory tract.

At least two distinct macrophage populations exist in the lung at homoeostasis, termed AM and interstitial macrophages (IM) that are characterised by their distinct locations and unique functions (Figure 1).[50] Located in the airway lumen, AM are characterised by high expression of CD206, CD11c, and SiglecF+, but

lack CD11b, which is expressed by other tissue resident macrophages.[51] IM conversely lack CD206 and SiglecF, are CD11b bright, express only low levels of CD11c, and reside in the lung parenchyma.[51] IM release cytokines associated with the adaptive immune response, such as IL-10, which exerts a regulatory role in the lung, whereas immunosuppressive highly phagocytic AM play a central role in maintaining immunological homoeostasis.[52] Indeed, in steady state, AM are largely quiescent, downregulating the phagocytic receptor Macrophage 1 antigen, and secrete nitric oxide, prostaglandin endoperoxide 2, and immunoregulatory cytokines IL-10 and TGFβ to prevent uncontrolled inflammation within the respiratory tract.

The renewal of AM populations in the steady state largely occurs by local precursor-cell proliferation, but during inflammation renewal occurs via incoming monocytes and is regulated through the C chemokine receptor type 2 (CCR2) and chemokine ligand 2 (CCL2) axis.[53] Of note is the functional phenotype of recently recruited monocytes contrasts significantly with that of lung-resident AM. Monocytes recruited to the alveolar space during inflammation display a proinflammatory phenotype with elevate levels of steady-state TNFα mRNA; increased neutrophil chemoattractants macrophage inflammatory protein 2 (MIP2), keratinocyte chemoattractant, and IFNγ-induced protein 10 (CXCL10); TLR4 upregulation; and the expression of various lysosomal cysteine proteases involved in extracellular matrix degradation and tissue remodelling processes.[54] Specifically, monocytes can function as efficient antigen-presenting cells (APC) before their maturation into immunosuppressive AM, which occurs over a period of days.[55] Interestingly, these 'converted' AM, which become increasingly similar to lung-resident AM, can persist for over 1 year after lung injury and cause profibrotic changes.[56] The recruited monocyte population is heterogeneous, including immature DC, which will also enhance T-cell responsiveness through exposure to granulocyte-macrophage colony-stimulating factor.[57]

Lung-Resident Dendritic Cells

In the steady state, lung-resident DC are critically involved in antigen uptake and processing in the lung but lack the capacity for efficient antigen presentation until they migrate to the lung-draining lymph nodes.[58] However, during inflammation, alveolar myeloid DC (AMDC) can become potent APC.[59] AMDC present with a phenotypic profile of high expression of major histocompatibility complex Class II and CD205, together with low expression of CD8, CD40, CD80, and CD86, similar to systemic DC. Other distinct subpopulations of lung DC have also been identified[60,61] within the airway mucosa but the main focus during inflammation is attributed to the AMDC pulmonary network. AMDC have a high turnover rate in the steady state, constantly transporting antigens from the mucosa to the lung-draining lymph nodes.[62]

During lung homeostasis, resident conventional DC (cDC) reside in the lung as two phenotypically and functionally distinct subsets: CD11b+CD103- (cDC2) and CD11b-CD103+ (cDC1).[63,64] cDC1 are located in the epithelial layer, extend their dendrites between epithelial cells to capture antigens in the airway lumen, and migrate to the lung-draining lymph nodes to cross-present to CD8+ T cells during respiratory viral infection.[65] cDC2 are located in the lamina propria and unable to directly penetrate the airway lumen and migrate to the lung-draining lymph nodes in a later stage of infection, shown to coincide with the peak of viral load in the lung tissue.[65]

pDC in the lungs play an immunoregulatory role by influencing regulatory T (Treg) cells[66] and have recently been implicated in tolerance induction to inhaled antigen.[67,68] Furthermore, the high capacity of pDC to produce IFNα in response to microbial stimuli suggests this subset of DC may play a critical role in the lung in antiviral immunity.[69-73] However, it is unlikely that pDC migrate out of lung tissues, but instead enter the lung-draining lymph node from the blood to respond and participate in local inflammation.

Tissue-Resident Memory Cells

The majority of lung T cells are non-circulating tissue-resident memory T cells (T_{RM}), which persist in stable frequencies for decades of human life. Lung T_{RM} were first identified as CD4+ T cells that were retained specifically in the lung in parabiosis studies, occupying specific airway niches.[74,75] Displaying a unique transcription profile[76,77] and resident in specific mucosal, barrier, and

lymphoid tissues, T_{RM} were distinguished as a distinct subset of effector memory T cells residing within the epithelium (Figure 1). T_{RM} are sufficient to generate local inflammation, even in the absence of T memory cells from secondary lymphoid organs.[78] Present in the healthy lung, T_{RM} cells express CD69 and CD103 to promote tissue retention, as well as a diverse T-cell receptor repertoire.[79,80] Recent studies reveal an important role for lung T_{RM} in rapid protective immune response to maintain tissue homeostasis upon exposure to a diverse range of inhaled antigenic material, and are also important in surveillance for tumours and persistent viruses. Mouse studies have revealed the central role of T_{RM} in multiple aspects of lung immunity including following influenza or respiratory syncytial virus infection[81-83] and in response to allergen exposure,[84,85] indicating high therapeutic potential.

Regulatory T Cells

Treg appear to be present from birth with their inducible phenotype influenced by local microbiota from early life.[86] Lung-resident Treg are central for the maintenance of immune tolerance to airborne antigen[87] and in the control of peripheral T-cell responses.[88] Crosstalk between AM and T cells is considered a mechanism through which inducible Treg cells are generated and allergic responses are dampened.[89] Treg cells have been shown as critical for lung homeostasis with adoptive transfer of inducible Treg cells inhibiting allergic inflammation and hyperreactivity via production of IL-10.[90] Treg cells were also shown to attenuate airway hyperresponsiveness through recruitment to the airway mucosa following the first wave of inflammation triggered by allergen inhalation, demonstrating a critical role of Treg cells in homeostasis to maintain healthy pulmonary function.[34]

T Helper 17 Cells

T helper (Th)17 cells provide critical immuno-regulation in the lung through the production of IL-17, IL-22, and IL-23. Although the role for Th17 cells in lung immune homeostasis remains poorly understood, Th17-derived IL-17 plays a critical response in early inflammation and pathogen clearance in the lung by mobilising neutrophils. Th17 cells are induced through the production of IL-6, IL-21, and TGFβ in mice and IL-6 and IL-1β in humans. Interestingly, Th17 and Treg cell differentiation in the lung appears to be mutually exclusive with TGFβ inducing Th17 and Treg cells, although IL-6 inhibits Treg-cell differentiation enabling the Th17 population.[91,92] It has been proposed that the reversal of Treg cell suppressive function that is induced by TLR activation may be a reflection of an increase in Th17 cell differentiation (involving IL-6 and TGFβ) rather than a decrease in the ability for suppression,[91] suggesting a role for Th17 cells in re-establishing homeostasis.

Innate Lymphoid Cells

Innate lymphoid cells (ILC) constitute several phenotypically distinct groups of innate lymphocytes that lack the usual lineage markers that define conventional cells, notably antigen-specific receptors thus ILC do not mediate antigen-specific responses.[93] ILC numbers are largely tissue-resident, enhanced at barrier surfaces, and thought to be vital for maintenance of tissue homeostasis, repair, and regulation of immunity (reviewed in Borger et al.[94]).[95] Like effector T cells, ILC have been classified according to the transcription factors that they express and the effector cytokines that they secrete ILC1 (T-bet), ILC2 (Gata3), ILC3 (Rorγt)[96] and can rapidly response to changes in the local tissue microenvironment.

ILC2 are the main population of ILC within the lung, shown to direct protective immunity during helminth infections: development of allergic inflammation, tissue repair, and maintaining metabolic homeostasis.[93,95,97] In an elegant series of parabiotic experiments using the ILC2 found within the lung were demonstrated to be of host origin, indicating residency.[98] Moreover, virtually all of the ILC2 and ILC1 identified were situated within the lung parenchyma rather than the circulation, with ILC2 being the major population. Somewhat surprisingly, even during episodes of inflammation such as during helminth infection, expansion of ILC2 was largely due to local proliferation rather than recruitment.[98] ILC2 accumulation in the lung can be facilitated by interaction with both local stromal cells as well as haematopoietic cells. Cytokines secreted by pulmonary epithelial cells such as IL-33 and TGFβ enhance the accumulation of ILC2 cells within the lung, particularly after encounter with allergen.[99,100] Interestingly, the majority of studies to date focus on ILC2, however, ILC3 are in fact

the most prevalent group in the human lung and their rapid secretion of IL-17A and IL-22 has led to their investigation in inflammatory and infectious diseases.[101] Interestingly, although the importance of ILC3 as a source of granulocyte-macrophage colony-stimulating factor, an important cytokine in pulmonary host defence, in the lung is unknown, ILC3 in the gut are known to orchestrate inflammation.

γδ-T Cells

γδ-T cells constitute 8–20% of resident pulmonary lymphocytes, where they respond to danger signals and facilitate orchestration of immune responses.[102] The abundance of γδ-T cells maintains lung tissue homeostasis. The lung is a major site for homing of γδ-T cells during in the perinatal period, with Vγ6$^+$ γδ-T cells the major γδ-T cell population from birth until 8–10 weeks of age, whereas Vγ4$^+$ γδ-T cells predominate from that age on.[103] In adult mice, γδ-T cells are divided into subsets expressing Vγ4$^+$ (45%), Vγ1$^+$ (15%), Vγ6$^+$ (20%), and Vγ7$^+$ (rare).[104,105] These γδ-T cells are present in all regions of the lung, except for the airway mucosa. Interestingly, Vγ4$^+$ and Vγ1$^+$ populations have a more parenchyma-biased distribution.[105] Evidence of lymphoid precursors present in the lungs indicates that these cells might undergo differentiation and selection in the lung environment.

The γδ-T cells residing in the lung are potent producers of IL-17 whereas γδ-T cells expressing a different T-cell receptor in the skin, gut, liver, spleen, uterus, and peripheral blood can produce IL-17 or IFN-γ.[106] IL-17 producing cells, such as ILC3, γδ-T cells, natural killer T cells, mucosal associated invariant T cells, and ILC3, as well as adaptive Th17 cells, play distinct roles in host defence against diverse pathogens.[107] The abundance of γδ-T cells in the lung supports tissue homeostasis, through potentially a similar IL-17/IL-22 axis as ILC3, although γδ-T cells have also been shown to play critical roles in bacterial clearance and the prevention of inflammation and lung fibrosis.[108]

In the lung, although little is known of the role of γδ-T cells in maintaining pulmonary homeostasis, γδ-T cells rapidly respond to pathogens as critical effector cells in innate host responses.[109] This now introduces the question of how γδ-T cells, along with other tissue-resident unconventional T cells (mucosal associated invariant T cells, natural killer T cells) functionally integrate with ILC to enhance the innate-like immune response (reviewed in Borger et al.[110]). Whether or not these innate-like lymphocytes coregulate one another or the adaptive T-cell arm, or function independently remains to be answered. Their enhanced sensitivity to the changing lung tissue microenvironment and rapid innate ability to respond to diverse antigens, in participation with the almost immediate ability of macrophages and neutrophils to phagocytose and degranulate and the highly specific response of the adaptive arm and generation of memory, demonstrates a highly complex spatiotemporal network exists in the lung immune system to maintain tissue homeostasis and protect from lung injury.

Together the cells of the innate and adaptive immune system provide diverse effector and regulatory mechanisms that maintain pulmonary homeostasis during the persistent challenges of aeroallergens, airborne pathogens, and noxious agents along the respiratory tract (Figure 2). The dysregulation of the exquisite balance between effector and regulatory immune processes is an important disease mechanism contributing to chronic lung disease such as COPD and asthma;[111,112] in viral, fungal, helminthic, and other pathogenic infections;[113] and in the development of lung cancer.[114] COPD, for example, is a pathologically complex disease with patients presenting with inflamed airways containing macrophages, neutrophils, DC, and CD8 T cells. The influx of these inflammatory effector cells and the activation of tissue-resident cells including ILC and γδ-T cells drive airway remodelling and parenchymal destruction through the secretion of inflammatory mediators such as reactive oxygen species; chemokines including IL-8, proinflammatory cytokine TNFα, IL-1β, IL-6, and IL-17; and proteases including matrix metalloproteinase and neutrophil elastase. Cigarette smoke, an established risk factor for COPD, has been shown to have a suppressive effect on innate immune cells within the respiratory tract and cause defects in the generation of adaptive immunity in the lung.[115,116] In this respect, although the immune cells that maintain tissue homeostasis and pulmonary function are still abundantly present, they are functionally deficient or abnormal.

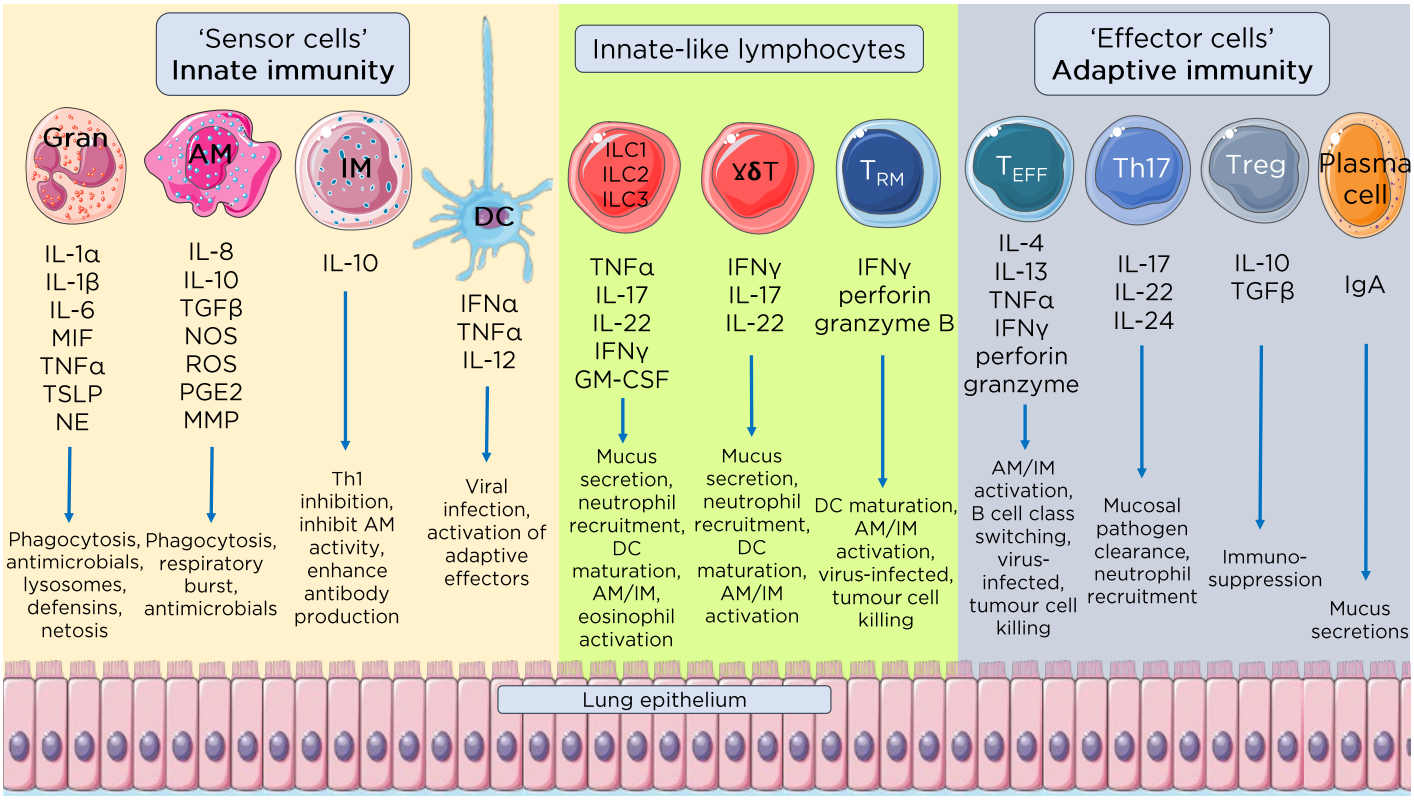

Figure 2: Effector and regulatory mechanisms that maintain pulmonary homeostasis.

Immune homeostasis in the lung requires an exquisite balance between effector cytokine and soluble factors with regulatory cytokines and humoral responses. The immediate innate response made of 'sensor cells' including granulocytes such as neutrophils and eosinophils, AM, IM, and DC, continually sample and respond to inhaled antigens to clear localised infections. This first and immediate line of immune defence secrete various factors such as IFN to clear pathogens, and other proinflammatory cytokines including IL-1, IL-6, and TGFβ. Tissue-resident innate-like lymphocytes, including ILC, γδ-T cells, and T_{RM} cells, bridge the innate and adaptive immune systems, secreting proinflammatory mediators and signals to recruit and activate effector cells from the adaptive immune system. Together these cytokines and soluble mediators serve to promote pathogen clearance, tissue repair and the maintenance of pulmonary immune homeostasis.

AM: alveolar macrophages; DC: dendritic cells; GM-CSF: granulocyte-macrophage colony-stimulating factor; Gran: granulocytes; IM: interstitial macrophages; MIF: macrophage migration inhibitory factor; MMP: matrix metallopeptidase; NE: neutrophil elastase; NOS: nitric oxide synthase; PGE2: prostaglandin E2; ROS: reactive oxygen species; T_{EFF}: effector T cells; TGFβ: transforming growth factor β; Th17: T helper 17; Treg: regulatory T cells; T_{RM}: tissue-resident memory T cells; TSLP: thymic stromal lymphoprotein.

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Therefore, it could be surmised that in chronic lung disease, and other lung pathologies, the immune sentinels responsible for pulmonary immune homeostasis have been detrimentally reprogrammed.

CONCLUDING REMARKS

Numerous immune cell populations contribute to the maintenance of pulmonary immune homeostasis, and in many cases exhibit phenotypic and functional features that appear specifically adapted to the unique local lung microenvironments. The immune cell network provides efficient surveillance in the lung, discriminating between innocuous and potentially pathogenic antigens due to the unique combination and spatiotemporal localisation of immune cells residing in the microanatomically distinct lung compartments.

To fully appreciate the maintenance of lung homeostasis, a greater understanding of the

regulation of leukocyte influx into the distinct lung compartments is still required. In particular it is still largely unknown how these immune cells directly interact with tissue-resident mucosal cells, and what directs migration between the distinct lung compartments to maintain pulmonary homeostasis. By understanding the spatiotemporal kinetics and organisation of the immune cell network in the lung, cells or process in specific compartments can be targeted therapeutically to return inflamed or diseased lungs to homeostasis.

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Risk Factors for Severe Coronavirus Disease (COVID-19)

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Abstract

Background: During the recent coronavirus disease (COVID-19) pandemic there have been several studies implicating an association between obesity, COVID-19 severity, and mortality. This retrospective study aims to investigate the association between obesity, other risk factors, and COVID-19 mortality of patients admitted over a 6-week period to the respiratory units at the authors' hospitals.

Methods: This is a retrospective study of 71 patients who were admitted into a respiratory unit over a 6-week period where the data were analysed for correlation between various risk factors, COVID-19 severity, and mortality. The statistical analysis was performed using excel statistics and SPSS (IBM, Armonk, New York, USA) statistical software. The significance was considered at $p<0.05$. The multivariate analysis, Z-test, Cox regression, Pearson correlation, and Kaplan–Meier analysis were used.

Results: The mean age of the patients was 65.8 years (range: 35.0–93.0 years) standard deviation (13.21) and the male to female ratio was 2.73 (52:19, respectively). The most frequent comorbidities were obesity (42/71; 59%), hypertension (36/71; 50%), diabetes (22/71; 31%), heart disease (13/71; 18%), respiratory disease (9/71; 13%), and cancer (8/71; 11%). The mean body weight was 83.7 kg (60.4–147.7 kg) and the mean BMI was 32.2 (22.0–53.0 kg/m^2). Smoking was reported in 8 (11%) of the patients. There were 20 (83%) mortalities among patients >70 years old ($p<0.0001$), 20 (83%) deaths among male patients ($p<0.0001$), 14 (58%) deaths among patients with a BMI >25 kg/m^2 ($p=0.001$), 17 (70%) deaths reported for patients with hypertension ($p=0.008$), 6 (25%) mortalities for patients with

cardiovascular disease (p=0.001), 14 (30%) deaths among patients who were mechanically ventilated (p=0.00028), and 5 (20%) mortalities among patients with cancer (p=0.003).

Conclusions: Obesity, cancer, mechanical ventilation, male sex, intensive care unit admission, cardiovascular disease, and hypertension are significant risk factors for mortality in patients with COVID-19.

INTRODUCTION

Obesity is suggested as a risk factor for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection,[1,2] though this has not been confirmed in randomised trials. In the outbreaks of the influenza virus H1N1 and SARS, obesity was reported in 23% of patients and was a predictor and risk factor for severe disease and poor outcomes.[3-5] This affinity is based on several underlying factors, mostly related to a defective immune system, antigen presentations, cellular and humoral responses, cytokines activation, interleukins interactions, immune system regulation, and adipose tissue inflammation.[6-10] According to the Intensive Care Units National Audit and Research Centre (ICNARC), once the infection is established in patients who are obese, it leads to severe outcomes in the majority.[11] The ICNARC data has shown that >73% of newly diagnosed cases of coronavirus disease (COVID-19) had a BMI >25 kg/m^2, 74% of patients needed advanced respiratory support, and nearly 50% died in an intensive care unit. The health systems in Western countries with high rates of obesity, including the UK, have experienced challenges whilst managing patients with COVID-19. Despite the huge resources and well-developed health infrastructures, the progression to organ failure and death in a significant number of patients, unfortunately, has been confirmed.[12,13] The primary endpoint of this article was to investigate obesity as a risk factor for mortality in COVID-19 patients. The secondary endpoints were to assess age, sex, diabetes, cancer, hypertension, smoking, and respiratory and cardiovascular diseases as risk factors for COVID-19 mortality.

METHODS

Study Design

This was a retrospective study of 71 consecutive patients with COVID-19 who were admitted and treated at a respiratory unit (RU) at the authors' hospitals. The data was initially retrospectively collected but subsequently populated prospectively during the hospital stay and then analysed. All patients showed severe symptoms of COVID-19 and tested positive for SARS-CoV-2 on a reverse transcriptase–PCR assay after a nasopharyngeal swab. All 71 patients (age range: 35–93 years) were admitted to the RU with hypoxaemia.

Setting

In the university hospitals, the RU was managed and supervised by a consultant respiratory physician. Patients were admitted to the intensive therapy unit (ITU) if they failed respiratory management.

Data Collection

The data were collected by the respiratory and ITU teams over a 6-week period. Initially retrospectively, then prospectively, the data were collected as the patient's clinical condition developed. The data were collected from case notes and clinical electronic systems; they were saved on Microsoft Excel files with a secured, encrypted password that could only be accessed by the research team. The anonymous data were then passed over to another research team to analyse.

Variables

The variables included age, sex, BMI, smoking, respiratory and cardiovascular disease, hypertension, diabetes, and cancer. The mortality was calculated for each of these risk factors. The data source was the daily patient records from the RU and ITU.

Bias

This is a retrospective study of a cohort of patients; there was no selection bias as all patients were included over the 6-week study

period. The clinical decisions were governed by clinical guidelines and supervised by experienced consultant physicians.

Quantitative Variables

The most important demographic features, comorbidities, and mortality rates were reported. The data were added to the Microsoft Excel file as they emerged, which was frequently both during admission and during progression of the disease.

Statistical Analysis

Microsoft Excel statistics and XLSTAT (Addinsoft, Paris, France) statistical software was used. The mean was used to compensate for missing data related to smoking and BMI. The rest of the data for all patients were available and there was no loss to follow-up. The significance was considered at $p<0.05$. Z-test, multivariate analysis, logistic regression, and correlation tests were used. Cox regression analysis was used to assess the survival and calculate the proportional hazard ratios. A Kaplan–Meier survival graph was produced to show the survival pattern (Figure 1).

RESULTS

All of the patients' data were included at all stages of the study. The mean age of the patients was 65.8 years (range: 35–93 years) and the male to female ratio was 2.73 (52:19). The most frequent comorbidities were diabetes (22/71; 31%), heart disease (13/71; 18%), hypertension (36/71; 50%), respiratory disease (9/71; 12.7%), and cancer (8/71; 11%).

The mean body weight was 83.7 kg (60.4–147.7 kg) and the mean BMI was 32.2 (standard deviation [SD]: 6.8; range: 22.0–52.0 kg/m^2). Seventeen patients (24%) were managed at Level 2 of care, while 54 were managed at Level 3 of care. The mean number of days needed by the patients to achieve >40% fraction of inspired oxygen (FiO_2) was 1.09 days (SD: 1.23). The mean O_2 after 12 hours of starting continuous positive airway pressure (CPAP) was 10.35 L/min (SD: 4.38); the partial pressure of oxygen before CPAP (SpO_2 pre-CPAP) was 93.60% (SD: 0.04); the FiO_2 (last pre-CPAP) was 69.80% (SD: 0.13); the SPO_2/FiO_2 ratio pre-CPAP was 1.40 (SD: 0.37); the mean respiratory rate pre-CPAP was 24.68 breaths per minute (SD: 4.97); the mean days on CPAP was 3.71 (SD: 2.23); and the mean maximum positive end-expiratory pressure (PEEP) was 12.78 cmH_2O (SD: 2.27).

Of the 71 patients, 25 (35%) were discharged, while 46 (65%) were intubated and managed at Level 3 of care.

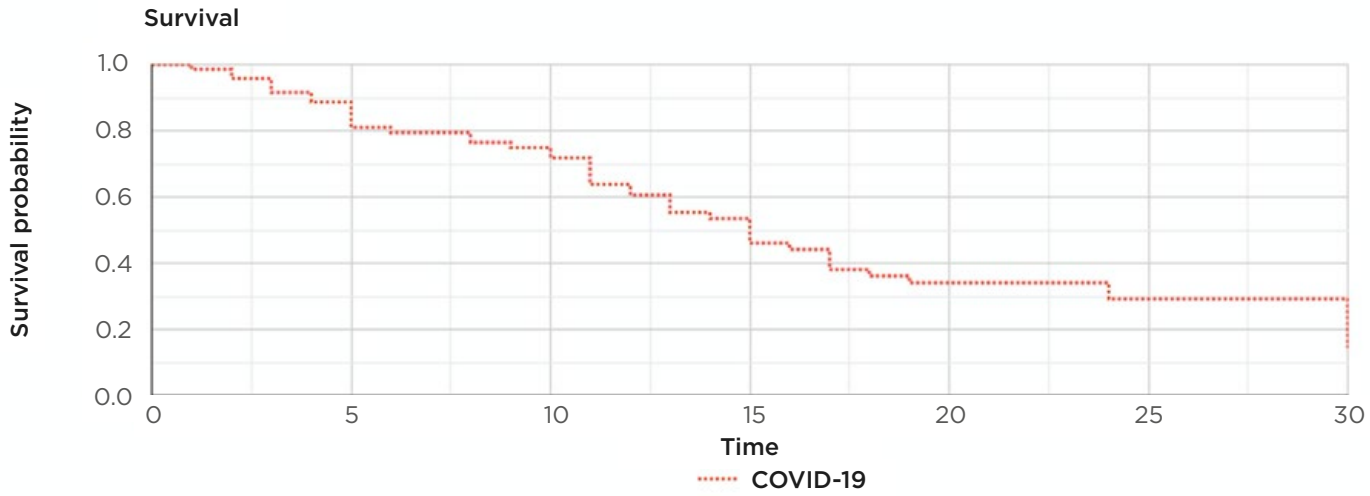

Figure 1: Kaplan–Meier survival graph.

COVID-19: coronavirus disease.

Twenty-eight patients (39%) were mechanically ventilated. Ten patients (14%) died in the RU and the total mortality up to the date of writing this report was 24 (34%). At present, 16 patients (23%) are still in hospital. The mean length of stay was 10.3 days (SD: 4.9), the mean C-reactive protein level on admission was 147.30 mg/L (SD: 99.93), the peak C-reactive protein was 264.42 mg/L (SD: 113.99), and the D-Dimer mean was 9,742 ng/mL (range: 224–80,000 ng/mL; SD: 22515) (Table 1). The incidence of obesity in this cohort of patients was 59%. The length of hospital stay ranged from 5 to 19 days (SD: 4.9), excluding the 16 patients still in hospital at the time of writing.

Table 1: Characteristic features and mortality.

	Number (%)	Standard deviation	Respiratory HDU outcome		p value
			Died/ITU n (%)	Discharged/alive n (%)	
Mean age (years)	65.8	13.2			<0.0001
>70	33 (46)		20 (83)	13 (39)	
<70	38 (54)		4 (17)	34 (89)	
Male	52 (73)	-	20 (83)	32 (61)	<0.0001
Female	19 (27)	-	4 (17)	15 (79)	0.17
Mean BW (kg)	83.65	22.1	-	-	-
BMI >25	56 (79)	-	14 (58)	42 (75)	0.001
BMI <25	15 (21)	-	6 (26)	9 (60)	
Mean BMI	32.2	6.8			
Diabetes	22 (31)	-	6 (25)	16 (72)	0.217
COPD	9 (13)	-	5 (20)	4 (44)	0.140
Smoking	21 (13)	-	9 (37)	12 (57)	0.352
Cancer	8 (11)	-	5 (20)	3 (38)	0.003
CVD	13 (18)	-	6 (25)	7 (54)	0.001
Hypertension	36 (50)	-	17 (70)	16 (44)	0.008
Level 2 of care	17 (24)	-	10 (14)	7 (10)	0.448
Level 3 of care	54 (76)	-	14 (19)	40 (56)	0.006
Mechanical ventilation	46 (65)	-	14 (30)	32 (70)	0.00028

BW: body weight; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; HDU: high dependency unit; ITU: intensive therapy unit.

Multivariate analysis showed a significant association between all the aforementioned risk factors (except chronic obstructive pulmonary disease [COPD] and diabetes; p=0.140 and p=0.217, respectively) and COVID-19 mortality (p=0.000172). There were 20 (83%) mortalities among patients >70 years old (p<0.0001) and 20 (83%) deaths among male patients (p<0.0001). There were 14 (58%) deaths among patients with a BMI >25 kg/m^2 (p=0.001), 17 (70%) deaths among patients with hypertension (p=0.008), 6 (25%) mortalities among patients with cardiovascular disease (p=0.001), 9 (37%) deaths among those who smoked (p<0.00001), and 5 (20%) mortalities among patients with cancer (p=0.003). On multi-regression analysis, BMI (p<0.0001), cancer (p=0.003), and smoking (p<0.0001) significantly predicted mortality (Table 1). Cox regression analysis showed an increased proportional hazard ratio for age, heart disease, hypertension, cancer, obesity, sex, and the need for mechanical ventilation (Table 2).

DISCUSSION

The most striking findings of this study are that obesity is pivotal in severe COVID-19 progression and mortality (p=0.043). Obesity is a complex disease with several factors increasing the likelihood of severe disease and mortality in cases of COVID-19, among them being a local prevalence of obesity; the associated comorbidities of obesity such as diabetes, cardiovascular, stroke, respiratory disease, and defective innate and adaptive immune responses; and the exposure of the patients to the virus because of their frequent hospital visits and need for medical support.[14-16] It is not surprising that a significant number of severe COVID-19 cases led to mortality in highly prevalent areas for obesity such as the USA[17] and the UK.[11]

A recent meta-analysis showed that obesity, age, critical illness, the need for advanced respiratory support, and severe comorbidities are risk factors for mortality in patients with COVID-19.[18] Obesity is thought to be a major risk factor for COVID-19 mortality because of the impaired immune response, cellular failure to control the infection, and the effect of adipose tissue mass, to which the virus affinity is higher than to the lung tissues.[19,20] The overexpression of inflammatory adipokines from visceral fat depots can affect the immune response, impair the chemotaxis, and alter the macrophage differentiation.[21] Other publications had confirmed the association between obesity and mortality and leading organisations such as the British Obesity and Metabolic Surgery Society (BOMSS) have called for increasing bariatric surgery capacity to protect patients with obesity and reduce the definitive risks if they go on to develop COVID-19.[22]

The mean age of the participants was of 65.8 years, and several studies on COVID-19 have confirmed that elderly people are likely to experience the severe form of the infection.[23,24] Other important features strongly associated with COVID-19 mortality are male sex, heart disease, respiratory disease, and cancer. Previous studies have also shown the vulnerability of hypertensive patients for severe infection.[25]

It is known that the virus attaches itself to cells via the angiotensin-converting enzyme-2 (ACE2) receptors for purposes of entry, replication, and subsequent shedding.[26] ACE2 are a usual target in the management of hypertension as their receptors are abundant in the lung, heart, kidney, and gastrointestinal tract. Administering ACE2 inhibitors blocks the receptors and reduces angiotensin-1. Angiotensin II receptor blockers are able to reduce inflammation and could diminish the potential for the development of either acute respiratory distress syndrome, myocarditis, or acute kidney injury, which is known to occur in patients with COVID-19.[27]

Several studies have reported hypertension as an indicator of severity without adjusting the confounding factors. The accurate association is not known and larger studies are needed to address this controversy.[28,29]

Smoking is frequently reported in cases of COVID-19, and it is a risk for severity, ITU admission, and mortality;[30] this is because smoking increases the levels of goblet cells and ACE2 receptors. Theoretically speaking, higher levels of smoking leads to additional ACE2 receptors which gives more opportunity for the SARS-CoV-2 to attach to cells.[31] If the viral load is high, then the expected outcome is a severe disease and possible mortality.

It is, however, not clear whether ex-smokers will be at as high a risk as current smokers, and more studies are needed to elucidate this.

Table 2: Cox regression analysis variables.

							95% CI for Exp(B)	
	B	**SE**	**Wald**	**DF**	**Sig.**	**Exp(B)**	**Lower**	**Upper**
Age	0.064	0.030	4.626	1	0.031	1.066	1.006	1.130
Smoking	-0.503	0.574	0.768	1	0.381	0.605	0.196	1.863
Diabetes	-0.113	0.585	0.037	1	0.847	0.893	0.284	2.812
Heart disease	0.554	0.594	0.867	1	0.352	1.740	0.543	5.578
Hypertension	1.215	0.562	4.677	1	0.031	3.369	1.121	10.131
Respiratory disease	-0.472	0.955	0.245	1	0.621	0.623	0.096	4.050
Cancer	1.261	0.743	2.882	1	0.090	3.529	0.823	15.136
BMI	0.072	0.765	0.009	1	0.925	1.074	0.240	4.817
Sex	0.382	0.625	0.373	1	0.541	1.465	0.430	4.988
Mechanical ventilation	0.418	0.546	0.585	1	0.445	1.518	0.521	4.428

B: exponential; CI: confidence interval; DF: Dickley–Fuller test; SE: standard error; sig: significance test; Wald: Wald test.

Again, confounding factors that need adjustment must be observed before jumping to the conclusion of significance as deemed by statistical tests.

Additionally, cardiovascular disease is a predictor for COVID-19 severity, ITU admission, and mortality. This again is linked to ACE2 receptors and progression to myocarditis, heart failure, and death.[32]

Patients with COPD are also at significant risk of poor COVID-19 disease progression and mortality. Many other studies have shown similar outcomes in patients with COPD and COVID-19,[24,33,34] where significant number of patients were admitted to the ITU or had to undergo CPAP ventilation.[35,36]

Patients with cancer are especially vulnerable to infection and severe outcomes because of poor general health, immunosuppression, and the type of cancer and anticancer treatment regimen they are following.[37,38] Cancer was significantly associated with mortality in the patients in this study (p=0.003).

In this study, diabetes was a predicter of mortality in linear regression; however, it did not reach statistical significance in multivariate analysis (p=0.491). Several reports on patients with diabetes have shown a strong association between vulnerability, severe disease progression, and mortality when presenting with COVID-19.[23,39-41] This is likely because of immunosuppression, defective metabolic systems, and associated morbidities of chronic complications of diabetes such as cardiovascular, renal, and cerebrovascular disease.

As this study is relatively small, caution should be taken when considering the generalisability of the results. It is, however, one of several studies to provide evidence on obesity as a risk factor for COVID-19 mortality.

Limitations

Firstly, this is a cohort of consecutive patients who were admitted to the RU for respiratory support and possible escalation to the ITU. It is a relatively small study; however, the sample representation was adequately powered for statistical analysis. Secondly, a significant number of patients are still in hospital and are therefore not available for mortality analysis.

CONCLUSIONS

This is one of several clinical studies to confirm obesity as a risk factor for COVID-19 mortality. Cancer, smoking, cardiovascular disease, and hypertension are also additional risk factors for mortality.

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Effects of Noninvasive Versus Invasive Mechanical Ventilation on Sleep in the Intensive Care Unit – A Pilot Study

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Abstract

Rationale: Use of noninvasive ventilation (NIV) has increased in intensive care units, but sleep during NIV has received little attention. The authors surmised that due to frequent air leaks and mask discomfort, patients receiving NIV would manifest poorer sleep quality than those receiving invasive mechanical ventilation (INV).

Methods: A prospective observational study on patients receiving NIV or INV for respiratory failure in a medical intensive care unit or coronary care unit. Patients were monitored by polysomnography for 24 hours with simultaneous collection of data on ventilator and environmental parameters.

Results: Eight subjects in each group were studied. Mean total sleep time was 7.29 +1.78 hours (range: 0.57–13.82) in the NIV versus 11.74 +0.65 hours (8.95–15.19) in the INV group (p=0.034). Sleep efficiency was lower in NIV than INV group (30.4% versus 53.3%, respectively; p=0.013). The NIV group had lighter sleep than the INV group (mean % of Stage 1: 36.9% versus 17.2% of total sleep time, respectively; p=0.000), whereas no significant differences were found for other stages. Median total arousal and awakening indexes were higher in the NIV group (16.8/hour versus 4.4/hour and 5.3/hour versus 2.1/hour, respectively; p=0.005), as well as spontaneous arousals and awakenings (p=0.006 and p=0.005, respectively). Sedation was provided mostly by intermittent bolus in the NIV group whereas often by infusion in the INV group.

Conclusion: Compared to INV, NIV in critically ill patients was associated with poorer quality and quantity of sleep. Future studies should determine whether adjustments in ventilator settings, mask type or fit, or use of sedation/analgaesia can improve sleep in patients receiving NIV.

INTRODUCTION

Disruption of sleep is remarkably common in critically ill patients.[1-3] Abnormalities of sleep in this population include sleep deprivation, sleep fragmentation, and alterations in sleep architecture and circadian rhythm. These abnormalities may lead to undesirable consequences, such as delirium, delayed weaning in intensive care units (ICU), or late noninvasive ventilation (NIV) failures.[4-6] Mechanical ventilation is one of the important factors associated with sleep disturbances in the ICU.[3,7,8]

NIV has been increasingly used in ICU.[9-11] Although recognition of the importance of poor sleep in mechanical ventilation patients is increasing, only a few studies have investigated the effect of NIV on sleep in patients with acute respiratory failure (ARF).[5,12] Earlier studies focussed on patients with chronic respiratory failure.[13,14] Air leaking was associated with frequent arousals during lighter stages of sleep and decreased sleep efficiency and durations of slow-wave sleep (SWS) and rapid eye movement (REM) sleep.[13,14] Sleep studies on hypercapnic ARF patients receiving NIV in the ICU showed similar sleep architecture changes.[5,12]

The authors hypothesised that because of frequent air leaks and mask discomfort, patients receiving NIV would manifest poorer sleep quality than those receiving invasive mechanical ventilation (INV). Therefore, they aimed to define and compare sleep characteristics in critically ill patients receiving NIV and INV during a 24-hour monitoring period.

METHODS

Patients

This prospective, observational, pilot study was conducted in critically ill adult patients undergoing INV or NIV for ARF in the medical ICU unit or coronary care unit (CCU) at Tufts Medical Center, Boston, Massachusetts, USA. The Institutional Review Board of Tufts Medical Center approved the study (Tufts ID #8053).[15] Written informed consent was obtained from all participants or their families.

All adult patients receiving NIV or INV for ARF in the medical ICU or CCU and anticipated to be continuing NIV for >8 hours/24 hours or INV for 24 hours were eligible and screened on the days when the primary researcher (Dr Ugurlu) was available. All patients were in private rooms that could be isolated from the nursing station through a sliding glass door.

Exclusion criteria are listed as presence of premorbid diseases that could interfere with application or interpretation of sleep monitoring (including central nervous system disorders, dementia, known sleep disorders); previous home treatment with bilevel positive airway pressure (BiPAP) or continuous positive airway pressure; depressed sensorium (Riker score: ≤2); presence of head trauma, psychiatric illness, anoxic brain injury, drug overdose, or uncontrolled seizure disorder; severe haemodynamic instability; recalcitrant hypoxaemia (inability to sustain oxygen saturation >88%); and tracheostomy.

All patient care decisions (supportive care and mechanical ventilation) were made by the ICU team and not by any investigator during the study. Respiratory therapists, nurses, and/or critical care physicians periodically checked patients to ensure that the subjects were adapted to the NIV use (proper mask fit, synchrony with ventilation, etc).

Polysomnography and Scoring

Continuous 24-hour standard polysomnography (PSG) utilising portable noninvasive PSG monitoring equipment (Grass Comet, West Warwick, Rhode Island, USA) was conducted with simultaneous monitoring of noise. The staff attending the study fixed displacing leads.

Sleep studies were continuously attended and scored manually according to standard criteria[16,17] by a registered PSG technologist and then reviewed in total by a sleep specialist blinded to mode of ventilation (Dr D'Ambrosio). Circadian sleep distribution was evaluated by separating the total recording time into a daytime segment (6 AM–10 PM) and a nocturnal segment (10 PM–6 AM).

Sleep efficiency was defined as the ratio of time asleep to total recording time. Total sleep time (TST) was defined as the sum of total time spent in any sleep stage during total recording time. The percentage of time spent in each sleep stage during TST was calculated. The sleep

fragmentation index was defined as the number of arousals and awakenings per hour of sleep. Arousals and awakenings caused by noise, patient care activities, patient–ventilator asynchronies (including auto-triggering, ineffective triggering, and double triggering, based on inductance plethysmography and airway pressure measurements), or mask leak (based on leak and airway pressure monitoring) were defined as those occurring within 3 seconds of termination of these events. The rest of the arousals or awakenings were defined as spontaneous.

Environmental Monitoring

Environmental noise was continuously monitored by a sound level meter (Extech Instruments, Nashua, New Hampshire, USA) secured to the head of the bed, and simultaneously recorded on the PSG. The ceiling fluorescent light turned on throughout the daytime and turned off at night, except during nursing care. The bedside environment was monitored by the staff, who recorded the time and duration of all activities (including interactions between the patients and the visitors or critical care team member, nursing care, and procedures) on the patient's bedside diary.

Data Collection

Data included demographics, date and time of hospital and ICU/CCU admission, admitting diagnosis, causal diagnosis, and reason for mechanical ventilation. Further data included type of mechanical ventilation, settings, sedation level, medications, last arterial blood gas measurement, and last chest X-ray findings. Acute physiology and chronic health evaluation II (APACHE II) score was calculated on the day of the sleep study using the most abnormal values during the 24-hour PSG period. Additionally, the investigator attending the sleep study recorded all pertinent events and times in a bedside log.

Statistical Analysis

This study was performed as a pilot and no previous study has compared sleep patterns during NIV and INV in critically ill patients. Accordingly, no power analysis was proposed. Statistical analysis was performed using SPSS statistical software (SPSS 17.0, Chicago, Illinois, USA). Continuous variables were expressed as median (interquartile range) or mean±standard error of mean with minimum and maximum values, based on the distribution of data. Variables were compared using chi-squared test or Mann–Whitney U test. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Patient Demographics

Out of 383 patients with ARF anticipated to continue using NIV or INV for ≥24 hours, 346 patients were excluded (central nervous system disorder/injury: 170; depressed sensorium: 51; tracheostomised: 33; previous home continuous positive airway pressure/BiPAP: 26; known sleep disorder: 22 [not using NIV at home]; severe haemodynamic instability: 17; unstable status: 17; legal issues: five [e.g., prisoner, no relatives]; diffuse skin lesions: three; recalcitrant hypoxaemia: two). Furthermore, 17 patients refused enrolment. Overall, 20 patients were enrolled to the study; however, a total of four patients were excluded after enrolment because of early extubation (<24 hours) in the INV group (three patients) or early intubation (<24 h) in the NIV group (one patient).

The study population characteristics are provided in Table 1. Chronic obstructive pulmonary disease and heart diseases (including coronary arterial disease, rhythm disorders, and congestive heart failure) were the predominant comorbidities in both the NIV and INV groups (Table 1). Although there was no statistically significant difference in the comparison of causal diagnoses, there tended to be more acute-on-chronic respiratory failure in the NIV group and more *de novo* respiratory failure in the INV group.

Characteristics of Mechanical Ventilation at Initiation of the Study

All patients in the NIV group were on BiPAP delivered through dedicated ventilators. Mean inspiratory and expiratory positive airway pressures were 11±0.7 (8–15) and 5.1±0.1 (5–6) cmH_2O, respectively. All INV patients were on volume-limited assist-control ventilation with a mean tidal volume of 507.9±24.6 (350–550) mL (7.1±0.3 mL/kg per ideal body weight), similar to NIV patients (441.3±24.4 [316–512] mL [7.8±0.7 mL/kg per ideal body weight]).

Table 1: Characteristics of the patients (N=16).

	Noninvasive ventilation group (n=8)	Invasive mechanical ventilation group (n=8)	p value
Age (years)	72.6±3.1 (54–85)	64.1±4.6 (38–78)	NS
Male (n [%])	3 (37.5)	8 (100)	0.013
BMI (kg/m^2)	25.7±6.37 (16.2–36.0)	26.8±8.22 (16.9–44.3)	NS
Location (MICU/CCU)	5/3	5/3	NS
Causes of ARF (n)			NS
Acute pulmonary oedema	2	1	
ARDS	0	2	
Cardiopulmonary arrest	0	1	
COPD exacerbation	1	0	
Haemoptysis	0	1	
Lung cancer	0	1	
Neuromuscular disease	1	0	
Pneumonia	1	1	
Pulmonary emboli	1	0	
Restrictive lung disease*	2	0	
Sepsis	0	1	
At the initiation of study: duration of MV† (day)	1 (1.00–3.25)	4 (1.00-5.00)	NS
Apache II score	20.4±2.3 (13–28)	13.4±1.9 (6–21)	0.039
Vitals			NS
Heart rate (bpm)	83.6±6.1 (58–105)	83.5±3.5 (68–97)	
Respiratory rate (bpm)	22.1±2.4 (10–32)	20.1±1.5 (13–25)	
Systolic blood pressure (mmHg)	106.5±5.3 (90–129)	114.8±6.3 (90–140)	
Diastolic blood pressure (mmHg)	55.6±5.2 (38–81)	56.9±3.2 (42–66)	
Arterial blood gases			
pH	7.25±0.03 (7.26±7.48)	7.44±0.01 (7.36–7.49)	0.022
P_aCO_2	49.4±5.6 (34–68)	42.4±1.1 (38–48)	NS
P_aO_2/FiO_2†	290 (220–410)	180 (160–240)	NS

*Restrictive lung disease was due to pleural effusion.

†Values are given in median (IQR). The rest of the values were given as mean±SEM (min–max).

ARDS: acute respiratory distress syndrome; ARF: acute respiratory failure; bpm: beats per minute; CCU: coronary care unit; COPD: chronic obstructive pulmonary disease; FiO_2: fraction of inspired oxygen; IQR: interquartile range; max: maximum; MICU: medical intensive care unit; min: minimum; MV: mechanical ventilation; NS: not significant (p>0.05); P_aCO_2: partial pressure of carbon dioxide; P_aO_2: partial pressure of oxygen; SEM: standard error of the mean.

Mean fraction of inspired oxygen and mean set respiratory rate in the NIV and INV groups were 52.5±7.5 versus 40±3.3% (p=0.14) and 10.5±1.1 versus 13.3±0.8 beats per minute (p=0.06), respectively.

Sleep Architecture of Patients

Compared to INV patients, NIV patients slept less and had lower sleep efficiency (Table 2).

Table 2: Comparison of sleep characteristics between patients treated with noninvasive ventilation and invasive mechanical ventilation.

	Noninvasive ventilation group	Invasive mechanical ventilation group	p value
TST (hours)	7.3±1.8 (0.6–13.8)	11.7±0.7 (9.0–15.2)	0.034
Day/night (% of TST)	57/43	60/40	NS
Sleep efficiency (%)			
Total	30.4±7.5 (2.4–57.6)	53.3±3.1 (37.5–64.0)	0.013
Daytime (6 AM–10 PM)	23.5±6.4 (3.7–51.6)	50.1±2.8 (34.9–57.4)	<0.001
Night-time (10 PM–6 AM)	44.2±10.3 (0.0–74)	58.9±5.0 (36.0–77.3)	NS
Stage 1 (% of TST)	36.9±3.3 (23.7–53.0)	17.2±2.8 (3.3–26.9)	<0.001
Stage 2 (% of TST)	57.1±3.1 (46.2–70.6)	64.8±6.2 (26.4–86.8)	NS
SWS* (% of TST)	1.4 (IQR 0.0–4.5)	9.5 (IQR 5.5–17.3)	0.04
REM* (% of TST)	0.6 (IQR 0.0–2.9)	0.0 (IQR 0.0–1.1)	NS
Total fragmentation index/hour	22.4 (IQR 14.0–39.5)	6.3 (IQR 5.2–11.4)	0.003
Arousal index*/hour	16.8 (IQR 9.1–31.8)	4.4 (IQR 3.7–8.5)	0.005
Spontaneous arousal index*	14.1 (IQR 7.4–17.9)	3.2 (IQR 2.2–4.2)	0.006
Ventilator asynchrony-air leak associated arousal index*	2.2 (IQR 0.1–10.9)	0.1 (IQR 0.0–1.5)	NS
Noise associated arousal index*	0.7 (IQR 0.1–1.1)	0.4 (IQR 0.2–0.5)	NS
Patient care associated arousal index*	0.5 (IQR 0.0–1.2)	0.6 (IQR 0.3–1.2)	NS
Awakening index*/hour	5.3 (IQR 4.9–6.8)	2.1 (IQR 1.7–3.0)	0.005
Spontaneous awakening index*	2.6 (IQR 2.0–4.9)	1.0 (IQR 0.6–1.4)	0.005
Ventilator asynchrony-air leak associated awakening index*	1.4 (IQR 0.0–1.7)	0.2 (IQR 0.1–0.2)	NS
Noise associated awakening index*	0.4 (IQR 0.1–0.7)	0.3 (IQR 0.1–0.3)	NS
Patient care associated awakening index	0.5±0.2 (0.0–1.7)	0.8±0.1 (0.3–1.4)	NS

*Values are given in median (IQR). Rest of the values are given as mean±SEM (min-max).
IQR: interquartile range; max: maximum; min: minimum; NS: not significant (p>0.05); REM: rapid eye movement; SEM: standard error of the mean; SWS: slow-wave sleep; TST: total sleep time.

Sleep efficiency was significantly lower during the daytime in the NIV group, but not during the night. The NIV group also had an increased mean percentage of Stage 1 sleep than the INV group and a reduced percent of SWS. When one patient with non-REM sleep that was inconsistent with normal due to the absence of typical Stage N2 sleep figures was excluded,[5] the significance for the difference of SWS was lost (p=0.07). REM sleep was virtually absent in both groups.

Sleep of NIV compared to INV patients was also more fragmented, with increased frequency of arousals and awakenings (Table 2). Although arousals as a result of ventilator asynchrony tended to be more frequent in NIV patients, the difference was not statistically significant. Only two NIV patients had respiratory event related arousals (7.4 and 8.4/hour) during spontaneous breathing and none during NIV use. Therefore, median number of arousals related to respiratory

events was negligible (0 in both groups; p>0.05). Sleep architecture and circadian rhythm varied greatly between patients (Figure 1).

Vital Signs and Duration of Noninvasive Ventilation Use

Vital signs (including heart rate, respiratory rate, diastolic blood pressure, and oxygen saturation) recorded hourly during the study were similar in both groups except for systolic blood pressure, which was lower in the NIV group than the INV group (median systolic blood pressure of 107 [100–112] versus 123 [112–125]; p=0.04).

NIV was applied continuously in two patients and intermittently in six patients. For those six patients, NIV was applied 70% of the total recording time with a mean sleep efficiency of 39%, and it was removed 30% of the time (with application of O_2 via nasal cannulae) with a mean sleep efficiency of 7.8% (p=0.045).

Use of Sedation and Analgesia

NIV patients received more intermittent sedation and less sedation overall than INV patients (p=0.001). Two of the NIV patients received no sedation; the other NIV patients received morphine (two patients), diphenhydramine, (two), lorazepam (one), quetiapine (one), and hydromorphone (one), all intermittently. The sedative agents used by the INV group were fentanyl (seven patients), propofol (three), midazolam (five), hydromorphone (two), quetiapine (one), and lorazepam (one). Two INV patients received only continuous sedation protocols, whereas six of them received not only continuous sedation, but also intermittent boluses.

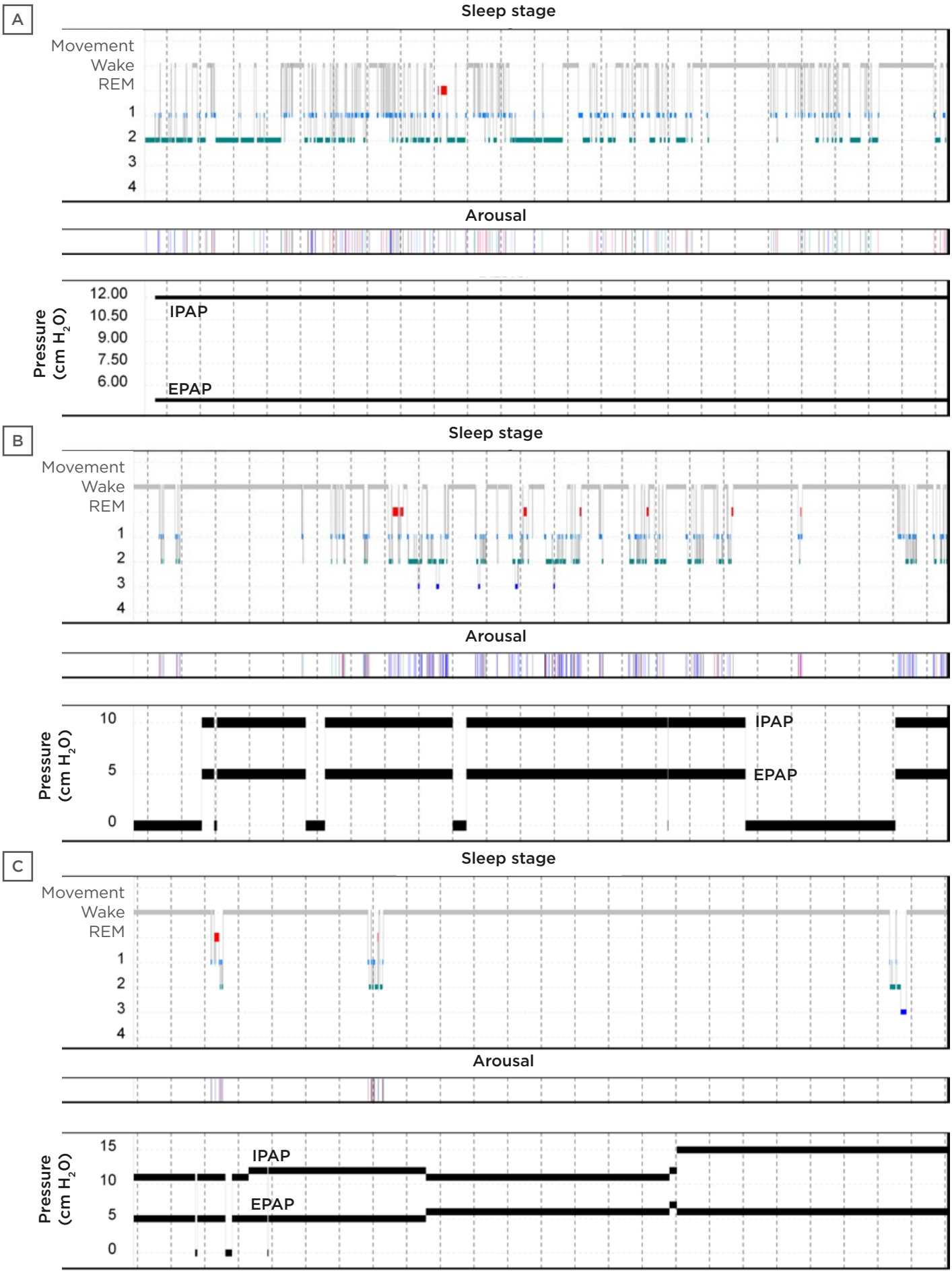
Long-Term Outcomes

Three of the NIV patients were intubated and eventually died (1–5 days and 4–11 days after the termination of the study, respectively), and two of the INV patients died (10 days after the termination of the study). The mean TST of the NIV patients requiring intubation was longer than other NIV patients, but this was not statistically significant (9.2±4.0 [1.2–13.8] versus 6.2±1.8 [0.6–10.7] hours, respectively; p>0.05), whereas the mean APACHE II score was higher on the day of the study (26.0±2.0 [22–28] versus 17.3±1.8 [13–22], respectively; p=0.02). Mean hospital and ICU lengths of stay were similar between the NIV and INV groups (18±1.1 [10–23] versus 19.8±3.1 [7–35] days, and 14.0±2.2 [5–21] versus 14.9±3.2 [5–34] days, respectively; p>0.05).

DISCUSSION

This first pilot study comparing sleep architecture in patients receiving NIV and INV for management of ARF in the ICU found that NIV patients 1) were sicker based on higher APACHE II scores and lower pH; 2) slept less and lighter in 24 hour; 3) had more fragmented sleep; and 4) received less sedation. Fragmentation of sleep was mainly due to spontaneous arousals and awakenings. Although arousals due to ventilator asynchronies (including asynchronies due to air leakages) were more common during NIV than INV use the difference was not significant. Noise and patient care contributed little to the sleep fragmentation. Lengths of stay and mortality outcomes were similar between groups although the number of patients was small.

Sleep abnormalities in critically ill patients have been repeatedly reported over the past three decades.[5,12,18-32] Most of the studies performed in intubated patients reported normal or near normal duration of sleep (6–8 hours/24 hours),[18-20,28,32] although some studies revealed a decreased TST,[20,22,23,31] and others showed longer durations of sleep.[21,24,30] In this study, patients on NIV had shorter TST with lower sleep efficiency than patients receiving INV. The TST of NIV patients from this study were similar to those reported for NIV patients previously,[5,12] whereas INV patients would have been considered 'long sleepers' as described by others.[21,24,30] The shorter TST of NIV compared to INV patients could be related to many factors including the higher severity of illness of this study's NIV population and more frequent and continuous use of sedatives in the INV patients. Furthermore, the NIV patients had received less ventilatory assistance than the INV patients (median 1st day versus 4th day) before enrolment and could have been less well acclimated. Furthermore, patients on both types of ventilation varied greatly in sleep duration, ranging from 0.6 to 15.2 hours over 24 hours. This corresponds with prior studies[18,19,32] and probably reflects the great variability between patients in acuity of illness, use of and responsiveness to medications, and many other possible factors.[7]


A
Sleep stage
Movement
Wake
REM
1
2
3
4
Arousal
Pressure (cm H_2O)
12.00
10.50
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6.00
IPAP
EPAP
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Sleep stage
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REM
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Arousal
Pressure (cm H_2O)
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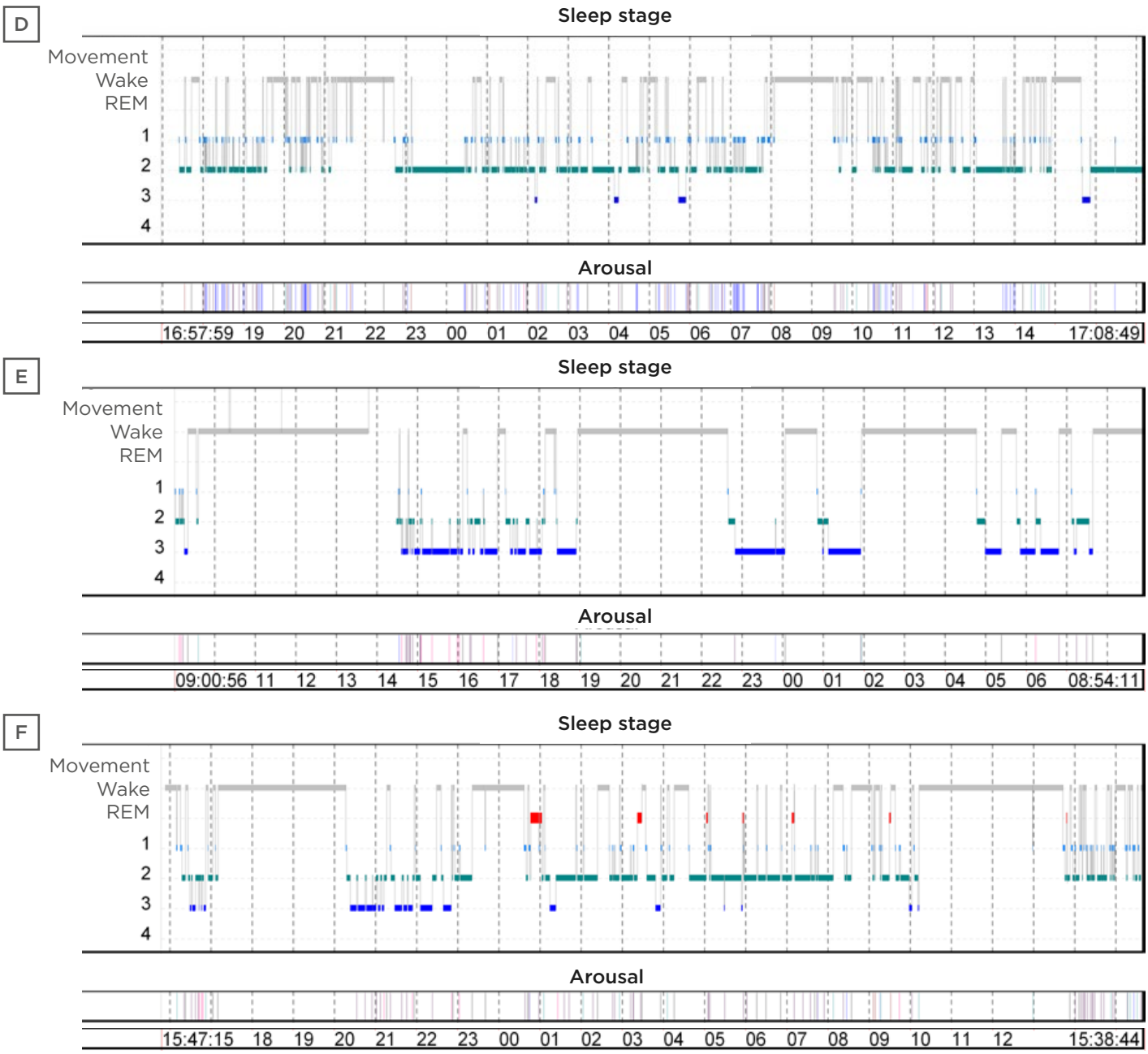

Figure 1: 24-hour hypnograms of six patients.

A, B, C in noninvasive ventilation group and **D, E, F** in invasive mechanical ventilation group (X axis is the timeline). The circadian rhythm was partly conserved in some patients (**B** and **F**) but lost in others (**A** and **D**). Total sleep time was severely decreased in two of the noninvasive ventilation patients who slept <2 hours (**C**). One of the patients on invasive mechanical ventilation had an abnormal sleep pattern with increased slow-wave sleep (**E**).

EPAP: expiratory positive airway pressure; IPAP: inspiratory positive airway pressure; REM: rapid eye movement.

Previous ICU studies have shown disruption of the circadian pattern with increased napping so that daytime sleep reached up to an average of 60% of TST in a 24-hour cycle.[18-20] Similarly, the patients of this study in both groups slept around 60% of the TST during the daytime.

Patients on mechanical ventilation in ICU generally have diminished sleep quality, characterised by an increase in the proportion of time spent in 'light' stages of sleep and a decrease in the proportion or even absence of slow wave or REM sleep.[19,23,24,31,32] Consistent with these observations, patients of this study, especially the ones on NIV, also manifested a greater than normal proportion of time spent in lighter stages of sleep. REM sleep was observed only in four NIV and two INV patients with a range

of 1.2 to 11.5% of TST. Still, sleep efficiency was better preserved during application of NIV compared to breaks off NIV, consistent with prior observations, but this might be related to increased patient activities during breaks.[12]

Two prior PSG studies have evaluated sleep in hypercapnic patients receiving NIV in an ICU for 17 hours.[5,12] Median TST was 5.8 hours with 68–74% of sleep occurring during at night. REM sleep deprivation (7–11% of TST) and severe sleep fragmentation (24–33/hour) were noted. Based on the assumption that patients were awake between 8 AM and 3 PM (because of nursing activities and diagnostic testing), the authors surmised that circadian rhythm and the proportion of SWS (22%) were better preserved with NIV compared to earlier studies on patients receiving INV.[18-20] The latter findings conflict with findings from this study. Here, sleep was directly compared during NIV and INV in contemporaneous patients in the same ICU rather than earlier studies and monitored for the entire 24 hours rather than 17 hours. Furthermore, patients had greater acuity of illness, more acidaemia (pH: 7.25 versus 7.32), an earlier period of observation during ventilator assistance and greater use of sedative/analgesic medications, which may account for some of the differences.

The study authors encountered more sleep fragmentation, attributable mainly to an increased number of arousals and awakenings, in NIV group compared to INV group. Common contributors to disrupted sleep include factors associated with the ICU environment, critical illness, medications, and mechanical ventilation.[1,3,8] The higher level of sleep disruptions with more frequent spontaneous arousals and awakenings during NIV compared to INV could have been related to the higher severity of critical illness in NIV patients, less frequent use of continuous sedation, or other unmeasured factors. On the other hand, it should be mentioned that the arousal index for both groups still seems to be within normal limits[33] and the sleep fragmentation index for the NIV group to be less than the prior studies (22/hour versus 33/hour),[5,12] which could be attributed to differences in severity of the disease, ventilator, or sedative management as mentioned above.

Patients on mechanical ventilation usually receive intermittent or continuous sedation to control agitation and to improve patient–ventilator interactions. Even though benzodiazepines and propofol at night can increase TST or decrease sleep fragmentation,[21,34,35] they can lead to significant disturbances of sleep architecture, with suppression of SWS and REM sleep.[4,7,36] While two of the NIV patients were not receiving any sedatives or analgesics, the rest were receiving less sedation on a more intermittent basis than INV patients. This difference could have contributed to the decreased quantity and quality of sleep in the NIV compared to the INV patients.

The presented study has a number of strengths including the complete and continuously observed PSG recordings for 24 hours, the prospective design, and the careful analysis including recording of noise and disruptions by caregivers. It also has important limitations including the small sample size that precludes the ability to draw inferences about the effects of disrupted sleep on clinical outcomes such as lengths of stay or mortality. Furthermore, patients were not randomised; therefore, selection bias was likely to create inevitable differences between the NIV and INV groups. Additionally, the authors were unable to control confounding variables such as use of medications and sedation level, severity of illness, fluctuations in patient illness, presence of undiagnosed sleep apnoea, activities of medical personnel, and clinical testing. On the other hand, the study was performed as a pilot to attract attention to this topic. The study was labour intensive, difficult to enrol (only 5% of screened patients), and technically challenging to administer in an ICU given interference with delivery of clinical care was prohibited. Furthermore, use of the Rechtsschaffen and Kales[16] sleep scoring manual has not been well validated in critically ill patients and is confounded by poor inter-observer reliability, except for REM sleep.[37]

CONCLUSION

The study demonstrated that compared to INV, critically ill patients using NIV for ARF had lower quantity and quality of sleep. These data are the first to suggest that sleep time and quality are compromised to a greater extent with NIV than INV. On the other hand, keeping the patient on NIV can protect against other adverse events

already described in literature related to INV. Therefore, future studies should determine whether adjustments in ventilator settings, mask type or fit, sedation/analgesia use, or other interventions can improve sleep in NIV patients.

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Cryobiopsy In Flexi-Rigid Pleuroscopy in a Region with Low Mesothelioma Prevalence

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Abstract

Background: The use of conventional flexible forceps during flex-rigid pleuroscopy can be challenging when sampling hard and thickened pleura. Pleuroscopic cryobiopsy is an emerging field, with various early studies demonstrating good yield and minimal complications.

Objectives: To review the authors' early experience of pleuroscopic cryobiopsy in their centre and highlight its utility in the diagnosis of mesothelioma.

Method: Six cases of undiagnosed pleural effusion that underwent pleuroscopic cryobiopsy via flexi-rigid pleuroscopy between July 2017 and June 2019 were retrospectively analysed.

Results: The cohort had a median age of 59 years, consisting of two females and four males with a median age of 57 years. Mean (aggregate) tissue sample diameter was 9.2±1.9 mm. Cryobiopsy established a definitive diagnosis in all six cases: one case of malignant mesothelioma, one pleural tuberculosis, two small cell carcinomas, and two adenocarcinomas. Immunohistochemical staining was performed in all five of the malignant samples (100%). There were no major complications reported.

Conclusions: Based on the case series, pleuroscopic cryobiopsy is a feasible adjunct to conventional forceps biopsy, a safe procedure in the authors' setting, gives high diagnostic yield, and enables differentiation between the different causes of exudative pleural effusion. A large, prospective study is required to validate this retrospective series.

INTRODUCTION

Following diagnostic thoracocentesis and closed pleural biopsy, 25% of pleural effusions remain undiagnosed,[1] requiring either pleuroscopy or video-assisted thoracic surgery (VATS). While VATS is considered the gold standard, pleuroscopy is a less invasive, simpler, and cost-effective alternative with a favourable diagnostic yield.[2] Furthermore, VATS is not always available,

and is sometimes contraindicated, especially in patients with high surgical risk or advanced metastatic malignancy.[2]

Rigid pleuroscopy demonstrates higher yields of 97.8% versus 73.3% for flexi-rigid pleuroscopy due to larger sample sizes, superiority in sampling fibrous pleura in suspected mesothelioma, and its effectiveness in adhesiolysis.[3] On the other hand, advantages for flexi-rigid pleuroscopy include less pain and easier maneuverability.[4,5] Efforts to increase yield of flexi-rigid pleuroscopy has led to the use of cryobiopsy, a technique previously validated for endobronchial and transbronchial biopsies.[6] Cryobiopsy through flexi-rigid pleuroscopy is an emerging technique which carries the promise of both larger sample size with preserved tissue architecture, while maintaining ease of manoeuvrability with a flexible pleuroscope.

In the Southeast Asia region, the incidence of mesothelioma is lower compared with European or Oceanian countries. Many benign pleural diseases mimic similar histopathological changes in mesothelioma;[7] therefore, proper acquisition of tissue is important in Malaysia to ensure a diagnosis of mesothelioma is not missed.

MATERIALS AND METHODS

Six patients with malignancy-suspicious pleural effusion who underwent pleuroscopic cryobiopsy at the authors' unit between July 2017 and June 2019 were analysed. In that period, a total of 244 patients underwent pleuroscopic biopsy: 14 via rigid pleuroscope, 224 via flexi-rigid pleuroscope using conventional forceps, and six via flexi-rigid pleuroscope using cryobiopsy. Written informed consent was obtained from all patients. Pleural fluid analysis was performed via ultrasound-guided diagnostic thoracocentesis prior to the procedure. Baseline blood investigations including coagulation profile were taken for each patient and ensured normal prior commencing the procedure.

Transthoracic ultrasound was performed on each patient to identify the safe entry site with the patient in lateral position with the abnormal side upwards. The procedure was performed under conscious sedation with intravenous midazolam and pethidine. Under aseptic technique, the entry site was infiltrated with local anaesthesia (2% lidocaine). Flexible electrocautery equipment were prepared for any potential bleeding complications.

A 1.5 cm incision was then made on the skin and blunt dissection was performed until the pleura was breached. A 11 mm metallic trocar was then inserted into the pleural cavity for pneumothorax induction. Pleuroscopy was performed using a flexi-rigid scope (LTF-160, Olympus, Tokyo, Japan) passed through the trocar. All pleural fluid was aspirated until clear to allow clear examination of the pleural cavity. Pleural fluid was sent for further analysis if initial diagnostic thoracocentesis data was inadequate.

After cautious examination of the pleural cavity, cryobiopsies were obtained at visibly abnormal areas using a 950 mm cryoprobe of either 1.9 or 2.4 mm diameter passed through the working channel of the pleuroscope in conjunction with the ERBECRYO®2 system (Erbe Medizintechnik, Tübingen, Germany). Carbon dioxide was used as cryogen. The tip of the cryoprobe was applied to the target biopsy sites and activated for a minimum time of 3 sec under direct vision, and pleural specimens were removed by extracting the cryoprobe and flexi-rigid scope together through the trocar. The specimen was thawed in normal saline, placed into formalin solution, and immediately sent to the laboratory for histopathological analysis. Meanwhile, the pleuroscope was reinserted into the pleural cavity to assess for any bleeding or complication. The biopsy procedure was repeated for a minimum of three times, given that no complications occurred. The decision to employ cryobiopsy was at the discretion of the endoscopist when specimen from forceps biopsy was deemed inadequate during intraprocedure.

CASE SERIES

Case 1

Case 1 was a 64-year-old indigenous Malaysian female who did not smoke and had no underlying medical illness. She presented with 1 week of progressively worsening shortness of breath on a background of 1 month of persistent non-productive cough and loss of appetite. When asked, she did not report any fever or night sweats. Clinically, she was not tachypnoeic but had finger clubbing and reduced air entry over

the left lower zone of the chest. Her vitals were unremarkable with a temperature of 36.6 °C and oxygen saturation of 97% under room air. Chest radiograph showed blunting of the left costophrenic angle and ultrasound of the thorax confirmed a left non-loculated pleural effusion. Her total white cell count was $6.7x10^9$ cells/L. Pleural fluid parameters were exudative (pH = 7.355; pleural fluid:serum protein ratio = 50/72 g/L; pleural fluid:serum lactate dehydrogenase [LDH] ratio = 1554/426 U/L; fluid glucose = 4.8 mmol/L); pleural fluid cytology showed no malignant cells. Pleuroscopy revealed multiple pleural and diaphragmatic nodules; cryobiopsy was performed with no major complication. Talc pleurodesis was applied prior to removal of the chest drain. Histopathological and immunohistochemical examination confirmed epidermal growth factor receptor-positive lung adenocarcinoma, and she was referred to the oncology team for commencement of tyrosine-kinase inhibitor therapy.

Case 2

Case 2 was a 59-year-old Malay male with a 50-pack per year smoking history, underlying hypertension, and dyslipidaemia, who presented with 1 week of right lateral chest pain and shortness of breath on a background of chronic dry cough of 2 months, accompanied by loss of weight and appetite. He did not have a history of fever. On clinical examination, he was tachypnoeic with a respiratory rate of 24 breaths per minute and oxygen saturation of 92% under room air. He had no finger clubbing; chest examination demonstrated reduced air entry over the right lower and middle zones. His temperature was 36.5 °C and his total white cell count was $7.7x10^9$ cells/L. Chest radiograph showed a right homogenous opacity with meniscus sign obliterating the right heart border. Ultrasound thorax confirmed a non-loculated right pleural effusion. Pleural fluid parameters were exudative (pH = 7.531; pleural fluid:serum protein ratio = 42/72 g/L; pleural fluid:serum LDH ratio = 722/894 U/L; pleural fluid glucose = 5.3 mmol/L); pleural fluid cytology showed no malignant cells. Pleuroscopy showed multiple visceral and parietal pleural nodules; cryobiopsy was performed with no major complication. Talc pleurodesis was applied prior to removal of the chest drain. Histopathological and immunohistochemical examination confirmed small cell carcinoma of the lung, and he was referred to the oncology team for further management.

Case 3

Case 3 was a 60-year-old indigenous Malaysian female who did not smoke and had a history of right breast carcinoma in 1999, for which she had a right mastectomy and subsequently had been in stable remission. In December 2017, she presented with 2 weeks of shortness of breath and right lateral chest discomfort for 3 days, but, when asked, did not report any fever, cough, night sweats, or overt loss of weight. On clinical examination, she had a respiratory rate of 23 breaths per minute, temperature of 36.2 °C, and oxygen saturation of 90% under room air, with chest examination demonstrating reduced air entry over the entire right thorax. Her total white cell count was $8.3x10^9$ cells/L. Chest radiograph revealed a 'white-out' appearance of the right lung. Ultrasound thorax confirmed a very large non-loculated right pleural effusion. Pleural fluid parameters were protein-discordant exudative (pH = 7.497; pleural fluid:serum protein ratio = 34/74 g/L; pleural fluid:serum LDH ratio = 472/400 U/L; pleural fluid glucose = 3.6 mmol/L); pleural fluid cytology was inconclusive, showing malignant cells. Pleuroscopy showed multiple diaphragmatic nodules; cryobiopsy was performed with no major complication. Talc pleurodesis was administered prior to chest tube removal. Histopathological and immunohistochemical examination confirmed metastatic adenocarcinoma secondary to her primary breast malignancy. She underwent palliative treatment under the oncology team. As of 18 months after the cryobiopsy, surveillance CT did not show further progression of disease.

Case 4

Case 4 was a 67-year-old Malay male who did not smoke but did have underlying Type 2 diabetes mellitus and was on insulin treatment. He presented in January 2019 with complaints of fever, shortness of breath, and loss of appetite for 2 weeks, associated with right lateral chest discomfort. He did not report any chronic cough or haemoptysis. On clinical examination, he had a respiratory rate of 22 breaths per minute, temperature of 37.1 °C, and oxygen saturation of 95% under room air, with chest examination

showing reduced air entry over the right lower zone. His total white cell was 6.8x10^9 cells/L. Chest radiograph showed a right homogenous opacity with meniscus sign partially obliterating the right heart border. Ultrasound thorax revealed a non-loculated pleural effusion. Pleural fluid parameters were exudative (pH = 7.466; pleural fluid:serum protein ratio = 59/78 g/L; pleural fluid:serum LDH ratio = 330/612 U/L; pleural fluid glucose = 10.38 mmol/L); pleural fluid cytology showed predominantly lymphocytic effusion. Sputum examination for acid-fast bacilli was negative. Pleural fluid and sputum culture for tuberculosis were negative. Pleuroscopy revealed multiple parietal pleural nodules, several of which were tangentially oriented; cryobiopsy was performed with no major complication. No talc pleurodesis was given in view of suspected tuberculous infection. Histopathological and immunohistochemical examination confirmed caseating granulomas; the patient was started on tuberculosis treatment, after which clinical improvement in terms of weight gain, symptom resolution, and radiological improvement as evidenced by eventual resolution of the effusion on chest radiographs were demonstrated.

Case 5

Case 5 was a 58-year-old Malay male who smoked but had no underlying medical illness. He presented in June 2019 with a 3-month history of chronic cough and loss of weight and appetite. He did not report fever and haemoptysis. Clinically, he had a respiratory rate of 24 breaths per minute, temperature of 37.0 °C, and oxygen saturation of 93% under room air. He was clinically clubbed, and chest examination revealed reduced air entry over the left lower and mid zone. Chest radiograph showed a left homogenous opacity with meniscus sign and obliteration of the left heart border. Ultrasound of the thorax showed a non-loculated left pleural effusion. His total white cell count was 9.9x10^9 cells/L. Pleural fluid parameters were exudative (pH = 7.394; pleural fluid:serum protein ratio = 45/77 g/L; pleural fluid LDH = 207 U/L; pleural fluid glucose = 6.8 mmol/L); pleural fluid cytology showed no malignant cells. Pleuroscopy revealed multiple pleural and diaphragmatic nodules; cryobiopsy was performed with no major complication. Talc pleurodesis was applied prior to removal of the chest drain. Histopathological and immunohistochemical examination confirmed small cell carcinoma of the lung. He was referred to the oncology team for further care.

Case 6

Case 6 was a 71-year-old indigenous Malaysian male who smoked and had a history of asbestos exposure. He presented in June 2019 with a 2-month history of progressive shortness of breath and dry cough, associated with loss of weight. He did not report fever or haemoptysis. Clinically, he had a respiratory rate of 23 breaths per minute, temperature of 36.8 °C, and oxygen saturation of 91% under room air. Chest examination revealed reduced air entry over the right lower and midzone. Chest radiograph revealed a right homogenous opacity with meniscus sign and obliteration of the right heart border. Ultrasound of the thorax showed a non-loculated right pleural effusion. His total white cell count was 7.9x10^9 cells/L. Pleural fluid parameters were exudative (pH = 7.258; pleural fluid:serum protein ratio = 42/73 g/L; pleural fluid:serum LDH ratio = 954/321 U/L; pleural fluid glucose = 5.1 mmol/L); pleural fluid cytology was inconclusive, showing atypical cells. Pleuroscopy showed scattered small hard nodules; cryobiopsy was performed with no major complication. Talc pleurodesis was applied prior to removal of the chest drain. Histopathological and immunohistochemical examination confirmed malignant mesothelioma, and the patient was referred to the oncology team for further management.

RESULTS

Baseline Demographic Data

A total of six patients of either indigenous Malaysian or Malay descent underwent pleuroscopic cryobiopsy (Table 1). Two were female and four were male, with a median age of 59 years (interquartile range: 56–67).

Characteristic of Pleural Effusion

Two (33.3%) of the effusions were left-sided, while four (66.7%) were right-sided. All effusions had a simple appearance on ultrasound.

Table 1: Characteristics of pleuroscopic cryobiopsy patients.

	Patient					
	1	2	3	4	5	6
Age (years)	61	56	57	67	56	69
Gender	Female	Male	Female	Male	Male	Male
Effusion laterality	Left	Right	Right	Right	Left	Right
Ultrasound appearance	Simple	Simple	Simple	Simple	Simple	Simple
Pleural fluid protein (g/dL)	50	42	34	59	45	42
Serum protein	72	72	74	78	77	73
Pleural fluid LDH	1554	722	472	330	207	954
Serum LDH	426	894	472	612	N/A	321
Pleural fluid pH	7.355	7.531	7.497	7.466	7.394	7.258
Pleural fluid glucose	4.8	5.3	3.6	10.38	6.8	5.09
Pleural fluid cytology	Not available	No malignant cells	Malignant cells	Lymphocytic effusion	No malignant cells	Atypical cells
Procedure time (min)	35	20	20	30	20	35
Appearance	Nodules	Nodules	Nodules	Nodules	Nodules	Nodules
Probe size (mm)	2.4	1.9	2.4	1.9	2.4	1.9
Complication	None	None	None	None	None	None
HPE	Lung adenocarcinoma	Small cell carcinoma	Lung adenocarcinoma	Caseating granuloma, negative ZN stain	Small cell carcinoma	Mesothelioma
IHC feasible?	Yes	Yes	Yes	No	Yes	Yes

HPE: histopathological examination; IHC: immunohistochemistry; LDH: lactate dehydrogenase; ZN: Ziehl–Neelsen.

Three (50.0%) patients had effusions occupying one-half of the hemithorax, two patients (33.3%) had effusions occupying less than one-half of the hemithorax, and one (16.7%) had a massive white-out effusion. Pleural fluid pH was elevated in Cases 2, 3, and 4. Five of the effusions were exudative, one was protein-discordant (Case 3). Median pleural fluid protein was 43.5 g/dL while median LDH was 597 IU/L. Pleural fluid cultures were negative in all samples. Cytology was inconclusive in all six specimens, with only one sample showing malignant cells (Case 3) and another showing atypical cells (Case 6).

Pleuroscopic Characteristic

All six cases (100%) had a nodular pleuroscopic appearance. A 1.9 mm probe was used in three cases (50%), while a 2.4mm probe was used in the other three cases (50%).

Table 2: Comparison to previous studies of pleuroscopic cryobiopsy.

Studies	Rozman et al.,[8] 2013	Thomas et al.,[9] 2015	Maturu et al.,[10] 2015	Chen et al.,[4] 2018	Tousheed et al.,[11] 2018	Dhooria et al.,[12] 2019	Present series
Number of subjects	15	22	6	92	87	50	6
Quality of sample							
Probe size	2.4 mm	2.4 mm	1.9 mm	1.9 mm	2.4 mm	2.4 mm	1.9/2.4 mm
Size (mm)	N/A	Median: 10 IQR: 7.0–15.8	Mean: 9.2±1.84	Mean: 9.4±4.9	Mean: 13.2±6.7	Median: 7.0	Mean: 9.2±1.9
Diagnostic yield (%)	15/15 (100)	20/22 (91)	6/6 (100)	91/92 (99)	86/87 (99)	39/50 (78)	6/6 (100)
IHC stain done (%)	13/13 (100%)	N/A	N/A	91/92 (99)	29/29 (100)	N/A	5/5 (100)

IHC: Immunohistochemistry; IQR: interquartile range; N/A: not available.

Median activation time and the number of exact activations were not recorded in the patients. The mean aggregate sample size was 9.2±1.9 mm (Table 2).[4,8-12] A definite histopathological diagnosis was obtained in all six cases. Five (83.3%) patients had confirmed malignancy (one adenocarcinoma lung, one adenocarcinoma breast, two small cell carcinomas, and one mesothelioma) and one (16.7%) patient was diagnosed with pleural tuberculosis. The five (83.3%) malignant samples were adequate for immunohistochemical staining. None of the six patients encountered major complications. The median procedural time was 25 minutes (range: 20–35 minutes).

DISCUSSION

Cryobiopsy is a technique that employs the use of a blunt probe cooled by nitrous oxide or carbon dioxide, which draws moisture out of surrounding tissue and freezes with it by creating a bond (Joule–Thomson effect).[13] In pleuroscopic biopsy, cryobiopsy was historically performed with a rigid probe via a second trocar, under direct rigid pleuroscopy examination.[13] Recent technological advancements have led to the flexible cryoprobe which can be inserted through the working channel of flexible endoscopes. The use of cryobiopsy in bronchoscopy has been validated in multiple studies for endobronchial biopsies and transbronchial biopsies with minimal additional bleeding risk.[6] Meanwhile, studies on cryobiopsy via flexi-rigid pleuroscopy have only recently burgeoned in the past decade, with studies citing comparable sample sizes and yield, preserved biopsy sample architecture allowing for immunohistochemical studies, and similar safety profile compared to conventional forceps biopsy via flexi-rigid pleuroscope.[4,5,8-12,14,15] To the authors' best knowledge, this is the first case series of pleuroscopic cryobiopsy in the Southeast Asia region.

Pleural fluid biochemical characteristics are poor differentiators of tuberculous and malignant pleural effusions,[16] as demonstrated in this case series. The higher pH values in Cases 2, 3, and 4 were likely due to exposure to air during collection via the suction port of the scope, causing artificial elevation of pH.[17] Pleural fluid cytology carries overall sensitivity of 67.2% in malignant pleural effusion of all types; of these, the sensitivity was 87.9% for adenocarcinomas but dropped to 45.5% in malignant mesothelioma.[18] In this series, none of the pleural fluid cytology results were conclusive;

only Cases 3 and 6 had abnormal fluid cytology showing malignant and atypical cells, respectively, which were later confirmed via cryobiopsy as adenocarcinoma and mesothelioma (Table 1). While the diagnostic accuracy of cytology in malignant mesothelioma has been shown to increase with the availability of an experienced cytopathologist in a region of high prevalence for mesothelioma,[18] this may not be applicable in the Southeast Asia region. This highlights the unreliability of pleural fluid cytology and the need for a definitive biopsy to clinch the diagnosis. While sensitivity and specificity of flexi-rigid pleuroscopy using conventional forceps in undiagnosed exudative pleural effusion is high,[5] increased false-negative results are seen in cases of thickened pleura.[19,20] Some factors that contribute to this include inadequate depth of biopsy sample[20] and the lack of mechanical power of the conventional forceps and a small cup size.[4,5]

Cryobiopsy poses a potential solution to this problem, having been shown to be non-inferior to conventional forceps in the diagnosis of malignant mesothelioma.[21] The crucial advantage lies in that it can acquire significantly greater depths of tissue than conventional forceps;[4,9,10,12] one study reported extrapleural fat in 65.2% of cryobiopsy samples as opposed to 40.8% in conventional forceps biopsy.[12] This was demonstrated in Case 6 (Table 1), whereby the patient's diagnosis of malignant mesothelioma was confidently obtained due to the demonstration of extrapleural fat, which is essential to visualise invasion of abnormal mesothelial cells in mesothelioma (Figure 1). In Southeast Asia, reported rates of non-specific pleuritis range from 12.0%[22] to 21.6%.[23]

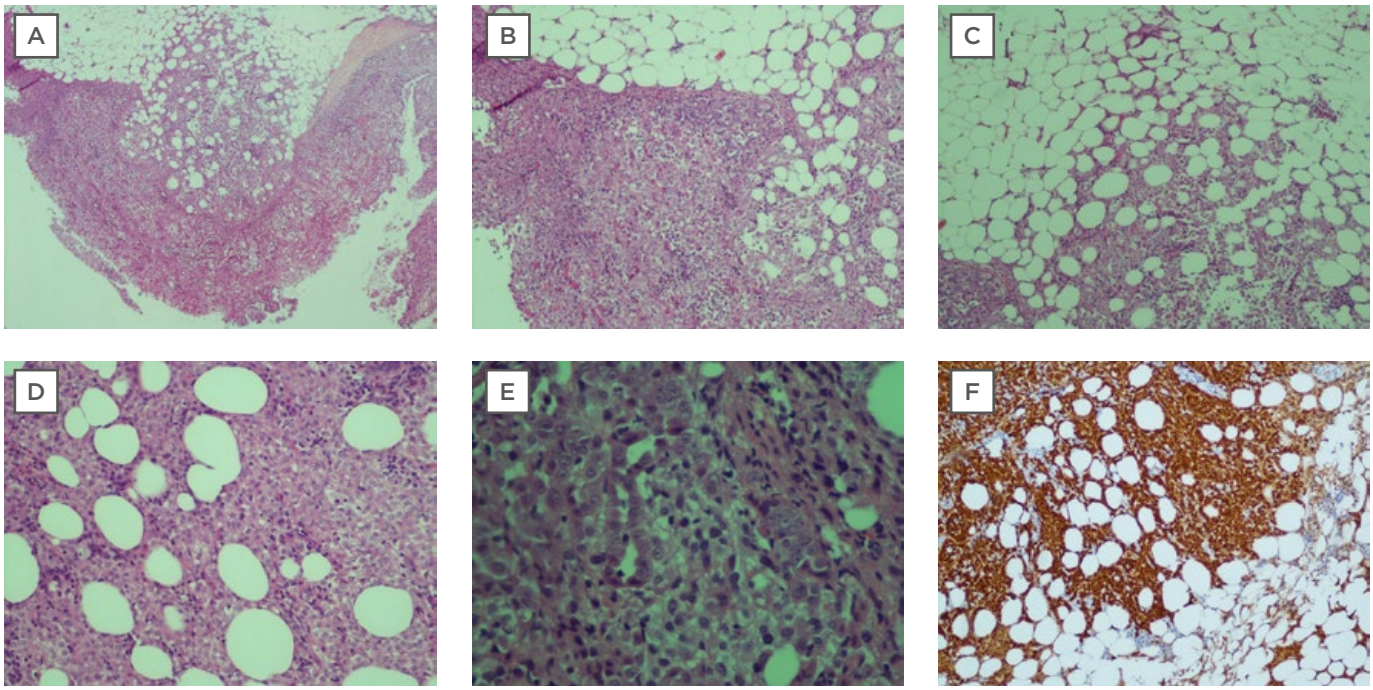

Figure 1: Cryobiopsy sample for Case 6 was conclusive for malignant mesothelioma.

A) Extrapleural adipose tissue is well demonstrated and there are no artefacts. There is marked increase of atypical mesothelial cells proliferation superficially, with infiltration into the underlying adipose tissue, which is indicative of malignancy (x40) H&E stain. **B)** The tumour cells are arranged in sheets (x200) H&E stain. **C)** Tumour cells are seen infiltrating into extrapleural adipose tissue (x200) H&E stain. **D)** Tumour cells infiltrating in between adipose cells (x400) H&E stain. **E)** The tumour cells show round vesicular nuclei with prominent nucleoli. Tubular formation is also noted. **F)** Immunohistochemical staining was positive for calretinin (d: ×200)

H&E: haemotoxylin and eosin.

Although long-term follow-up on these cases did not frequently reveal a diagnosis of mesothelioma,[20] it is prudent to consider the possibility that the low prevalence of mesothelioma in Southeast Asia may be partly contributed by shallow biopsies leading to inconclusive or alternative diagnoses. Further research could look into the value of cryobiopsy in non-specific pleuritis.

Moreover, certain varieties of mesothelioma such as desmoplastic mesothelioma make conventional biopsy extremely difficult because they are often smooth and non-nodular macroscopically. In such cases, one author has proposed a combination of incisions via electrocautery technique followed by cryobiopsy.[21] Another author has suggested creating a break in the pleura with forceps prior to cryobiopsy,[9] but this has to be weighed against the risk of bleeding. The present authors have yet to implement these combined methods in their pleuroscopic setting; further studies are needed to validate them.

The second advantage of the cryoprobe is its ability to biopsy samples from lesions positioned tangentially to the instrument.[4,10] As opposed to conventional forceps, which only allow forward sampling, cryoprobe can obtain tissue in a 360° manner laterally.[24] Similarly, in the experience with Case 4, nodules that were tangentially oriented despite having the pleuroscope at maximal angulation were much easier to sample with cryoprobe than conventional forceps. Third, in terms of technical difficulty, there is no significant difference in operator-rated difficulty when comparing cryobiopsy to conventional forceps technique;[12] this is promising and may encourage more pulmonologists to adopt it in the future, although studies on its learning curve are lacking. The authors' limited experience with pleuroscopic cryobiopsy was not a major deterrent to obtaining accurate diagnosis, as evidenced by good sample sizes comparable to other larger studies, and successful histopathological diagnosis in all six of their patients (Table 2).

The most dreaded complication of cryobiopsy is always major bleeding, which was not encountered in these six cases (Table 1). Early studies have not described any significant risks of major bleeding, but various authors have advocated gentle withdrawing of the probe as essential to prevent severe haemorrhage.[4,8-11] Furthermore, one author opined that in cases when the probe was already attached to the tissue but could not be gently removed, the probe should be allowed to unfreeze and resume with a shorter period of freezing.[8] Freezing time of the cryoprobe should be variable, to be adjusted throughout the procedure, as to not take tissue samples deeper than the muscle layer to reduce the risk of bleeding or nerve injury.[21]

One of the limitations of the authors' study is that biopsy was only performed on visibly abnormal areas for at least three passes. Expert recommendations advocate at least five biopsies carried out over abnormal and normal pleura to ensure adequate tissue quality and quantity.[25,26] However, these recommendations were made in regard to conventional forceps rather than cryobiopsy. In Case 6, three cryobiopsies were performed, comparable to prior studies which performed a range of one to four cryobiopsies per patient.[4,8-11,14,16] The optimal number of cryobiopsies needed to balance yield and the risk of bleeding remains uncertain, this is a potential area for future research.

Another limitation of this study was that pleural biopsy for tuberculosis culture was not routinely sent. The gold standard of diagnosing pleural tuberculosis is the isolation of *Mycobacterium tuberculosis* in either pleural fluid or pleural tissue by culture, or demonstration of caseating granulomas in histology.[27] Tuberculosis culture is important for drug sensitivity testing, but has a sensitivity of only 68.7% as opposed to 100.0% in pleuroscopy.[28] Furthermore, there is often a delay in waiting for culture results. In tuberculous endemic regions at the hand of an experienced investigator, tuberculous pleurisy usually presents with characteristic inflammatory patterns on pleuroscopy, such as caseous, sago-like nodules, or fibrin deposits and loculations.[29] As demonstrated in Case 4, representative appearance on pleuroscopy combined with histological finding of granuloma was sufficient to clinch the diagnosis of pleural tuberculosis. A demonstrated therapeutic response to antituberculous medication further reinforced the diagnosis of pleural tuberculous in this cohort of patients.

CONCLUSION

In conclusion, pleuroscopic cryobiopsy was feasible with no major complications in the six subjects; samples were comparable in size to those in previous studies and had preserved tissue architecture, allowing for histopathological confirmation of diagnosis and immunohistochemistry studies. Pleuroscopic cryobiopsy may prove useful both in the diagnosis of malignant mesothelioma in regions of low prevalence or in centres where cytological analysis is unreliable or unavailable.

STATEMENT OF ETHICS

Subjects have given their written informed consent for publication of this case report and accompanying images. This article does not contain any studies with human participants or animals performed by any of the authors. The authors have no ethical conflicts to disclose.

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