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RESPIRATORY

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RESPIRATORY

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RESPIRATORY 5.1
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Welcome

A very warm welcome to the 2017 edition of *EMJ Respiratory*, which delves into the cutting-edge research and hot topics presented and discussed at the 27th European Respiratory Society (ERS) International Congress. We are delighted to present an exciting Congress Review section, detailing the highlights from the 5-day assembly of world-leading experts. The Abstract Review section presents ongoing research projects destined to shape the way respiratory issues are treated in the future. Alongside this, you will find thought-provoking research advances detailed within peer-reviewed articles, as well as interviews with esteemed members of the *EMJ Respiratory* Editorial Board.

This year, the ERS congress returned to Italy for the first time in 17 years, taking place in the stunning city of Milan. The opening ceremony proved unmissable, as awards were presented to distinguished researchers, including Prof Luigi Allegra, Dr Sally Wenzel, Dr Bart Lambrecht, Dr MeiLan Han, and Prof Vincent Cottin, for their contributions to the field. An astonishing 21,080 academics were in attendance and, with numerous sessions being live-streamed across the globe, more people than ever were able to experience the event first hand. Further details of the congress, recent news updates, and clinical trial results can be found within our comprehensive Congress Review section inside.

The Abstract Review section features details of ongoing research projects presented at the congress and are written by the researchers themselves. Such topics include details of a focussed investigation into the management of anti-neutrophil cytoplasmic antibody-associated vasculitis, conducted by Nagarajan et al. Alongside this, Orlova et al. have detailed their extensive evaluation of the factors that promote silicomycobacteriosis manifestation, paying particular interest to diagnosis and prognosis. *EMJ Respiratory 5.1* also contains fascinating interviews with members of the Editorial Board who detail their prospective views on asthma and chronic obstructive pulmonary disease.

Furthermore, this eJournal contains the latest, high-quality, peer-reviewed articles detailing novel research projects and reviews. The Editor's Pick for this issue is the impressive review of past and present techniques for the investigation of allergen testing in asthma patients, providing improvements to current methodologies and future directions for allergen testing, courtesy of Blais et al. In addition, Glover and Glossop have penned an intriguing analysis of considerations and current practises for the extubation of patients who have undergone invasive mechanical ventilation, with the aim of developing these techniques, preventing reintubation, and improving patient outcomes.

We sincerely hope that you find this edition of *EMJ Respiratory* as stimulating and engaging as we do and that it highlights the key areas of research within the field of respiratory medicine. We are already looking forward to next year's ERS congress in the spectacular city of Paris, France.

Kind regards,

Spencer Gore

Director, European Medical Journal

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Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A (HAV) and parvovirus B19 virus. Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived proteinase inhibitors. It is strongly recommended that every time Respreeza is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. Home-treatment: There are limited data regarding the use of Respreeza in home-treatment/self-administration. Potential risks associated with home-treatment/selfadministration are related to the handling and administration of the medicinal product as well as to the handling of adverse reactions, particularly hypersensitivity. Patients should be informed of signs of hypersensitivity reactions. The decision of whether a patient is suitable for home-treatment/self-administration is made by the treating doctor, who should ensure appropriate training is provided (e.g. regarding reconstitution, use of transfer device or filter, assembly of intravenous tubing, infusion techniques, maintenance of a treatment diary, identification of adverse reactions and measures to be taken in case such reactions occur), and the use is reviewed at regular intervals. Smoking: Tobacco smoke is an important risk factor for the development and progression of emphysema. Therefore cessation of smoking (> 6 months) and the avoidance of environmental tobacco smoke and air pollution are strongly recommended. **Interactions:** No interactions of Respreeza with other medicinal products are known so far. **Fertility, pregnancy and lactation:** Pregnancy: No animal reproduction studies have been conducted with Respreeza and its safety for use in human pregnancy has not been established in controlled clinical trials. Since alpha1-proteinase inhibitor is an endogenous human protein, it is considered unlikely that Respreeza will cause harm to the foetus when given at recommended doses. However, Respreeza should be given with caution to pregnant women. Lactation: It is unknown whether Respreeza / metabolites are excreted in human milk. The excretion of human alpha1-proteinase inhibitor in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue / discontinue therapy with Respreeza should be made, taking into account the benefit of breast-feeding to the child and the benefit of human alpha1-proteinase inhibitor therapy to the woman. Fertility: No animal fertility studies have been conducted with Respreeza and its effect on human fertility has not been established in controlled clinical trials. Since human alpha1-proteinase inhibitor is an endogenous human protein, no adverse effects on fertility are expected when given at recommended doses. **Effects on ability to drive and use machines:** Respreeza may have a minor influence on the ability to drive and use machines. Adverse reactions such as dizziness may occur following administration of Respreeza. **Undesirable effects:** Blood and lymphatic system disorders. *Unknown:* Lymph node pain. Immune system disorders. *Uncommon:* Hypersensitivity reactions (including tachycardia, hypotension, confusion, syncope, oxygen consumption decreased and pharyngeal oedema); *Very rare:* Anaphylactic reactions. Nervous system disorders. *Common:* Dizziness, headache; *Uncommon:* Paraesthesia; *Very rare:* Hypoaesthesia. Eye disorders. *Unknown:* Eye swelling. Vascular disorders. *Uncommon:* Flushing. Respiratory, thoracic and mediastinal disorders. *Uncommon:* Dyspnoea. Gastrointestinal disorders. *Uncommon:* Nausea; *Not known:* Lip swelling. Skin and subcutaneous tissue disorders. *Uncommon:* Urticaria, rash (including exfoliative and generalized); *Very rare:* Hyperhidrosis, pruritus; *Not known:* Face swelling. General disorders and administration site conditions. *Uncommon:* Asthenia, infusion-site reactions (including infusion site hematoma); *Very rare:* Chest pain, chills, pyrexia. **Reporting of suspected adverse reactions:** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health-care professionals are asked to report any suspected adverse reactions. **Prescription status:** Prescription-only drug. **Marketing Authorization Holder:** CSL Behring GmbH, Emil-von-Behring-Str. 76, 35041 Marburg, Germany. **Date of information:** August 2015.

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Foreword

Dr Antonio Rossi

IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy.

Dear Colleagues,

It is my pleasure to extend to you a very warm welcome to this latest edition of *EMJ Respiratory*, which will round off a year of discoveries and innovative treatment strategies in the field of respiratory disease.

This year's Annual European Respiratory Society (ERS) International Congress took place in Milan, 9th–13th September 2017. Enthusiastic researchers, clinicians, general practitioners, and allied health professionals working in the field of respiratory diseases came from all over the world and shared their experiences and the latest significant advances in the field, to strengthen or initiate clinical and scientific networks for future work. The programme addressed the needs of all respiratory professionals, stimulating debate and shedding new light on advances in the field. The results from numerous studies regarding basic and clinical lung health and disease were widely discussed throughout the impressive event, and are heavily featured in this issue of the journal.

This publication contains a compendium of interesting and perceptive peer-reviewed articles, encompassing a variety of respiratory topics. These include reports about extubation and the post-extubation management in intensive care patients, to past, present, and future directions in the management of allergen-induced asthma. An updated review looks at the growing body of evidence concerning the removal of airway stents and related complications. A further review discusses the pathology, presentation, staging, and treatments of thymomas and thymic carcinomas. Other articles focus on the barriers associated with the diagnostic delay of lung cancer and e-cigarette use in the West Indies.

> "This publication contains a compendium of interesting and perceptive peer-reviewed articles, encompassing a variety of respiratory topics."

On behalf of the Editorial Board and the staff of the European Medical Journal, I would like to thank all the authors for their efforts in contributing to the publication of this new issue.

Finally, I am confident that you will find this latest issue of the journal an entertaining and meaningful read, and that the topics will set off interesting discussions.

Yours sincerely,

Antonio Rossi

Staff Physician, Division of Medical Oncology, Scientific Institute for Research and Health, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy.

ERS ANNUAL CONGRESS 2017

MICO,
MILAN, ITALY
9TH–13TH SEPTEMBER 2017

Welcome to the European Medical Journal review of the 27th Annual Meeting of the European Respiratory Society

Citation: EMJ Respir. 2017;5[1]:10-23. Congress Review.

Milan, Italy, a city renowned for its style and beauty, provided a splendid setting for the 27th ERS International Congress. As the attendees discovered, Milan is about much more than just fashion, with magnificent architecture, such as the Milan cathedral, a vibrant opera scene, including the Scala Opera house, and a tradition and history to rival cities worldwide.

A highly entertaining opening ceremony began with some typically beautiful Italian opera signing, including a rendition of the world famous 'La donna e mobile' by Luciano Pavarotti. This was followed by a wonderfully crafted video that showed the congress Chair Prof Francesco Blasi, and Co-Chair Prof Stefano Centanni in various scenic locations in Milan, with Prof Blasi appearing to sing the famous Pavarotti piece 'Nessun Dorma' and Prof Centanni driving an Alfa Romeo car! This last homage was particularly fitting, as the location of this event, the MiCo congress centre, was formerly the factory of Alfa Romeo.

During his address at the ceremony, Prof Blasi expressed his excitement that the largest respiratory event in the world was returning to Italy for the first time in 17 years. He also gave a final figure on the number of participants for this year's congress, totalling a whopping 21,080. ERS President Prof Guy Joos was also on hand to inform the captivated audience about some of the aims, work, and campaigns of the society. "We have the mission to promote lung health in order to help our patients and to drive the standards for respiratory medicine. To do so we are concentrating on three different pillars: the activities of science, education, and efficacy," he said.

During the action-packed opening ceremony, there were also a number of awards presented to respiratory health individuals who had distinguished themselves in their respective specialisms. Firstly, Prof Luigi Allegra, regarded as one of the founding fathers of the ERS, received the ERS Congress Chair Award for his contributions to research and training in the area of lung disorders, as well as his commitment to the care of patients with such conditions. The ERS Presidential Award went to Dr Sally Wenzel, who was recognised for the pioneering work and exceptional contributions she has made to the field of asthma.

Next, the ERS Gold Medal was given to three researchers for making an outstanding contribution to their respective fields of asthma, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis. The recipients of the prizes (and €50,000 each) were Dr Bart Lambrecht, Dr MeiLan Han, and Prof Vincent Cottin. The orator of this year's Sadoul lecture, which honours senior scientists of great standing, was Dr Dirkje S. Postma, and was delivered on Sunday 10th September. Prof Stefano Nava then accepted the ERS Educational Award for his contribution to respiratory education. Following this, the Chair of the European Lung Foundation (ELF), Mr Dan Smyth, came on stage to hand the 2017 ELF Award to Prof Colin Sullivan for his work in improving the lives of patients with sleep apnoea. These were just some of the awards bestowed at the 2017 ERS congress, highlighting the impressive work and advances taking place within the field.

> "We have the mission to promote lung health in order to help our patients and to drive the standards for respiratory medicine. To do so we are concentrating on three different pillars: the activities of science, education, and efficacy..."

As always, there was a tremendous amount of research presented throughout the 5 days of the congress, enhancing knowledge and displaying the new treatment options that have recently emerged for the many types of respiratory conditions that exist, using some innovative methods to spread the messages as far as possible. For example, live sessions were streamed to other continents, including to Latin America for the first time. It was a truly ground-breaking congress and we hope this theme continues at next year's ERS annual meeting, which will be held in Paris, France.

Asthma Symptoms Potentially Reduced by Park Access

DISTANCE to the nearest park has been correlated with the number of days children with asthma who live in the city present with asthma symptoms, according to results presented at the ERS congress and reported in a ERS press release dated 8th September 2017. It was found that the closer children lived to a park, the fewer asthma symptom days (ASD) they tended to have. This Baltimore-based study (Maryland, USA) enrolled 196 children, the majority of whom were male (66%), African American (95%), and Medicaid insured (95%), which meant they were from a population at high risk of asthma-related mortality. The children had a mean age of 6.4 years. The home address of each child was noted and then marked on a map of Baltimore that featured the locations of city parks. This geocoded map was then used to calculate the distance to the closest park, and it was found that the mean distance to the closest park was 826 ft.

ASD were assessed by means of questioning the child's primary caregiver on the number of days their child had presented with symptoms such as chest pain, wheezing, and shortness of breath. The researchers conducted a multivariate analysis to model ASD against park distance and discerned that there was a significant association between a shorter distance to the nearest park and a reduced number of ASD (standardised β=0.15; p=0.042). This corresponded to one extra ASD for every additional 305 m from the park; a child who lived next door to a park had 5 ASD on average, whereas a child whose home was 305 m away had an average of 6 ASD. Drilling down into the data further, a stronger association was found for children aged 6–12 years compared with those aged 3–5 years (standardised β=0.32; p=0.002). The researchers speculated that the reason for this was because older children had more freedom to choose where they wanted to go and hence were more likely to take advantage of their proximity to local green space. In the 6–12 years old group, a multivariate analysis was conducted to control for second-hand smoke exposure and short-acting beta agonist use. It was found that distance to park remained independently associated with ASD (standardised β=0.30; p=0.003).

> "They will also help healthcare providers to take a more holistic view of their patients by understanding how access to green space might affect health."

The researchers hoped that their research would be taken into account by urban planners and that it would lead to additional city parks. Commenting further on the findings, the study's presenter, Kelli DePriest, Johns Hopkins University School of Nursing and Medicine, Baltimore, Maryland, USA, also suggested they should be considered by healthcare providers. She pronounced: "They will also help healthcare providers to take a more holistic view of their patients by understanding how access to green space might affect health." Looking to the future, there are plans to further explore the relationship between green space and asthma symptoms by considering different types of green space, such as gardens.

Respiratory Infections Linked with Asthma and Lung Function

RISK of both asthma and decreased lung function in later life is increased with respiratory tract infections in early life. These results, from the Generation R Study Group at Erasmus MC University Medical Centre, Rotterdam, Netherlands, were presented at the ERS congress 2017, and reported in a ERS press release dated 10th September 2017. Asthma and lung function are two different respiratory measures that are not necessarily fully related. Lung function is a measure of an individual's ability to breathe, usually determined using a spirometer, which measures forced viral capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow at 75% of FVC (FEF_{75}). On the other hand, asthma is a condition characterised by spasms of the bronchi in the lungs and may not greatly affect lung function.

The meta-analysis included 154,942 children from across Europe for whom data were available regarding respiratory tract infections (RTI) from 6 months to 5 years of age, lung function, and/or asthma. Lung function was monitored using a spirometer as the children grew older. The study included both upper RTI as well as lower RTI. The results highlighted that the presence of an upper RTI was not associated with worsened lung function, but the children had a 1.5-fold increased risk of developing asthma. The presence of a lower RTI, however, was associated with

worsened lung function, with lower FVC, FEV_1, and FEF_{75} scores, and also resulted in a two-to-four-fold increased risk of asthma.

> “These findings support the hypothesis that early-life respiratory tract infections may influence the development of respiratory illnesses in the longer term...”

Dr Evelien van Meel, Erasmus MC University Medical Centre, concluded: “These findings support the hypothesis that early-life respiratory tract infections may influence the development of respiratory illnesses in the longer term,” but went on to say: “However, at this stage we cannot say for certain whether the relationship is causal.” The researchers hope to perform future studies that determine the percentage of associations between RTI and asthma, which can be explained by lung function changes, including whether these associations alter when considering early life wheezing. They also hope to analyse how paracetamol, antibiotics, and second-hand smoke exposure affect these relationships.

Asthmatic Children More Likely to be Prescribed Unnecessary Antibiotics

CHILDREN with asthma are more likely to be prescribed antibiotics compared to non-asthmatic children, even if there is no symptomatic evidence that they need them, according to a multi-national study presented at the ERS 2017 congress and reported in a ERS press release dated 11th September 2017.

It has been well publicised that the overuse and misuse of antibiotics leads to a rise in difficult-to-treat infections. Dr Esmé Baan, Department of Medical Informatics, Erasmus University, Rotterdam, Netherlands, explained that asthmatic children already face day-to-day difficulties, such as not being able to play with their peers and having to take days off school. Dr Baan went on to comment: “We do not want to compound this with prescribing drugs that will not help and may be harmful.”

> “...we saw that, in children with asthma, most of the antibiotic prescriptions in children were intended for asthma exacerbations or bronchitis, which are often caused by a virus rather than bacteria.”

The study consisted of 1.5 million (including around 150,000 with asthma) and 375,000 (including around 30,000 with asthma) children from the UK and the Netherlands, respectively. The Netherlands and the UK both follow the same international guidelines on asthma treatment; however, antibiotic prescriptions were twice as common in the UK compared to the Netherlands. Researchers also found that children with asthma were approximately 1.6-times more likely to be prescribed antibiotics compared to those without asthma.

On an annual basis, per 1,000 children with asthma, 374 and 197 were prescribed antibiotics from the UK and the Netherlands, respectively, compared to 250 and 126 non-asthmatic children, respectively. With the trend for prescribing antibiotics to asthmatic children being so similar between the two countries, the researchers believed that this trend may also be similar in other countries. The Netherlands prescribes some of the lowest numbers of antibiotics in the world and, as such, the researchers expressed concern that the situation in countries where antibiotics are prescribed more frequently, such as Italy, Spain, Portugal, and Greece, could be worse.

Dr Baan explained: “Antibiotics should only be given when there is clear evidence of a bacterial infection, such as for pneumonia. However, we saw that, in children with asthma, most of the antibiotic prescriptions in children were intended for asthma exacerbations or bronchitis, which are often caused by a virus rather than bacteria.” Dr Baan acknowledged: “It can be difficult for a general practitioner (GP) to differentiate between a deterioration in asthma symptoms and a bacterial respiratory infection,” and this was the reason why researchers believed asthmatic children are being overprescribed antibiotics. Dr Baan concluded by noting that sometimes antibiotics are genuinely needed, but discouraged doctors from prescribing unnecessary antibiotics, in order to reduce the risk of drug-resistant infections.

Nicotine-Containing E-Cigarettes Linked to Arterial Stiffness

PRELIMINARY results from a recent study have shown that the use of nicotine-containing e-cigarettes leads to arterial stiffening in healthy volunteers, heightening the risk of cardiovascular disease. With numbers of e-cigarette users soaring, the implications of the study are vital for understanding the possible adverse effects of the smoking substitutes, which are often marketed as less harmful than traditional cigarettes.

> “...our research concerns a very large population and our results may prevent future health problems for a huge number of people.”

A ERS press release dated 11th September 2017 reported the study, which was conducted by Dr Magnus Lundbäck, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden. Dr Lundbäck and colleagues randomised 15 healthy, young volunteers to use e-cigarettes with or without nicotine for 30 minutes on alternate days. The volunteers were noted to be seldom smokers, not smoking >10 cigarettes per month, and none of them had used e-cigarettes prior to the study. The volunteers' average age was 26 years; 59% of volunteers were female. Blood pressure, heart rate, and arterial stiffness were all measured immediately after smoking, and then again 2 hours and 4 hours later. The team noted that volunteers who had smoked nicotine-containing e-cigarettes demonstrated a significant increase in blood pressure, heart rate, and arterial stiffness in the 30 minutes immediately following smoking. Volunteers who smoked e-cigarettes without nicotine, however, were not affected in this way.

Commenting on the sharp spike in heart rate, blood pressure, and arterial stiffness, Dr Lundbäck stated: “It is very important that the results of this and other studies reach the general public and the health care professionals working in preventive health care, for example in smoking cessation. Our results underline the necessity of maintaining a critical and cautious attitude towards e-cigarettes, especially for health care professionals,” adding: “The marketing campaigns of the e-cigarettes industry target current cigarette smokers and offer a product for smoking cessation. However, several studies question the e-cigarette as a means of smoking cessation, and there is a high risk of double use, where people use both e-cigarettes and conventional cigarettes. Furthermore, the e-cigarette industry also targets non-smokers, with designs and flavours that appeal to a large crowd.”

Dr Lundbäck concluded: “Therefore, our research concerns a very large population and our results may prevent future health problems for a huge number of people. It is of the utmost importance to investigate further the possible long-term effects of daily e-cigarette use through studies that are funded independently of the e-cigarette industry.”

Potential Risks of E-Cigarettes

AN EXAMINATION of e-cigarettes and their usage has revealed potentially associated risks, according to the results of two studies recently presented at the ERS congress, as reported in a ERS press release dated 11th September 2017. It was also suggested that these risks were heightened if e-cigarette

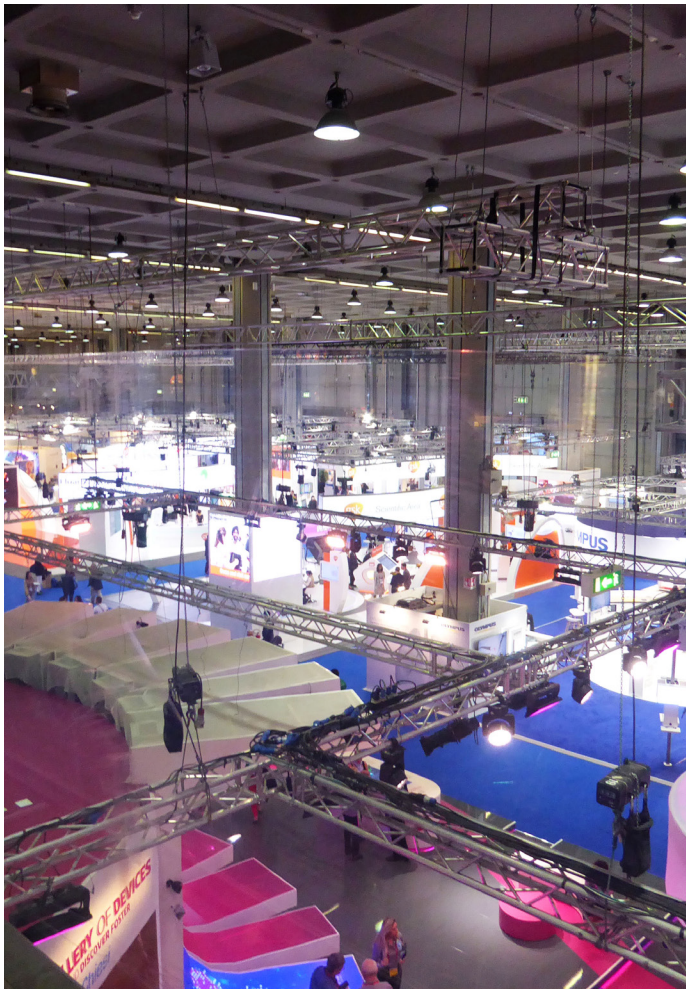
usage was combined with the smoking of conventional cigarettes. It is hoped that these studies will provide some measure of guidance to doctors and the users of e-cigarettes.

> “...doctors should inform their patients that e-cigarettes may contain respiratory irritants.”

The first study examined the content of e-cigarette refills. The researchers picked a random sample of the most popular e-cigarette brands across nine European countries, including the UK, Spain, Romania, Poland, Hungary, and Germany. This resulted in a selection of 122 liquids that were analysed to determine their chemical composition and their respective quantities. Every one of the 122 liquids tested was found to contain at least one substance that the United Nations (UN) classification system identified as presenting some level of risk to health. For instance, 26.3% of samples contained methyl cyclopentanolone and 8.7% contained α-ionone. The classification of both of these substances indicates that they “may cause allergy or asthma symptoms or breathing difficulties if inhaled.” Furthermore, there were several substances found that were classified as: “able to cause respiratory irritation.” These included menthol (42.9% of samples), ethyl vanillin (16.5%), and acetyl pyrazine (8.2%).

Commenting on the findings of this study, the lead author, Dr Constantine Vardavas, University of Crete, Crete, Greece, declared: “Based on this work, we also think users should be aware that e-cigarettes are not risk-free and that doctors should inform their patients that e-cigarettes may contain respiratory irritants.” He also commented that there is currently limited information available on the influence that the components of e-cigarette liquids may have on respiratory health, which represents an area for further consideration in the future.

The second study presented at the ERS congress surveyed >30,000 individuals residing in Sweden. The questionnaire was designed to obtain information on their smoking habits, including the use of e-cigarettes, and respiratory symptoms.

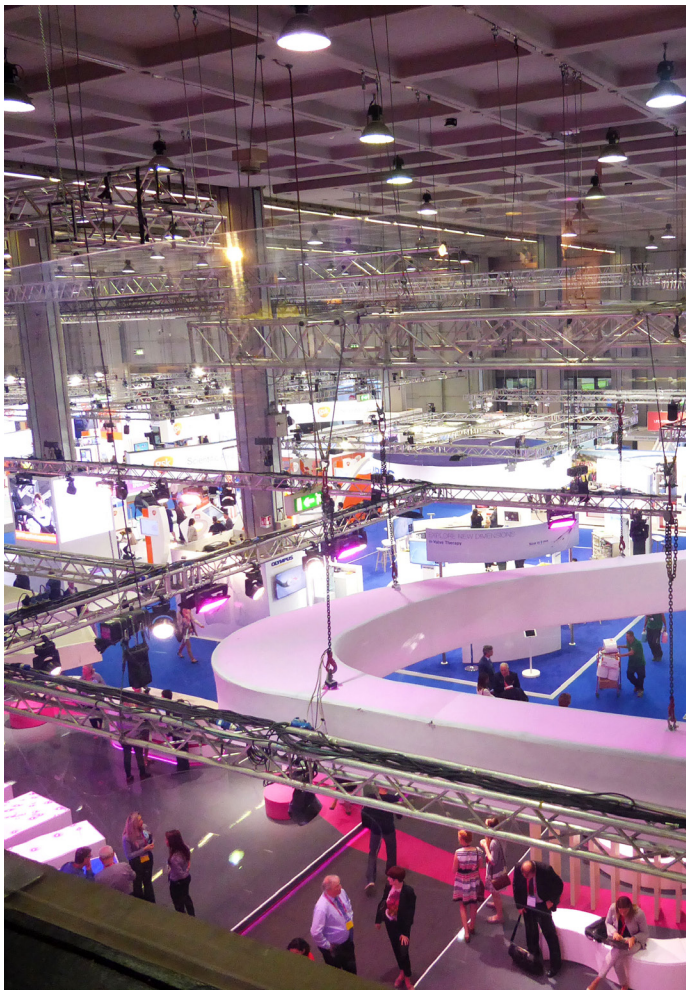


The breakdown of results showed that 11% of respondents smoked purely conventional cigarettes, 0.6% smoked only e-cigarettes, and 1.2% smoked both conventional and e-cigarettes. Upon examining the reported respiratory symptoms, it was revealed that the 1.2% of individuals who smoked both types of cigarette were the most likely to present with respiratory symptoms. Indeed, 56% of dual users reported respiratory symptoms. This compared with 46% of conventional cigarette smokers, 34% of e-cigarette smokers, and 26% of non-smokers ($p<0.001$).

The researchers added the caveat that the results did not prove that dual usage was responsible for increased incidence of respiratory symptoms. For instance, it was noted that smokers currently presenting with respiratory symptoms might be concurrently using e-cigarettes as part of a smoking cessation process. More studies are needed to establish the impact of e-cigarettes on respiratory health, although the results of these two studies contribute to the growing body of evidence that e-cigarettes should not be marketed as a safe alternative to conventional cigarettes.

Second-Hand Smoke Exposure Increased in Workplaces Around Europe

INCREASED numbers of individuals who work indoors are exposed to second-hand smoke at work, despite widespread smoking bans, according to new findings presented at the ERS congress 2017 and reported in a ERS press release dated 9th September 2017. New no-smoking laws have been enforced in several countries throughout the European Union (EU), but some countries are better at enforcing these laws than others. The bans came about following numerous research projects that established the risks of second-hand smoke exposure, including progression to coronary heart disease, stroke, and lung cancer, with a combined responsibility for >600,000 deaths around the world each year.



> “Our results suggest there is still a lot more work to be done to protect people in some parts of Europe.”

A survey including >55,000 people from within the EU formed the basis of the study. Approximately half of these people completed the study in 2009, with the remaining half in 2014. The results found that in 2014, 25.1% of respondents were exposed to second-hand smoke in bars, compared to 45.1% of respondents in 2009, a significant decrease. Following the same trend, 11.8% of respondents were exposed to second-hand smoke in restaurants in 2014, compared to 30.2% in 2009. In contrast, 27.5% of respondents were exposed to second-hand smoke within their workplace in 2014, compared to 23.8% of respondents in 2009. The researchers suggest that these results are due to difficulties in regard to complaints being made in the workplace, as well as major differences in the levels of legislation enforcement between different countries. Dr Filippos Filippidis, Imperial College London, London, UK, said: "Our results suggest there is still a lot more work to be done to protect people in some parts of Europe." He further explained: "This research is an essential way for us to monitor the progress that EU countries are making in upholding smoke-free laws."

The researchers aim to continue their research on second-hand smoke exposure around Europe, with efforts being made to determine why some countries do not enforce legislations as well as others. Once these results are established, better legislation can be encouraged, ultimately reducing second-hand smoke exposure and providing a huge step forward for public health.

Regular Use of Disinfectant is Associated with COPD

NURSES who regularly use disinfectants for tasks, such as cleaning surfaces, are at a higher risk of developing chronic obstructive pulmonary disease (COPD), according to a study presented at the ERS 2017 congress and reported in a ERS press release dated 11th September 2017. The study analysed data from 55,185 female registered nurses enrolled in the US Nurses' Health Study II, initiated in 1989. Dr Orianne Dumas, INSERM, Villejuif, France, and colleagues studied practising nurses who had no prior history of COPD from 2009 until May 2017. A questionnaire was used to evaluate disinfectant exposure, as well as a matrix that assigned exposure to disinfectants by job or task. The data were adjusted for smoking habits, age, BMI, and ethnicity.

> "...we need to investigate the impact on COPD of lifetime occupational exposure to chemicals and clarify the role of each specific disinfectant."

During the 8-year study period, 663 nurses were diagnosed with COPD. Dr Dumas commented on the results, saying: "We found that nurses who use disinfectants to clean surfaces on a regular basis, at least once a week, had a 22% increased risk of developing COPD." Researchers also assessed different types of disinfectant and their relationship

with COPD risk, including glutaraldehyde (for medical instruments), bleach, hydrogen peroxide, alcohol, and quaternary ammonium compounds (for floors and surfaces). The increased risk of COPD ranged from 24–32% ($p<0.05$). Of the study population, 37% used disinfectants to clean surfaces and 19% cleaned medical instruments with disinfectant on a weekly basis.

The affect disinfectants have on asthma among healthcare workers has been well documented, but there has been significantly less consideration on COPD risk. Dr Dumas commented: "To the best of our knowledge, we are the first to report a link between disinfectants and COPD among healthcare workers, and to investigate specific chemicals that may underlie this association." She went on to say: "These are preliminary findings and more research needs to be carried out. In particular, we need to investigate the impact on COPD of lifetime occupational exposure to chemicals and clarify the role of each specific disinfectant." Dr Dumas emphasised that these results are only observational and provide only an associated risk at this stage. Further research is required to assess the lifelong exposure risk and to understand whether this correlation is, in fact, a causational link. It is hoped that these findings will be utilised in the development of updated guidelines on cleaning and disinfection in healthcare settings that take into account the potential associated risks.

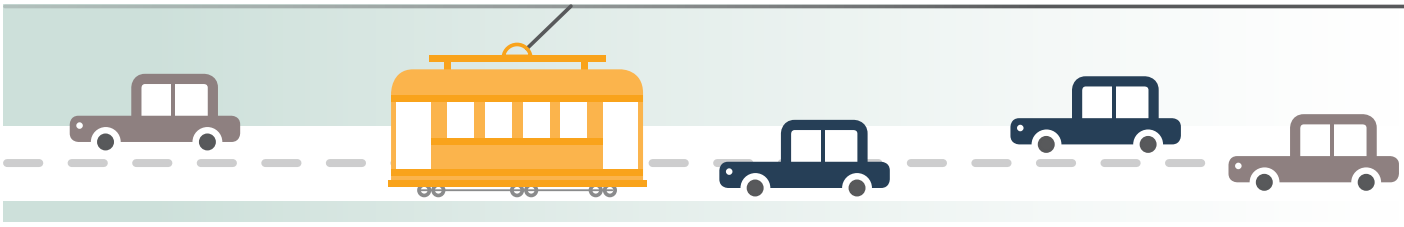
Effects of Asthma on Fertility Investigated

A SERIES of studies have analysed the association of asthma and fertility, a ERS press release dated 12th September 2017 has reported. The studies, carried out in Denmark and Australia, looked at the association between asthma diagnoses and time to pregnancy, and the link between maternal e-cigarette vaping and offspring risk of allergic asthma, respectively.

In the study from Denmark, 744 pregnant women were enrolled in the study at Hvidovre Hospital, Hvidovre, Denmark. Eligibility criteria included: i) a diagnosis of asthma, ii) had their first visit to the respiratory clinic in the first 18 weeks of pregnancy, and iii) had given birth between 2007 and 2013. Each participant under these criteria was studied alongside three consecutive non-asthmatic women who gave birth at the same hospital. The average age in the asthmatic and control groups was 31.3 years (range: 17–44) and 30.9 years (range: 17–45), respectively. Results were adjusted to account for differences in age, BMI, smoking status, previous children, and relationship status; however, it was noted that there were possible differences in income, lifestyle, and socioeconomic status. It was also noted whether the births were the result of spontaneous conception, or whether the mother had undergone assisted reproductive therapy, such as *in vitro* fertilisation (IVF), or intrauterine insemination. The team found that 12% of the asthmatic women had undergone fertility treatment compared to 7% of the control group participants.

Prof Charlotte Suppli Ulrik, Department of Respiratory Medicine, Hvidovre Hospital, Hvidovre, Denmark, commented: "We don't have the hard-core evidence, but based on what we know, it seems very likely that good asthma control will improve fertility in women with asthma by reducing the time it takes to become pregnant and, therefore, the need for fertility treatment." Following these results, Prof Suppli Ulrik and colleagues are now hoping to further study this association and to assess the effects of effective asthma control on fertility.

The second study to be presented looked at maternal e-cigarette vaping and the risk of allergic asthma in offspring by exposing female mice to vapour both with and without nicotine, and normal room air prior to mating and during gestation and lactation.



Following this, offspring were exposed to an ovalbumin-based allergen in order to develop asthma. Additionally, the team exposed *in vitro* human cells to e-cigarette liquid of a range of concentrations and assessed mitochondrial function.

> "...it seems very likely that good asthma control will improve fertility in women with asthma by reducing the time it takes to become pregnant and, therefore, the need for fertility treatment."

Commenting on the results of the study, Dr Pawan Sharma, University of Technology, Sydney, Australia, explained: "Our study found that maternal vaping increased the risk and severity of allergic asthma in offspring. We also found that the detrimental effects of vaping were partially mediated through impairment of mitochondrial function, which affects cellular respiration, and were independent of nicotine. This means that vaping, even without nicotine present, has a demonstrated negative impact on cell function."

Hormone Replacement Therapy for Preservation of Lung Function

AN INHIBITION of the decline of lung function in middle-aged women can be achieved by the use of hormone replacement therapy (HRT) as a therapeutic option, according to research recently presented at the ERS congress and reported in a ERS press release dated 12th September 2017. Lung function begins to decline after people reach their mid-twenties. Currently, a variety of factors are known to influence the speed of this decline, with the menopause having been identified as an accelerating factor.

In this research, data was used from the European Community Respiratory Health Survey, which followed 3,714 women for a period of approximately 20 years up to 2010. When the women initially joined the survey, they had their lung function assessed by measurement of forced vital capacity (FVC). This measurement was repeated 20 years later.

In this study, the researchers identified 236 women who took long-term HRT, which was defined as ≥2 years of treatment, and then matched them by characteristics including age at menopause, smoking behaviour, age, weight, height, and baseline lung function, with 236 women who had never undergone HRT. After adjusting for additional factors, such as length of follow-up time and type of spirometer, it was found that, over the study's duration, the women in the long-term HRT group had lost an average of 46 mL less lung volume when compared to the women in the control group. It was noted that 46 mL was approximately the lung volume that would be lost if a woman smoked a pack of cigarettes every day for 3 years; however, the researchers were at pains to point out that HRT should not be a substitute for quitting smoking.

> "Our findings show that female sex hormones are important for the preservation of lung function in middle-aged women."

Dr Kai Triebner, University of Bergen, Bergen, Norway, announced the headline discovery: "Our findings show that female sex hormones are important for the preservation of lung function in middle-aged women." However, when placing the results of their study into a holistic health context, the researchers discussed some of the other health impacts associated with HRT: it has a protective effect against osteoporosis and can alleviate menopausal symptoms but, on the other hand, has also been associated with increased risk of breast cancer and heart and blood vessel problems. Therefore, this finding should form part of a personalised treatment approach for women going through the menopausal transition, as the exact therapeutic option will depend on the individual situation and risk factors.

Lifestyle Changes Improve Asthma Symptoms in Non-Obese Patients

DIETARY and exercise changes could positively affect quality of life and symptoms in non-obese asthma patients, as shown by new research presented at the ERS congress 2017 and reported in a ERS press release dated 13th September 2017. As asthma is a relatively common condition, affecting

approximately one-in-ten individuals in the Western world on a long-term basis, new developments in management are important. Currently, daily medicine is the main method of controlling symptoms, with patients usually reluctant to participate in exercise for fears of exacerbating their symptoms.

The study randomly assigned 149 patients into four groups: i) consumption of a high protein diet with a low glycaemic index (to maintain blood sugar levels) and at least six portions of fruit and vegetables each day, ii) participation in three exercise classes at hospital per week, including both high intensity activities to increase the heart rate and more relaxed activities, iii) combination of the above diet and exercise programmes, and iv) a control group involving none of the above. The study lasted 8 weeks, with 125 patients completing the full study duration. Patients were questioned regarding their symptoms, quality of life, fitness level, strength, and lung capacity.

The study deemed high intensity exercise safe for asthma patients. There was no definite improvement in patient lung function; however, the combination of the diet and exercise allowed better patient control of symptoms and improved quality of life and fitness levels. Patients in the combination diet and exercise group defined their asthma symptom score as 50% better on average than those in the control group. Although patients in the individual diet and exercise groups also rated their scores higher than the control group, (by an average of 30%), these results were not found to be statistically significant. Dr Louise Lindhardt Toennesen, Bispebjerg University Hospital, Copenhagen, Denmark, stated: "Our research suggests that people with asthma should be encouraged to eat a healthy diet and to take part in physical activity." Future research will investigate these results in the long-term. The researchers hope to establish particular diets and exercises that have the best outcome for asthma symptoms, with the ultimate aim of replacing daily asthma medicine with improved diet and increased exercise.

> "Our research suggests that people with asthma should be encouraged to eat a healthy diet and to take part in physical activity."

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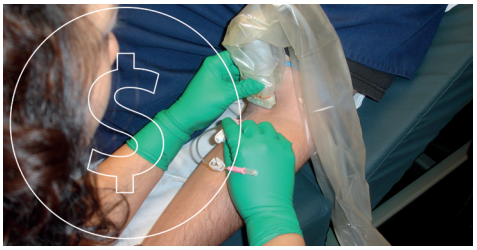

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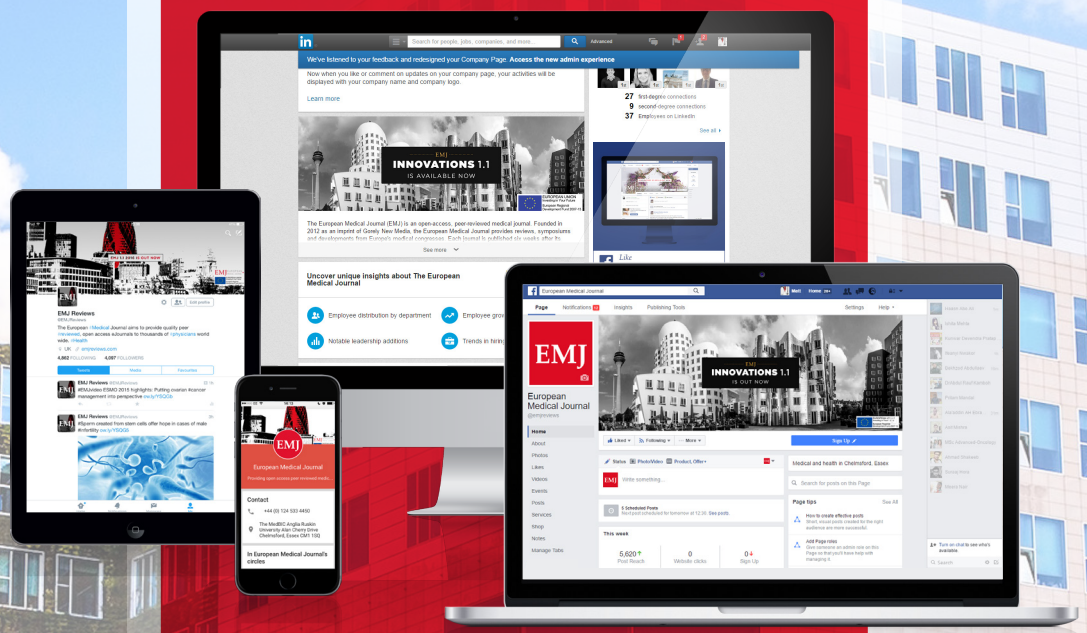

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Peter Barnes

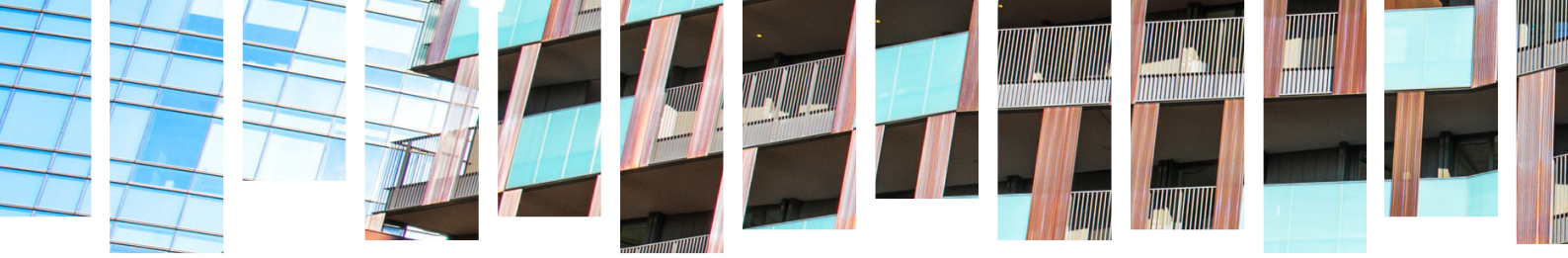
Professor of Thoracic Medicine and Head of Respiratory Medicine, National Heart and Lung Institute, Imperial College London; Honorary Consultant Physician, Royal Brompton Hospital, London, UK; Past President, European Respiratory Society (2013-2014).

On Tuesday 25th July, Prof Peter Barnes, from the world-renowned National Heart and Lung Institute, London, UK, kindly gave us some of his time to discuss topics such as his entry into the field, his current role, his past achievements, and his views on respiratory health and its future, amongst many other elements. As a specialist in asthma and chronic obstructive pulmonary disease (COPD), Prof Barnes has undertaken copious research projects and published an extensive number of articles on these diseases.

Prof Barnes first explained the rather unusual route he took into his career in respiratory medicine. "Well, like many things in life, it came about by chance," he recalled. "I had been training in general medicine at University College Hospital [London, UK], and I was working in a number of different specialities as a medical registrar. I was quite keen to do general medicine, but I applied for different specialty posts in different areas, like gastroenterology and cardiology, and I never got any of these posts. I then applied for a post in respiratory medicine, which I also didn't get, but the person in charge of respiratory medicine, Neil Pride from Hammersmith, phoned me at home and said I needed to do some research if I was going to get one of these speciality training posts, and said that he could arrange for a research post in respiratory. I was quite reluctant to do it, because I didn't really want to do research, but I did it, working with Colin Dollery in clinical pharmacology on a project on drugs for asthma, and got really involved in research. And then I just continued doing research after that."

When Prof Barnes began his research on asthma, the main method for treating the condition was with bronchodilators, to reduce bronchoconstriction, and therefore much of the research undertaken was with the aim of understanding the causes of bronchoconstriction. However, Prof Barnes instead looked at other mechanisms for the disease: "The work that I did really highlighted the importance of chronic inflammation in the airways of people with asthma and the role of inflammatory cells and mediators in producing the clinical features of asthma. We worked a lot on inflammatory mechanisms, the role of nerves in asthmatic inflammation, and the role of particular cells and mediators including cytokines and chemokines. So, we did a lot of work on mechanisms, but also worked on understanding how the treatments for asthma worked; for example, using beta-2 agonists as bronchodilators, but also having other effects on the airways." He continued: "But I suppose the main area that we focussed on was how corticosteroids worked, because it was known that corticosteroids were the most effective treatments for asthma and inhaled steroids really had revolutionised asthma therapy. So, we did a lot of work to understand the molecular mechanisms of steroids in asthma and to show that they were able to switch off activated inflammatory genes, by reversing acetylation of core histones that allowed inflammatory gene expression, by recruiting histone deacetylase 2 (HDAC2) to deacetylate the histones and therefore suppress inflammatory genes; we did a lot of work looking at those mechanisms."

> "...I suppose the main area that we focussed on was how corticosteroids worked, because it was known that corticosteroids were the most effective treatments for asthma and inhaled steroids really had revolutionised asthma therapy."



In addition to asthma, Prof Barnes has also conducted much research on the pathogenesis of COPD. Unlike with asthma, corticosteroids are not effective at treating COPD, so Prof Barnes and colleagues sought to understand and then discover ways of overcoming such resistance. "We looked at the mechanisms of corticosteroid resistance and found that, in COPD and in people with severe asthma, the HDAC2 mechanism was disrupted because oxidative stress activated a PI3-kinase which phosphorylated HDAC2, leading to its degradation, which meant that steroids were not able to then switch off inflammatory genes. We worked out ways to overcome this resistance by blocking the PI3-kinase pathway with drugs, such as theophylline and other classes of drug," he said.

Prof Barnes has also played a particularly prominent role in the development of new treatments for asthma and COPD. "I think we worked on all of the currently available treatments in some way, trying to understand how they work and how they should be better used," he recounted. "I suppose the early work focussed on inhaled steroids and why these were very effective treatments in asthma. So, we have a lot of clinical studies with inhaled steroids showing that they were extremely effective in suppressing inflammation in asthma, and this led to more widespread use of inhaled steroids. This has really been very important for improving the management of asthma in general, so I think this work had broad implications for how we currently manage asthma."

The development and research on anticholinergic drugs was also something that is associated with Prof Barnes. "Another treatment that we worked on was anticholinergics and we did the key pharmacology research that led to the development of the long-acting anticholinergic drug, tiotropium bromide, which is now probably the number one drug used in the management of COPD. We showed the importance of cholinergic tone in the airways of COPD patients, and that blocking this tone gave bronchodilation and also led to reduced air trapping in COPD. So, this was really based on the work that we did looking at muscarinic receptors in COPD and how they can be blocked for a prolonged period. It also led to the development of another long-acting muscarinic antagonist, called glycopyrrolate, which was used as an oral drug for a long time before, but we studied its effects on the lung muscarinic receptors and showed that it had a long duration of action, like tiotropium. So, we gave it by inhalation and found that it had a similar long duration anticholinergic effect and bronchodilator action," explained Prof Barnes.

We then discussed possible factors related to the continuously increasing prevalence of asthma and COPD, particularly in the developed world, despite the improvements in treatment. With regard to asthma, while no definite reasons can be attributed to the increase, Prof Barnes described in depth his belief that the lifestyle and environmental features of Western societies are key reasons. One such factor is the lack of immunity in children living in these societies due to a low exposure to bacteria. "When people live in cleaner environments and have more widespread use of antibiotics, then they seem to have an increased risk of allergy," he explained. "That seems to be the most likely explanation, because you can see in Germany, for example, that asthma was very uncommon in East Germany, but common in West Germany; but once Germany reunified, then asthma became much more common in East Germany. You can see it in an even more extreme case in Africa, where asthma is almost unknown in rural African communities, but becomes quite common in big cities, where people are not exposed to the same sort of dirty environment. There are probably other factors as well, and I suppose it is best summarised by a Western lifestyle being associated with an increased risk of asthma."

> "We looked at the mechanisms of corticosteroid resistance and found that, in COPD and in people with severe asthma, the HDAC2 mechanism was disrupted because oxidative stress activated a PI3-kinase, which meant that steroids were not able to then switch off inflammatory genes."

> “I think a problem that is still ongoing is the poor public understanding of respiratory diseases and the low perception of respiratory disease compared to diseases like heart disease, diabetes, and cancer...”

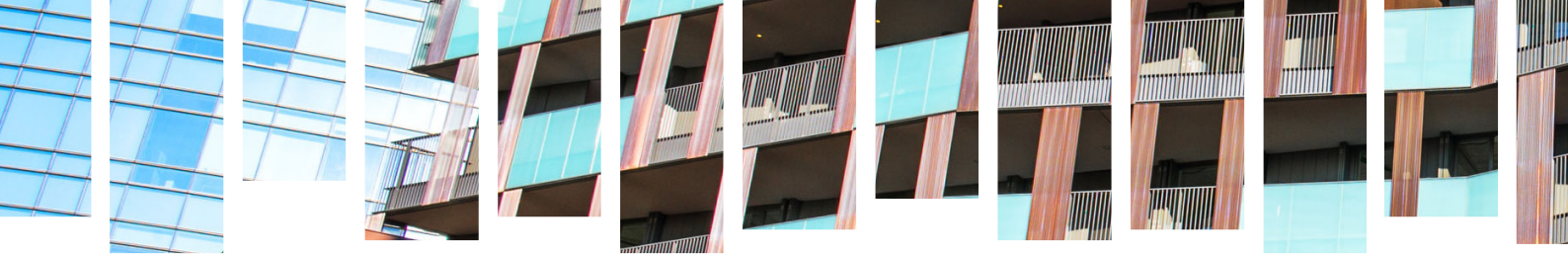
Other features associated with a Western society that are probable contributors to the onset of the condition, described by Prof Barnes in our discussion, include diet, with fewer antioxidants and less fish consumed in these population groups. These contributing factors to the onset of asthma are therefore very difficult to counteract: “Basically, you could say that you want to have a non-Western lifestyle, so you want to live in a dirty environment, and you want to have food that has more fruit and vegetables and fish, and not to be exposed to air pollution, living outside an urban environment, for example. But these are quite difficult lifestyle choices for people to make.”

The situation with regard to COPD is different, with the development of the condition certainly easier to prevent in younger people, with smoking widely believed to be a contributing factor. However, this has not prevented an increase in the incidence of COPD in recent times. Prof Barnes provided an insightful analysis as to why this may be the case: “The reason we see an increase in COPD, despite a reduction in smoking in the community, is that people live longer now. They are not dying of diseases that would kill people before they develop COPD, and we know that COPD is a disease of more elderly people, and may in fact be linked to accelerated ageing of the lung. In developing countries, COPD is quite often seen in people who have never smoked, and this may be due to indoor air pollution, due to biomass smoke being used in poorly ventilated houses, and this is probably just as common a risk factor in developing countries as cigarette smoking. So, there is a lot of COPD throughout the world, and the prediction is that it will go on increasing as people live longer because they are not dying of other diseases,” he outlined.

While this increase due to an increasingly ageing society is inevitable, successful changes have been implemented to reduce the incidence in younger people, both in developing and developed nations. “In the case of COPD, the main cause is cigarette smoking, so reducing cigarette smoking in the population has been very important,” he held. “Stopping smoking in public places for example, and now in cars so that people are not exposed to passive smoking. All of these things are important. In developing countries, there has been a lot of research into cleaner forms of cooking, so better ventilation for the houses but also using cooking stoves that produce less smoke. There are ways to reduce exposure.”

Prof Barnes went on to state his concerns about what he sees as an under-recognition and indeed a lack of understanding of respiratory conditions in general, but in particular asthma and COPD. This is an issue he is particularly passionate about, and something that he believes requires urgent action: “I think a problem that is still ongoing is the poor public understanding of respiratory diseases and the low perception of respiratory disease compared to diseases like heart disease, diabetes, and cancer, which have much more publicity, and this is partly because people think that diseases like asthma may not be very important. But, in fact, asthma is still killing people. About 1,000 people die from asthma in the UK every year, including young people, and, actually, deaths from asthma are increasing in young people, even with good treatments, because people don’t actually take the treatments. So, this is an ongoing problem and we need to increase public awareness.” He continued: “But it’s even worse in the case of COPD, because people in the general public are not very knowledgeable about this disease. They probably know it better as chronic bronchitis and emphysema.”

The lack of public awareness surrounding these diseases has had a negative knock-on effect on the state of research in these areas, according to the respiratory specialist. “Because there has been a poor public understanding, this has led to less



research funding, so the charities that support respiratory research have far less money than the charities supporting heart disease, neurological diseases like Alzheimer's, and diabetes," he explained. "There is a relative lack of research, which I think is a big problem for this area. And, of course, it makes it more difficult to attract good people into respiratory medicine if there is less research funding. I think we need to make the public, and politicians, much more aware of the importance of lung diseases; asthma is the most common chronic disease in the world and COPD is the third most common cause of death in developed countries. These are major diseases, but are largely ignored."

Following this theme, Prof Barnes stated his desire for more medical students to pursue a career in respiratory health and emphasised why it is such an important and valuable specialism for them to follow. "A thing to say to medical students in general is that respiratory diseases are very important. I've already talked about how common asthma and COPD are, but lung cancer is the most common cancer leading to death in the UK and there are many other important respiratory diseases including infections, pneumonia, and tuberculosis, as well as chronic fibrotic lung diseases. Cystic fibrosis is the most common genetic disease in the UK and that mainly affects the lungs. So, it's very important that medical students can see the importance of respiratory diseases, because these will be very important in general practice. Many medical students will end up as general practitioners (GP), and respiratory diseases are amongst the most common diseases that are leading to patients going to see their GP."

He concluded: "In terms of respiratory medicine as a speciality, there's a lot of potential because it covers a broad range of diseases, so it's more often to general medicine, and many respiratory diseases are associated with other diseases. So, people get a very broad knowledge of medicine and they're probably more general than other specialities like endocrinology, cardiology, and neurology, which are probably a lot more specialised. The research in respiratory medicine is very interesting, because we still don't understand a lot about most of the diseases in respiratory medicine, so there are a lot of challenges for people in research. I think it's a very good speciality for people to choose, because it gives them a very varied career."

Jacques Bouchard

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

Q: Firstly, there have been significant developments in the guidelines for chronic obstructive pulmonary disease (COPD) management recently, have these affected your day-to-day medical activities?

A: I think the most important change with the new COPD guidelines 2017 is the revised, combined COPD assessment. The 'ABCD assessment' tool is mostly based on the patient's symptoms and not just the spirometric impairment. It is very important to know more about not only the frequency of exacerbation and how many during the past year but also the severity of those included and if the patient has been admitted or not. We also have to take note of the biomarkers, including blood eosinophilia.

Q: With the popularity of vaporisers surging over the last few years as alternatives to smoking cigarettes, do you think this will have any effect on the development of respiratory diseases, and if so why?

A: At this stage, we do not know enough about those vaporisers. So, I think the best way is to wait until new data become available and try to stay away from these new alternative devices.

> The problem is exactly the same that it was 20 years ago: adherence to treatment still continues to be the most important challenge.

Q: You kindly participated in an interview 2 years ago for our 2015 *EMJ Respiratory 3.2* eJournal; in that interview you alluded to the reluctance of the Quebec government to provide reimbursement for new drugs; in the last 2 years have you seen any change in this?

A: No major changes have been made since then. I have personally been involved, since the last year, in the scientific committee to suggest which drugs will be available free of charge from the government health insurance plan. Our analysis should include all published data in accordance with international guidelines. As with many other governments in the world, the rationale for reimbursement of a new drug should include many aspects, including price, and also a well-demonstrated benefit for the patient.

Q: We know you have been heavily involved with the Quebec Asthma Education Network, which merged with the COPD programme to form the Quebec Asthma and COPD Network. Are you still just as heavily involved in the programme? And what changes have you seen in the subjects being covered in the programme?

A: I, of course, am still involved. We are now reviewing the educational programme for educators according to the new Gold Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines 2017. We educate more COPD patients than ever and are also writing more COPD action plans. Asthmatic patients are younger than in the past and allergy is playing an important part in the educational process.

Q: The Quebec Asthma and COPD Network (QACN) has helped develop >100 asthma and COPD education centres and regularly trains the educators for these institutions. Unfortunately, despite the availability of this service, referral for asthma education is still infrequent. Why do you think this is still the case?

A: The problem is exactly the same that it was 20 years ago: adherence to treatment still continues to be the most important challenge. Patients continue to misunderstand the importance of treating the inflammatory underlying process of their disease and are in search of fast relief to solve their problems rapidly.

Q: In your previous interview you touched on the importance of collaboration in science, what role do you think congresses such as the European Respiratory Society (ERS) annual congress play in national and international collaboration?

A: These medical international congresses are very important for stimulating exchange with both colleagues or healthcare professionals. It is important to know all the new incoming data that may challenge our personal practice and enhance the quality of treatment of our patients.

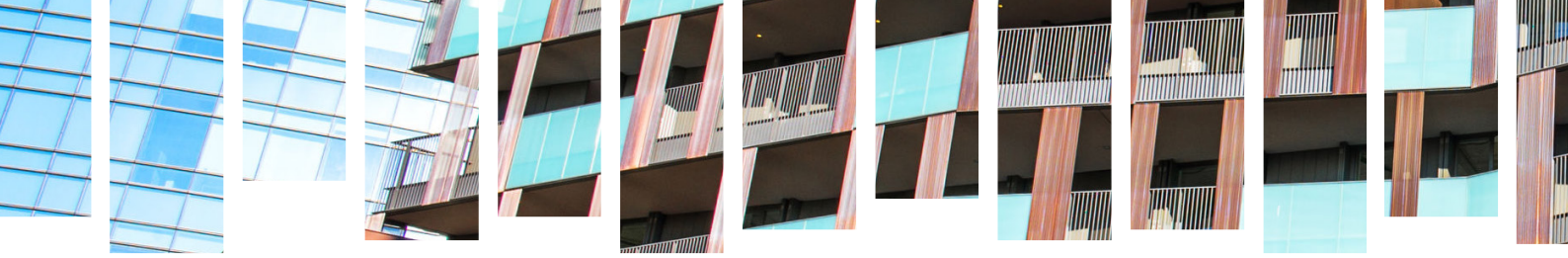
Q: Over the next decade, what do you envision to be the main morbidity inducing respiratory disease and what can be done to try and combat this?

A: Smoking cessation was, and will be, the most challenging issue. Education and smoking cessation campaigns will be the measure to reinforce this.

Q: At the moment, could you tell us what disease or therapeutic area you are currently focussing on?

A: The most challenging issue, for the moment, is to educate family physicians to properly use new drugs and devices both in asthma and COPD. I am working hard to create some new and innovative educational programmes.

> As with many other governments in the world, the rationale for reimbursement of a new drug should include many aspects, including price, and also a well-demonstrated benefit for the patient.



Q: Is there a specific factor that you believe is preventing the advancement of respiratory treatment and you would like to see abolished?

A: We surely have to define some new markers for the treatment of both obstructive diseases. As an example, continuing to use improvement in the forced expiratory volume in one second as a marker of success is the wrong way forward. We should use the symptoms assessment questionnaires more, which are still probably only one part of the answer. I will admit this is a very sensitive question.

Q: Finally, if time and money were no object, what respiratory related disease would you like to see cured and why?

A: COPD for sure! Sometimes, it can be a very bad disease and in some patients, severe chronic respiratory failure is very difficult to deal with in regard to medical and social aspects.

> “The most challenging issue, for the moment, is to educate family physicians to properly use new drugs and devices both in asthma and COPD. I am working hard to create some new and innovative educational programmes.”

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TRANSITIONING CLINICAL DATA INTO PATIENT CARE: RECENT REAL-LIFE EXPERIENCES WITH ALPHA 1

This satellite symposium took place on 11th September 2017, as part of the European Respiratory Society (ERS) International Congress in Milan, Italy

Chairpersons

Jan Stolk,[1] Berend Stoel[1]

Speakers

David Parr,[2] Joachim H. Ficker,[3] Charlie Strange,[4] Jan Stolk[1]

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Disclosure: Dr Stolk has acted as a consultant to CSL Behring and Kamada. Dr Stoel has acted as a consultant to BioClinica, CSL Behring, Baxalta, and Kamada. Prof Parr has acted as a consultant and is on the advisory boards for CSL Behring and Kamada, has given lecture presentations for CSL Behring and Grifols, and has attended conferences for CSL Behring. Prof Ficker is a member of the RAPID clinical trial programme study group funded by CSL Behring, has had research grants from CSL Behring, and has received personal fees and non-financial support from CSL Behring and Grifols. Prof Strange has received present and past grants from the Alpha 1 Foundation, CSL Behring, Grifols, the NIH, PneumRx, Pulmonx, and Shire; and has acted as a consultant for AstraZeneca, Baxalta, CSL Behring, Grifols, Abeona, and Pulmonx.

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MEETING SUMMARY

The symposium explored the use of state-of-the-art technologies in building the evidence for Alpha 1 Antitrypsin (AAT) efficacy, namely the use of computed tomography (CT) and recent developments in regional lung density analysis, and current challenges and data gaps for the management of AAT deficiency (AATD). The vital importance of registries in building our knowledge and understanding of AATD and its management were also discussed. Dr Stolk opened the symposium with a brief overview of AATD and the results of the RAPID clinical trial programme, which provided evidence for the efficacy of AAT therapy in slowing the rate of lung density loss in AATD. Prof Parr then presented the rationale and methodology for assessing regional lung density changes, as measured by CT, and the potential clinical relevance of regional treatment variability in AATD. Prof Ficker addressed the clinical implications for AATD treatment, in light of data from the RAPID clinical trial programme, and provided an overview of the current challenges for treating patients with AATD, including questions surrounding when to commence AAT therapy and how the potential life-extending effect of AAT therapy can be assessed and quantified. Finally, the importance of registries was discussed; Prof Strange provided an overview of the USA Alpha 1 Foundation registry and presented key published data. In addition, he discussed current and future initiatives. Dr Stolk considered the European Alpha 1 International Registry (AIR) and presented the results of recent projects supported by this registry.

Welcome and Introduction

Doctor Jan Stolk

AATD, a hereditary disorder characterised by reduced levels of functional AAT, results in excess lung protease activity and increases the risk for development of chronic obstructive pulmonary disease (COPD). Patients present with early-onset emphysema characterised by loss of lung density and is more prominent in the lower lobes. Lung densitometry assessed by CT scanning has been used to measure disease progression and demonstrate treatment efficacy in clinical trials of AAT.

Results of the RAPID clinical trial programme, consisting of RAPID-RCT followed by the open-label extension RAPID-OLE, provided evidence for the efficacy of Respreeza® in slowing the rate of lung density loss (Figure 1). RAPID-RCT, which randomised 180 patients with AATD and forced expiratory volume in 1 second (FEV_1) 35–70% predicted, to either Respreeza (n=93; intravenous AAT 60 mg/kg body weight per week) or placebo (n=87), showed that the annual rate of lung density decline at total lung capacity was significantly reduced in the Respreeza group (-1.45 g/L/year) compared to the placebo group (-2.19 g/L/year; p=0.03).[1]

Patients who received either Respreeza (n=76) or placebo (n=64) in RAPID-RCT were then included in the 2-year open-label extension trial, RAPID-OLE.[2] Results showed that between Months 24 and 48, the rate of lung density loss was reduced in the delayed-start group compared to placebo in Months 0–24.

This means that patients who initially received placebo during RAPID-RCT experienced a disease-modifying reduction in the progression of emphysema (from -2.26 g/L to -1.26 g/L per year) that was similar to that of actively treated patients. This slowing of lung density loss was highly statistically significant (p=0.001). For the early-start group, (i.e. patients who had received Respreeza during RAPID-RCT), no significant difference was seen over 4 years (-1.51g/L/year to -1.63 g/L/year), and their treatment effect was maintained during this time period.

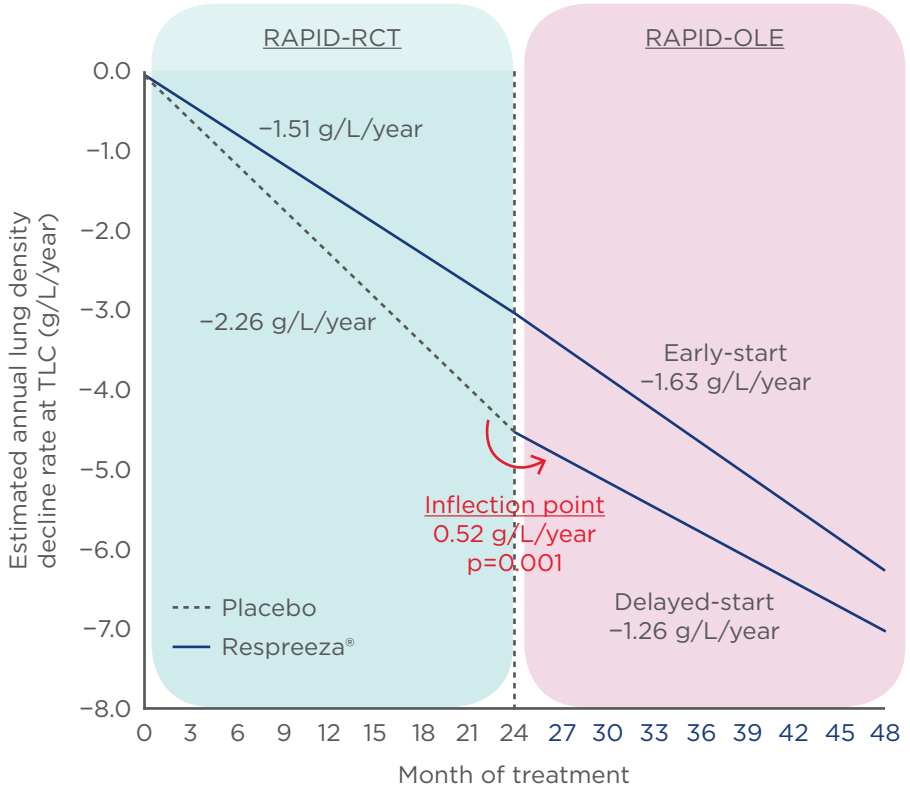

Figure 1: RAPID clinical trial programme results.
Annual lung density decline rate of whole lung densitometry (volume-adjusted PD15) at total lung capacity during 48 months of treatment (completer population).
OLE: open label extension study; RCT: randomised controlled trial; TLC: total lung capacity.
Adapted from McElvaney et al.[2]

However, some questions still remain, including how CT changes relate to clinical outcomes and how registries can support efforts to improve treatment.

Regional Lung Density and Imaging: Latest Findings from the RAPID Extension Trial

Professor David Parr

Prof Parr opened his presentation by describing the principles of CT lung densitometry, explaining that CT scanners are tissue densitometers that produce images comprising pixels corresponding to a volume of lung tissue, hence the term voxel. Each voxel has a computed value of density relative to water measured in Hounsfield units (HU); the density of water is 0 HU, air is -1,000 HU, and normal lung density is between -550 HU and -950 HU. Emphysema results in tissue loss and hyperinflation that leads to loss of lung density that is generally accepted as abnormal when it falls below -950 HU. CT densitometry has been validated as a measure of emphysema against pathology and a variety of clinical parameters. In AATD, two pivotal studies have shown that loss of CT lung density correlates with decline in health status over time[3] and with decline in FEV_1.[4]

The EXACTLE study was an exploratory study of the use of whole lung CT densitometry to assess therapeutic effects of AAT therapy and was not powered to show a treatment effect.[5] However, in a post hoc analysis of EXACTLE data, Parr et al.[6] showed that differences in treatment effect between patients receiving AAT therapy and those given placebo were evident when the basal region of the lung was sampled (p=0.040), but not in the central (p=0.155) and apical (p=0.673) regions.[6] Similar results were reported in a post hoc analysis of data from the RAPID clinical trial programme;[7,8] the greatest treatment effects (i.e. difference between placebo and AAT therapy) occurred in the basal lung regions.

Prof Parr went on to explore potential explanations for these observations. A histopathological study from the 1970s[9] investigating whole lung specimens from patients with COPD showed that centrilobular emphysema was more frequently located towards the apex of the lung, while panlobular emphysema was found towards the base. Furthermore, a study from the 1990s showed the coefficient of variation of interalveolar wall distance was significantly higher for the same mean linear intercept in centrilobular emphysema than panlobular emphysema.[10] Such data suggest distinct pathological subtypes of emphysema.[4]

These two histopathological subtypes of emphysema also coexist in patients with AATD; about one-third of patients with panlobular emphysema due to AATD also have centrilobular emphysema evident on CT,[11] and the pattern of emphysema distribution also influences the physiological impairment. In a quantitative CT scan study of two groups of patients with either predominantly basal or apical emphysema, basal distribution was associated with relatively greater impairment of airflow but less impairment of gas exchange than apical distribution.[12] Such data suggest that centrilobular and panlobular emphysema are distinct pathological subtypes with potentially different pathogenesis. However, regional lung density changes on CT in patients with emphysema may arise from regional volume changes or from tissue loss. Consequently, interpretation of regional density changes in a group of patients may be misleading and further studies are required to characterise the natural history of emphysema progression in individual patients.

Clinical Implications and Challenges for the Treatment of Alpha 1 Antitrypsin Deficiency

Professor Joachim H. Ficker

A meta-analysis of five classical studies,[13] including 1,509 patients, demonstrated that patients with AATD receiving AAT therapy show less decline in FEV_1 (Figure 2).

FEV_1 is a measure of bronchial obstruction that reflects many different pathological changes and, as such, is a poor predictor of the degree and progression of emphysema. However, for patients with AATD, the primary aim is to reduce progression of emphysema and researchers need to understand how to best measure this; therefore, it is important to understand how FEV_1 changes relate to emphysema progression.

It has been shown that expiratory air flow limitation in emphysema is, in part, due to the loss of elastic recoil.[14] During the development of emphysema,

bronchial tethering, which secures patency of the airways, is lost, leading to a checked valve phenomenon of dynamic airway collapse. This can be visualised on CT scans by the different forms of the bronchi during inspiration and expiration, and relates to a characteristically deformed flow-volume loop and reduced FEV_1.[15] Such data indicate that FEV_1 is not a direct measurement of emphysema, but represents an indirect measurement of airway collapse due to loss of elastic recoil.

In addition, the decline in FEV_1 found in patients with AATD is not linear. A study of 100 patients with AATD, grouped according to baseline FEV_1 (mild, moderate, severe, and very severe disease), showed FEV_1 decline over 3 years was greatest for those with moderate disease.[16] In mild disease, loss of elastic recoil does not reach the threshold required for bronchial collapse and in severe disease there is nearly total airway collapse and emphysema progression causes no further loss of FEV_1. In line with this, there is little change in FEV_1 in both early-stage and late-stage disease, with time during long-term follow-up indicating that FEV_1 is an insensitive measure of emphysema progression in comparison to CT lung density.[17,18]

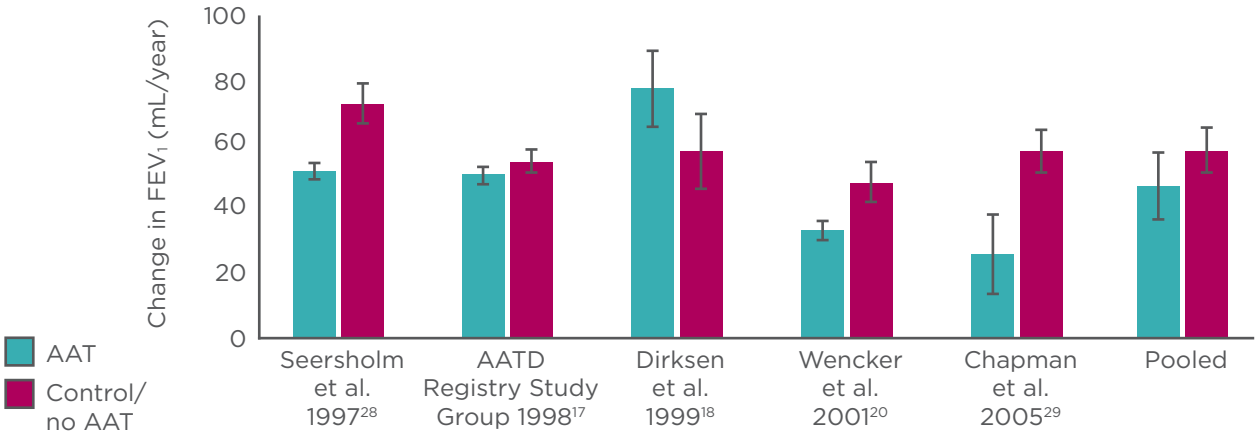

Figure 2: Effect of Alpha 1 Antitrypsin therapy on forced expiratory volume in 1 second.
Meta-analysis: the pooled results imply that therapy with AAT slows the loss of lung function.[13]
AAT: Alpha 1 Antitrypsin; AATD: Alpha 1 Antitrypsin deficiency; FEV_1: forced expiratory volume in 1 second.

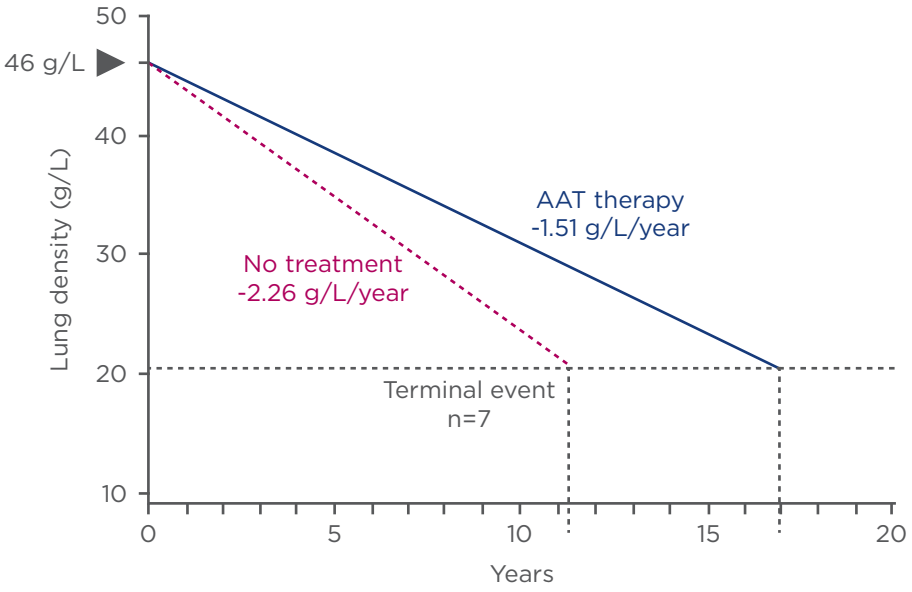

Figure 3: Time to respiratory crisis.
Earlier treatment start may result in a more pronounced effect.
AAT: Alpha 1 Antitrypsin.
Adapted from McElvaney et al.[2]

Using change in lung density as a primary endpoint, the RAPID clinical trial programme demonstrated that emphysema progression can be significantly reduced by AAT replacement therapy.[1,2] Long-term changes in lung density were similar in all degrees of lung function impairment and active treatment was associated with a significant lung density preservation ($p<0.001$ between placebo and active treatments) independent of baseline FEV_1.[19]

A post hoc analysis of data from the RAPID clinical trial programme[2] suggests that patients receiving AAT therapy will achieve critical lung densities (average final recorded lung density of approximately 21 g/L), where terminal events such as death or lung transplantation occur around 5.6 years later than those patients not receiving treatment (Figure 3).

Such extrapolation suggests that differences in lung density decline might ultimately translate into overall survival differences. Therefore, early introduction of treatment in all patients with emphysema-related AATD may delay time to respiratory crisis.

Whether different AATD phenotypes should be handled in different ways needs to be addressed. Data suggest that AAT therapy provides a particular benefit in arresting disease progression in patients with rapidly deteriorating emphysema.[2,20] Furthermore, data from the Danish AATD registry showed a marked difference in survival between index (those who present with symptoms) and non-index (those diagnosed via a family member) cases, with a mean age of death of 49.4 years for index cases versus 69.3 years for non-index cases.[21]

In addition to rapid decliners and index versus non-index cases, other AATD phenotypes include genotypes with intermediate AAT levels and rare alleles with very low levels (PIZ [Null], and PI [Null, Null]). A paper by Ferrarotti et al.[22] reviewed 6,057 individuals enrolled in the Swiss Cohort Study on Air Pollution (SAPALDIA) and showed that AAT serum levels vary according to different genotype classes in the general population, and that certain allele combinations of the *SERPINA1* gene (PI*SZ, PI*ZZ, and Null/Null) increase the risk of emphysema. These data suggest that rather than basing AAT therapy dose on body weight alone, additional phenotypic characteristics might have to be considered when choosing the optimal dose for treatment. In line with this hypothesis, patients may need higher doses during exacerbations. Planned and ongoing studies will investigate the currently licensed dose of 60 mg/kg body weight against the efficacy of higher doses of AAT therapy.

It is important to introduce outcomes into clinical trials that matter to patients. To date, the only patient-centred outcomes used have been hospital admissions (EXACTLE study)[5] and extrapolating reductions in lung density decline to mortality (RAPID clinical trial programme).[2] However, it is difficult to recruit sufficient numbers of patients into clinical trials of rare diseases such as AATD, and long-term observational studies based on registries may be more practical than traditional randomised trials for gathering data on patient-centred outcomes and may offer additional insights.

Going Beyond the Trials: Strengthening Clinical Evidence

Professor Charlie Strange

With 7,000 different rare diseases affecting 10% of the population, understanding the course of the disease and the development of treatments may be a daunting task, particularly if the number of affected individuals is very small. Registries can be an important research tool that can also facilitate recruitment to clinical trials.

One of the best examples of a registry is the USA Cystic Fibrosis Foundation Registry, which tracks the health outcomes of roughly 28,000 patients with cystic fibrosis each year, producing a snapshot of the therapies received and overall health outcomes. The foundation, which employs >50 people, also manages the largest cystic fibrosis clinical trials network in the world.

Membership of the USA Alpha 1 Foundation registry increased from 500 members in 1998 to 6,416 individuals in 2017. The rapid growth can be attributed, in part, to a USA primary care initiative that tested patients with COPD for AATD. Significant publications have come from the registry, and include a study of individuals with severe AATD showing that, in addition to cigarette smoking, male sex, previous asthma, chronic bronchitis, and pneumonia diagnoses represent risk factors for severe COPD.[23]

The USA Alpha 1 Foundation is currently developing a new registry that will include information on genotype, diagnostic history, FEV_1 category, lung

function, outcomes, therapies, visit type, and vitals, as well as a biorepository for samples. The registry will also contain an integrated informatics for biology at the bedside tool (known as i2b2) to enable exploratory analysis of the registry. It will also include a facility to allow the larger Alpha 1 community, such as patients and researchers, to review anonymised data upon request. Additionally, the Alpha 1 Global community is attempting to synchronise registry fields around the world to enable shared data collection and the gathering of a larger database. There is a need to focus on long-term outcomes, including quality of life and mortality.

Greater emphasis is being placed on patient engagement, for example with the work of the Patient-Centred Outcomes Research Institute (PCORI). This trust fund receives $150 million per year and has the mission to examine the relative health outcomes, clinical effectiveness, and appropriateness of different medical treatments. Patient engagement is important because it helps improve patient recruitment and retention rates, patient understanding of results, and enhances trust between researchers and participants. A 2013 PCORI survey revealed that barriers to engagement from the patient perspective include lack of time (43%), concerns about privacy (36%), and work, school, or care giving commitments (33%), while facilitators included helping others with their medical condition (68%), learning about their health (63%), helping the next generation (57%), and getting paid (56%). From the clinician's perspective, barriers included lack of time (79%), payment (47%), and research training (35%), while facilitators included helping patients receive better care (79%), getting paid (78%), and contributing to scientific knowledge (61%).[24]

Going forward, it will be important to make as much data public as possible, and use political will to integrate as many data sources as possible.

Clinical Implications and Challenges for Treatment of Alpha 1 Antitrypsin Deficiency

Doctor Jan Stolk

More than 10 European Union (EU) member states currently contribute data to the European AIR. The registry was founded in 1996 by chest physicians following publication of a World Health Organization (WHO) report on AATD.[25] Data of individuals with genotypes ZZ, SZ, or rare variants are being considered. The minimal data set includes information about demography, smoking habits, primary reason for AAT analysis (e.g. respiratory symptoms or family screening), medical history, information about AAT therapy, spirometry, and qualitative information on liver enzymes. Soon after AIR was started in 1997, it had 540 subjects, and after a rapid period of expansion the numbers reached 5,389 subjects in 2016.

AIR data show the median age of diagnosis is similar for men and women (46.54 years and 46.65 years, respectively) and similar for ZZ, SZ, and rare genotypes (46.39 years, 48.97 years, and 46.68 years, respectively). With regard to phenotype, 84.6% of participants are ZZ (n=4,388), 11.9% SZ (n=617), and 3.5% rare variants (n=179), of which the greatest contribution comes from patients with a Null/Null genotype. Additional registry data show a median age of respiratory symptom onset of 40 years, differing for the three subgroups (40 years for ZZ, 45 years for SZ, and 39 years for rare variants). On average there was a 7-year delay between onset of respiratory symptoms and AATD diagnosis. A USA study showed that 44% of patients reported seeing at least three physicians before an initial diagnosis was made.[26]

The registry also showed that quality of life, as assessed by the St George's Respiratory Questionnaire (SGRQ) at baseline, was worse for smokers and ex-smokers compared to never-smokers and index cases versus non-index cases, respectively.[27] The registry has investigated a subpopulation of patients with one of the 32 AAT Null mutations currently known, which result in an absence of AAT in the serum.[27] A matched analysis of Null AATD patients and ZZ and SZ patients from the AIR registry (based on age and sex) showed Null patients have significantly lower lung function values than SZ and ZZ individuals (p=0.001 for both FEV_1 and the coefficient of diffusion of carbon monoxide).[27]

In order to investigate the effect of treatment with AAT in this very small population of patients with Null mutations, the registry compared patients with a minimum of 6 years of follow-up on treatment in Italy, Spain, or France (n=10) with those who had received no treatment in the Netherlands due to lack of reimbursement (n=12). Results showed an average annual loss of FEV_1 for untreated patients of 76 mL/year

versus 12 mL/year for treated patients. This suggests that in selected populations with ultra-rare mutations, AAT therapy protects against FEV_1 decline. It would be impossible to explore such therapy in a randomised trial due to the rarity of the phenotype.

The AIR registry has provided a rich source of data for analysis of the clinical characteristics of AATD. However, quality control of data represents a particular challenge.

Summary

Doctor Berend Stoel

Providing an overview of the symposium, Dr Stoel said that it has taken 25 years from the first clinical study that utilised CT densitometry to measure emphysema progression in AATD until the publication of the RAPID study demonstrating that AAT therapy slows lung tissue destruction. CT densitometry is a sensitive method for assessing lung tissue but has downsides, including exposure to X-rays and the need for stringent quality control. In future, it is hoped that more specific blood biomarkers that are sensitive to changes in disease severity and progression will become available to replace CT scanning.

Alpha 1 registries represent real-world clinical practice. They can be used for recruiting patients to clinical trials and describing natural progression of disease in different phenotypes. Identification of phenotypes that benefit most from therapy could help define the patient groups who should be eligible for AAT therapy reimbursement.

Question and Answer Session

Q: How should we approach the evaluation of survival without treatment? What clinical outcome markers should be used and are these affordable for registries?

A: Considering how to approach the issue of patients who do not receive AAT therapy, Prof Strange said the National Heart, Lung, and Blood Institute (NHLBI) registry enrolled patients with and without AAT therapy over 5 years and had shown a mortality signal. However, the finding was downplayed because it was not derived from a prospective randomised trial. The signal was strong and it would have taken only 2 years of treatment to show this mortality difference. A caveat, he said, was that mortality largely occurred in patients with FEV_1 <30% predicted at baseline, making it important to perform studies in the most severely affected patients. However, with the associated comorbidities in these patients this may not be possible. In future, the USA registry plans to collect death certificates for cause of death and also declines in lung function.

Q: Should biomarker data, similar to that found in the RAPID study relating to elastin degradation, be used as an endpoint in future clinical studies?

A: The RAPID study demonstrated that elastin degradation breakdown products, desmosine (DES) and isodesmosine (IDES), were significantly reduced following AAT treatment. Furthermore, levels of DES/IDES could be related to CT density. Prof Parr said studies demonstrate placebo patients experience greater loss of lung mass than patients receiving AAT therapy. A complication, however, is that disease progression causes hyperexpansion of the lungs, which reduces density even in the absence of a change in lung mass. Observations of changes in both lung mass and elastin biomarkers suggest changes occur at the tissue level.

Q: Would studies focussing on data from lower lobe lung segments allow fewer patients to be enrolled and shorter follow-up periods?

A: Prof Parr stated that, while statistical data is better in the lower part of the lung, investigators should still monitor the entire lung. This is because it is impossible to judge whether any density changes occurring in the lower lung are due to a real loss of lung density or due to changes in other parts of the lung. Such limited data, he felt, would be unlikely to convince regulators.

Q: Should guidelines be changed to allow treatment to be continued even in patients with very low FEV_1 % predicted?

A: Prof Ficker commented that AAT therapy should be started as early as possible to preserve lung structure, and he did not see any reason to stop treatment when the patient declined. The situation, he said, was analogous to osteoporosis, where treatments are started as soon as possible to preserve bone mass.

Q: What new data could be used to persuade healthcare payers to support reimbursement of AAT therapy?

A: Regarding healthcare payer data, Prof Strange felt that it would be valuable to have data on the effects of AAT therapy on exacerbation frequency as this influences healthcare utilisation and cost. It was important, he added, for databases to capture real-life patient experiences, including exacerbations.

Prof Ficker underlined differences in Europe, where AAT therapy is not reimbursed in Scandinavia and the UK. One of the aims of the European Reference Network for Rare Diseases, he said, was to harmonise treatment reimbursement across EU member states.

Q: Where in the field of COPD is the best data on patient exacerbations?

A: Prof Strange answered that the Alpha 1 Foundation runs a programme called Alpha Net, which asks patients to answer an Alpha Net exacerbation questionnaire every month. The scheme, which has been running for 10 years, has allowed real-world data to be captured that is only just starting to be mined.

Q: Would investigators be ready to enrol AATD subjects with normal lung function into placebo-controlled trials?

A: Prof Parr commented that treating patients with normal lung function was fine; however, it would be hard to justify if they did not show emphysema on CT scans, as they were not considered at-risk. Prof Strange felt that in gene therapy trials it would be justifiable for patients with normal lung function to be considered as candidates for therapy. Prof Ficker said that all alpha 1 patients showing evidence of emphysema should be treated.

REFERENCES

1. Chapman K 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):360-8.

2. McElvaney NG et al. Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: An open-label extension trial (RAPID-OLE). Lancet Respir Med. 2017;5(1):51-60.

3. Stolk J et al. Correlation between annual change in health status and computer tomography derived lung density in subjects with α1-antitrypsin deficiency. Thorax. 2003;58(12):1027-30.

4. Parr DG et al. Validation of computed tomographic lung densitometry for moitoring emphysema in α1-antitrypsin deficiency. Thorax. 2006;61(6):485-90.

5. Dirksen A et al. Exploring the role of CT densitometry: A randomised study of augmentation therapy in α1- antitrypsin deficiency. Eur Respr J. 2009;33(6): 1345-53.

6. Parr DG et al. Exploring the optimum approach to the use of CT densitometry in a randomised placebo-controlled study of augmentation therapy in alpha 1-antitrypsin deficiency. Respir Res. 2009; 10:75.

7. Parr DG et al. Effect of alpha-1 proteinase inhibitor (A1 -PI) therapy on changes in regional lung density: A post-hoc analysis of the RAPID trial. Abstract P1242. ATS 2016, 13-18 May, 2016.

8. Reed D. The effect of alpha1-proteinase inhibitor therapy on changes in regional lung density: Post-Hoc analysis of the RAPID/RAPID extension trial. Abstract 109. ATS 2017. 19-24 May, 2017.

9. Anderson AE Jr, Foraker AG. Centrilobular emphysema and panlobular emphysema: Two different diseases. Thorax. 1973;28(5):547-50.

10. Kim WD et al. Centrilobular and panlobular emphysema in smokers. Two distinct morphologic and functional entities. Am Rev Respir Dis. 1991;144(6): 1385-90.

11. Parr DG et al. Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2007;176(12):1215-21.

12. Parr DG et al. Pattern of emphysema distribution in alpha 1 antitrypsin deficiency influences lung function impairment. Am J Respir Crit Care Med. 2004;170(1):1172-8.

13. Chapman KR et al. Augmentation therapy for alpha1 antitrypsin defiency: A meta-analysis. COPD. 2009;6(3):177-84.

14. Barnes PJ. Chronic obstructive pulmonary disease. N Eng J Med. 2000;343(4):269-80.

15. Kurosawa H, Kohzuki M. Images in clinical medicine: Dynamic airway narrowing. N Eng J Med. 2004;350(10): 1036.

16. Dawkins PA. Rate of progression of lung function impairment in α1-antitrypsin deficiency. Eur Respr J. 2009;33(6): 1338-44.

17. The Alpha-1 Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. Am J Respir Crit Care Med. 1998;158(1):49-59.

18. Dirksen A et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. Am J Respir Crit Care Med. 1999;160(5Pt1):1468-72.

19. Ficker J. Alpha 1 antitrypsin (A1-PI) treatment slows emphysema progression independent of baseline FEV_1. Abstract OA3416. ERS 2017. 9-13 September, 2017.

20. Wencker M et al. Longitudinal follow-up of patients with a1-protease inhibitor defiency before and during therapy with IV α1-protease inhibitor. Chest. 2001; 119(3):737-44.

21. Seersholm N et al. Survival of patients with severe α1-antitrypsin deficiency with special reference to non-index cases. Thorax. 1994;49(7):695-8.

22. Ferrarotti I et al. Serum levels and genotype distribution of α1-antitrypsin in the general population. Thorax. 2012;67(8):669-74.

23. Demeo DL. Determinants of airflow obstruction in severe alpha-1-antitrypsin deficiency. Thorax. 2007;62(9):806-13.

24. PCORI. Patient and clinician views on CER and engagement in research: A panel discussion on PCORI survey results. Available at: https://www.pcori.org/events/2013/patient-and-clinician-views-cer-and-engagement-research-panel-discussion-new-pcori. Last accessed: 16 October 2017.

25. Alpha 1-antitrypsin deficiency: Memorandum from a WHO meeting. Bull World Heal Organ. 1997;75(5):397-415.

26. Stoller JK et al. Physical and social

impact of alpha 1-antitrypsin deficiency: Results of a survey. Cleve Clin J Med. 1994;61(6):461-7.

27. Fregonese L et al. Alpha1-antitrypsin null mutations and severity of emphysema. Respir Med. 2008;102(6): 876-84.

28. Seersholm N et al. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Eur Respir J. 1997;10:2260-3.

29. Chapman KR et al. Slower lung function decline during augmentation therapy in patients with alpha1-antitrypsin deficiency (A1ATD): Results from the Canadian Air Registry. Proc Thorac Soc. 2005;2:A808.

NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE: CURRENT STATE OF KNOWLEDGE AND FUTURE DIRECTIONS

The two symposia reviewed here took place on 11th and 12th September 2017, as part of the European Respiratory Society (ERS) International Congress in Milan, Italy

Chairpersons

James Chalmers,[1] Charles Haworth,[2] David Griffith[3]

Speakers

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MEETING SUMMARY

The main objectives of the two symposia were to raise awareness of nontuberculous mycobacterial lung disease (NTM-LD); evaluate the key microbiological and clinical aspects of the disease, including its association with other conditions, such as bronchiectasis and common coinfections; outline the current treatment and management strategies; and review data from clinical trials of new therapies and how these could shape future management strategies. Dr Chalmers, Dr Griffith, and Dr Haworth opened the symposia by introducing NTM-LD and providing a brief overview of the key topics. Dr Ringshausen focussed on the epidemiology, prevalence, and burden of NTM-LD, and briefly discussed pathophysiology. Dr van Ingen outlined the microbiological diagnosis of NTM-LD, in particular the importance of molecular identification and drug susceptibility testing (DST). Dr Aliberti introduced bronchiectasis, outlined the relationship between the two diseases, and discussed the clinical relevance of comorbid disease. Dr Aksamit addressed the assessment and management of co-isolated NTM and other respiratory pathogens. Dr Griffith and Dr Loebinger each summarised the current treatment and management strategies, and reviewed the latest research regarding new therapies and what this could mean for the future. Dr Koh closed the symposium by outlining the latest clinical research on the natural history of NTM-LD from a global perspective.

Prevalence and Burden: Why Care About Nontuberculous Mycobacterial Lung Disease?

Doctor Felix Ringshausen

The epidemiology of NTM-LD is difficult to predict, as it is not a reportable disease and surveillance systems do not exist. One initiative in the Netherlands gathered data from >20,000 laboratory isolates from 30 different countries and found that *Mycobacterium avium* complex (MAC) was the most frequently isolated NTM (47% of isolates), although the predominant species and strain varied between countries.[1] A retrospective cohort of NTM-LD over 25 years in Denmark demonstrated no increase in disease burden or incidence, and identified children aged 0–4 years as having the highest incidence of NTM disease.[2] In contrast, a study of burden and trends of NTM-LD-associated hospitalisations in Germany showed a significant increase in incidence from 2005–2011. Chronic obstructive pulmonary disease (COPD) was identified as the most frequent NTM-LD-associated condition (28.9% of hospitalisations), and the average annual increase in this patient population was 4.8% (Figure 1).[3] Likewise, in a USA study of insurance claims data from 1997–2007, the prevalence of NTM-LD increased annually by 8.2%.[4] A similar study in Germany that used health insurance claims data showed that the prevalence of NTM-LD increased from 2.3 to 3.3 cases/100,000 population from 2009–2014 and that >50% of patients had concomitant COPD. The highest prevalence rates were among patients aged ≥80 years, with a rate of 9.4 and 9.6/100,000 for men and women, respectively.[5]

To explore the burden of NTM-LD in Germany, Diel et al.[6] carried out an analysis of 125 patients with NTM-LD, compared with 1,250 matched control patients. The incidence rate of NTM-LD was 2.6/100,000. The mean direct expenditure per patient with NTM-LD was four-fold that of matched controls (€39,559 versus €10,006), while hospitalisations were three times higher in patients with NTM-LD compared with matched controls and accounted for 63% of total costs. Attributable annual direct costs and indirect work-loss costs in patients with NTM-LD were €9,093 and €1,221 per patient, respectively. It was also found that 74% of patients with NTM-LD received antibiotics (29 different regimens were prescribed) and 12% were prescribed macrolide monotherapy. The mortality rate in patients with NTM-LD was higher than in matched controls, 22.4% and 6.0%, respectively, which was increased with concomitant COPD (41.5%).

Pathogenesis of Nontuberculous Mycobacterium Lung Disease

The pathogenesis of NTM-LD differs according to the pathogen, with species, subspecies, virulence/resistance mechanisms, and interactions with other pathogens all influencing factors. Environmental factors, such as temperature, evapotranspiration, pH, water chlorine content, biofilms, and soil mineral matter, also play a role, along with host factors, such as the presence of structural or genetic immunological diseases and certain phenotypes.

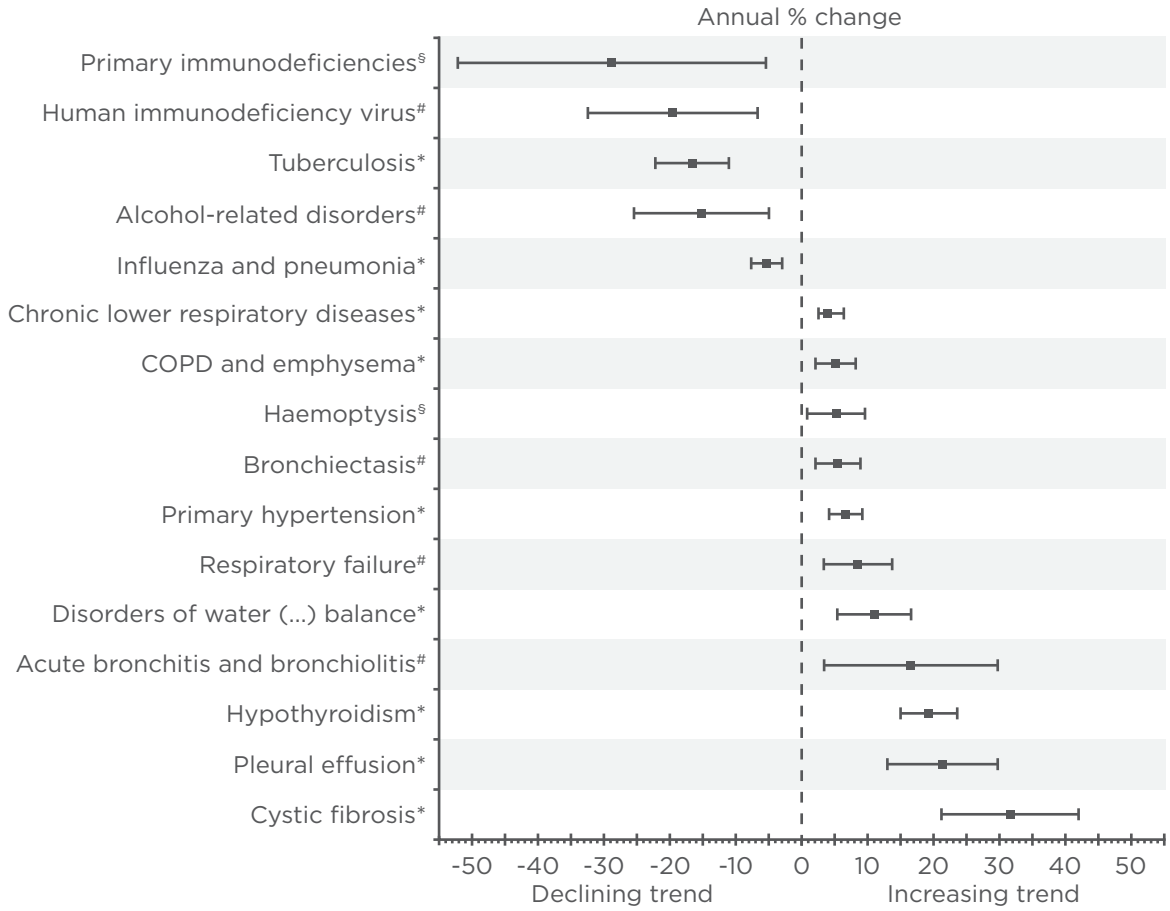

Figure 1: Average annual percentage change of the rate of associated primary and secondary diagnoses per 1,000 hospitalised patients with any diagnosis of nontuberculous mycobacterium lung disease. Bars indicate 95% confidence intervals calculated from Poisson log-linear regression (Wald statistics). Non-significant trends from 2005–2011 are not shown.
*Statistical significance at p<0.001; #Statistical significance at p<0.01; §Statistical significance at p<0.05.
COPD: chronic obstructive pulmonary disease.
Adapted from Ringshausen et al.[3]

Microbiological Diagnosis of Nontuberculous Mycobacterium Lung Disease

Doctor Jakko van Ingen

Laboratory diagnosis of NTM-LD should involve mycobacterial culture on liquid and solid media at 30°C and 37°C, respectively, and partnership with a reference lab should allow culture with supplemented media, molecular identification of NTM to species level, and guideline-compliant drug susceptibility testing (DST). Molecular detection of resistance-conferring mutations and next-generation sequencing of NTM in clinical specimens should be on the research agenda. The clinical relevance of NTM isolates differs by species, so correct species identification is crucial to allow treatment to be evidence-based.

Although there are no validated commercial assays, a study comparing the correlation between polymerase chain reaction (PCR) and culture demonstrated that in smear-positive specimens, PCR detection of NTM had 100% sensitivity and 97% specificity, while in smear-negative specimens it had 50% sensitivity and 90% specificity.[7] Identification of isolated NTM using molecular methods is important for rapid diagnosis and treatment decisions. Fibrocavitary disease (FCD) is easier to diagnose microbiologically, as sputum cultures are often positive and direct Ziehl–Neelsen staining of sputum often reveals acid-fast bacilli (AFB). Nodular bronchiectatic (NB)-LD is harder to diagnose as it has a lower bacterial burden and the sensitivity of direct staining, PCR, and culture is lower. A series of sputum samples or even a bronchoalveolar lavage sample may be required to

find the causative NTM and meet the microbiological criteria for NTM-LD diagnosis.

Drug Susceptibility Testing

There is a myth that for NTM, results of *in vitro* DST do not correlate with outcomes of treatment *in vivo*.[8-14] There is, however, sufficient evidence from clinical studies that susceptibility to macrolides and amikacin is correlated to outcomes of treatment. For rifampicin and ethambutol, which are prescribed for their synergy and not their individual effects, the activity against MAC *in vitro* is not important and should not be reported by laboratories.

Overall, it is important to have a multidisciplinary team to treat NTM-LD, including a pharmacist and a microbiology team who can identify to the species level and partner with reference laboratories. Quality control should be stringent and DST should be carried out according to existing guidelines.

Bronchiectasis as a Friend of Nontuberculous Mycobacterium and Vice Versa

Doctor Stefano Aliberti

Bronchiectasis is a disease with an increasing prevalence and incidence worldwide.[15] Historically, it has been neglected, which has contributed to a lack of awareness and licenced treatments, with guidelines recommending reliance on real-life experience to manage the disease. Symptoms of bronchiectasis include chronic cough, haemoptysis, purulent sputum, wheeze, tiredness, and recurrent lower respiratory tract infections. However, it is a highly heterogeneous disease with variable aetiology, radiological findings, and pulmonary function. Chronic infection plays a crucial role in the vicious cycle of bronchiectasis pathophysiology; infection increases inflammation and leads to airway damage and development of bronchiectasis, which impairs lung defences and leaves the patient vulnerable to chronic infection.[16]

In 2016, the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) released a statement outlining research priorities in bronchiectasis, the third highest priority being the prevalence and characteristics of microbiological colonisation and chronic and acute infection (including NTM) in patients across Europe.[17] The European Bronchiectasis Registry enrolled 9,123 patients from 27 countries and found that <5% of patients were infected with NTM.[18]

Nontuberculous Mycobacterium and Bronchiectasis: A Specific Clinical Phenotype

Among patients with bronchiectasis, there is a clear phenotype for those that have NTM: elderly (>60 years of age), female, with a low BMI, scoliosis, mitral valve prolapse, and no pre-existing LD. An interesting association exists between NTM-LD and cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation. The clinical course is a prolonged cough with fatigue and weight loss, and radiology showing bronchiectasis with nodules particularly in the middle and upper lobes.

Prevalence of Nontuberculous Mycobacterium in Bronchiectasis

The prevalence of NTM in bronchiectasis varies between countries and study type (Table 1), and evaluation of the data is limited by low sample size, variable study periods, geographic locations, and the fact that most of the data are from case series, retrospective analyses, or databases.

Table 1: Prevalence of nontuberculous mycobacterium in bronchiectasis.[19-24]

Country	Type of study	Year	Total patients (N)	Prevalence of NTM, n (%)
UK	Prospective	2002	94	8 (9)
UK	Prospective	2005	50	1 (2)
Spain	Retrospective	2002–2010	218	18 (8)
Italy	Prospective	2014	32	32 (12)
N/A	Meta-analysis	N/A	N/A	N/A (9)

N/A: not applicable; NTM: nontuberculous mycobacteria.

Sputum Culture for Mycobacteria in Bronchiectasis

The Italian national audit of patients with bronchiectasis across 32 hospitals during 2014–2015 enrolled 1,361 patients (53% female; average age 70 years) and found that sputum culture during the stable period was performed in <30% of patients, and only 50% of cultures were for mycobacteria.[25] In a prospective, observational, single-centre study from 2012–2015, 261 adults with bronchiectasis were identified (59% female; average age 69 years), of which 52% underwent bronchoscopy, 12% had NTM-LD (59% identified by fetal bovine serum and 41% from sputum), 4% had coinfection with *Pseudomonas aeruginosa*, and none were resistant to macrolides. Patients with NTM-LD were more likely to have cylindrical bronchiectasis (p=0.048), a 'tree-in-bud' pattern (p=0.011) on radiology, and a history of weight loss (p=0.045) compared with those infected with *P. aeruginosa*.[23]

Additionally, NTM-LD in bronchiectasis can be complicated by coinfection with other bacteria (such as *P. aeruginosa*), and fungi (such as *Aspergillus*).[19,26] The presence of *CFTR* gene polymorphisms without cystic fibrosis (CF) may predispose to NTM infection by increasing the risk of bronchiectasis.[27]

American Thoracic Society Diagnostic Criteria

The American Thoracic Society (ATS) guidelines recommend that the following diagnostic criteria are met for diagnosis of NTM-LD: symptoms compatible with NTM-LD, radiology compatible with NTM-LD (e.g. cavities, nodules), ≥3 respiratory samples over ≥1 week, and ≥2 positive cultures with the same species (identified on both solid and liquid media plus molecular methods). For patients with bronchiectasis, the diagnosis of NTM-LD is very difficult as they already have the clinical and radiological criteria due to bronchiectasis.[28]

In conclusion, the diagnosis of NTM in patients with pre-existing bronchiectasis can be challenging. Cultures should be taken before macrolide therapy is initiated, and resistance should be monitored.

How to Assess and Manage the Co-Isolation of Nontuberculous Mycobacteria with Other Potential Respiratory Pathogens

Doctor Timothy Aksamit

The isolation of *Mycobacterium tuberculosis* and NTM is common, and the presence of multiple organisms is not rare. As a general rule, tuberculosis (TB) should be treated first and then NTM-LD reassessed. Notably, not all smear-positive disease is NTM (in the USA only 14% of smear-positive isolates were NTM).[29] A recent report supported the recommendation to restrict investigations to sputum smear-positive patients;[30] however, NTM should be considered when TB is being investigated. For example, in a cohort of patients with multiple drug-resistant TB in Cambodia, 409 patients were identified, of whom 46% were examined for culture. Two-thirds of the samples were culture-positive; 25% for NTM and 75% for *M. tuberculosis*.[31]

It is very common to isolate multiple NTM in one sample. For example, in a retrospective National Jewish Group study of 107 patients with NTM-LD, over half (55%) of patients had coexistent or previous MAC infection,[13] whereas in another study of patients with CF, the initial isolate was almost always a single organism.[32]

A study of patients with MAC lung disease (MAC-LD) explored the significance of *Mycobacterium abscessus* subspecies *abscessus* (MAA) infection. In total, 29% of patients had MAA infection and the time from MAC-LD diagnosis to first MAA was between 9.9 and 11.3 months. Patients with MAA infections were more likely to have new or enlarging cavitary lesions on MAC therapy than those without coinfection (38% versus 0%, respectively).[33] Treatment for MAC and MAA coinfection should include ethambutol, rifampin, a macrolide, amikacin, cefoxitin, and imipenem.

Aspergillus is a fungus that is more common in patients with NTM-LD than those without; the US Bronchiectasis Research Registry demonstrated that *Aspergillus* was present in 21% of patients with NTM-LD, versus 16% without.[33] A cohort of patients with CF showed that 30% versus 8% of patients with and without NTM-LD, respectively, also had *Aspergillus* infection.[32] Similarly, a retrospective study that compared 30 patients with NTM-LD and 61 patients with bronchiectasis without NTM-LD found that *Aspergillus* was present in 20% versus 0% of patients with and without NTM-LD, respectively.[26] In the ATS Fungal Statement in 2011, voriconazole, itraconazole, posaconazole, amphotericin, and caspofungin were identified as treatments for *Aspergillus* infection;[34] however, drug–drug interactions between NTM-LD and *Aspergillus* therapies limit the number of options. Although treatment with dose-adjusted antifungals and rifabutin has been carried out, along with therapeutic drug monitoring,[35] it is not generally

advised. Other options are to delay NTM treatment until *Aspergillus* infection is cured or to use alternative strategies that exclude rifamycin/rifabutin.

In conclusion, coinfection in NTM-LD is not uncommon, although the impact on natural history is yet to be established. Careful screening and regular monitoring for other pathogens is crucial for the care of patients with NTM-LD. Complex multidrug regimens that bear several drug–drug interactions are the only options currently available, and therapeutic drug monitoring should be utilised when treatment is prescribed.

Management of Nontuberculous Mycobacterium Treatment and New Strategies

Doctor David Griffith and Doctor Michael Loebinger

There are several factors that should be considered when making the decision whether to treat NTM-LD or not, such as whether NTM-LD is associated with cavities, the symptoms of the patient, pulmonary comorbidities, short and long-term prognosis, and the patient's wishes. Additionally, at present there are a number of impediments to effective NTM-LD therapy, such as the long duration of therapy required, multiple drug cocktails, ongoing exposure to NTM from the environment, innate and acquired antibiotic resistance, poor clinical response to drugs, and patient factors (such as comorbid conditions).

Nontuberculous Mycobacterium Drug Resistance

Drug resistance can be either innate, i.e. natural drug resistance that is not readily associated with *in vitro* measures of resistance, such as minimal inhibitory concentrations (MIC) (for example, inducible macrolide resistance through the *erm* gene) or acquired, where isolates are selected with naturally occurring mutations that confer resistance to specific antibiotics. Some species of NTM, such as *M. abscessus*, MAC, and *Mycobacterium simiae*, show 'cryptic' resistance, whereby *in vitro* susceptibility results do not correlate with *in vivo* treatment response. However, some species, such as *Mycobacterium kansasii (rmp)*, *Mycobacterium marinum, Mycobacterium szulgai*, and *Mycobacterium fortuitum (erm)*, show good correlations between *in vitro* susceptibility and treatment response.

Treatment of Nontuberculous Mycobacterium

It is recommended to carry out initial *in vitro* susceptibility testing for NTM isolates to guide therapy, for example, to test the effectiveness of macrolides and amikacin against MAC. Gene mutations that confer resistance among NTM include the *23S rRNA* gene and *16S rRNA* gene in MAC, which confer resistance to macrolides and amikacin, respectively, the *rpoβ* gene in *M. kansasii*, which confers resistance to rifamycins, and the *23S rRNA* gene in MAA/*M. abscessus* subspecies *massiliense* (MAM), which confers resistance to macrolides. Inadequate therapy in such cases results in acquired mutational resistance and can cause profound negative consequences for the treatment of NTM-LD.

In a study of 71 patients with *M. massiliense* LD, patients received oral macrolides along with 4 or 2 weeks initial intravenous (IV) amikacin and cefoxitin (or imipenem). Patients were treated for 24 months (4-week IV group) or for ≥12 months after negative sputum culture conversion (2-week IV group). Response rates after 12 months were 89% versus 100% for symptoms, 79% versus 91% for computed tomography (CT) scanning, and 100% versus 91% for negative sputum culture results in the 4 and 2-week IV groups, respectively. Acquired macrolide resistance developed in 2 patients in the 2-week IV group. Genotyping analysis for patients who failed to convert sputum culture to negative, or those with positive culture after successful treatment, revealed that most episodes were due to reinfection with different genotypes of *M. massiliense*.[36] In an editorial by Griffith and Aksamit,[37] the authors outlined that *M. massiliense* without an active *erm* gene is responsive to macrolide treatment, and that the primary mechanism of macrolide resistance is acquired mutational resistance. This is noteworthy as it is inevitable that some patients treated with macrolide monotherapy will develop resistance and become treatment-refractory.

The pharmacokinetic and pharmacodynamic indices of MAC therapy are often suboptimal, although currently there is no correlation with treatment outcome and no demonstrated correlation between circulating MAC drug levels and treatment outcome. There is also no correlation between MIC for *rmp/emb/stm* and response to therapy and no MIC cut-offs designating susceptible and resistant MAC strains for any antibiotics other than macrolides and amikacin. Additionally, inappropriate dependence on *in vitro* susceptibility results may have adverse

consequences. Macrolides and amikacin treatment success for MAC correlates with *in vitro* MIC; with macrolides the susceptible MIC is ≤8 µg/mL and resistance MIC is ≥32 µg/mL, and with amikacin the susceptible MIC is ≤64 µg/mL and resistance MIC is >64 µg/mL.

The ATS guidelines on NTM recommend the following for NTM-LD for ≥12 months with sputum culture negativity on therapy:[28]

- NB disease: macrolide/ethambutol/rifamycin; intermittent
- Cavitary disease: macrolide/EMB/rifamycin ± injectable; daily
- Severe or previously treated disease: macrolide/EMB/rifamycin/injectable; daily
- Surgery for selected patients

Current treatment strategies for MAC-LD include a combination of rifampicin, ethambutol, azithromycin, and clarithromycin with the addition of IV amikacin or ≤3 months nebulised amikacin for severe cases. Antibiotic treatment should continue for ≥12 months after culture conversion (unpublished data). Treatment of *M. abscessus* LD should involve an initial phase of ≥1 month of IV amikacin, IV tigecycline, and, where tolerated, IV imipenem plus oral macrolide followed by a continuation phase of nebulised amikacin, oral macrolide, and 1–3 oral antibiotics guided by drug susceptibility and patient tolerance. Despite use of these regimens, mortality remains high, with a 5-year all-cause mortality reported between 23–70% in a variety of retrospective cohort studies of different mycobacterial species.[38-41] In addition to the high mortality rates, significant numbers of patients remain refractory with continued isolation of mycobacteria. The highest culture conversion success rates are generally with *M. kansasii*, and the worst outcomes for *Mycobacterium xenopi* or *M. abscessus*. A recent meta-analysis of 16 studies and 1,462 patients suggested a sustained conversion rate of 60% in MAC-LD.[42,43]

A retrospective single-centre study aimed to validate the appropriateness of current treatment for MAC-LD. In total, 180 patients with NB-LD completed >12 months of macrolide/azalide multidrug therapy. Sputum conversion to culture-negativity occurred in 86% of patients, with no differences between clarithromycin or azithromycin regimens. Treatment regimen modification occurred more frequently with daily (80%) versus intermittent (1%) therapy. Microbiological recurrences during therapy occurred in 14% of patients: 73% with reinfection MAC isolates and 27% with true relapse isolates. Overall treatment success was achieved in 84% of patients. Following completion of therapy, microbiological recurrences occurred in 48%: 75% reinfection isolates and 25% true relapse isolates.[44] A similar study in South Korea of 217 patients with NB MAC-LD found that rates of symptomatic improvement, radiographic improvement, and sputum culture conversion were not different between daily therapy and intermittent therapy (75% versus 82%, 68% versus 73%, and 76% versus 67%, respectively). Modification of the initial antibiotic regimen occurred more frequently in the daily therapy group than in the intermittent therapy group (46% versus 21%).[45]

Overall, current guidelines for macrolide/azalide-based regimens for NB MAC-LD show favourable microbiological outcomes and do not promote macrolide resistance. Daily and intermittent regimens are equally effective, although intermittent regimens have fewer side effects. Microbiological recurrences are common and mostly due to unique MAC genotypes. However, there is a lack of adherence to guidelines in the USA, Europe, and Japan.[46,47]

Cavitary *Mycobacterium Avium* Complex Nontuberculous Mycobacterium Lung Disease

Cavitary MAC NTM-LD is a smoking COPD-related disease that is likely associated with long-term respiratory impairment and requires aggressive therapy. Appropriate therapy includes parenteral agents, surgery, smoking cessation, and avoidance of macrolide resistance. Patients should be advised that smoking during treatment can inhibit a favourable treatment response.

A National Institutes of Health (NIH) study of mortality among patients with NTM-LD demonstrated that FCD and pulmonary hypertension (PH) were significant risk factors for death in NTM-LD. Median survival for patients with FCD was 9.0 years versus 13.1 years with no FCD (p=0.006), and 6.8 years for patients with PH versus >18 years for those without PH (p=0.048).[48]

Surgery for Nontuberculous Mycobacterium Lung Disease

Surgery is indicated for NTM-LD if medication is unresponsive (due to resistance or large cavities) or if the patient has uncontrolled symptoms, haemoptysis, or highly damaged lung tissue.

The Nontuberculous Mycobacterium Lung Disease Drug Pipeline

New drugs for NTM-LD should be tested using sputum conversion, duration of therapy, and symptomatic improvement as endpoints. Currently, liposomal amikacin inhalation (LAI) is under investigation for the treatment of NTM-LD and the U.S. Food and Drug Administration (FDA)-approved drugs (bedaquiline, linezolid, tedizolid, clofazimine) are being studied for potential use.

There is some evidence that a proportion of patients with stable NTM-LD do not require treatment and culture-convert spontaneously. In an observational study by Hwang et al.,[49] 93 patients (out of 420) with MAC-LD were untreated and followed up for a median of 5.6 years. Of these patients, 51.6% showed spontaneous sputum conversion.

Nebulised Amikacin

A study of nebulised amikacin in 20 patients with MAC or *M. abscessus* suggested some response to therapy, with 5 patients demonstrating negative cultures after treatment.[50]

Liposomal Amikacin Inhalation

In a Phase II study, the efficacy and safety of LAI 590 mg once-daily versus placebo was assessed for 84 days with an additional open-label treatment period of 84 days. The primary endpoint was reduction in NTM growth by semi-quantitative sputum cultures. The primary endpoint was not achieved, although a greater proportion of patients in the LAI group demonstrated ≥1 negative sputum culture (32% versus 9%; p=0.006) and improvement in 6-minute-walk test at Day 84. Most adverse events were respiratory (hoarseness and bronchospasm) and led to drug discontinuation in some patients. Of those who achieved culture conversion after 3–6 months of LAI, 82.4% had negative sputum culture at 12 months after LAI discontinuation.[11]

The Phase III CONVERT study of LAI therapy enrolled 336 patients with NTM-LD caused by MAC who were treatment refractory for ≥6 months of guideline-based therapy (GBT). Top line results have been released that show the primary endpoint, culture conversion, was met (29% LAI + GBT versus 9% GBT-placebo; p<0.0001).[51]

Bedaquiline

Bedaquiline is a drug used to treat TB and has been investigated for potential use in NTM-LD. A study of untreated MAC isolates MIC_{90} with bedaquiline 0.004–0.008 µg/mL using Clinical and Laboratory Standards Institute methods demonstrated no difference between *M. avium* and *Mycobacterium intracellulare*.[52] Preliminary results of an open case series of off-label bedaquiline use in 10 patients with MAC or *M. abscessus* LD showed some symptomatic benefit; however, microbiological and radiological outcomes were mixed.[53]

Linezolid and Tedizolid

Linezolid is indicated in the British Thoracic Society (BTS) guidelines for possible use against *M. abscessus* disease, although clinical evidence of efficacy is lacking. One study assessed the tolerability of linezolid for NTM-LD; cytopenia, peripheral neuropathy, and optic neuropathy were identified as significant adverse events.[54]

In a further study, the potency of tedizolid was compared with linezolid using *in vitro* testing of 170 NTM isolates, including resistant strains. Tedizolid demonstrated a greater *in vitro* potency compared with linezolid (Table 2), which indicated its use as a potential treatment for NTM infections.[55]

Table 2: *In vitro* susceptibility results of tedizolid against nontuberculous mycobacterium.[55]

Linezolid		Tedizolid	
MAA	32 µg/mL	MAA	8 µg/mL
MAM	32 µg/mL	MAM	4 µg/mL
MAC	32 µg/mL	MAC	8 µg/mL
Mycobacterium simiae	64 µg/mL	*Mycobacterium simiae*	8 µg/mL

MAA: *Mycobacterium abscessus* subspecies *abscessus*; MAC: *Mycobacterium avium* complex; MAM: *M. abscessus* subspecies *massiliense*.

Clofazimine-containing regimens have been shown to be effective when compared with rifampin-containing regimens for the treatment of MAC-LD in a study of 107 patients and may be a suitable alternative.[56]

Other Strategies

In addition to new drugs, different treatment paradigms may be needed to improve treatment success. Presently, treatment is advised for 1 year following culture conversion. Despite apparent treatment success, high relapse and reinfection rates ≤48% have been reported.[44] It is possible that longer treatment periods may be needed for patients with higher relapse rates (such as those with cavitary disease) or prophylactic treatment post eradication may reduce the risk of reinfection. NTM are ubiquitous in the environment, so preventing exposure is challenging; however, certain cleaning regimens may be more effective at environmental eradication of NTM.

An increase in precision medicine and targeting specific treatments to certain individuals is likely to occur in the future. For example, patients with specific predispositions or susceptibilities to NTM-LD may benefit from a treatment approach that addresses the host in addition to the microbe, such as with the use of immunomodulators. Additionally, as we learn more about the microbes with technologies such as sequencing, treatments directly affecting virulence targets, biofilms, and the microbiome are likely to develop.

The Natural History of Untreated Nontuberculous Mycobacterium Lung Disease: A Global Perspective

Doctor Won-Jung Koh

The natural history of untreated pulmonary TB was studied in 126 AFB smear-positive patients in South India from 1961–1968 when no treatment was available. At the end of the study, 49% of patients had died, 18% had chronic disease, and 33% were cured without treatment.[57] This study was not powered to detect NTM; however, more recent studies have provided better understanding of the natural history of NTM-LD.

MAC (*M. avium* and *M. intracellulare*) and *M. abscessus* complex (MABC) (*M. abscessus* and *M. massiliense*) are the most common causes of NTM-LD (approximately 90% of cases); therefore, natural history studies have focussed on these four pathogens. Fibrocavitary NTM-LD is typically caused by *M. intracellulare* and *M. massiliense* and patients are generally middle-aged/elderly males with underlying pulmonary disorders such as COPD and TB. Chest X-ray and CT scans show thin-walled apical cavity in the upper lobes of the lung, which, if left untreated, can progress in 1–2 years to cause extensive lung damage and death. NB NTM-LD is typically caused by *M. intracellulare* and patients are generally middle-aged/elderly females without underlying pulmonary disorders, who do not smoke. A high-resolution CT scan shows multiple small nodules (<5 mm) and bronchiectasis in both lungs, and the course of disease is indolent with slow progression.

Mycobacterium Avium Complex Lung Disease Mortality

In a retrospective study of 634 Japanese patients with MAC-LD, 76%, 21%, and 3% had NB-LD, fibrocavitary LD, or other forms of NTM-LD, respectively. Kaplan-Meier curves of all-cause mortality according to radiographic features showed that the survival rate of patients with FCD was significantly lower than those with NB-LD or other forms of NTM-LD ($p<0.001$).[40] In a similar study of 782 patients with NB MAC-LD, 85% had non-cavitary disease and 15% of patients had cavitary disease. Ten-year survival rates were significantly lower for patients with cavitary disease (25%) compared with those without cavitary disease (0.8%); ($p<0.001$).[58] Taken together, these results demonstrate that cavitation is an important prognostic factor in both FCD and NB-LD.

Nontuberculous Mycobacterium Lung Disease Treatment Decision

The ATS guidelines state that a diagnosis of NTM-LD does not necessarily lead to the initiation of treatment; they recommend that the decision to initiate treatment for patients with NTM-LD should be based on risk-to-benefit analysis that takes into account patient symptoms, radiographic findings (such as severity and progression), and microbiological results versus the adverse effects of multiple potentially toxic drugs.[28] In clinical practice, the proportion of patients who receive treatment for NTM-LD varies according to the country: population-based studies in the USA, the Netherlands, and Germany found that 19%, 57%, and 75% of patients received treatment, respectively.[6,59,60]

Mycobacterium Avium Complex Lung Disease and *Mycobacterium Abscessus* Complex Lung Disease Progression

Hospital-based studies evaluating progression of MAC-LD (defined as initiation of therapy) showed that 43% of 392 patients in the USA were started on treatment,[61] 53% of 72 patients with NB-LD in Japan showed progressive disease on chest X-ray at 10 years follow-up,[62] and 51% of 67 patients with NB-LD in South Korea had progressive disease at 5-year follow-up.[63] In these patients, risk factors for progression included low BMI, cavitation, and extensive involvement of lung segments on CT scans.[62,63]

In a South Korean hospital-based study of 590 patients with newly diagnosed MAC-LD, 55% of patients had *M. avium* LD and 45% had *M. intracellulare* LD. Of those with *M. avium* LD, 45% received treatment within 3 years, compared with 65% of those with *M. intracellulare* LD. Risk factors for progression were FCD, positive AFB smear, and *M. intracellulare* LD.[64] In another study from South Korea, 63% of 488 patients with MAC-LD received treatment within 3 years of diagnosis. In these patients, risk factors for progression included low BMI, systemic symptoms, FCD, positive AFB smear, and extensive disease. In total, 24% of patients did not receive treatment for ≥3 years following diagnosis, of whom 5% received treatment after 3 years of stable disease and 19% did not receive any treatment. Of those who received no treatment after 3 years, 52% had spontaneous negative culture conversion (representative of 10% of the full study population). Factors associated with spontaneous culture conversion were high BMI, negative AFB smear, and transient anti-TB medication for at least 1 month.[49] A similar study in Taiwan retrospectively enrolled 450 patients with MAC-LD who had ≥2 positive sputum cultures. In total, 126 patients received microbiological follow-up, of which 60% had consistent positive culture and 40% had negative culture (representative of 11% of the full study population). Interestingly, only 12% of the study population received treatment, so the majority of negative conversions occurred without treatment. Factors associated with microbiological persistence included low BMI and positive AFB smear; conversely, factors associated with spontaneous negative culture conversion included high BMI and negative AFB smear.[65] In a South Korean study of 1,021 patients with newly diagnosed non-cavitary NB MAC-LD or MABC-LD, 55% and 45% of patients were treated and untreated, respectively. Of those who were untreated, 65% had persistent positive culture, compared with 35% who had spontaneous negative culture conversion (representative of 15% of the full study population) (unpublished data).

Studies evaluating progression of MABC-LD, which was defined as initiation of therapy, showed that ≤47% of patients in South Korea[14,66] and ≤55% of patients in Taiwan[67,68] received treatment. The clinical outcomes of MAC and MABC-LD are very similar; as demonstrated in a hospital-based study in South Korea that followed 150 patients with NTM-LD (73% MAC, 21% MABC). Findings showed that there was no difference in 3-year progression rate (approximately 42%) between the two patient groups.[69] Laboratory studies have suggested that there is an association between mycobacterial genotypes and disease progression,[70-72] which could be useful for predicting the clinical course following diagnosis; however, genomic analysis is not available in routine clinical practice in most countries.

In summary, clinical studies report that approximately 40–60% of patients with MAC or MABC-LD are treated within 3 years of diagnosis and 40–60% are untreated. The most commonly reported risk factors associated with progression or treatment initiation are poor nutritional status (low BMI), increased disease severity (cavitary and extensive disease), and high bacterial burden (positive AFB smear). Between 35% and 50% of untreated patients (10–15% of all initially diagnosed patients) have spontaneous negative culture conversion, which is associated with a high BMI and low bacterial burden. Overall, the decision to treat NTM-LD should be based on the individual patient and the risks and benefits of treatment; those with cavitary disease should be treated following diagnosis, whereas those with non-cavitary disease should be assessed further to ascertain if treatment is necessary (general and nutritional conditions, symptoms, chest X-ray and CT scans, and bacterial burden).

REFERENCES

1. Hoefsloot W et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: An NTM-NET collaborative study. Eur Respir J. 2013;42(6):1604-13.

2. Hermansen TS et al. Nontuberculous mycobacteria in Denmark, incidence and clinical importance during the last quarter-century. Sci Rep. 2017;7(1):6696.

3. Ringshausen FC et al. Burden and trends of hospitalisations associated with pulmonary non-tuberculous mycobacterial infections in Germany, 2005-2011. BMC Infect Dis. 2013;13:231.

4. Adjemian J et al. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med. 2012;185(8):881-6.

5. Ringshausen FC et al. Prevalence of nontuberculous mycobacterial pulmonary disease, Germany, 2009-2014. Emerg Infect Dis. 2016;22(6):1102-5.

6. Diel R et al. Burden of non-tuberculous mycobacterial pulmonary disease in Germany. Eur Respir J. 2017;49(4).

7. Peter-Getzlaff S et al. Detection and identification of Mycobacterium spp. in clinical specimens by combining the Roche Cobas Amplicor Mycobacterium tuberculosis assay with Mycobacterium genus detection and nucleic acid sequencing. J Clin Microbiol. 2010; 48(11):3943-8.

8. Tanaka E et al. Effect of clarithromycin regimen for Mycobacterium avium complex pulmonary disease. Am J Respir Crit Care Med. 1999;160(3):866-72.

9. Chaisson RE et al. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic Mycobacterium avium complex disease in patients with HIV infection. AIDS. 1997; 11(3):311-7.

10. Brown-Elliott BA et al. In vitro activity of amikacin against isolates of Mycobacterium avium complex with proposed MIC breakpoints and finding of a 16S rRNA gene mutation in treated isolates. J Clin Microbiol. 2013;51(10): 3389-94.

11. Olivier KN et al. Randomized trial of liposomal amikacin for inhalation in nontuberculous mycobacterial lung disease. Am J Respir Crit Care Med. 2017; 195(6):814-23.

12. Wallace RJ Jr. et al. Treatment of nonpulmonary infections due to Mycobacterium fortuitum and Mycobacterium chelonei on the basis of in vitro susceptibilities. J Infect Dis. 1985;152(3):500-14.

13. Jarand J et al. Clinical and microbiologic outcomes in patients receiving treatment for Mycobacterium abscessus pulmonary disease. Clin Infect Dis. 2011;52(5):565-71.

14. Jeon K et al. Antibiotic treatment of Mycobacterium abscessus lung disease: A retrospective analysis of 65 patients. Am J Respir Crit Care Med. 2009;180(9): 896-902.

15. Weycker D et al. Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. Chron Respir Dis. 2017: 1479972317709649.

16. Cole PJ. Inflammation: A two-edged sword--the model of bronchiectasis. Eur J Respir Dis Suppl. 1986;147:6-15.

17. Aliberti S et al. Research priorities in bronchiectasis: A consensus statement from the EMBARC Clinical Research Collaboration. Eur Respir J. 2016;48(3):632-47.

18. Chalmers JD et al. The EMBARC European Bronchiectasis Registry: Protocol for an international observational study. ERJ Open Res. 2016;2(1).

19. Wickremasinghe M et al. Non-tuberculous mycobacteria in patients with bronchiectasis. Thorax. 2005;60(12): 1045-51.

20. Fowler SJ et al. Nontuberculous mycobacteria in bronchiectasis: Prevalence and patient characteristics. Eur Respir J. 2006;28(6):1204-10.

21. Bilton D. Update on non-cystic fibrosis bronchiectasis. Curr Opin Pulm Med. 2008;14(6):595-9.

22. Chu H et al. Prevalence of nontuberculous mycobacteria in patients with bronchiectasis: A meta-analysis. Arch Med Sci. 2014;10(4):661-8.

23. Faverio P et al. Characterizing non-tuberculous mycobacteria infection in bronchiectasis. Int J Mol Sci. 2016;17(11).

24. Máiz L et al. Prevalence and factors associated with nontuberculous mycobacteria in non-cystic fibrosis bronchiectasis: A multicenter observational study. BMC Infect Dis. 2016;16(1):437.

25. Aliberti S et al. Quality standards for the management of bronchiectasis in Italy: A national audit. Eur Respir J. 2016;48(1):244-8.

26. Kunst H et al. Nontuberculous mycobacterial disease and Aspergillus-related lung disease in bronchiectasis. ur Respir J. 2006;28(2):352-7.

27. Bienvenu T et al. Cystic fibrosis transmembrane conductance regulator channel dysfunction in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2010;181(10):1078-84.

28. Griffith DE et al. An official ATS/ IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.

29. Kendall BA et al. Isolation of non-tuberculous mycobacteria from the sputum of patients with active tuberculosis. Int J Tuberc Lung Dis. 2010; 14(5):654-6.

30. Dean AS et al. Sputum smear microscopy result: A predictor for drug-resistant tuberculosis? Int J Tuberc Lung Dis. 2016;20(7):864-5.

31. Khann S et al. Linkage of presumptive multidrug resistant tuberculosis (MDR-TB) patients to diagnostic and treatment services in Cambodia. PLoS One. 2013;8(4):e59903.

32. Martiniano SL et al. Clinical significance of a first positive nontuberculous mycobacteria culture in cystic fibrosis. Ann Am Thorac Soc. 2014;11(1):36-44.

33. Griffith DE et al. The significance of Mycobacterium abscessus subspecies abscessus isolation during Mycobacterium avium complex lung disease therapy. Chest. 2015;147(5): 1369-75.

34. Limper AH et al. An official American Thoracic Society statement: Treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med. 2011;183(1):96-128.

35. Schwiesow JN et al. Concomitant use of voriconazole and rifabutin in a patient with multiple infections. Pharmacotherapy. 2008;28(8):1076-80.

36. Koh WJ et al. Oral macrolide therapy following short-term combination antibiotic treatment of Mycobacterium massiliense lung disease. Chest. 2016; 150(6):1211-21.

37. Griffith DE, Aksamit TR. Nontuberculous mycobacterial disease therapy: Take it to the limit one more time. Chest. 2016;150(6):1177–8.

38. Andrejak C et al. Mycobacterium xenopi pulmonary infections: A multicentric retrospective study of 136 cases in north-east France. Thorax. 2009; 64(4):291-6.

39. Andrejak C et al. Nontuberculous pulmonary mycobacteriosis in Denmark: Incidence and prognostic factors. Am J Respir Crit Care Med. 2010;181(5):514-21.

40. Hayashi M et al. Prognostic factors of 634 HIV-negative patients with Mycobacterium avium complex lung disease. Am J Respir Crit Care Med. 2012; 185(5):575-83.

41. Griffith DE et al. Clinical and molecular analysis of macrolide resistance in Mycobacterium avium complex lung disease. Am J Respir Crit Care Med. 2006; 174(8):928-34.

42. Diel R et al. Microbiological and clinical outcomes of treating non-mycobacterium avium complex nontuberculous mycobacterial pulmonary disease: A Systematic Review and Meta-Analysis. Chest. 2017;152(1): 120-42.

43. Kwak N et al. Treatment outcomes of mycobacterium avium complex lung disease: A systematic review and meta-analysis. Clin Infect Dis. 2017. [Epub ahead of print].

44. Wallace RJ Jr. et al. Macrolide/Azalide therapy for nodular/bronchiectatic mycobacterium avium complex lung disease. Chest. 2014;146(2):276-82.

45. Jeong BH et al. Intermittent antibiotic therapy for nodular bronchiectatic Mycobacterium avium complex lung disease. Am J Respir Crit Care Med. 2015; 191(1):96-103.

46. Adjemian J et al. Lack of adherence to evidence-based treatment guidelines for nontuberculous mycobacterial lung disease. Ann Am Thorac Soc. 2014;11(1): 9-16.

47. van Ingen J et al. Poor adherence to management guidelines in nontuberculous mycobacterial pulmonary diseases. Eur Respir J. 2017;49(2).

48. Fleshner M et al. Mortality among patients with pulmonary non-tuberculous mycobacteria disease. Int J Tuberc Lung Dis. 2016;20(5):582-7.

49. Hwang JA et al. Natural history of Mycobacterium avium complex lung disease in untreated patients with stable course. Eur Respir J. 2017;49(3).

50. Olivier KN et al. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. Ann Am Thorac Soc. 2014;11(1):30-5.

51. Insmed. Insmed announces positive top-line results from Phase 3 CONVERT study of ALIS (Amikacin Liposome Inhalation Suspension) in adult patients with treatment-refractory nontuberculous mycobacterial (NTM) lung disease caused by mycobacterium avium complex (MAC). September 5, 2017. Available at: http://investor.insmed.com/releasedetail.cfm?releaseid=1039069. Last accessed: 26 September 2017.

52. Brown-Elliott BA et al. In vitro susceptibility testing of bedaquiline against Mycobacterium avium complex. Antimicrob Agents Chemother. 2017;61(2).

53. Philley JV et al. Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. Chest. 2015; 148(2):499-506.

54. Winthrop KL et al. The tolerability of linezolid in the treatment of nontuberculous mycobacterial disease. Eur Respir J. 2015;45(4):1177-9.

55. Brown-Elliott BA et al. In vitro susceptibility testing of tedizolid against nontuberculous mycobacteria. J Clin Microbiol. 2017;55(6):1747-54.

56. Jarand J et al. Long-term follow-up of Mycobacterium avium complex lung disease in patients treated with regimens including clofazimine and/or rifampin. Chest. 2016;149(5):1285-93.

57. Tuberculosis in a rural population of South India: A five-year epidemiological study. Bull World Health Organ. 1974; 51(5):473-88.

58. Gochi M et al. Retrospective study of the predictors of mortality and radiographic deterioration in 782 patients with nodular/bronchiectatic Mycobacterium avium complex lungdisease. BMJ Open. 2015; 5(8):e008058.

59. Prevots DR et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am J Respir Crit Care Med. 2010;182(7):970-6.

60. van Ingen J et al. Clinical relevance of non-tuberculous mycobacteria isolated in the Nijmegen-Arnhem region, The Netherlands. Thorax. 2009;64(6):502-6.

61. Boyle DP et al. Comparison of clinical features, virulence, and relapse among Mycobacterium avium complex species. Am J Respir Crit Care Med. 2015;191(11):1310-7.

62. Kitada S et al. Long-term radiographic outcome of nodular bronchiectatic Mycobacterium avium complex pulmonary disease. Int J Tuberc Lung Dis. 2012;16(5):660-4.

63. Kim SJ et al. Risk factors for deterioration of nodular bronchiectatic Mycobacterium avium complex lung disease. Int J Tuberc Lung Dis. 2014; 18(6):730-6.

64. Koh WJ et al. Clinical significance of the differentiation between Mycobacterium avium and M ycobacterium intracellulare in M avium complex lung disease. Chest. 2012;142(6): 1482-8.

65. Pan SW et al. Microbiological persistence in patients with Mycobacterium avium complex lung disease: The predictors and the impact on radiographic progression. Clin Infect Dis. 2017;65(6):927-34.

66. Lyu J et al. Outcomes in patients with Mycobacterium abscessus pulmonary disease treated with long-term injectable drugs. Respir Med. 2011;105(5):781-7.

67. Huang YC et al. Clinical outcome of Mycobacterium abscessus infection and antimicrobial susceptibility testing. J Microbiol Immunol Infect. 2010;43(5): 401-6.

68. Lee MR et al. Risk factors for Mycobacterium chelonae-abscessus pulmonary disease persistence and deterioration. J Infect. 2012;64(2):228-30.

69. Kim SJ et al. Characteristics associated with progression in patients with of nontuberculous mycobacterial lung disease: A prospective cohort study. BMC Pulm Med. 2017;17(1):5.

70. Kikuchi T et al. Association between mycobacterial genotypes and disease progression in Mycobacterium avium pulmonary infection. Thorax. 2009; 64(10):901-7.

71. Uchiya KI et al. Comparative genome analyses of Mycobacterium avium reveal genomic features of its subspecies and strains that cause progression of pulmonary disease. Sci Rep. 2017;7:39750.

72. Shin SJ et al. Mycobacterial genotypes are associated with clinical manifestation and progression of lung disease caused by Mycobacterium abscessus and Mycobacterium massiliense. Clin Infect Dis. 2013;57(1): 32-9.

CELLULAR STRUCTURE OF THE INDUCED SPUTUM IN THE COMBINATION OF BRONCHIAL ASTHMA AND OBESITY IN PATIENTS OF A YOUNG AGE

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Keywords: Bronchial asthma, obesity, induced sputum, neutrophilic inflammation, biophenotype.

According to the World Health Organization (WHO), obesity is approaching pandemic levels. It has now been indisputably proven that obesity increases the risk of developing bronchial asthma and worsens patients' control over their condition. Simultaneously, an unmanageable phenotype with implications of dependence on a dose or resistance to inhaled glucocorticosteroids is formed. Today, studying the cellular structure of the induced sputum, as an effective, non-invasive method of assessment of inflammation in a bronchial tree, is of particular importance. The aim of this study was to estimate the changes in cellular structure in the induced sputum of young patients with bronchial asthma and the relationship between structures and BMI.

MATERIAL AND METHODS

The study examined 164 patients with asthma of varying severity; subjects ranged from 18–44 years of age and were divided into two groups, dependent on BMI. Group 1 included patients with a BMI of 18–25 kg/m^2 and Group 2 had a BMI of 30–40 kg/m^2. The control group included 40 healthy volunteers. The study assessed the existence of excess weight and degree of obesity, the parameters of respiratory function, and the cellular structure of the induced sputum.

RESULTS

Obesity and asthma were found to coexist, with obese patients experiencing moderate-to-severe asthma ($p<0.001$). In this group, bronchial obstruction expression was more significant when compared with patients from Group 1 ($p<0.05$). It was shown that obesity is interconnected with the depression of forced expiratory volume in 1 second/forced vital capacity, and the increase of residual volume (RV), RV/total lung capacity, and resistance of respiratory tracts on exhalation, in comparison with the control group ($p=0.004$). Analysis of peripheral blood indicated a higher content of neutrophils in obese patients ($p<0.05$). The analysis of cellular structure of the induced sputum showed prevalence of eosinophilic inflammation in Group 1, whereas Group 2 patients more often expressed a paucigranulated biotype.

In patients with mild bronchial asthma and a BMI of <25 kg/m^2, nearly one-quarter of patients (23%) had paucigranulated inflammation biotype, and the majority (77%) were treated for eosinophilic inflammation. In patients with moderate bronchial asthma from this group, the analysis of cellular structure of the induced sputum was characterised by almost equal separation of eosinophilic (55%) and paucigranulated (45%) biotypes. Patients with severe asthma were observed to also have eosinophilic inflammation.

Among patients from Group 2, the paucigranulated endotype was registered in 99% of patients with mild asthma, 67% of patients with moderate asthma, and 40% with severe asthma. In severe asthma cases with obesity, 60% expressed neutrophilic inflammation. Thus, the severity of bronchial asthma in combination with obesity is associated with the heterogeneity of inflammation biophenotypes. Furthermore, the maintenance of neutrophils increases with statistical significance, parallel to the severity of asthma and the process of

bronchial obstruction. The increase of neutrophilic inflammation in patients with asthma and excess body weight aggravates the current disease, which is followed by reduced control over the disease, deterioration in bronchial permeability, and an increase of pulmonary hyperinflation.

VASCULAR ENDOTHELIAL GROWTH FACTOR INDUCES EXTRACELLULAR MATRIX SYNTHESIS AND FIBROBLAST ACTIVITY IN HUMAN LUNG FIBROBLASTS

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Keywords: Vascular endothelial growth factor (VEGF), chronic obstructive pulmonary disease (COPD), vascular remodelling, extracellular matrix (ECM), lung fibroblasts.

Pulmonary vascular remodelling is common in chronic lung disorders.[1] Alterations in vascular and parenchymal structures may impair gas exchange in alveoli, resulting in hypoxic conditions and systemic complications. Comorbidities in cardiovascular disease have negative impacts on clinical course and disease prognosis,[2] as discussed at the European Respiratory Society (ERS) congress. Nowadays, it is observed that mesenchymal cells, such as fibroblasts, have the potential to contribute to airway and vascular remodelling, as well as associated fibrosis.[3] Fibroblasts are key players in regulating the homeostasis of the extracellular matrix (ECM) by constituting a rich source of growth factors and inflammatory mediators, including vascular endothelial growth factor (VEGF).[4] VEGF is a key mediator in vascular remodelling processes, promoting angiogenesis, and is implicated in chronic obstructive pulmonary disease (COPD) progression.[1] Abnormal fibroblast activation may cause pathological tissue remodelling. We have previously shown that patients with COPD[5] and patients with bronchiolitis obliterans syndrome (BOS) (chronic lung allograft dysfunction after lung transplantation)[6] have an altered fibroblast phenotype. New treatment strategies are warranted to target vascular remodelling processes in chronic lung disorders.

The overall goal of our research was to find potential biomarkers and highlight the importance of the ECM for disease progression and treatment strategies towards personalised medicine.[7] In our abstract, we hypothesised that the vascular mediator VEGF could have an important effect on fibroblast function and ongoing remodelling processes. We investigated if there were differences in VEGF synthesis between distally derived lung fibroblasts from patients with severe COPD and patients with BOS, compared with healthy control subjects, as well as whether VEGF could be a biomarker for ongoing remodelling processes. We could not detect any significant differences in synthesis of VEGF from fibroblasts in patients with severe COPD compared to healthy control subjects; whereas, fibroblasts from patients with BOS had elevated levels of VEGF. Histological findings also indicated increased expression of VEGF receptor 2 in lung tissue from patients with BOS, compared to control subjects. We were interested to further understand the role of VEGF in fibroblast function and therefore evaluated how VEGF affected cell migration, proliferation, and ECM synthesis. Our obtained data indicated that the levels of VEGF synthesised by the pulmonary fibroblasts promoted migration and proliferation of the fibroblasts, and increased ECM synthesis

of the proteoglycans biglycan and perlecan.[8] These ECM proteoglycans are important for cell migration and basal membrane formation in vessels. We concluded that VEGF may have a crucial role in autocrine and paracrine signalling, such as between endothelial cells and fibroblasts, in remodelling processes in the distal lung compartments. However, further studies are needed to highlight the role of VEGF during disease progression and if VEGF could be a potential biomarker for ongoing remodelling processes.

REFERENCES

1. Harkness LM et al. Pulmonary vascular changes in asthma and COPD. Pulm Pharmacol Ther. 2014;29(2):144-55.
2. Faner R et al. Network medicine, multimorbidity and the lung in the elderly. Eur Respir J. 2014;44(3):775-88.
3. Postma DS, Timens W. Remodeling in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006; 3(5):434-9.
4. Burgess JK et al. The extracellular matrix - the under-recognised element in lung disease? J Pathol. 2016;240(4): 397-409.
5. Larsson-Callerfelt AK et al. Defective alterations in the collagen network to prostacyclin in COPD lung fibroblasts. Respir Res. 2013;14:21.
6. Andersson-Sjoland A et al. Fibroblast phenotypes and their activity are changed in the wound healing process after lung transplantation. J Heart Lung Transplant. 2011;30(8):945-54.
7. Woodruff PG et al. Current concepts in targeting chronic obstructive pulmonary disease pharmacotherapy: Making progress towards personalised management. Lancet. 2015; 385(9979):1789-98.
8. Westergren-Thorsson G et al. VEGF synthesis is induced by prostacyclin and TGF-β in distal lung fibroblasts from COPD patients and control subjects: Implications for pulmonary vascular remodelling. Respirology. 2017. [Epub ahead of print].

PATIENT AND PUBLIC INVOLVEMENT AND ITS VITAL ROLE IN THE TANDEM COPD STUDY: A RANDOMISED CONTROLLED TRIAL

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Keywords: Patient and public involvement (PPI), chronic obstructive pulmonary disease (COPD), cognitive behavioural therapy, anxiety, depression, pulmonary rehabilitation.

Chronic obstructive pulmonary disease (COPD) is a progressive, irreversible condition, characterised by symptoms of breathlessness, cough, sputum production, and fatigue; additionally, many patients suffer from anxiety and depression.[1,2] Anxiety can range from 10–50%[3] of patients; furthermore, people with severe COPD are 2.5-times more likely to develop depression compared to those with mild disease.[4] These comorbidities are associated with increased likelihood of exacerbations, more frequent and longer hospital admissions, and poor quality of life.[5,6] Pulmonary rehabilitation is an effective and cost-effective, but underutilised, treatment to reduce the burden of COPD.[7,8]

TANDEM (Tailored intervention for ANxiety and DEpression Management in COPD) is a UK multicentre randomised controlled study evaluating the effectiveness and cost-effectiveness of a cognitive behavioural approach intervention, that links and optimises the benefits of routine pulmonary rehabilitation, with the aim of reducing mild-to-moderate anxiety and/or depression in people with COPD.

Patient and public involvement (PPI) is when research is carried out with, or by, members of the public rather than 'to', 'about', or 'for' them.[9] In the UK, PPI is mandated in publicly funded research in order to make studies more effective and credible.[10] The aim of PPI in TANDEM was to involve patients with COPD and carers in the design and implementation of the study to improve the relevance and overall quality of the research.

METHODS

Potential advisors were identified via established patient networks and through promotion of TANDEM on social media outlets. Those who expressed interest were volunteer lung support groups affiliated to the British Lung Foundation (BLF) and a dedicated hospital-based PPI committee in Greater London and Leicestershire, UK. Prior to their engagement in the study, patients were given a brief presentation about the study and what it might involve. In the first 14 months we spent a total of 10.5 days on PPI activities.

RESULTS

PPI advisors (N=59) belong to two volunteer lung support groups, two exercise groups for patients with lung disease, and one dedicated PPI group. Advice was sought in groups or individually for different aspects of the research process.

Before the Study

- Invited to join the study steering group
- Invited to comment on a lay summary on the proposed research design, intervention, and terminology for the funding application

During the Study

- Provided advice on the personal and clear language used to describe the study and the design of the study leaflets used for study promotion among potential participants. Incorporating the words 'chronic bronchitis' and 'emphysema' in addition to COPD was suggested, as these are more recognisable terms, and replacing the description 'psychological therapy' with 'one-to-one sessions with a healthcare professional' was advised
- Assisted in planning the duration, frequency, and location of intervention delivery and provided examples for patient hand-outs on the meaning of anxiety and depression
- Piloted the outcome data collection. It was found that the average time to complete the study questionnaire was 35 minutes, and it was not burdensome to complete

The attendees at the European Respiratory Society (ERS) congress gave positive feedback regarding the visualised representation of how and where PPI activity was utilised in the study.

CONCLUSION/REFLECTION

Our PPI advisors contributed significantly to the design and implementation of the TANDEM study. The advisors will continue to be involved until study completion and results dissemination. Experiences at the ERS congress demonstrated that attendees recognised the importance and value of embedding PPI in research. Published PPI reporting checklists[10] may help researchers to design PPI for a study or to assess the use of PPI in their study.

REFERENCES

1. National Collaborating Centre for Chronic Conditions; Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Appendix D: Economics costs of COPD to the NHS. Thorax. 2004;59(Suppl 1):i192-4.

2. Cassidy S et al. Attendance at pulmonary rehabilitation classes: An exploration of demographic, physiological and psychological factors that predict completion of treatment. Chron Respir Dis. 2014;11(2):95-102.

3. Willgoss TG, Yohannes AM. Anxiety disorders in patients with COPD: a systematic review. Respir Care. 2013;58(8):858-66.

4. Cafarella PA et al. Treatments for anxiety and depression in patients with chronic obstructive pulmonary disease: A literature review. Respirology. 2012;17(4):627-38.

5. Ng TP et al. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med. 2007;167(1):60-7.

6. Laurin C et al. Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. Am J Respir Crit Care Med. 2012;185(9):918-23.

7. Bolton CE et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax. 2013;68(Suppl 2):ii1-30.

8. Hogg L et al. Effectiveness, attendance, and completion of an integrated, system-wide pulmonary rehabilitation service for COPD: Prospective observational study. COPD. 2012;9(5): 546-54.
9. INVOLVE. What is public involvment in research? 2017. Available at: http://www.invo.org.uk/find-out-more/what-is-public-involvement-in-research-2/. Last accessed: 19 September 2017.
10. Staniszewska S et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. BMJ. 2017;354:j3453.

THE RISK OF STROKE EVALUATED BY THE CHA_2DS_2-VASc SCALE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND CARDIOVASCULAR COMORBIDITY

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Keywords: Chronic obstructive pulmonary disease (COPD), scale CHA_2DS_2-VASc, risk of stroke, Charlson Comorbidity Index (CCI).

Chronic obstructive pulmonary disease (COPD), along with other respiratory problems, is accompanied by major cardiovascular comorbid conditions (hypertension, heart failure, atrial fibrillation). The risk of stroke in patients with atrial fibrillation is 5–7-times that of patients with sinus rhythm. Therefore, it is very important to assess the risk of stroke in COPD patients with cardiovascular comorbidities. The CHA_2DS_2-VASc scale has been used to predict stroke. The abbreviation of the scale name CHA_2DS_2-VASc is formed from the first letters of the risk factors: Congestive heart failure/left ventricle dysfunction, Hypertension, Age ≥75, Diabetes mellitus, Stroke/transient ischaemic attack/thromboembolism history, Vascular disease, Age 65–74, and Sex (female). Two points or more on the CHA_2DS_2-VASc scale means a high risk of stroke. It is important to quantify and objectively assess comorbidity. For this purpose, the Charlson Comorbidity Index (CCI) is widely used.

METHODS

A total of 215 COPD patients were examined. The investigated group comprised patients with a long experience of smoking. In the study group, men predominated (97%) and the average age of patients was 62.21±7.12 years. The risk of stroke was studied by the CHA_2DS_2-VASc scale.

RESULTS

Among the cardiovascular comorbidities, hypertension predominated (detected in 59% of patients with COPD). Atrial fibrillation was noted in 10.24% of patients. In the group of Stage 2 COPD patients with atrial fibrillation, the mean age was 63.50±7.02 years and the expected stroke rate for the year was 3.50±1.77. In the group of Stage 3–4 COPD patients with atrial fibrillation, the mean age was 66.18±7.05 years, and the expected stroke rate for the year 3.12±0.73. The CCI increased with worsening of the COPD stage.

CONCLUSION

A significant correlation was found between the stroke rate for the year (percentage measured by CHA_2DS_2-VASc scale) and the CCI (direct, strong connection; correlation coefficient: 0.89; $p<0.005$). A direct, strong relationship was established between the expected rate of strokes for the year and the number of cigarette packs smoked per year (correlation coefficient: 0.84; $p<0.005$).

RELATIONSHIP BETWEEN VITAMIN D AND SEVERITY IN COPD PATIENTS

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Keywords: Vitamin D, chronic obstructive pulmonary disease (COPD), infection, dyspnoea.

INTRODUCTION

Vitamin D deficiency is a common, underdiagnosed condition that has received increased attention around the world.[1] The Endocrine Society guidelines and the Institute of Medicine (IOM) recommend screening in populations at risk, as no evidence currently exists to support screening at a population level.[2] Candidates for vitamin D screening include those who are at a specific risk of vitamin D deficiency and patients who are experiencing, or are at risk of, specific medical conditions associated with hypovitaminosis D.[1,2] Decreased vitamin D levels strongly interact with different pathogenic mechanisms in chronic obstructive pulmonary disease (COPD).

METHODS

From September 2015 to August 2016, serum vitamin D was analysed and COPD Assessment Tests (CAT) were completed in a total of 55 patients. COPD patients can be categorised in different stages of severity, into mild, moderate, severe, and very severe disease, according to their forced expiratory volume in the first second (FEV_1) score.[3,4] Nowadays, COPD classification includes CAT, dyspnoea scale, and number of exacerbations the patient experiences per year.[3]

With the progressive loss of pulmonary function, patients become more prone to acute exacerbation[5] of their disease, which frequently requires hospitalisation, and may lead to respiratory failure and death,[6] as well as a faster decline in FEV_1.[7] The systemic consequences of Vitamin D deficiency appear when serum levels do not reach 30 ng/mL. Furthermore, vitamin D boosts the innate immune response upon infection. Vitamin D may control many pathways within pathogenic mechanisms.[6] It appears to act on innate immune cells and it can reduce the expression of toll-like receptors (TLR), which are critical in the induction of the early immune response and the priming of the adaptive immune system.[5,7] High levels of vitamin D are potent inhibitors of dendritic cell maturation, with lower expression levels of major histocompatibility complex (MHC) Class II molecules, downregulation of costimulatory molecules, and lower production of proinflammatory cytokines.[3]

RESULTS

The mean age was 66.44 (±11.86 years), with a total of 39 males and 16 females. The prevalence of vitamin D deficiency (<30 ng/mL) was 98.4%. Vitamin D average was 14.33 ng/mL in males and 14.4 ng/mL in females. There was an association between CAT D, the most severe score, and vitamin D (p=0.016).

CONCLUSION

There is a high prevalence of vitamin D deficiency in patients with COPD (98.4%). There was an association between CAT D and vitamin D (p=0.016). The question remains as to whether deficit or preventing adequate vitamin D supplementation can reverse the course of the disease. Vitamin D strongly interacts with different pathogenic mechanisms in COPD.[7] Prevalence of vitamin D deficiency is particularly high in COPD patients and increases with the severity of COPD. This finding may potentially be a way of preventing further deterioration of pulmonary function.

Reduced vitamin D levels may thus enhance proinflammatory pathways, reduce the downregulation of T cells, and impair the innate defence against bacteria and viruses, possibly leading to clinical disease onset and/or further pulmonary deterioration.[3] Randomised controlled trials are needed to explore the systemic consequences in the pathogenesis of COPD exacerbation/infections/deterioration.

REFERENCES

1. Holick M. High prevalence of vitamin D inadequacy and implications for Health. Mayo Clin Proc. 2006;81(3):353-73.
2. Millen AE, Bodnar LM. Vitamin D assessment in population-based studies: A review of the issues. Am J Clin Nutr. 2008; 87(4):1102S-5S.
3. Chalmers JD et al. Vitamin D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. Thorax. 2013;68(1):39-47.
4. Schwalfenberg G. Not enough vitamin D: Health consequences for Canadians. Can Fam Physician. 2007;53(5):841-54.
5. Hossein-nezhad A et al. Vitamin D for health: A global perspective. Mayo Clin Proc. 2013;88(7):720-55.
6. Niewoehner DE. The role of systemic corticosteroids in acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Med. 2002;1(4):243-8.
7. Donaldson GC, Wedzicha JA. The causes and consequences of seasonal variation in COPD exacerbations. Int J Chron Obstruct Pulmon Dis. 2014;9:1101-10.

IDENTIFICATION OF HIGH-RISK FACTORS FOR DEVELOPMENT OF ACTIVE TUBERCULOSIS IN CHILDREN WITH LATENT TUBERCULOSIS INFECTIONS

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Keywords: Latent tuberculosis infection (LTI), children, immunologic methods, tuberculosis (TB).

INTRODUCTION

Children with latent tuberculosis infection (LTI) represent a group of patients who are at risk of developing active tuberculosis (TB).[1-3] The use of new immunological tests, such as Diaskintest® (Generium Pharmaceutical, Moscow, Russia), which uses a recombinant tuberculosis allergen based on *Mycobacterium tuberculosis* specific proteins: ESAT-6 and CFP-10, and QuantiFERON® (Qiagen, Hilden, Germany), an immunological skin test, can improve diagnosis of LTI in children who have received the Bacillus Calmette–Guérin (BCG) vaccination.[4] The identification of risk factors for developing active TB in children with LTI is important for adequate maintenance of the disease. In a cohort retrospective-prospective study with multifactor analysis, we examined 624 children with LTI at 6 and 12 months and analysed risk factors for active TB development in these children.

METHODS

The St. Petersburg Research Institute of Phthisiopulmonology conducted a retrospective-prospective study during 2013–2016, involving 624 children (0–14 years old) with positive results from a tuberculin skin test and who had received the BCG vaccination. After complex diagnosis, 269 children were recognised as healthy, 127 (19.4%) children were diagnosed with LTI, and 258 (37.2%) were diagnosed with lung TB. We examined the children with LTI at both 6 and 12 months. The diagnostic complex included clinical assessment, immunological tests (Diaskintest), radiological methods including computed tomography (CT), and bacteriological methods. Multifactor analysis was applied to identify risk factors for children with LTI who were also at a high risk of developing active TB. Statistical analysis was performed by Statistic 7.0 and GraphPad Prism 6, and a chi-square test was used.

Table 1: Risk factors for developing active tuberculosis in children with latent tuberculosis infection.

Risk factors	OR	RR	95% CI	PV+	PV-
Low BMI	0.31	1.009	0.682–1.491	53.7	46.8
Non-effective BCG vaccination	0.63	0.793	0.502–1.292	43.2	45.5
Concomitant pathology	**1.95**	**1.364***	**1.044–1.781**	**71.4**	**54.4**
Low social status	1.23	1.121	0.640–1.234	63.0	60.9
TB contact	**3.40**	**1.553***	**1.191–2.023**	**78.6**	**59.4**
Lack of chemoprophylaxis	**2.53**	**1.458***	**1.090–1.949**	**71.7**	**60.0**

BCG: Bacillus Calmette–Guérin; BMI: body mass index; CI: confidence interval; OR: odds ratio; PV+: positive predictive test; PV-: negative predictive test; RR: relative risk; TB: tuberculosis.
*p<0.01 in comparison risk factors.

Table 2: Influence of risk factors for the development of active tuberculosis in children with latent tuberculosis infection.

Risk factors	Influence risk factors n (%)	RR	OR
TB contact (n=42)	32 (76.2)	0.7	3.2
Concomitant pathology (n=35)	26 (74.3)	0.7	2.8
Lack of chemoprophylaxis (n=66)	31 (46.9)	0.5	0.9

OR: odds ratio; RR: relative risk; TB: tuberculosis.

RESULTS

After observation, active lung TB was diagnosed in 76 (59.1%) children who had LTI at initial diagnosis; the relative risk (RR) was 0.6 and the chance of developing active disease (odds ratio [OR]) was 1.5. The analysis indicated the risk factors that could contribute to the development of TB in children with LTI. The most relevant high-risk factors for active TB development in children with LTI included the presence of comorbidities (OR: 1.95; RR: 1.36; 95% confidence interval [CI]: 1.044–1.781), close contact with TB patients (OR: 3.40; RR: 1.553; 95% CI: 1.191–2.023), and absence of chemoprophylaxis (OR: 2.53; RR: 1.458; 95% CI: 1.090–1.949) (Table 1).

With regard to the children who developed active TB at 12 months, the risk factors also included the presence of comorbidities (74.3%; OR: 3.2), close contact with TB patients (76.2%; OR: 2.8), and the absence of chemoprophylaxis (76.6%; OR: 0.9) (Table 2). There are different schemes of chemoprophylaxis which differ in duration (3 and 6 months), as well as in the combination of anti-tuberculosis drugs (isoniazid, isoniazid and pyrazinamide, and isoniazid and rifampicin). However, in 48.1% (n=61) of cases, the parents of children with LTI refused chemoprophylaxis on their child's behalf. Children who had a coincidence of comorbidities and close contact with TB patients developed active TB in 91.0% of cases.

CONCLUSION

From our study, we concluded that children with LTI with the presence of comorbidities, close contact with TB patients, and who did not receive chemoprophylaxis were at a high risk of developing active TB within 1 year.

REFERENCES

1. Venturini E et al. What steps do we need to take to improve diagnosis of tuberculosis in children? Expert Rev Anti Infect Ther. 2015;13(7):907-22.

2. Logsdon S et al. Successful rifampin desensitization in a pediatric patient with latent tuberculosis. Pediatr Allergy Immunol. 2014;25(4):404-5.

3. Amanatidou V et al. Latent tuberculosis infection in children: Diagnostic approaches. Eur J Clin Microbiol Infect Dis. 2012; 31(7):1285-94.

4. Starshinova A et al. The diagnosis of latent of latent tuberculosis infection in children with new immunologic tests. Eur Respir J. 2013;42(S57):603.

A CASE SERIES OF LONG-TERM AZITHROMYCIN THERAPY EFFECT ON EOSINOPHIL COUNT IN COPD

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Keywords: Chronic obstructive pulmonary disease (COPD), eosinophils, azithromycin.

INTRODUCTION

Long-term macrolide therapy is a treatment option in chronic obstructive pulmonary disease (COPD) patients with frequent exacerbations. Long-term azithromycin therapy in COPD patients can reduce COPD exacerbation frequency and improve quality of life.[1,2] However, treatment response is heterogenous and the modulation of inflammation by macrolides is not fully understood.

CASE SERIES

After an exceptional clinical response to macrolide therapy in a patient with COPD at our centre, it was noted that the peripheral blood eosinophil count (PBE) increased steadily while on macrolide therapy. Sputum mediator analysis using Luminex platforms (Luminex Corporation, Chicago, Illinois, USA) was performed on the same patient's sputum samples before, during, and after azithromycin therapy (Figure 1). During azithromycin therapy, interleukin (IL)-8, IL-17A, thymic stromal lymphopoietin, and tumour necrosis factor-alpha decreased, IL-5 and IL-33 increased, and there was not much change in IL-4 and IL-13 levels during azithromycin therapy.

A retrospective case series review of the effect of long-term macrolide therapy on PBE levels in COPD patients was performed. All COPD patients attending the COPD clinic at our Trust who started long-term macrolide therapy (azithromycin) in 2016 were included (N=16), and anonymised data was audited. The dose of azithromycin used was 250 mg three times a week (n=15) and 250 mg daily (n=1). The overall mean PBE increased during azithromycin therapy (mean change in mean PBE was 0.05; standard deviation: 0.18). There was no significant difference between sex (p=0.51), mean age (p=0.44), smoking status (p=0.66), and mean forced expiratory volume in the 1st second at the start of azithromycin therapy (p=0.55) between patients who had an overall increase in PBE and in those who had an overall decrease in PBE, although numbers were small. There was a reduction in the mean COPD exacerbation frequency in patients with a mean rise in PBE

during azithromycin therapy (decreased from 15.5 to 2.1 exacerbations per year). In the group of patients who had a mean decrease in PBE, there were inadequate data available on exacerbations.

DISCUSSION

COPD is typically associated with T helper 1 inflammation with a neutrophilic response, while asthma is characterised by T helper 2 (T2) inflammation,[3] although eosinophilic inflammation in COPD is recognised.[4] Eosinophilic inflammation is mainly propagated by T2 cytokines such as IL-4, IL-5, and IL-13. In the index case, during azithromycin therapy, IL-8, IL-17A, thymic stromal lymphopoietin, and tumour necrosis factor-alpha decreased, reflecting an overall decrease in the inflammatory burden. IL-5 and IL-33 increased during therapy, which was expected given the associated rise in eosinophils, and there was not much change in IL-4 and IL-13 levels during azithromycin therapy, although the baseline levels were elevated, possibly reflecting an alternative mechanism for T2 inflammation in COPD.

In COPD, a PBE <2% is associated with an increased risk of developing pneumonia independent of inhaled corticosteroid use,[5] and COPD patients with a PBE ≥2% have greater improvements in their health-related quality of life and faster recovery after receiving oral corticosteroids during an exacerbation, whilst inhaled corticosteroids decrease exacerbations at stable state.[6]

COPD is heterogeneous and inflammation can be variable.[3] Long-term azithromycin may affect the underlying inflammatory COPD phenotypes, suppressing the T helper 1 neutrophilic inflammation, with an increase in the T2 eosinophilic inflammation, possibly indicating more steroid-responsive disease; however, larger studies are required to further investigate this.

REFERENCES

1. Albert RK et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365(8):689-98.
2. Han MK et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. Am J Respir Crit Care Med. 2014;189(12):1503-8.
3. George L, Brightling CE. Eosinophilic airway inflammation: Role in asthma and chronic obstructive pulmonary disease. Ther Adv Chronic Dis. 2016;7(1):34-51.
4. Bafadhel M et al. Acute exacerbations of chronic obstructive pulmonary disease: Identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med. 2011;184(6):662-71.
5. Hogg JC et al. What drives the peripheral lung-remodeling process in chronic obstructive pulmonary disease? Proc Am Thorac Soc. 2009;6(8):668-72.
6. Bafadhel M et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease. A randomized placebo-controlled trial. Am J Respir Crit Care Med. 2012;186(1):48-55.

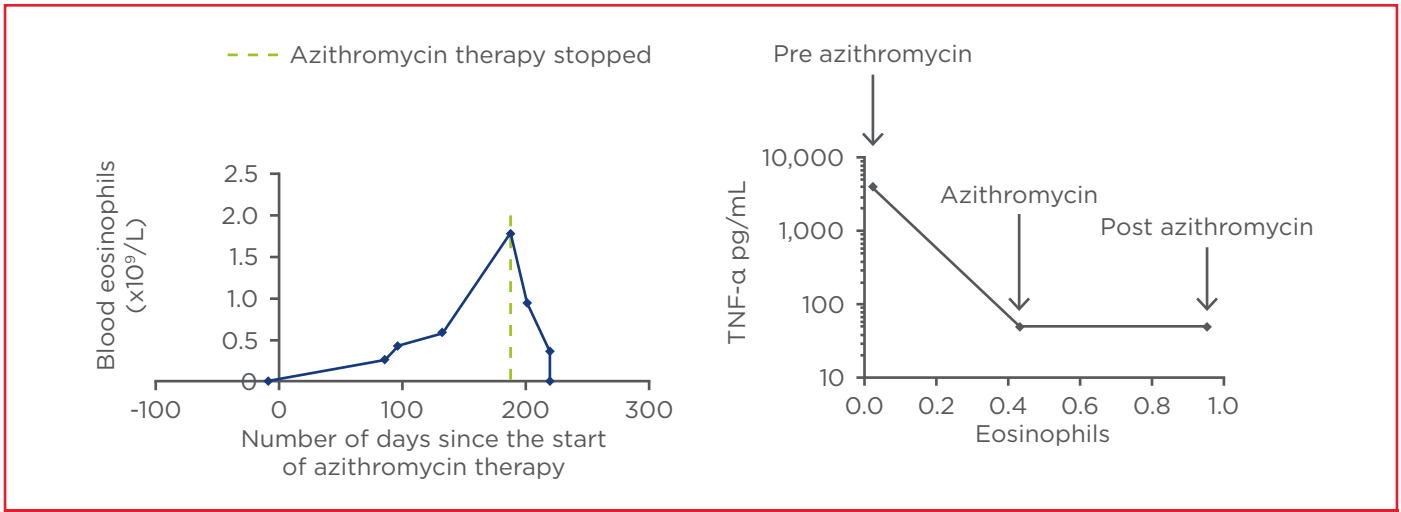

Figure 1: The results of the sputum mediator analysis using Luminex platforms performed on the index patient's sputum samples from before, during, and after azithromycin therapy.
TNF-α: tumour necrosis factor-alpha.

SILICOMYCOBACTERIOSIS: DIAGNOSIS AND PROGNOSIS, FOLLOW-UP AT 2.5 YEARS

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Keywords: Silicomycobacteriosis (SM), silicotuberculosis, computed tomography (CT), lung function, fibrobronchoscopy, cardiopulmonary haemodynamic.

One of the most serious complications of silicosis is mycobacteriosis, specifically tuberculosis and, although rare, conditions due to atypical mycobacterium. The incidence of tuberculosis in silicosis cases was 21.8-fold higher than in the general population.[1] Among 284 patients with silicosis at the Metallurgical Plant in the Kemerovo region, Russia, silicotuberculosis was present in 19.1% of cases.[2] The relationship between the changes in functional parameters and the type of exposure factor is not clear.

AIM

The aim of the study was to evaluate the factors contributing to silicomycobacteriosis (SM) manifestation during 2.5 years of observation.

MATERIALS AND METHODS

Among 250 patients with pneumoconiosis, 32 SM patients (12.8%; 30 with silicotuberculosis, 2 with SM due to atypical mycobacterium) were examined. Of those, 23 were men and 9 were women, the mean age was 61.1±1.7 years, and 36.7% were smokers. Ten of the patients worked as miners and 22 were foundry workers. In difficult diagnostic cases (n=15), the diagnosis was confirmed histologically. SM was the main primary diagnosis (81%). In four cases (13%), SM developed 10–45 years after the diagnosis of silicosis. In 2 patients, silicosis was developed in the presence of inactive tuberculosis. X-ray, computed tomography (CT), complex lung function examination, echocardiography, perfusion scintigraphy, and fibrobronchoscopy were performed. Nine patients received specific therapy (8 during the observation and 1 received a preventive course for >5 years following initial examination). Twelve patients were followed for 2.5±0.8 years (0.5–4.4 years).

RESULTS

SM was diagnosed 1.5±0.5 years after the observed X-ray changes. Fibrobronchoscopy revealed scar-pigmental changes (0.94), infiltration of the bronchial mucosa (0.06), and stenosis of the bronchi (0.33). Obstructive function disorders (0.44; 14/32) were more common than restrictive function disorders (0.19; 2/32; $p<0.05$). A reduced diffusing capacity of the lungs for carbon monoxide (DLCO) (0.29; 5/17), combined local-diffuse reduction of pulmonary perfusion (0.86; 6/7), pulmonary arterial hypertension (0.54; 16/24), and cor pulmonale (0.46; 11/24) were revealed. Predominant CT signs were: nodule (94%), reticular opacities (56%), and lymphadenopathy with calcifications (41%); rare signs included infiltration (13%) and cavity (6%). A follow-up study revealed stable lung volumes, while DLCO was decreased (Figure 1). Pulmonary arterial hypertension (0.75; 9/12) and cor pulmonale (0.83; 10/12; $p<0.05$) were detected in patients more often than at the first examination (0.42; 5/12 for both parameters), possibly as a result of the fibrosis progression. Anti-tuberculosis therapy led to positive X-ray dynamics (0.28) and stabilisation (0.42).

CONCLUSION

SM accounts for 12.8% of patients with pneumoconiosis and was the primary diagnosis in

81% of cases; it was also reported as a complication of silicosis caused by tuberculosis in 13% of cases. Preventive courses of specific treatment improve the prognosis of SM. Annual echocardiography and DLCO monitoring should be carried out to control SM progression.

REFERENCES

1. Farazi A, Jabbarias M. Silico-tuberculosis and associated risk factors in central province of Iran. Pan Afr Med J. 2015;20:333.

2. Zakharenkov VV et al. Peculiarities of silicotuberculosis in the workers of ferrous metallurgy enterprises. 2012. Available at: http://byulleten.com/en/2017/06/27/peculiarities-of-silicotuberculosis-in-the-workers-of-ferrous-metallurgy-enterprises/ [In Russian]. Last accessed: 21 September 2017.

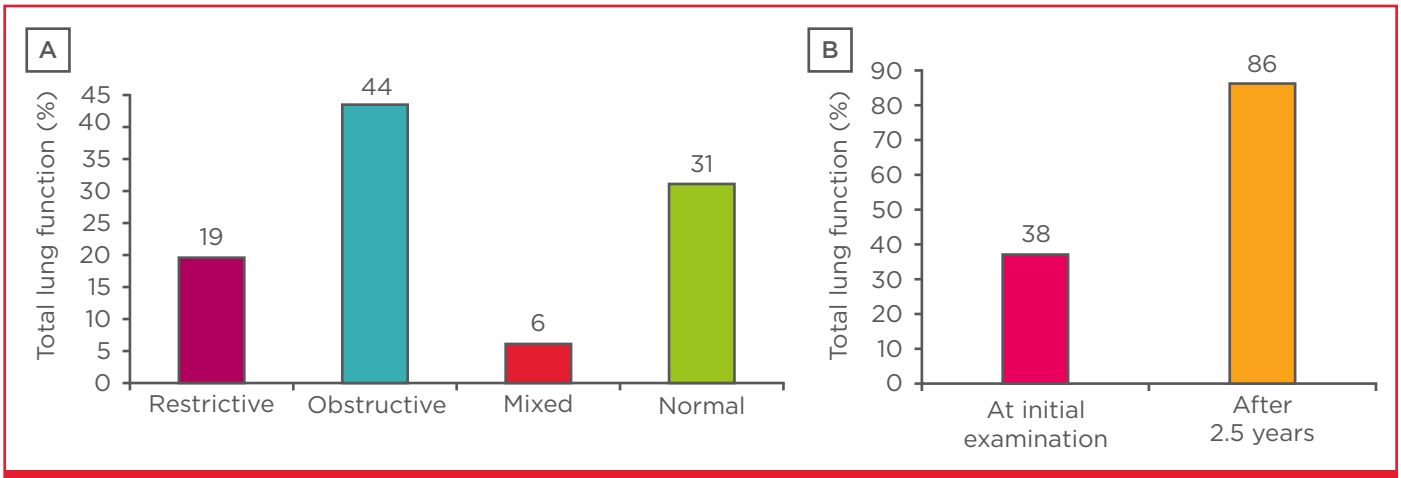

Figure 1: A) Lung function in silicomycobacteriosis patients (n=17). B) The frequency of decrease in the diffusing capacity of the lungs for carbon monoxide during observation of silicomycobacteriosis patients (n=12).

ASSOCIATION OF LONGITUDINAL CHANGES OF COPD ASSESSMENT TEST WITH EXACERBATION RISK: INSIGHT INTO THE DISCUSSION AT THE EUROPEAN RESPIRATORY SOCIETY INTERNATIONAL CONGRESS 2017

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Keywords: Telemonitoring, telemedicine, chronic obstructive pulmonary disease (COPD) management, acute exacerbations of COPD, COPD assessment test.

BACKGROUND

The chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) well reflects the functional status of COPD patients;[1-4] however, there are only scarce data regarding the evolution of the CAT over time.[5] Our aim was to investigate the evolution of the CAT in a telehealth care (THC) cohort of COPD patients and to evaluate the potential of repeated CAT-measurements to predict exacerbations. Furthermore, we wanted to evaluate a possible learning effect of filling out the CAT.

METHODS

The CAT was measured once per week, over a period of <1 year, in 40 COPD patients undergoing THC intervention. The evolution of the CAT was analysed using linear regression. The association between the evolution of the CAT and the occurrence of exacerbations was evaluated using the Andersen-Gill formulation of the Cox proportional hazards model for the analysis of recurrent time-to-event data with time-varying predictors. We modelled the CAT kinetics using the 4-parameter Brain-Cousens hormesis non-linear model. This model describes an initial increasing/decreasing phase followed by stabilisation. In order to decide whether or not a learning effect existed, we compared the goodness of fit obtained by this model with that obtained using linear regression.

RESULTS

The median CAT at study inclusion was 17 (interquartile range: 13–22) points. Analysis of the data highlighted that 25% of patients showed a significant negative slope, 38% had a stable course, and 38% had a significant positive slope. A significant, positive association was found between the change in CAT scores over time and the risk of exacerbations (hazard ratio: 1.08; 95% confidence interval: 1.03–1.13; p<0.001). There was an 8% increase of the risk of exacerbation per unit increase in CAT. We detected a significant learning effect of filling out the CAT in 18% of patients with a median learning phase of five filled questionnaires.

CONCLUSIONS

Of the patients, 63% experienced a stable or improved CAT while being monitored with THC. This promising finding could indicate the potential of our proposed THC procedure to significantly improve health-related quality of life. A significant positive association was found between the evolution of the CAT over time and the risk of exacerbation. The CAT could serve as a marker for exacerbation risk when assessed in a longitudinal fashion. Roughly one-fifth of patients needed to learn how to complete the CAT several times before reliable results could be obtained.

INPUT FROM THE PRESENTATION AT THE EUROPEAN RESPIRATORY SOCIETY CONGRESS

The poster presentation was well accepted by the audience with large amounts of interest, and positive comments sparked a fruitful discussion. The audience and the chair persons appreciated the novel method of measuring the CAT score in a longitudinal fashion which, until now, has rarely been performed or published. They agreed that measuring the CAT repeatedly and calculating a slope could serve as a prediction tool for exacerbations. The second novel aspect of the learning effect of filling out the CAT was also received with interest. One issue was how to get more patients to use this kind of THC platform, because only a minority of screened patients were included. Many of the older generations in Switzerland have no internet access and therefore could not take part in our intervention; this will be resolved over the years by supplying more people with online access. The second most common reason for not participating was a rather restrictive attitude regarding study participations in general. This should be addressed by motivating patients; for example, by highlighting the immediate personal benefits. Also, concerns regarding data safety and privacy must be addressed.

REFERENCES

1. Jones PW et al. Development and first validation of the COPD assessment test. Eur Respir J. 2009;34(3):648-54.

2. Gulart AA et al. Does the COPD assessment test reflect functional status in patients with COPD? Chron Respir Dis. 2016;14(1):37-44.
3. Gupta N et al. The COPD assessment test: A systematic review. Eur Respir J. 2014;44(4):873-84.
4. Smid DE et al. Responsiveness and MCID estimates for CAT, CCQ, and HADS in patients with COPD undergoing pulmonary rehabilitation: A prospective analysis. J Am Med Dir Assoc. 2017;18(1):53-8.
5. Buhl R et al. A year in the life of German patients with COPD: The DACCORD observational study. Int J Chron Obstruct Pulmon Dis. 2016;11(1):1639-46.

MANAGEMENT OF ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIS: A SINGLE-CENTRE PERSPECTIVE FROM A RESPIRATORY CLINIC

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Keywords: Vasculitis, immunosuppression, autoimmune disease, pulmonary vascular disease.

INTRODUCTION

Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) causes small and medium-vessel destruction. The 2012 revised Chapel Hill Consensus[1] describes three main types of AAV: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The British Society for Rheumatology (BSR) aims to arrest disease progression, whilst minimising the risks of immunosuppression by advocating treatment with rituximab and intravenous (IV) cyclophosphamide.[2]

AIMS AND METHODS

We reviewed the management of patients with AAV in our respiratory clinic until March 2015, comparing our management with BSR guidelines. We investigated morbidity data and long-term outcomes for patients.

RESULTS

The study involved 30 patients with GPA, 15 with MPA, 5 with EGPA, and 2 who had unclear diagnoses. The lungs, kidneys, and upper respiratory tract were the most commonly affected areas. Glucocorticoids and IV or oral cyclophosphamide were the mainstay drugs used for induction. Prednisolone and azathioprine were most commonly used for maintenance. No patients with EGPA relapsed; 5 patients with MPA relapsed, including 2 who relapsed whilst on-drug. One of these patients had IV methylprednisolone induction and 1 was given oral prednisolone and rituximab; these patients were maintained at relapse with the use of prednisolone and prednisolone/rituximab, respectively.

In addition, 10 patients with GPA relapsed, of whom 2 experienced two relapses. Eight of these relapses were on-drug and the mean time to relapse was 32.3 months. For patients who relapsed on-drug, the methods of induction included 3 patients with IV cyclophosphamide, 2 with prednisolone/cyclophosphamide, 1 with prednisolone, 1 with IV cyclophosphamide/rituximab, and 1 with prednisolone/cyclophosphamide/rituximab. Maintenance therapies used before relapse included 5 patients treated with azathioprine/prednisolone, 2 with mycophenolate/prednisolone, and 1 with prednisolone only.

DISCUSSION

Figure 1 shows the treatment guidelines for AAV. The CYCLOPS trial showed the non-inferiority of treatment with pulsed IV cyclophosphamide, with a

less cumulative dose (to reduce urothelial toxicity) and fewer instances of leukopenia;[3] however, the relapse rate was higher.[4] We reported no cases of haemorrhagic cystitis; however, 1 patient induced on oral cyclophosphamide developed bladder cancer.

Six, two, and one patient(s) with GPA, MPA, and EGPA, respectively, had refractory disease, and therefore a secondary rituximab induction was added. One GPA patient subsequently relapsed. One patient with GPA and another with MPA relapsed after primary rituximab induction.

The RAVE trial[5] demonstrated the non-inferiority of a shorter induction with rituximab at 18 months compared to prednisolone/cyclophosphamide induction with maintenance using azathioprine. Rituximab treatment resulted in reduced immunosuppression overall and was more likely to be successful in inducing remission in relapsing disease, particularly in proteinase 3-AAV.[6] Six patients on rituximab developed hypogammaglobulinaemia and 5 experienced B cell depletion. There is a ~25% risk of hypogammaglobulinemia associated with rituximab use.

Two patients developed an aspergillus infection and 1 presented with cytomegalovirus colitis whilst immunosuppressed. The highest mortality from infection is within the 1st year of treatment, when immunosuppression is maximal. Infection independently predicts early mortality, and respiratory tract infection is especially problematic. In addition, 1 patient with EGPA died from pneumonia and pseudomembranous colitis and 5 patients in the MPA group died (1 with vanishing duct syndrome from cyclophosphamide treatment, 1 at index from respiratory and renal failure, and 1 due to a perforated colon), compared to 2 patients with GPA (1 with granulomatous aortic valve stenosis and heart failure).

Aggressively treating active disease limits the irreversible damage caused by the condition. Furthermore, it is also important to minimise immunosuppression via relapse prevention.

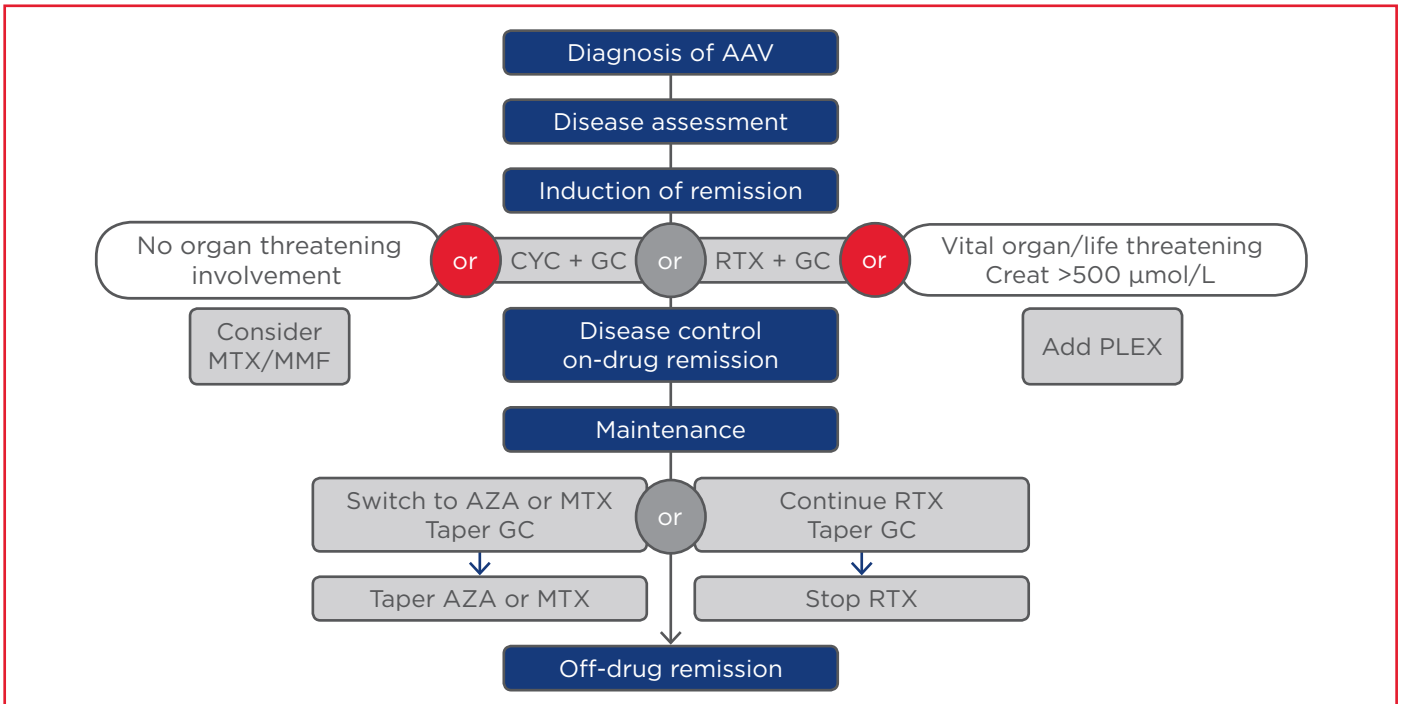

Figure 1: The treatment guidelines for anti-neutrophil cytoplasmic antibody-associated vasculitis.
AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; AZA: azathioprine; CYC: cyclophosphamide; GC: glucocorticosteroids; MMF: mycophenolate; MTX: methotrexate; PLEX: plasma exchange; RTX: rituximab.

However, immunosuppression can be as problematic as AAV itself. Use of the Birmingham Vasculitis Activity Score is recommended to measure active disease, with remission defined as a Birmingham Vasculitis Activity Score of 0. The Vasculitis Damage Index measures the irreversible damage caused by both the disease process and immunosuppression. By using the above scores, we will be able to differentiate pre-existing irreversible damage from new activity, thereby reducing cumulative immunosuppression and its side effects.

REFERENCES

1. Jennette JC et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1-11.
2. Ntatsaki E et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology. 2014;53(12):2306-9.
3. de Groot K et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomised trial. Ann Intern Med. 2009;150(10):670-80.
4. Harper L et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. Ann Rheum Dis. 2012;71(6):955-60.
5. Stone J et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. NEJM. 2010;363(3):221-32.
6. Unizony S et al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. Ann Rheum Dis. 2016;75(6):1166-9.

EDITOR'S PICK

Over the years, the study of the pathophysiology and pharmacology of allergen-induced asthma has been based on several allergen inhalation challenge models, which have specific benefits and disadvantages. In this issue of the journal, an interesting review provided by Blais et al. covers the utility of different allergen models in tailoring a clinical approach for treating allergic asthma, as well as a look at future directions for allergen challenge testing.

Dr Antonio Rossi

ALLERGEN CHALLENGE TESTING IN ATOPIC ASTHMA PHARMACEUTICAL RESEARCH: PAST, PRESENT, AND FUTURE DIRECTIONS

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ABSTRACT

Over the years, various allergen inhalation challenge models have been developed to study the pathophysiology and pharmacology of allergen-induced asthma. Each allergen challenge method possesses unique benefits and disadvantages. The classic allergen challenge model is useful for assessing the efficacy of new treatments but does not reflect real-world repeated exposure and excludes approximately 50% of allergic asthmatics (i.e. those who do not exhibit a late asthmatic response). The early response model, while also artificial, is less time-consuming and allows for the generation of dose-response data but does not assess the late response or related sequelae. The repeated low-dose allergen model was developed with the purpose of mimicking natural exposure for induction of airway inflammation and airway hyperresponsiveness. However, this method does not consistently produce airway inflammation and is less practical to perform due to the number of study visits required. The segmental allergen model is the only one to allow direct sampling of airway secretions for airway inflammation studies, but it is highly invasive and requires special training and equipment. Attempts have been made to establish a repeated high-dose allergen model for the assessment of drug effects on symptoms and rescue medication use, but participant safety remains a concern and it is also less practical than the classic method. The most difficult allergen model to perform is the natural exposure method, for which standardisation may not be possible given the number of environmental factors that must be controlled or measured. Modifications to these allergen models could improve their clinical relevance and identify their specific, tailored applications in pharmaceutical research of allergic asthma.

Keywords: Allergic asthma, early asthmatic response (EAR), late asthmatic response (LAR), classic allergen challenge, repeated low-dose allergen challenge, repeated high-dose allergen challenge, environmental allergen challenge, EAR allergen challenge, segmental allergen challenge.

INTRODUCTION

Asthma is a common chronic respiratory condition that physically, mentally, and financially affects approximately 300 million people worldwide.[1] Over the last 30 years, significant research findings have transformed our knowledge of the causes, pathophysiology, symptoms, and treatments for asthma, but much has yet to be investigated or further elucidated. In atopic asthma, mechanisms and novel respiratory medications are studied through inhaled allergen challenge testing. This communication will briefly review the history of the allergen challenge and the various experimental models that have been used for allergen challenge testing. Recommendations for minor changes in the commonly used classic model will also be made.

EVOLUTION OF THE ALLERGEN CHALLENGE

The allergen challenge model has undergone several changes in the last century as a result of advancements made in technology and research. Early allergen challenges measured fluctuations in vital capacity to observe the allergic response and any treatment or hyposensitisation effects.[2] The forced expiratory volume in 1 second (FEV_1), invented by Tiffeneau in 1947,[3] has since become the standard lung function parameter assessed; the FEV_1 is significantly more sensitive and does not require the induction of a high, likely uncomfortable, and potentially unsafe level of bronchoconstriction.[4]

Mid-20th century allergen challenge testing entailed administering nebulised allergen extracts via a bell spirometer/air pump/nebuliser circuit, through which dose delivery depended on inhalation time.[2] Such experiments identified multiple key factors involved in the allergic response that are still clinically relevant today. The primary endpoint of these historic studies was the change in the immediate or early asthmatic response (EAR).[5] In the 1950s, studies identified the late asthmatic response (LAR),[5-7] which peaks several hours after allergen exposure.

Originally, allergen challenge testing was used to diagnose allergic sensitivities and possibly hyposensitise patients to their allergies.[5] Its use for assessing and comparing drug effects was relatively new in the 1950s,[2] but has since become its primary application. It was subsequently discovered that airway hyperresponsiveness (AHR) to non-specific or direct-acting stimuli (e.g. methacholine) increased with allergen exposure and was associated with the LAR.[8,9] Current allergen challenges include baseline and post-allergen measurements of AHR, typically through methacholine challenge testing (MCT). Differences in the levels of inflammatory factors in the bronchoalveolar lavage and sputum samples of asthmatics post-allergen were also observed in the late 20th century.[10,11] Most modern pharmaceutical allergen challenge protocols require dual responders and investigate therapeutic efficacy, focussing on the LAR and airway inflammation.[12] A number of challenge models are used (Table 1).

CLASSIC ALLERGEN CHALLENGE MODEL

In comparison to historical methods, the classic allergen challenge model involves more precise methodologies.[13] When using the 2-minute tidal breathing method, a safe starting allergen concentration is deduced through MCT and skin prick test results, from which the provocative concentration of allergen causing a 20% fall in FEV_1 (PC_{20}) can be predicted.[14] The starting concentration is 3–4 doubling concentrations less than the predicted allergen PC_{20} and is held constant for each allergen challenge for the duration of the study.[15] Doubling concentrations of allergen are administered over 2 minutes of tidal breathing and a single FEV_1 measurement is obtained 10 minutes post inhalation. Administration of the next concentration begins 12 minutes after the start of the previous, and this process repeats until a 20% fall in FEV_1, relative to the highest baseline FEV_1, is achieved.[12]

When using the dosimeter method, a set pattern of allergen doses is administered via a dosimeter.[16–18] FEV_1 measurements are recorded 10 minutes post allergen inhalation,[16,17] or at 5, 10, and 15 minutes post-dose before the next inhalation.[18] Testing is typically continued until the FEV_1 falls by at least 20% from baseline and a cumulative provocative dose (PD_{20}) is obtained.[16–18] The same inhalation pattern or a single inhalation challenge using only the cumulative dose of allergen is then used for subsequent challenges.

For both methods, after allergen inhalation is complete, FEV_1 measurements are captured at set time points up to 7 hours (or longer) to follow the potential development of an LAR. This model is commonly used to investigate drug effects on the

LAR, usually as changes in maximal decrease in FEV_1 and/or area under the FEV_1 curve, provided the same dose of allergen has been administered before and after the intervention under investigation. The model also allows for secondary investigations of changes to the EAR, as well as allergen-induced late sequelae, including increases in airway inflammation[10,11] and in AHR to methacholine.[8,10]

Table 1: Allergen challenge models and their advantages and disadvantages.

Allergen challenge model	Brief description	Advantages	Disadvantages
Classic (2-minute tidal breathing and dosimeter methods)	• Doubling concentrations or set doses of allergen administered until 20% fall in FEV_1 • FEV_1 followed by ≥7 hours until LAR • AHR, sputum, and serum (7 and 24 hours)	• Captures the entire response (EAR, LAR, changes in airway inflammation, and AHR) • Although not ideal, can be performed in participants using daily stable-dose ICS	• Excludes EAR-only responders (≥50% of asthmatics) • Does not resemble natural allergen exposure • EAR and LAR definitions not consistent • No testing between the EAR and LAR
Repeated low-dose	• Administration of low-dose allergen daily, usually >1 week, to induce airway inflammation and AHR	• May more closely resemble repeated low-dose natural exposure • More rapid recovery following challenge	• Does not consistently induce asthma symptoms or airway inflammation • Not practical for standard use, particularly when the entire challenge needs to be repeated 2–3 times
Repeated high-dose	• Repeated classic allergen model in short-time frame (e.g. 4x separated by 48 hours)	• Induces asthma exacerbation (i.e. increased medication use and symptoms) • Resembles repeated natural exposure to symptomatic levels of allergen • Animal models in asthma research typically tested through this method • Induces EAR and LAR	• Safety a concern • Not practical for repeat studies given length and frequency of study visits • Can produce severe symptoms and airway inflammation
Segmental (bronchoscopic)	• Challenge administered by bronchoscopy followed by direct sampling of airway secretions via bronchoscopic BAL	• Only method to allow direct sampling and analysis of immune response to allergen	• Cannot quantitate AHR • Highly invasive • Requires special equipment and trained staff • Limited concentration range of allergen
Natural exposure	• Simulated allergic environment for timed exposure (e.g. room with residing cats)	• Mimics natural allergen exposure • Induces EAR, LAR, AHR, and increased IgE and eosinophils	• Time-consuming • Requires rigid safety considerations and protocols • Standardisation difficult as many factors must be controlled and/or measured in simulated environment
EAR	• Administration of doubling concentrations of allergen until 20% fall in FEV_1 to measure PC_{15}/PC_{20} • Following treatment PC_{15} re-established and treatment effect assessed as dose shift	• Practical and quick to perform • Ease of repeatability • Greater availability of participants (EAR-only and dual responders) • Improved discrimination between treatments with large inhibition of EAR	• Does not allow assessment of LAR and the sequelae, which are considered clinically more important

AHR: airway hyperresponsiveness; BAL: bronchoalveolar lavage; EAR: early asthmatic response; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LAR: late asthmatic response; PC_{15}/PC_{20}, provocative concentration causing a 15/20% fall in FEV_1.

Despite standard use in pharmaceutical research, classic allergen challenge methods are not flawless. Current study protocols are designed to exclude non-LAR responders; this is problematic, because ≥50% of allergic asthmatics do not develop an LAR, possibly due to the allergen type and/or dose administered.[12,19] For example, multiple studies have reported that asthmatics allergic to house dust mites are significantly more likely to develop an LAR, which is often also of higher magnitude compared to other allergic triggers.[17,20,21] Nonetheless, the exclusion of isolated EAR responders calls into question the generalisability of study findings; however, this model is highly appropriate for studies strictly focused on the LAR. Additional concerns with this model are that the dose delivered may not resemble environmental allergy exposure[19] and that there is a lack of standardisation when defining the EAR and the LAR. The EAR has been defined as a 20% fall in FEV_1 within 5–30 minutes,[19,22,23] 10–30 minutes,[24,25] 0–1 hour,[26] 0–2 hours,[27,28] or 0–3 hours post-allergen;[29] the LAR has been defined as a minimum 15% fall in FEV_1 2–8 hours,[19] 3–7 hours,[27,29,30] 3–8 hours,[28] 4–10 hours,[24,25] 2.5–10 hours,[18] 3–10 hours,[26] or 3–24 hours post-allergen.[31] Studies of this nature have also been limited in that researchers have not performed experiments in the period between the EAR and LAR because of the risk of influencing the development of their primary study endpoint, the LAR.

REPEATED LOW-DOSE ALLERGEN CHALLENGE MODEL

Some researchers have focussed on establishing a reproducible approach for performing repeated low-dose allergen challenges. Their rationale is that many asthmatics are regularly exposed to a low level of their allergen, which increases airway inflammation and AHR.[30,32] This model entails the administration of the allergen PC_5 pre-determined through a screening classic allergen challenge.[30,32,33]

Sulakvelidze et al.[32] designed and tested administering a dose of allergen in the morning for 5 consecutive days, with MCT and sputum induction performed at screening and on the afternoon of Days 1, 3, and 5 of the trial. Changes in symptomology and rescue medication use were assessed through questionnaires. A slight drop in baseline FEV_1 was observed, but significant increases in airway eosinophil and interleukin (IL)-5 levels, AHR, asthma symptoms, and rescue therapy use occurred. All effects subsided within 3 days, which is a more rapid recovery than following a classic allergen challenge. De Kluijver et al.[33] completed a similar study but dosing was performed for 10 business days over 2 consecutive weeks. Overall, it was found that this protocol produced a significant increase in airway inflammation (i.e. exhaled nitrous oxide, sputum eosinophils, and sputum IL-5) without increasing symptomology or AHR.

Palmqvist et al.[30] explored the effects of repeated low-dose allergen exposure on the allergic response to a high-dose challenge. Participants underwent 7 consecutive days of repeated low-dose cat allergen challenge, followed 48 hours later by a single high-dose challenge (i.e. cumulative dose from screening) to determine the effect, if any, on the LAR. Repeated low-dose allergen exposure resulted in a small but significant reduction in the high-dose challenge LAR (30%), even though airway responsiveness to methacholine and the number of sputum eosinophils had significantly increased following the final low dose challenge performed 2 days earlier.

Despite the perceived immunotherapeutic effect, the low-dose approach has several disadvantages. It does not consistently induce asthma symptoms,[18] which precludes the concomitant investigation of treatment effects on the allergic response and on patient symptomology. This method also does not consistently induce elevated airway inflammation,[18] making it, in its current form, less reproducible than the classic method. Lastly, it is not practical for standard use, as it requires several more study visits than the standard high-dose method.

REPEATED HIGH-DOSE ALLERGEN CHALLENGE MODEL

The repeated high-dose model is meant to mimic environmental exposure to a significant level of allergen, thereby inducing an asthma exacerbation, sustained airway eosinophilic inflammation, and structural remodelling.[18] The other testing models do not resemble the situation where patients are repeatedly exposed to symptomatic levels of their allergen. Additional rationale for this method is that animal models of asthma used in early pharmaceutical studies are often tested through repeated high-dose allergen challenges,[18] and so following a similar procedure in humans would allow for more appropriate transferring of findings between species.

Grainge and Howarth[18] investigated a repeated high-dose allergen challenge protocol that entailed three classic allergen challenges at 48-hour intervals. In case sensitisation was to develop, the last two allergen challenges were performed starting with the dose equivalent to half the PD_{15} of the first challenge. It was subsequently found that no priming or desensitisation occurred, and the dose of allergen administered across the three challenges was equivalent. The researchers also observed a significant increase in the frequency of symptoms and rescue therapy use, while the baseline FEV_1, EAR, and LAR values did not significantly change over the course of the trial. Unfortunately, this study did not investigate changes in AHR or airway inflammation.

Only this allergen model seems to produce significant increases in the frequency of symptoms and rescue medication use; however, safety remains a primary concern with this approach and its feasibility in the research setting is questionable, as it requires multiple long allergen challenges in a short timeframe. Another limitation is interpretation of changes in PD_{15} across a treatment period. It is possible that incidental exposures to stimuli altering responsiveness to allergens may have unknowingly occurred during the interval (i.e. 48 hours) between challenges. Others have assessed shortening the interval between repeated high-dose challenges, which produced severe symptoms and airway inflammation, raising safety and ethical concerns for routine use of this type of protocol.[16] Altogether, more research is needed on this approach to allergen testing before it can be used as a common laboratory technique.

SEGMENTAL ALLERGEN CHALLENGE MODEL

As the most invasive allergen challenge method, the segmental allergen model, also known as the local allergen challenge, is particularly useful for investigating the pathogenesis of asthma at the cellular level.[34] It allows for direct sampling of airway secretions through bronchoalveolar lavage and so the immune response to allergen can be more thoroughly studied through analysis of specific cells, mediators, and cytokines in bronchoalveolar lavage fluid.[16,35]

Metzger et al.[35] assessed the allergic response in asthmatics through a local allergen challenge. Participants first underwent MCT and a classic allergen challenge to establish the baseline AHR and allergic response. They then underwent a control bronchoalveolar lavage and bronchoscopy prior to the local allergen challenge. Increasing concentrations of allergen aliquots were administered via the bronchoscope until there was a visible airway response to the allergen, at which point airway secretions were collected for analysis. Participants returned 2–4 days later for one last bronchoalveolar lavage. The airway secretions were then analysed for the level of macrophages, lymphocytes, neutrophils, basophils, mast cells, and eosinophils present. It was not possible, however, to quantify the level of airway narrowing produced.

Although this model is unique in its ability to directly observe changes in the airway at the cellular level, it is not practical to perform as it is highly invasive and requires specially trained staff and specialised equipment.[34] It also does not allow for the administration of relatively high concentrations of allergen locally, as the endpoint is the visual change in airway response, which may occur at lower concentrations of allergen. As such, the segmental allergen challenge testing is not often used and is only implemented in a narrow research context.

NATURAL EXPOSURE ALLERGEN CHALLENGE MODEL

A natural exposure allergen challenge has also been attempted and this should most closely resemble true environmental exposure. However, several problems arose with this methodology; many factors must be rigorously controlled and can be difficult to measure, such as the dose and particle sizes of allergen received, the setting of exposure, the duration of the challenge, and the target endpoint.[31]

Arvidsson et al.[31] completed a crossover study to compare allergen challenge results from the classic model and a natural exposure method. The 'natural' allergic environment consisted of a sitting room where cats had lived for ≥10 years. The approximate allergen dose was calculated through analyses of air samples and settled dust. During the natural exposure challenge, participants spent ≤3 hours in the unventilated room and were exposed to live cats for approximately 20% of the provocation time. FEV_1 measurements were captured every 15 minutes until an FEV_1 fall of 20% was achieved. After the natural exposure challenge, the FEV_1 was measured hourly until bedtime and at 24 hours post-allergen. It was found that with the natural exposure method, 60% of participants

developed an EAR and 47% developed an LAR. Overall, the two allergen models did not produce differences in sputum content, specific immunoglobulin E (IgE) levels, or sputum eosinophils, and 65% of the sample produced similar EAR and LAR responses to both methods. It was also observed that the results with the two models became significantly more comparable when participants who experienced a 10–15% fall in FEV_1 in the late phase were included as late responders.

Unfortunately, the natural exposure model is difficult to perform, is time-consuming, and requires rigid safety considerations and protocols. As such, it remains the least feasible allergen challenge model for regular use in pharmaceutical research.

EARLY ASTHMATIC RESPONSE ALLERGEN CHALLENGE MODEL

Several experimental asthma treatments have targeted inflammatory mediators involved in the EAR (e.g. IgE, histamine, leukotrienes) of which the EAR allergen challenge method was most appropriate.[36-38] This model is similar to the classic allergen model in terms of the calculation for the starting allergen concentration and the use of 2-minute tidal breathing at 12-minute intervals. However, the final concentration administered is not necessarily the same for each challenge; doubling allergen concentrations are administered until the desired percent fall in FEV_1 (typically 15% or 20%) is achieved; this allows for assessment of a dose response and quantitation of therapeutic benefit by way of dose shift in allergen PC_{15} or PC_{20}. As a safety precaution for those who may develop a late response, inhaled corticosteroids (ICS) are routinely administered to attenuate the response once the maximal EAR has been captured or, if the recovery phase is important to the study design, administration of ICS can be extended ≤3 hours after the last allergen inhalation.[39]

Advantages to this model include its practicality (i.e. shorter study visits), its ease of repeatability, the greater availability of subjects (i.e. EAR-only and dual responders are both eligible), and its improved discrimination between drugs that have a large (>50–75%) inhibitory effect on the EAR.[34,36] The main limitation of this method is that it prevents the examination of any aspect of the LAR.

POTENTIAL FUTURE DIRECTIONS FOR ALLERGEN CHALLENGE TESTING

As our knowledge expands, research techniques are repeatedly updated in order to continue to grow our understanding of physiological mechanisms. The allergen challenge model is no exception. For example, in pharmaceutical research, the classic allergen model typically excludes participants who do not develop an LAR, which represents approximately 50% (30–70%) of allergic asthmatics.[12,19] Considering that the treatments tested with this methodology will also be used in EAR-only responders, it seems inappropriate to exclude them from important drug trials investigating efficacy. In addition, the LAR is dependent on the allergen and/or the dose used for testing.[12,19] We recommend that the current methodology be updated to include the enrolment of both dual EAR/LAR responders and EAR-only responders to gain a better understanding of the allergic response and how to treat it. A potential method for doing so is the merging of the classic and EAR allergen models into one method with two study groups: early responders and dual responders.

Another shortcoming of classic standard methodology and assessing dual responders is the limitation for collecting sputum or measuring AHR during the time frame between the EAR and LAR, as an intervention performed has the potential to influence the development of the LAR. If we include early responders, we may be able to gain insight into allergen-induced increases in AHR since early responders show an increase at 3 hours post allergen challenge.[40] At 24 hours post challenge, early responders have also shown increased AHR,[41] as well as increased eosinophils and fractional exhaled nitric oxide,[42] but without developing a classic LAR. By using a method that incorporates both the classic dual and EAR models (i.e. follow only to 3 hours), or by including EAR-only responders in the classic model (i.e. follow for 7–10 hours and include 24-hour assessments), it may be possible to obtain new insights into the mechanism(s) of allergic asthma.

An additional alteration to the classic allergen challenge could be a change in the definition of an LAR response. There are presently different definitions for the classification of a LAR, but one feature that remains relatively standard is that the FEV_1 must fall by ≥15% from baseline during the LAR timeframe. While some studies require that such a

percentage fall only happens once, others require that it occurs twice or three times, possibly even consecutively. It has been remarked that the LAR has an arbitrary cut-off point of 15%, which likely has little clinical significance and could be reduced.[31] Some studies have shown that the inclusion of participants who fell between 10–15% during the LAR time frame strengthened the data set, especially considering that these participants showed similar results to those who had met the current LAR criteria.[31,42] Future allergen challenge models could potentially reduce the cut-off point for defining the LAR to 10% without negatively influencing study outcomes.

Future studies should also aim to develop a practical set of tests and patient history questionnaires to phenotype asthmatics. At present, the application of research findings in clinics relies heavily on mean data of study samples that include several disease phenotypes. As a result, variances in treatment effects based on phenotype are not observed through current allergen testing methods,[43] which could otherwise help to reduce the time and expense of finding the right therapeutic intervention for a given patient.

Further research must be conducted on repeated low-dose, repeated high-dose, and natural exposure allergen challenge models to improve their standardisation, feasibility, and repeatability; the repeated low-dose method must be modified to produce consistent airway inflammation; the repeated high-dose allergen model requires a safe protocol that is characterised for its effects on all aspects of the allergic response (i.e. inflammation, AHR, EAR, and LAR); and the natural exposure allergen model cannot (at least not thus far) be conducted in a regulated manner with most allergen types. Nonetheless, the exploration of these models for future use could prove beneficial for clinical trials of particular drug types.

CONCLUSION

Several allergen challenge techniques have been developed or considered, each with its benefits and shortcomings (Table 1). The classic model triggers an EAR, LAR, airway inflammation, and AHR, and requires the smallest number of study visits. However, it does not accurately simulate natural allergic exposure. The EAR model is more feasible, eases participant recruitment, and better discriminates drug effects. It does not, however, allow for the investigation of the LAR. The repeated low and high-dose allergen challenges more closely resemble environmental exposure but the former method produces inconsistent results and the latter raises safety concerns. The segmental method is unique in that it allows direct sampling of airway secretions, but it is invasive and requires special training. Lastly, the natural exposure allergen model most closely emulates the natural allergic situation, but is the least practical. Future studies could improve these methods to maximise their clinical relevance and better identify beneficial treatment options for different asthma phenotypes.

REFERENCES

1. Global Initiative for Asthma. Global Strategy For Asthma Management and Prevention. 2016. Available at: http://ginasthma.org/wp-content/uploads/2016/04/wms-GINA-2016-main-report-final.pdf. Last accessed: 13 July 2017.

2. Herxheimer H. Induced asthma in man. Lancet. 1951;1(6669):1337-41.

3. Tiffeneau R, Pinelli A. Air circulant et air captif dans l'exploration de la fonction ventilatrice pulmonaire. Paris Méd. 1947; 37(52):624-8.

4. Citron KM et al. Inhalation tests of bronchial hypersensitivity in pollen asthma. Thorax. 1958;13(3):229-32.

5. Herxheimer H. Bronchial hypersensitization and hyposensitization in man. Int Arch Allergy Appl Immunol. 1951;2(1):40-59.

6. Herxheimer H. The late bronchial reaction in induced asthma. Int Arch Allergy Appl Immunol. 1952;3(4):323-8.

7. Herxheimer H. Bronchial obstruction induced by allergens, histamine and acetyl-beta-methylcholinechloride. Int Arch Allergy Appl Immunol. 1951; 2(1):27-39.

8. Cockcroft DW et al. Allergen-induced increase in non-allergic bronchial reactivity. Clin Allergy. 1977;7(6):503-13.

9. Cartier A et al. Allergen-induced increase in bronchial responsiveness to histamine: Relationship to the late asthmatic response and change in airway caliber. J Allergy Clin Immunol. 1982; 70(3):170-7.

10. De Monchy JG et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. Am Rev Respir Dis. 1985;131(3):373-6.

11. Pin I et al. Changes in the cellular profile of induced sputum after allergen-induced asthmatic responses. Am Rev Respir Dis. 1992;145(6):1265-9.

12. Boulet LP et al.; Clinical Investigative Collaboration, Canadian Network of Centers of Excellence AllerGen. The allergen bronchoprovocation model: An important tool for the investigation of new asthma anti-inflammatory therapies. Allergy. 2007;62(10):1101-10.

13. Cockcroft DW et al. Understanding allergic asthma from allergen inhalation tests. Can Respir J. 2007;14(7):414-8.

14. Cockcroft DW et al. The links between allergen skin test sensitivity, airway responsiveness and airway response to allergen. Allergy. 2005;60:56-9.

15. Diamant Z et al. Inhaled allergen bronchoprovocation tests. J Allergy Clin Immunol. 2013;132(5)1045-55.

16. Schulze J et al. Airway responses and inflammation in subjects with asthma after four days of repeated high-single-dose allergen challenge. Respir Res. 2012; 13(1):78-89.

17. Schulze J et al. Bronchial allergen challenges in children – safety and predictors. Pediatr Allergy Immunol. 2013; 24(1):19-27.

18. Grainge C, Howarth PH. Repeated high-dose inhalation allergen challenge in asthma. Clin Respir J. 2011;5:150-5.

19. Scheerens H et al. The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge. Clin Exp Allergy. 2013;44(1):38-46.

20. Hatzivlassiou M et al. The allergen specificity of the late asthmatic reaction. Allergy. 2010;65(3):355-8.

21. Warner JO. Significance of late reactions after bronchial challenge with house dust mite. Arch Dis Child. 1976; 51(12):905-11.

22. Singh D et al. The inhaled phosphodiesterase 4 inhibitor GSK256066 reduces allergen challenge responses in asthma. Respir Res. 2010;11(1):26.

23. Singh D et al. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. Eur Respir J. 2012;41(1):46-52.

24. Leaker BR et al. The effects of the novel SHIP1 activator AQX-1125 on allergen-induced responses in mild-to-moderate asthma. Clin Exp Allergy. 2014;44(9): 1146-53.

25. Richards DB et al. Treatment with a peroxisomal proliferator activated receptor gamma agonist has a modest effect in the allergen challenge model in asthma: A randomised controlled trial. Respir Med. 2010;104(5):668-74.

26. Diamant Z et al. Setipiprant, a selective CRTH2 antagonist, reduces allergen-induced airway responses in allergic asthmatics. Clin Exp Allergy. 2014; 44(8):1044-52.

27. Gauvreau GM et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N Engl J Med. 2014; 370(22):2102-10.

28. Heijink IH et al. Effect of ciclesonide treatment on allergen-induced changes in T cell regulation in asthma. Int Arch Allergy Immunol. 2008;145(2):111-21.

29. Gauvreau GM et al. A nonsteroidal glucocorticoid receptor agonist inhibits allergen-induced late asthmatic responses. Am J Respir Crit Care Med. 2015;191(2):161-7.

30. Palmqvist M et al. Reduced late asthmatic response by repeated low-dose allergen exposure. Eur Respir J. 2001; 17:872-80.

31. Arvidsson MB et al. Early and late phase asthmatic response in lower airways of cat-allergic asthmatic patients - a comparison between experimental and environmental allergen challenge. Allergy. 2007;62(5):488-94.

32. Sulakvelidze I et al. Increases in airway eosinophils and interleukin-5 with minimal bronchoconstriction during repeated low-dose allergen challenge in atopic asthmatics. Eur Respir J. 1998;11(4):821-7.

33. De Kluijver J et al. Asymptomatic worsening of airway inflammation during low-dose allergen exposure in asthma: Protection by inhaled steroids. Am J Respir Crit Care Med. 2002;166(3): 294-300.

34. Cockcroft DW, "Bronchial Challenge Testing," Adkinson Jr NF et al. (eds.), Middleton's Allergy Principles and Practice Volume 2 (2008) 7th edition. Philadelphia: Mosby Elsevier,pp. 1303-5.

35. Metzger WJ et al. Local allergen challenge and bronchoalveolar lavage of allergic asthmatic lungs. Am Rev Respir Dis. 1987;135(2):433-40.

36. Davis BE et al. Effect of combined montelukast and desloratadine on the early asthmatic response to inhaled allergen. J Allergy Clin Immunol. 2005; 116(4):768-72.

37. Gauvreau GM et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. J Allergy Clin Immunol. 2016;138(4):1051-9.

38. Boulet LP et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med. 1997;155(6): 1835-40.

39. Cockcroft DW et al. Beclomethasone given after the early asthmatic response inhibits the late response and the increased methacholine responsiveness and cromolyn does not. J Allergy Clin Immunol. 1993;91(6):1163-8.

40. Amakye DO et al. Refractoriness to inhaled mannitol 3 hours after allergen challenge. Ann Allergy Asthma Immunol. 2013;111(3):182-4.

41. Davis BE et al. Airway responsiveness to mannitol 24h after allergen challenge in atopic asthmatics. Allergy. 2015;70(6):682-8.

42. Nomani S et al. Allergen inhalation challenge, refractoriness and the effects of ibuprofen. Allergy Asthma Clin Immunol. 2016;12:24.

43. Robinson DS. Inhaled allergen challenge in assessment of biologics for asthma. Clin Exp Allergy. 2014;44(1):2-5.

'NO STENT LEFT BEHIND': A REVIEW OF STENT REMOVAL AND RELATED COMPLICATIONS

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ABSTRACT

Recently, there have been enormous developments in the endoscopic management of central airway obstruction secondary to benign or malignant processes. Airway stents are an essential component of such management. They provide rapid relief to patients with central airway obstruction. However, like any other foreign object introduced into the body, airway stents have their own complications. These can range from benign, such as increased coughing, to fatal, due to massive haemorrhage. Placement of a stent is a temporary bridging therapy to allow the patient to undergo chemotherapy or radiotherapeutic management. Airway stents should not be left *in situ* for long, as they themselves can become a disease in patients who already have life-limiting diseases. Hence, the motto at our centre is 'no stent left behind', with the only caveat being that they are left behind when the removal itself could cause death. In this paper, we will review the recent literature covering the removal of airway stents. We also describe our experience with airway stents removal. We conclude that efforts should be made to remove all airway stents when the primary disease is controlled. No stent left behind!

Keywords: Endoscopy, airway stents removal, airway stenosis.

INTRODUCTION

Over the last few decades, there has been enormous development in the endoscopic management of central airway obstruction secondary to benign or malignant conditions.[1] Airway stents have become an integral part of the endoscopic management of inoperable conditions causing central airway obstruction.[2,3] They are specifically designed to mimic the airway, in order to restore patency.[4]

Previous reports have described certain features of an ideal airway stent: re-establish the airway; minimal morbidity and mortality; limited migration, while being easily removable if necessary; maintain luminal patency without causing ischaemia or erosion into adjacent structures; minimal granulation tissue (GT) formation; easy to place; and affordable.[5,6] Unfortunately, the perfect stent has yet to be found; every stent available has its own advantages and disadvantages. Similar to any device introduced into the body, stents have their own complications and indications to be removed.[7] Due to an increase in the use of stents, in 2005 the U.S. Food and Drug Administration (FDA) published an advisory on the use of metallic stents in patients with benign airway diseases.[8] The advisory clearly recommended that in patients with benign airway compression, self-expandable metallic stents (SEMAS) should only be used after thoroughly exploring all other treatment options and the insertion and removal of SEMAS, if this is the only option available, should be done by a physician trained or experienced in metallic tracheal stent procedures. The stent of choice for these patients continues to be silicone stents.

Removal of stents is not without complications. There are reports of hospitalisations and intensive care unit admissions in 78% and 39% airway stent removal cases, respectively. The estimated median

total cost per stent removal in the same study was $10,700 (range: $3,700–69,800).[8] This paper reviews the recent literature for the removal of airway stents. As there are numerous reviews on stent insertion, they will not be discussed in this paper.[5,9] We also describe our experience with airway stent removal.

METHODOLOGY

A search on PubMed and Google Scholar was performed in November 2016, using the keywords 'airway stents', 'tracheobronchial stent', and 'stent removal'. Relevant articles were reviewed from 1990 until November 2016. There were 42 articles published that discussed airway stents. Eight were excluded as they discussed surgical removal and reconstruction of the tracheobronchial tree.

At our centre, we use partially and fully covered stents, as well as silicone stents. Table 1 outlines our experience with stents, and Figure 1 outlines our protocol for the evaluation for stent placement and its subsequent removal. We recently removed a tracheal stent from a patient that was inserted 26 years ago for trauma-related tracheomalacia and resulted in obstruction of the trachea with GT (Figure 2A and 2B). Figure 3 shows a CT scan image of a patient before and after stent removal. Figure 4 depicts a migrated stent.

Table 1: Our overall experience with airway stents.

Indication for insertion	Partially covered SEMAS		Fully covered SEMAS		Silicone		Patient deaths potentially attributable to the stent
	(a)	(b)	(a)	(b)	(a)	(b)	
Malignant CAO	35	23	25	25	15	15	4/68
Benign CAO	0	0	1	1	28	28	0/0
Tracheomalacia	0	0	0	0	11	11*	1/1
Tracheobronchial fistulas	0	0	1	1	5	0	0/1

(a) Deployed; (b) Removed; (*) Removed and replaced.
CAO: central airway obstruction; SEMAS: self-expandable metallic stents.

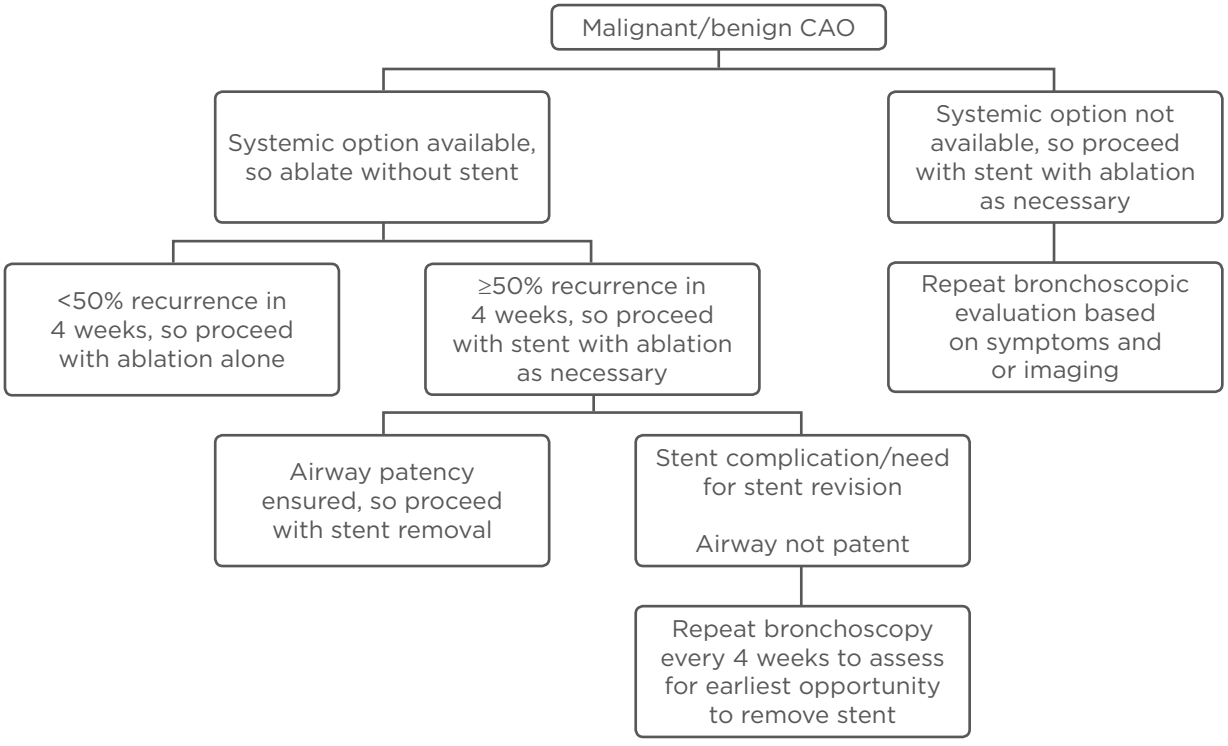

Figure 1: Our approach to central airway obstruction.
CAO: central airway obstruction.

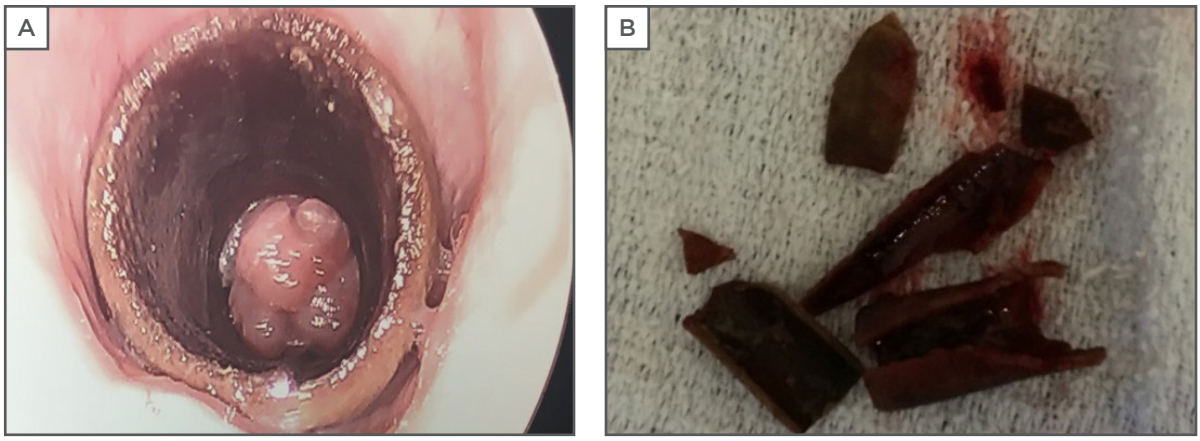

Figure 2: Silicone stent.
A) The silicone stent is almost completely occluded with granulation tissue at the site of tethering suture. The stent was present within the patient for 26 years. B) The silicone stent *ex vivo*. The stent fragmented upon removal (to our knowledge, at 26 years this is the longest a stent has remained within a patient).

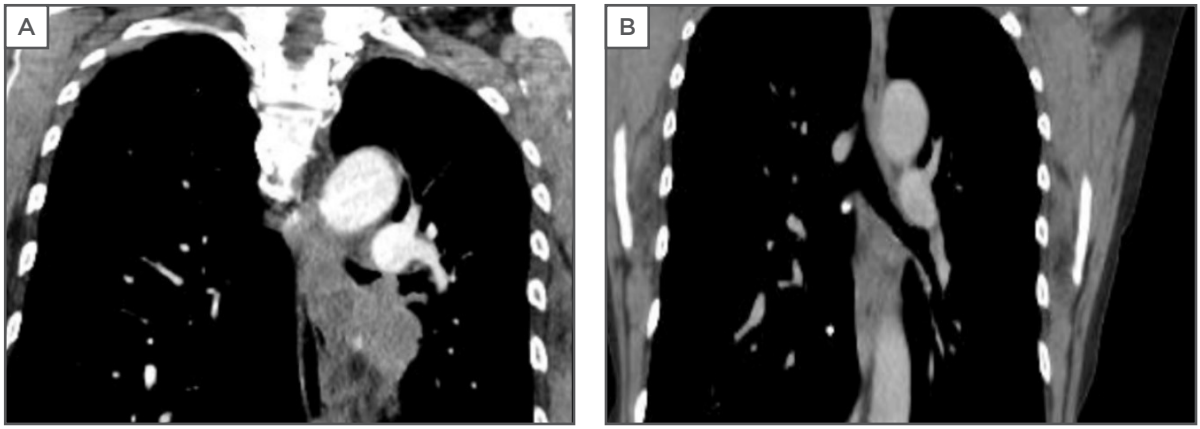

Figure 3: A) Computed tomography scan image showing recurrent obstruction secondary to adenocarcinoma of the lung. B) Computed tomography scan image after stent removal, after 4 months on erlotinib treatment.

INDICATIONS FOR STENTS REMOVAL

As use of airway stents gains popularity, complications are subsequently becoming more frequent.[6] Removal of stents is considered when they are either not necessary or a major complication is imminent. Incidences of complications vary widely, from 13–72% in various reports.[10,11] The complications are related to stent type, location of stenosis, and type of stenosis. Chhajed et al.[12] showed that patients who develop tracheobronchial stenosis after pulmonary transplantation had reduced survival rates in the event of tracheobronchial stent complications. Certain complications occur more frequently in one type of stent compared to others. For example, SEMAS are associated with higher rates of GT formation, stent fracture, erosion into adjacent structures, and bacterial colonisation compared to other types of stents.[8,13-15]

COMMON COMPLICATIONS SECONDARY TO AIRWAY STENTS

Migration

Migration is one of the most common complications associated with stents.[6] Silicone stents are more likely to migrate than metal stents and can even be expelled from the airway. This complication can be explained by the nature of the stent. Silicone stents usually maintain their predetermined shape and diameter, whereas metal stents expand to fit the airway when deployed.[6,16]

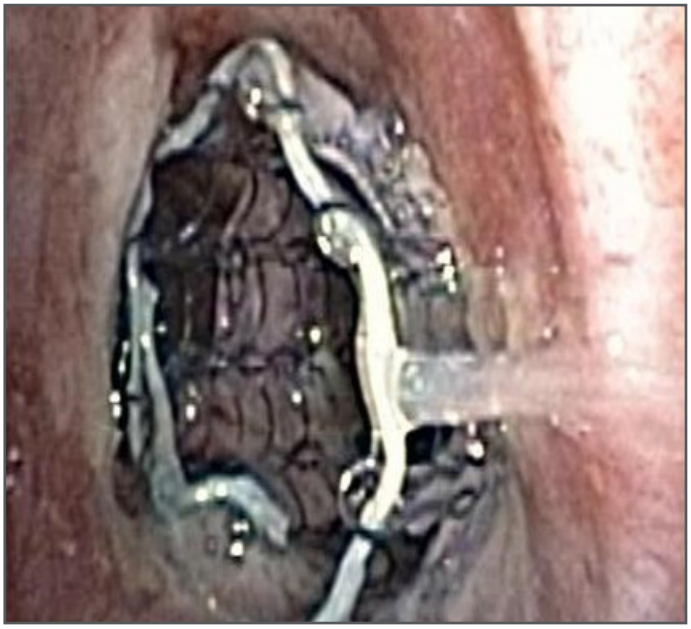

Figure 4: A bronchoscopic image demonstrating a migrated, partially covered SEMAS obstructing the left main bronchus.
SEMAS: self-expandable metallic stent.

Granulation Tissue

Formation of GT is more likely to form at the proximal and distal end of a stent and, in severe cases, granulation can cause in-stent stenosis (Figure 2).[17] In addition to causing obstruction, GT can serve as a nidus for bacterial growth.[18] In a study conducted by Wang et al.,[19] granuloma formation was found to be the most common complication of both covered metallic stents (CMS) and uncovered metallic stents (UCMS). It was also noted that the location of GT was different between the two groups. GT was common at the end of CMS, whereas it occurred as an in-growth in UCMS.[19]

Impaired Mucociliary Function

Similar to GT, lack of mucociliary clearance can lead to obstruction and infection of the stent. Unlike plastic stents, metallic stents permit mucosalisation through their interstices, which could preserve mucociliary function.[20,21]

Stent Fracture

Although stent fractures are an uncommon complication, when they do occur it is usually with metal stents. Stent breakage requires urgent removal to minimise the upper airway effects of stent collapse and subsequent distal fragmentation of metallic pieces.[6,16]

Patient Intolerance

Some patients do not tolerate long-term stent placement. Stiff, longer stents are not as well tolerated as short, flexible, compliant stents. In addition, proximally placed stents are not as well tolerated as distal trachea-bronchial stents.[6] We once managed a patient who had a hybrid Y stent placed for tracheobronchomalacia with marked airway narrowing; the patient's stent had to be removed the same day, as they could not tolerate the stent *in situ* and had suffered a persistent cough.

Haemoptysis

Balloon-expandable metal stents are more likely to erode the tracheobronchial tree and lacerate major blood vessels if they over-expand, or have a shear force that is being exerted at the bronchial wall.[22]

Another indication for stent removal is when it is no longer required. In a study performed by Wang et al.,[19] 35% of the CMS and 16.7% of the UCMS were removed when they had achieved their goal of allowing for therapy.[19] In a separate series, it was reported that 21 of 48 prosthesis removals were justified by an apparent cure.[23] However, Buiret et al.[24] only reported two removals that were justified by an apparent resolution of the stenosis.

PREDICTORS OF STENTS REMOVAL

Buiret et al.[24] performed a broad study evaluating several stent brands. It was found that the only significant predictive factor for prosthesis removal was the brand of the prosthesis.[24] Contrary to the study by Saad et al.,[25] this finding was independent of the benign or malignant nature and precise cause of the stenosis, and independent of the type of prosthesis (for example, non-expandable, expandable covered, or uncovered). Buiret et al.[24] reported the stability of each separate brand of prosthesis (the hazard ratio [HR] represents the probability of maintenance of the prosthesis): Ultraflex (HR: 1), covered Wallstent (HR: 2.496), Cook (HR: 8.701), Hanarostent (HR: 9.372), Aboulker (HR: 10.424), Tracheobronxane (HR: 10.626), Novatech Silmet (HR: 17.750), uncovered Wallstent (HR: 57.8), Novatech Y (HR: 88.268), and Rush Y (HR: 122.902).[24]

Dasgupta et al.[26] assessed 37 patients and reported that the longer a patient has an airway stent fitted, the greater the risk of complications. They noted a complication rate of 0.06 per patient month, with 19 complications in 318 months.

Most of the complications encountered in the series were obstructive granulomas and non-obstructing GT (two patients).

TECHNIQUES AND CHOICE OF ANAESTHESIA IN STENT REMOVAL

Three basic steps have been described to remove a stent: a) assessing degree of incorporation, b) freeing the stent from the mucosa, and c) removing the stent from the airway.[1] Nashef et al.[27] reported their experience in removing four Gianturco stents and described the procedure as "...similar to that of rolling spaghetti on a fork, but much more difficult and at least equally messy."

At our institute, we place silicone tracheobronchial stents, hybrid and silicone Y stents, and fully covered and partially covered SEMAS. After placement, as per Figure 1, we perform routine surveys of the airways with flexible bronchoscopy every 4–6 weeks, based on patient comfort and factors that may impact scheduling. The stents are evaluated for the presence of any criteria for removal, be it a complication or resolution of the disease that required a stent. Once the decision is made to remove, we plan the removal based on the difficulty level, judged by the stent and airway interphase.

Simple Removals

When the stent is fairly free in the airway or a 'floating stent', we intubate with the rigid bronchoscopy and grasp-roll-remove the stent. We re-intubate to clean the debris and determine that the patient does not need another stent. These removals have not been associated with any complication. Silicone stents and fully covered SEMAS are usually easy to remove.

Moderately Difficult Removals

These are usually partially covered stents.

- If the stent appears to have a significant ingrowth with GT, we treat the GT with cryo-therapy or heat ablative therapy (argon plasma coagulation or laser). This reduces the stent incorporation into the airway wall, making them easier to remove.
- If the stent's edge could potentially cause airway injury, we slide the bevel of the rigid scope gently between the stent and the airway and remove. If injury occurs, we place a silicone stent across the breach and remove it in 2 weeks.
- Development of a tracheaoesophageal fistula has occurred once and was treated via removal of the offending stent, and replacement with a Y silicone stent.

Extremely Difficult Removals

These always occur with UCMS. We do not place them within our institute but have had referrals for incorporated stent removals. These stents should only be approached with multidisciplinary planning, including radiologic and bronchoscopic evaluation, in concert with cardiothoracic surgery backup. The stents have to be removed in a piecemeal fashion, with short segments removed at a time. Bleeding usually occurs and can lead to a breach in the airway or vascular system that may require emergent thoracic surgery. For indications that require a bare metal stent placement, the removal should be within 2 weeks.

Removal Based on Stent Types

Silicone stents

These tend to be the easiest to remove. We grasp the proximal end, roll the stent with the forceps, and then pull the stent out.

Self-expandable metallic stents

- Fully covered: these are reliably easy to remove, similar to the silicone stents. We use the same technique; the proximal end is grasped, the stent rolled, and then pulled through, using a rigid bronchoscope.
- Partially covered: these tend to be a little more difficult to remove after the first 28 days. However, we evaluate the stents every 4–6 weeks until the need for the stent is resolved. Once the decision is made to remove the stent, it is done either in a one-step method, for partially covered SEMAS that are free from any significant GT, or endothelialisation. Alternatively, if there is significant GT involvement of the uncovered part of the stent, we treat the GT with cryotherapy or ablation and then reevaluate within a week. We have been able to remove all but one stent completely intact when using the two-step method. For the one case where this was not possible, the distal end of the stent was unravelled, and took multiple attempts to remove all wires from the airway.

We recommend all stents be removed in operative rooms under general anaesthesia; any other site

places the patient under undue risk. We have not yet had to admit or observe any of our stent removals ≥2 hours post operation. No major complications have been noted after the removal at our institution.

COMPLICATIONS OF STENT REMOVAL

Complications of stent removal include bleeding, mucosal tears with or without bleeding, re-obstruction requiring new stent placement, GT behind the stent, damage to the bronchoscope, damage to the pulmonary artery, pneumothorax, postoperative mechanical ventilation, retained stent pieces and unsuccessful removal, and death.[1] In a retrospective analysis performed in 43 patients with 47 tracheobronchial stents, Wang et al.[28] reported two major post-removal complications: profuse haemorrhage (n=4) and mucosal tear (n=15). In a report by Kao et al.,[29] a critical airway obstruction occurred during the removal of a welded tracheal stent using rigid bronchoscopy, which required urgent use of cardiopulmonary bypass. The remaining pieces of the stents were removed successfully by directly opening the trachea.

FACTORS PREDICTING STENT REMOVAL-RELATED COMPLICATIONS

Many authors reported factors that predict complications of the stent removal. Murgu et al.[30] reported three factors that can predict post-removal complications: type of stent, duration of indwelling stent, and initial indication for stent placement. Such data is important as it could prepare the physician for the complications. The type of stent was studied and was found to have prognostic significance in stent removal complications. Uncovered SEMAS have a higher removal complication rate than covered ones, due to tumour ingrowth, GT, or endothelialisation.[30] Reports by Wang et al.[28] and Chan et al.[31] revealed a higher failure rate with uncovered versus covered stents. Wang et al.[28] reported that the proportion of failed removal was 2.8-times higher for uncovered SEMAS than for covered SEMAS. Stent fracture during removal is more common with uncovered SEMAS, possibly due to stent embedding and/or GT.[28]

Duration of indwelling stent is another predictor of stent removal-related complications.[8,30,32] Alazemi et al.[8] noted no major complications in SEMAS that were removed within 30 days of insertion. A similar trend was observed by Thornton et al.[33] Although only two patients (5%) in their series required additional therapeutic interventions within 30 days after their SEMAS placement, 15 patients (38%) developed significant complications after 30 days (mechanical stent failure and stent obstruction) requiring additional intervention. While Lunn et al.[32] found that complications related to SEMAS removal increased for every additional month they had been in place, Shah et al.[34] did not find a relation between the development of complications and length of stent placement.

Initial indication for stent placement can also predict post-removal complications. Patients who had their SEMAS initially placed for underlying benign diseases were more likely to experience complications, need for hospitalisation, longer hospital stay, and had higher total costs associated with their stent removal.[8,30,32] The reasons are likely related to longer survival and thus more time for the development of the complications, including embedding in the airway wall, GT formation, stent fatigue, and fracture. Stent removal in such cases can be difficult and hazardous, as it can result in mucosal tears, severe bleeding, re-obstruction, and respiratory failure with the need for postoperative mechanical ventilation, and tension pneumothorax.[32] Stents are a benefit for patients struggling with central airway obstruction; however, constant vigilance is required to ensure complications do not arise.

CONCLUSION

Removing a tracheobronchial stent can have significant risks that may lead to major complications. Once placed, constant vigilance is necessary to judge the correct time to remove the stent. Careful and strategic planning is required by the physician performing the initial stent placement and/or removal. No stent should ever be left behind once it is not needed. We eagerly await the development of biodegradable stents and custom designed stents. These could obviate some of the complications that are associated with airway stents, which, in turn, would decrease the burden on the healthcare system as well as the patients.

REFERENCES

1. Doyle DJ et al. Anesthesia and airway management for removing pulmonary self-expanding metallic stents. J Clin Anesth. 2009;21(7):529-32.

2. Ernst A et al. Central airway obstruction. Am J Respir Crit Care Med. 2004;169(12):1278-97.

3. Lund ME et al. Airway stenting: Applications and practice management considerations. Chest. 2007;131(2):579-87.

4. Ranu H, Madden BP. Endobronchial stenting in the management of large airway pathology. Postgrad Med J. 2009; 85(1010):682-7.

5. Chin CS et al. Airway stents. Ann Thorac Surg. 2008;85(2):S792-6.

6. Zakaluzny SA et al. Complications of tracheobronchial airway stents. Otolaryngol Head Neck Surg. 2003; 128(4):478-88.

7. Murthy SC et al. Removal of self-expandable metallic stents: Is it possible? Semin Respir Crit Care Med. 2004;25(4):381-5.

8. Alazemi S et al. Outcomes, health-care resources use, and costs of endoscopic removal of metallic airway stents. Chest. 2010;138(2):350-6.

9. Casal RF. Update in airway stents. Curr Opin Pulm Med. 2010;16(4):321-8.

10. Lemaire A et al. Outcomes of tracheobronchial stents in patients with malignant airway disease. Ann Thorac Surg. 2005;80(2):434-7.

11. Kapoor BS et al. Endobronchial stent placement for the management of airway complications after lung transplantation. J Vasc Interv Radiol. 2007;18(5):629-32.

12. Chhajed PN et al. Interventional bronchoscopy for the management of airway complications following lung transplantation. Chest. 2001;120(6): 1894-9.

13. Burningham AR et al. Metallic tracheal stents: complications associated with long-term use in the upper airway. Ann Otol Rhinol Laryngol. 2002;111(4):285-90.

14. Miyamoto T et al. Successful surgical management of a tracheopulmonary artery fistula caused by an intratracheal expandable metal stent. Jpn J Thorac Cardiovasc Surg. 2001;49(10):632-4.

15. Noppen M et al. Bacterial colonization of central airways after stenting. Am J Respir Crit Care Med. 1999;160(2):672-7.

16. Rafanan AL, Mehta AC. Stenting of the tracheobronchial tree. Radiol Clin North Am. 2000;38(2):395-408.

17. Filler RM et al. Tracheobronchial stenting for the treatment of airway obstruction. J Pediatr Surg. 1998;33(2):304-11.

18. Jacobs JP et al. The role of airway stents in the management of pediatric tracheal, carinal, and bronchial disease. Eur J Cardiothorac Surg. 2000;18(5): 505-12.

19. Wang H et al. Endoscopic removal of metallic airway stents. J Bronchology Interv Pulmonol. 2011;18(1):31-7.

20. Furman RH et al. The use of balloon-expandable metallic stents in the treatment of pediatric tracheomalacia and bronchomalacia. Arch Otolaryngol Head Neck Surg. 1999;125(2):203-7.

21. Ruegemer JL et al. Effect of the Palmaz balloon-expandable metallic stent in the trachea of pigs. Otolaryngol Head Neck Surg. 1999;121(1):92-7.

22. Urschel JD. Delayed massive hemoptysis after expandable bronchial stent placement. J Laparoendosc Adv Surg Tech A. 1999;9(2):155-8.

23. Martinez-Ballarin JI et al. Silicone stents in the management of benign tracheobronchial stenoses. Tolerance and early results in 63 patients. Chest. 1996;109(3):626-9.

24. Buiret G et al. Determination of predictive factors of tracheobronchial prosthesis removal: stent brands are crucial. Ann Otol Rhinol Laryngol. 2011; 120(5):307-13.

25. Saad CP et al. Self-expandable metallic airway stents and flexible bronchoscopy: long-term outcomes analysis. Chest. 2003;124(5):1993-9.

26. Dasgupta A et al. Self-expandable metallic airway stent insertion employing flexible bronchoscopy: preliminary results. Chest. 1998;114(1):106-9.

27. Nashef SA et al. Expanding wire stents in benign tracheobronchial disease: indications and complications. Ann Thorac Surg. 1992;54(5):937-40.

28. Wang HW et al. [Endoscopic retrieval of metallic stents in patients with airway diseases]. Zhonghua Yi Xue Za Zhi. 2010;90(20):1411-5. (In Chinese).

29. Kao SC et al. Welded tracheal stent removal in a child under cardiopulmonary bypass. Br J Anaesth. 2003;91(2):294-6.

30. Murgu S, Stoy S. The when, the how and the why of metallic stent removal. J Bronchology Interv Pulmonol. 2016;23(4):266-71.

31. Chan AL, et al. Do airway metallic stents for benign lesions confer too costly a benefit? BMC Pulm Med. 2008;8:7.

32. Lunn W et al. Endoscopic removal of metallic airway stents. Chest. 2005; 127(6):2106-12.

33. Thornton RH et al. Outcomes of tracheobronchial stent placement for benign disease. Radiology. 2006; 240(1):273-82.

34. Shah SK et al. Removal of self-expanding metallic stents. J Bronchology Interv Pulmonol. 2016;23(4):279-82.

MANAGING EXTUBATION AND THE POST EXTUBATION PERIOD IN THE INTENSIVE CARE UNIT

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ABSTRACT

The process of successfully weaning patients from invasive mechanical ventilation is a great challenge for all healthcare providers working in critical care. Despite several recent advances in the care of intensive care patients, failed extubation remains a significant problem that may result in poor patient outcomes. A lack of consensus in many areas regarding clinical approach to extubation and the peri-extubation period exists, and the numerous strategies described in this review add to the complexity of the decision faced by the clinicians involved.

The process of weaning and timing of extubation may be improved by implementation of a consistent multidisciplinary approach to weaning, with a number of easily identifiable risk factors available to support clinical decision making. There are also many known risk factors that can be used to predict the likelihood of extubation failure; whilst these factors may not be easily modifiable, they do allow the identification of patients at a high risk of extubation failure who may require more detailed care and planning post extubation. Finally, a number of strategies, including non-invasive ventilation and high flow nasal oxygen therapy, are available to support carefully selected groups in the post extubation period. Evidence is emerging linking these adjuncts to a reduction in the risk of extubation failure. This article will discuss these risk factors and the evidence supporting their use in this challenging patient group.

Keywords: Extubation, extubation failure, spontaneous breathing trial (SBT), non-invasive ventilation (NIV), high flow nasal oxygen therapy (HFNOT).

INTRODUCTION

The process of weaning from invasive mechanical ventilation (IMV), including discontinuation of IMV and removal of the endotracheal tube or tracheostomy from a patient's airway, is an integral step in the management of a patient in the intensive care unit (ICU). Guidance on the optimal strategies and timing of weaning are varied and the process is beset by potential complications. Extubation failure is arguably the most serious complication of weaning and is defined as the need for reintubation within a 48-hour period of initial removal of the patient from IMV.[1] Extubation failure is associated with several adverse healthcare-related outcomes and is thus of great significance to both healthcare providers and patients.

Despite numerous advances in intensive care management in recent years, extubation failure rates have remained relatively unchanged over the last decade, with ≤25% of patients extubated in an ICU requiring reintubation within 48 hours.[2] It is widely reported that reintubation secondary to post extubation respiratory failure is associated with several adverse outcomes, including increased hospital length of stay and mortality.[3,4] These risks, however, must be balanced against the risks associated with continued and prolonged IMV, which, in turn, may be associated with significant complications.[5]

Several approaches have been studied to improve the process of weaning from IMV by facilitating a successful transition from IMV to spontaneous ventilation. These range from careful patient selection to supportive treatments to minimise the

risk of failure following extubation. This article will review the current evidence behind these strategies and discuss the challenges encountered when extubating patients in the ICU.

WHEN TO EXTUBATE

It is not disputed that in the acute setting, both intubation and IMV are essential as well as life-saving interventions that are mainstays of care in critically ill patients.[6] However, it is also well documented that prolonged IMV is associated with a number of adverse outcomes, including ventilator associated pneumonia, ICU-acquired weakness, and increased hospital length of stay.[5,7] Several stages of mechanical ventilation have been proposed (Figure 1), with the weaning process beginning after reversal of the precipitating cause that led to intubation.[1] Weaning encompasses the patient journey from the initiation of reducing ventilator support to the removal of the endotracheal tube.[8]

This transition from IMV to spontaneous breathing in the critical care population is often complex with multiple confounding factors to consider[9] and differs significantly from the process of waking and extubation following general anaesthesia for surgical procedures. Patients starting the weaning process early and extubating rapidly have lower rates of mortality and morbidity.[5] Despite awareness of this, weaning from IMV in the ICU is often delayed, which increases the risk of patient complications as well as the cost and stress on already stretched healthcare resources.[1,5,10] The rationale that weaning can often be started earlier in the ICU is supported by the findings of Epstein et al.,[11] who found that ≤50% of patients accidentally extubated in the ICU did not require subsequent reintubation.

Despite the presence of several studies comparing different methods of weaning, no real consensus as to the optimal weaning method exists. Some authors promote gradual reduction in pressure support (PS)[12] over a period of time until patients reach a point of being comfortable on little or no PS; other studies suggest that daily spontaneous breathing trials (SBT) (often via a T-piece) are just as effective.[13,14] Perhaps of greatest importance when faced with such a challenging clinical problem is a multi-disciplinary team approach. The inclusion of nursing staff, physiotherapists, and specialists in the rehabilitation process to help deliver care, giving different perspectives, is thought to have a beneficial effect on clinical outcomes in weaning patients.[15] Thorough assessment, consistency in practice, adherence to principles of best practice, established care bundles such as ventilator-associated pneumonia prevention, and consideration of each patient's individual care, are all vital elements when planning a weaning strategy.[9]

Liberation from mechanical ventilation via the process of extubation is arguably the pivotal event within the weaning process and must be performed at an early enough stage to limit the risks of prolonged IMV but not so early as to increase the risk of extubation failure and all its associated complications. As such, it is vital that clinicians consider a large amount of clinical and patient factors prior to making the decision to proceed to extubation. This decision involves an evaluation of the patients' ability to breath spontaneously and consideration of other factors, such as how and when to extubate, the potential for airway difficulty in the event of extubation failure, and what interventions may be available to prevent life threatening complications. Despite principally pertaining to anaesthesia practice, it would be naïve of the intensivist to disregard the Difficult Airway Society[16] guidance on extubation, which is relevant to critical care practice. This guidance highlights the issues that may be easily overlooked, including assessing for previous airway difficulty and optimisation of non-patient factors, including location, the presence of skilled personnel, and the availability of emergency airway equipment, such as airway exchange catheters and laryngeal mask airways. Patient position is also important, with semi upright positions being preferred to facilitate spontaneous breathing and relative ease of reintubation if required.[16,17] The 4th National Audit Project (NAP4) of the Royal College of Anaesthetists[18] highlighted critical care as a high-risk area for adverse airway events, with poor identification of at-risk patients, insufficient planning, and inadequate skilled personnel reported as triggers of such events. It is therefore paramount that those involved in the extubation process are fully aware of the potential pitfalls of airway management and are trained accordingly.[16]

In contemporary critical care practice, there has been a move away from performing early tracheostomy to facilitate faster weaning, based on the findings of several large and robust studies,[19,20] and as such it is becoming less common for the procedure to be performed in patients ventilated for <10 days.

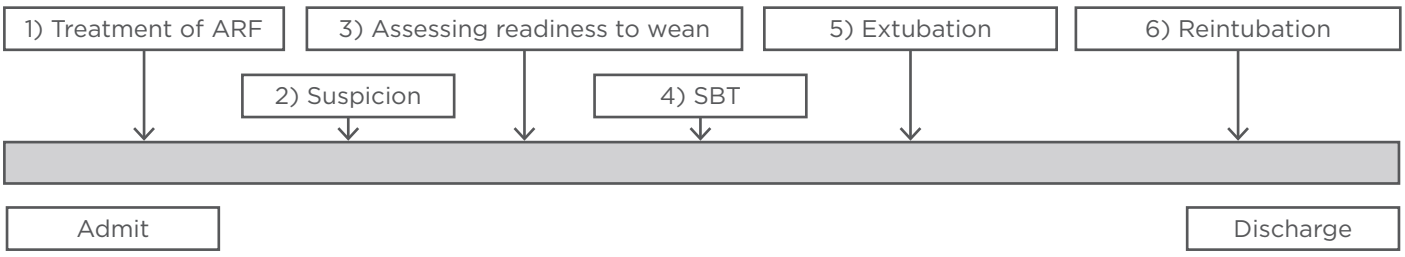

Figure 1: Stages of mechanical ventilation.
ARF: acute respiratory failure; SBT: spontaneous breathing trial.
Adapted from Boles et al.[1]

However, there remains a cohort of critical care patients, including those with known upper airway obstruction or neurological conditions resulting in lasting bulbar dysfunction, in whom an early tracheostomy without attempted extubation may be beneficial. This prevents patients in whom successful extubation is highly unlikely being exposed to the often significant risks associated with a failed extubation.

Measures of respiratory muscle strength and capacity, such as the rapid shallow breathing index (RSBI) and maximal inspiratory pressure, correlate inconsistently with a patient's ability to successfully extubate. Additionally, individual clinician judgement has been demonstrated to have a low sensitivity and specificity in predicting success.[5] Thus, the currently favoured approach is to conduct a SBT lasting between 30 minutes and 2 hours and assess the patient's clinical response during this period. During a SBT the patient breathes with little or no inspiratory PS, using 5–8 cmH_20 PS or a T-piece attached to the ventilator circuit.[6] Again, no clear consensus exists regarding the most appropriate mode or duration of SBT;[6] however, it has been suggested that application of no additional inspiratory PS yields greater validity in the SBT due to its more realistic resemblance of spontaneous breathing. Furthermore, studies have demonstrated that most SBT failures occur within 30 minutes,[21,22] suggesting that a successful SBT of 30 minutes is as good an indicator of successful extubation as one of 120 minutes. Failure of an SBT is commonly defined by the presence of worsening physiological parameters, such as tachycardia, tachypnoea, hypertension, agitation, and anxiety,[8] or a deterioration in gas exchange or ventilatory parameters,[12,13] and should be followed by a period of patient stabilisation on increased ventilator support before a further SBT is considered.

A recent systematic review conducted by the American College of Chest Physicians (ACCP) and American Thoracic Society (ATS),[6] concluded that, for patients ventilated for >24 hours, an SBT with PS of 5–8 cmH_20, rather than a T-piece trial, increased the success of the SBT and subsequent extubation and thus may represent a reasonable approach to assessing readiness to extubate.

PREDICTORS OF SUCCESS AND FAILURE

Despite robust patient assessment with daily sedation holds and SBT, extubation failure remains a significant problem, with reintubation rates remaining as high as 25%.[23] This implies that a SBT alone is not the sole consideration when making the decision to extubate, and it is equally important to attempt to identify patients at a high risk of extubation failure prior to discontinuing IMV. Unfortunately, this remains a difficult clinical decision, with no one test available to perfectly recreate post extubation conditions.[3,4] Clinicians must endeavour to balance the risk of delayed versus premature extubation, both of which are associated with significant increases in poor outcomes,[24] and attempt to use as much information as they can relating to the risk of failed extubation in their patients to guide decision making.[25]

Many of the historical studies investigating extubation failure have been small single-centre trials of low-risk individuals, which lessens the validity of their findings when applied to the wider ICU population.[3] A 2006 study[4] exploring risk factors for failed extubation following a successful SBT revealed an extubation failure rate of 13.4% for those passing an SBT, which was in concordance with previously documented figures. Work of breathing, hypoxia, respiratory acidosis, retained secretions, reduced conscious level, and hypotension were all reported as risk factors

for reintubation in this study. Although this is noteworthy and useful information, there remains the issue of how modifiable or preventable such risk factors are in clinical practice and to what degree these problems may be treatable prior to extubation failure occurring.

A positive fluid balance is widely recognised to have a detrimental effect on extubation success; a finding supported by studies suggesting that congestive cardiac failure patients have higher reintubation rates.[26-28] Furthermore, positive fluid balance is associated with longer periods of IMV[29] and, therefore, may compound the increased risk of extubation failure with the increased morbidity and mortality that occurs secondary to prolonged mechanical ventilation. B-type natriuretic peptide levels have recently been associated with weaning duration. Elevated B-type natriuretic peptide levels at SBT may predict extubation failure[30] and thus could potentially be used to rule out cardiac dysfunction as a source of weaning and extubation failure.

Upper airway obstruction, or oedema, is also an important cause of extubation failure, especially in those patients who successfully pass an SBT and appear to have adequate respiratory mechanics, with one study quoting airway patency as a direct cause of extubation failure in ≤38% of patients.[31] In the presence of a negative cuff leak test, steroid administration may reduce the prevalence of stridor and reduce the rate of reintubation[32] and, thus, should be considered in all patients undergoing extubation with clinical signs of upper airway oedema. The duration of suggested steroid regimes in the literature varies, although a large meta-analysis of 14 studies[33] suggested that steroids should be administered ≥12 hours prior to extubation and for ≤24 hours after. Should concerns exist regarding airway patency without an endotracheal tube or tracheostomy *in situ*, extubation should not be attempted and the opinion of an ear, nose, and throat surgeon should be sought.

The RSBI has been extensively investigated in relation to failed extubation, with several studies supporting its reliability as a predictor of failed extubation.[34] One study concluded that an RSBI >105 was an independent risk factor for failed extubation, with reintubation rates increasing from 11% to 18%.[4] Thus, it seems reasonable to measure RSBI, where possible, prior to making decisions regarding extubation of patients, but it is also vital to consider that while RSBI may be a reliable indicator of respiratory muscle capacity, it does not make any assessment of the airway problems highlighted above and should not be used in isolation as a marker of suitability for extubation.

Risk factors resistant to modification, such as age, pneumonia (as the cause for mechanical ventilation), conscious level, cardiovascular disease, and respiratory disease,[35,36] may not be parameters that can be influenced or changed by clinical care but remain important factors in clinical decision making. Recognition of these factors allows early identification of patients at a high risk of extubation failure and thus enables clinicians to dedicate more attention and resources to patients in the extubation period to achieve the best possible patient outcomes.

Other risk factors less confidently associated with extubation failure include cough strength, secretion load, the presence of delirium, and ICU-acquired polyneuromyopathy. These factors have limited and somewhat conflicting evidence of association, with further studies necessary to define their predictive value in extubation failure.[37,38] A summary of the risk factors for extubation failure and the strength of supporting evidence are shown in Figure 2.

HIGH-RISK PATIENTS AND NON-INVASIVE VENTILATION

Having identified those at a high risk of extubation failure, measures must be taken to avert complications in the post extubation period. Non-invasive ventilation (NIV) may be used to provide respiratory support without the need for tracheal intubation in a wide range of recently extubated patients.[39] This may be in the form of continuous positive airway pressure or non-invasive positive pressure ventilation. Its use in the post extubation period falls into three distinct patient groups that will be addressed separately; namely, as an aid to early extubation, as a prophylactic measure in high-risk extubations, and finally as a treatment for post extubation respiratory distress.[40]

Early extubation and progression to NIV for continued weaning in patients who have failed an SBT but are suitable for weaning has been demonstrated to reduce the length of IMV time and risks associated with ongoing IMV in selected patient groups.[41] This effect appears to be most prominent in patients with chronic obstructive pulmonary disease (COPD) and has been replicated

in several randomised controlled trials and meta-analyses.[42,43] A large multicentre study by Girault et al.[44] that recruited from a more general population of ICU patients found no significant difference in reintubation rates between patients extubated early onto NIV versus conventional weaning, with time spent in the weaning phase increased in the NIV group. It has been suggested that the use of NIV in this way is not presently recommended for general ICU populations but may be an appropriate course of action in patients with chronic respiratory disease, which is supported by recent guidance from the British Thoracic Society (BTS) as a strategy for weaning patients with known COPD.[45]

Prophylactic use of NIV post extubation has been extensively studied in patients deemed to be at a high risk of extubation failure. This has been demonstrated in a number of studies to significantly reduce reintubation rates when used before the onset of post extubation respiratory distress.[23,46,47] The ACCP, ATS,[6] and BTS[45] all present comparable advice stating that patients receiving >24 hours of mechanical ventilation who are at a high risk of extubation failure should receive prophylactic NIV immediately post extubation. Although some debate exists as to what actually constitutes a high risk of extubation failure,[48] with several different definitions used in different studies, there is a general consensus on a number of factors that warrant prophylactic post extubation NIV: being a smoker, age >65 years, known respiratory or cardiovascular disease, poor cough.[23]

NIV in acute respiratory failure caused by pathologies such as exacerbations of COPD[49] and pulmonary oedema[50] is an established treatment that can prevent the need for mechanical ventilation. However, the use of NIV in the treatment of post extubation respiratory failure has been shown to be both ineffective and potentially detrimental. It has been suggested that NIV used in this setting may lead to delays in reintubation once respiratory compromise has occurred, which in turn may increase patient morbidity and mortality;[51] as such, its use is not supported in this setting.

POST EXTUBATION HIGH-FLOW NASAL OXYGEN THERAPY

Following extubation, the conventional method of preventing hypoxia is application of controlled oxygen therapy (COT), usually via a facemask with the fraction of inspired oxygen targeted to a physiological parameter. Facemask oxygen, however, can be cumbersome and is associated with variable levels of oxygen delivery dependent upon the user's peak inspiratory flow. In addition, mucosal drying may occur secondary to a lack of humidification,[52] increasing the risk of extubation failure secondary to secretion retention. High flow nasal oxygen therapy (HFNOT) is a relatively new development in adult populations offering humidified, warmed oxygen at flow rates ≤60 L/min.[53] This may be beneficial to recently extubated patients by providing more accurate oxygen concentrations, generating positive end expiratory pressure and improving gas exchange.[54]

Several studies have investigated HFNOT use in post extubation ICU populations. Maggiore et al.[53] reported improved oxygenation and fewer desaturations compared to COT, perhaps due to improved patient tolerance of the nasal delivery system, and a non-significant trend towards reduced reintubation rates. Hernandez et al.[55] concluded that low-risk patients treated with HFNOT had lower reintubation rates and less commonly developed post extubation respiratory failure compared to those treated with COT.

Figure 2: Risk factors for extubation failure following invasive mechanical ventilation.
ICU: intensive care unit; IMV: invasive mechanical ventilation; RSBI: rapid shallow breathing index.

A more recent study,[56] terminated early due to recruitment issues, found no significant difference in the frequency of post extubation respiratory failure, time to respiratory failure, or length of ICU and hospital stay with HFNOT.

A recently published meta-analysis examining the role of reintubation in post extubation patients suggested that HFNOT is more effective at preventing reintubation than COT[57] and may be as effective as NIV in this setting but without the side effects and patient tolerance problems that may hamper effective NIV delivery. It is important to note that one of the larger studies in the data pool excluded patient groups known to respond well to post extubation NIV, such as those with COPD and cardiogenic pulmonary oedema; thus, the impact of NIV may have been underestimated in this trial.

The use of HFNOT in post extubation patients is a promising development, particularly in those patients deemed at a low risk of developing extubation failure or where NIV intolerance may be an issue. The precise role of HFNOT and how it may be used alongside NIV to achieve optimal clinical outcomes requires further clarification, and robust trials are needed in this important area.

CONCLUSION

Despite many recent advances in ICU practice, optimal management of extubation remains a significant challenge to healthcare providers and carries a significant weight of morbidity and mortality should extubation failure occur. Several weaning strategies are well described in the literature, with an organised approach and consistency in practice seemingly more important than the weaning method used. Although a number of factors are described that may predict extubation failure, few of these are easily modifiable and no universal consensus exists to guide clinicians on when exactly to extubate.

A number of interventions are available to support patients who have been recently extubated, and in particular the timely application of NIV may be greatly beneficial, especially in patients with chronic lung disease or when risk factors present for extubation failure. There is also growing interest in the use of HFNOT in lower-risk patients, and this therapy may play a useful role in carefully selected post extubation populations.

It is evident from the literature that careful planning and assessment at every stage of the patient journey through the ICU, from an organised multi-disciplinary team approach to weaning, through to provision of suitable respiratory support following extubation, are essential to achieve the best possible outcomes in this challenging patient group. Further work is warranted to more clearly define and stratify the risk to patients of extubation in the ICU and identify which treatment strategies should be most effectively used to improve patient outcomes in this challenging area of contemporary practice.

REFERENCES

1. Boles JM et al. Weaning from mechanical ventilation. Eur Respir J. 2007;29(5):1033-56.

2. Thille AW, Boissier F. At the critical time of deciding on extubation, it is too late to assess patient breathlessness. Am J Respir Crit Care Med. 2016;193(12):1438-9.

3. Thille AW et al. Weaning from the ventilator and extubation in ICU. Curr Opin Crit Care. 2013;19(1):57-64.

4. Frutos-Vivar F et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. Chest. 2006;130(6):1664-71.

5. Blackwood B et al. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis. BMJ. 2011;342:c7237.

6. Ouellette DR et al. Liberation from mechanical ventilation in critically ill adults: An official American College of Chest Physicians/American Thoracic Society clinical practice guideline: Inspiratory pressure augmentation during spontaneous breathing trials, protocols minimizing sedation, and noninvasive ventilation immediately after extubation. Chest. 2017;151(1):166-80.

7. Coplin WM et al. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med. 2000;161(5):1530-6.

8. Schultz MJ. Weaning from mechanical ventilation: Stay poised between load and strength. Anesthesiology. 2010;113(2): 273-5.

9. Henneman E et al. Using a collaborative weaning plan to decrease duration of mechanical ventilation and length of stay in the intensive care unit for patients receiving long-term ventilation. Am J Crit Care. 2002;11(2):132-40.

10. Ely EW et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med. 1996;335(25):1864-9.

11. Epstein SK. Preventing postextubation respiratory failure. Crit Care Med. 2006; 34(5):1547-8.

12. Brochard L et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med. 1994;150(4):896-903.

13. Esteban A et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Eng J Med. 1995;332:345-50.

14. Vitacca M et al. Comparison of two methods for weaning patients with chronic obstructive pulmonary disease requiring mechanical ventilation for

more than 15 days. Am J Respir Critical Care Med. 2001;164(2):225-30.

15. Chan PK et al. Practising evidence-based medicine: The design and implementation of a multidisciplinary team-driven extubation protocol. Crit Care. 2001;5(6):349-54.

16. Frerk C et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. B J Anaesth. 2015;115(6):827-48.

17. Popat M et al.; Membership of the Difficult Airway Society Extubation Guidelines Group. Difficult Airway Society Guidelines for the management of tracheal extubation. Anaesthesia. 2012; 67(3):318-40.

18. Cook TM et al.; Fourth National Audit Project. Major complications of airway management in the UK: Results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: Anaesthesia. B J Anaesth. 2011;106(5): 617-31.

19. Young D et al. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: The TracMan randomized trial. JAMA. 2013;309(20):2121-9.

20. Terragni PP et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: A randomized controlled trial. JAMA. 2010;303(15): 1483-9.

21. Esteban A et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med. 1997; 156(2 Pt 1):459-65.

22. Perren A et al. Protocol-directed weaning from mechanical ventilation: Clinical outcome in patients randomized for a 30-min or 120-min trial with pressure support ventilation. Intensive Care Med. 2002;28(8):1058-63.

23. Thille AW et al. Easily identified at-risk patients for extubation failure may benefit from noninvasive ventilation: a prospective before-after study. Crit Care. 2016;20:48.

24. Thille AW et al. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med. 2011;39(12): 2612-8.

25. Frutos-Vivar F et al. Outcome of reintubated patients after scheduled extubation. J Crit Care. 2011;26(5):502-9.

26. Upadya A et al. Fluid balance and weaning outcomes. Intensive Care Med. 2005;31(12):1643-7.

27. Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. Am J Respir Crit Care Med. 1998;158(2):489-93.

28. Cabello B et al. Physiological comparison of three spontaneous breathing trials in difficult-to-wean patients. Intensive Care Med. 2010;36(7): 1171-9.

29. Wiedemann HP et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354(24):2564-75.

30. Mekontso Dessap A et al. Natriuretic peptide-driven fluid management during ventilator weaning: A randomized controlled trial. Am J Respir Crit Care Med. 2012;186(12):1256-63.

31. Francois B et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial. Lancet. 2007;369(9567):1083-9.

32. Pluijms WA et al. Postextubation laryngeal edema and stridor resulting in respiratory failure in critically ill adult patients: Updated review. Crit Care. 2015; 19:295.

33. McCaffrey J et al. Corticosteroids to prevent extubation failure: A systematic review and meta-analysis. Intensive Care Med. 2009;35(6):977-86.

34. Bien MY et al. Breathing pattern variability: A weaning predictor in postoperative patients recovering from systemic inflammatory response syndrome. Intensive Care Med. 2004; 30(2):241-7.

35. Namen AM et al. Predictors of successful extubation in neurosurgical patients. Am J Respir Crit Care Med. 2001;163(3 Pt 1):658-64.

36. Salam A et al. Neurologic status, cough, secretions and extubation outcomes. Intensive Care Med. 2004; 30(7):1334-9.

37. Smina M et al. Cough peak flows and extubation outcomes. Chest. 2003; 124(1):262-8.

38. Khamiees M et al. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. Chest. 2001;120(4): 1262-70.

39. Glossop AJ et al. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the postoperative period: a meta-analysis. Br J Anaesth. 2012;109(3):305-14.

40. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374(9685):250-9.

41. Ferrer M et al. Noninvasive ventilation during persistent weaning failure. a randomized controlled trial. Am J Respir Crit Care Medicine. 2003;168(1):70-6.

42. Burns KE et al. Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: Meta-analysis and systematic review. BMJ. 2009;338:b1574.

43. Burns KE et al. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: A Cochrane systematic review. CMAJ. 2014;186(3):E112-22.

44. Girault C et al. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: A randomized multicenter trial. Am J Respir Crit Care Med. 2011;184(6):672-9.

45. Davidson AC et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71 Suppl 2:ii1-35.

46. Ferrer M et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173(2):164-70.

47. Nava S et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33(11):2465-70.

48. Glossop AJ, Esquinas AM. Using noninvasive ventilation to prevent extubation failure: it is good news, but do we really know what "high risk" means? Crit Care. 2016;20(1):213.

49. Keenan SP et al. Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: A meta-analysis. Crit Care Med. 1997;25(10):1685-92.

50. Winck JC et al. Efficacy and safety of non-invasive ventilation in the treatment of acute cardiogenic pulmonary edema--a systematic review and meta-analysis. Crit Care. 2006;10(2):R69.

51. Esteban A et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004; 350(24):2452-60.

52. Gotera C et al. Clinical evidence on high flow oxygen therapy and active humidification in adults. Rev Port Pneumol. 2013;19(5):217-27.

53. Maggiore SM et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190(3):282-8.

54. Nishimura M. High-flow nasal cannula oxygen therapy in adults. J Intensive Care. 2015;3(1):15.

55. Hernandez G et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: A randomized clinical trial. JAMA. 2016; 315(13):1354-61.

56. Fernandez R et al. High-flow nasal cannula to prevent postextubation respiratory failure in high-risk non-hypercapnic patients: a randomized multicenter trial. Ann Intensive Care. 2017; 7(1):47.

57. Huang HW et al. Effect of high-flow nasal cannula oxygen therapy versus conventional oxygen therapy and noninvasive ventilation on reintubation rate in adult patients after extubation: A systematic review and meta-analysis of randomized controlled trials. J Intensive Care Med. 2017:885066617705118.

A PATIENT PERSPECTIVE: IDENTIFYING AND UNDERSTANDING THE BARRIERS ASSOCIATED WITH THE DIAGNOSTIC DELAY OF LUNG CANCER

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ABSTRACT

Lung cancer is the most common cancer worldwide and is a fundamental health problem in the UK. Mortality rates are much higher in the UK than other European countries, with overall 5-year survival rates in England and Wales currently as low as 7%. Reducing diagnostic delays may increase the proportion of early stage lung cancer and improve survival, yet the literature surrounding these issues suggests that many people continue to wait a considerable time before presenting symptoms to a clinician. To gain an in-depth understanding into the factors that may influence this delay, this review aims to explore some of the social and psychological barriers that patients face in seeking medical attention for lung cancer symptoms. Likewise, with the majority of lung cancer cases strongly linked to tobacco use, the impact of smoking status and whether it has an effect on an individual's pathway to diagnosis is imperative to this review. The evidence found suggests that delays in symptom reporting are attributed to low perceptions of risk and a difficulty in recognising lung cancer symptoms early, especially when other comorbidities are present. Additionally, the de-normalisation of smoking appears to have confused understanding regarding risk and reinforced blame and stigma, which ultimately hinders help-seeking behaviours. Future research is thus required to develop strategies and interventions that raise awareness of lung cancer symptoms and empower people to engage in help-seeking behaviours.

Keywords: Lung cancer, symptom recognition, diagnostic delay, barriers, patient perspective, stigma, knowledge and awareness, smoking status, demographic factors, late stage.

INTRODUCTION

Lung cancer is the primary cause of cancer mortality,[1] with an estimated 1.6 million new diagnoses and 1.4 million deaths annually.[2] Despite advances in treatment, survival rates in the UK are vastly below the average rates of Europe and America; only 25% of patients with lung cancer in England and Wales survive 1 year post diagnosis, with 7% surviving ≥5 years.[3,4] For those with early stage lung cancer, curative treatment is more likely to be successful,[5] yet only 11% of patients in the UK receive surgery.[4,6] Differences in mortality are largely dependent on lung cancer staging at the time of presentation.[7] Stage I non-small cell lung cancer patients have an average 1-year survival following diagnosis of 58–73%, compared to the 2–13% average survival of those with Stage IV.[7,8]

To maximise patient survival, the barriers that lead to late stage diagnosis need to be considered, including delays in seeking medical attention, the presence of comorbidities, and emotional impacts.[9]

Associated with this is the use of tobacco, with approximately 90% of lung cancer diagnoses linked to cigarette smoking.[6] Typically, a lifetime smoker is 20-times more likely to be at risk of developing lung cancer compared to a non-smoker.[6] A recent UK prospective study[10] indicated that smokers have larger tumours at the time of diagnosis and increased presence of metastatic disease compared with non-smokers.[11] While it is biologically plausible that nicotine can accelerate abnormal cell development,[6] this progression in smokers may also be due to psychological and behavioural factors, such as difficulties in recognising symptoms.[3,4,12]

THE PROBLEM: CONSEQUENCES OF A LATE DIAGNOSIS

Delays in patient recognition of symptoms may often lead to late diagnosis, resulting in the advancement of the tumour or presence of metastatic disease.[13,14] The likely impact of a diagnostic delay on survival has been a significant part of a UK national government strategy;[15] however, despite the initiation of several lung cancer campaigns aimed to enhance public awareness of primary symptoms, the delay between identification of symptoms and help-seeking behaviours remains extensive.[16] Based on survey data collected from 172 NHS trusts in England and 3 in Scotland, patients reported delays of 117 days between initial onset of symptoms and diagnosis, with 98–99 days being accounted for by patients delaying in consulting their primary care physician.[4,17] Individual reports however may vary dramatically, with symptoms being recalled anywhere between 4 and 24 months prior to diagnosis.[18] Given the retrospective and self-reporting nature of these studies, the potential for recall bias cannot be discounted.[4,17,19] Likewise, since a proportion of patients either passed away or were clinically unwell prior to completing questionnaires, a different type of bias may have been present.[4,7,12,19] The methodological difficulty of recruiting lung cancer patients due to the rapid clinical decline in condition may further render the data unrepresentative of this population.[12,17] In addition, there is the prospect of confounding data, since details of diagnostic stage, comorbidities, and histological type of cancer were not collected.[4,17,19]

Cross-cultural variations across 16 countries have shown differences in the delay in symptom reporting, which ranges from 7 days to 6 months.[12] Several suggestions have been made to explain this difference: the accessibility to economic resources in the area examined, patient compliance with scheduled appointments, and late presentation of symptoms.[12,14] Due to the range of potential factors, it is difficult to draw any concrete conclusions as to whether delays across European countries, including the UK, are a consequence of the patient or the healthcare system.[12,14] Nonetheless, the considerable delays that lung cancer patients experience accentuate the need for stronger evidence-based clinical epidemiology of presenting symptoms.[20] While this body of evidence is growing,[4,8,13,21] further exploration into the factors that contribute to this delay, particularly in the UK and considering smoking status as a factor, are required.[18,20,22]

LACK OF SYMPTOM AWARENESS AND ASSOCIATED FACTORS

Although lung cancer is regularly identified in asymptomatic individuals who present for other health difficulties,[2] some individuals explicitly experience indications of lung cancer in the early stages yet rarely associate the symptoms with malignancy.[18,23] For patients who do experience symptoms, these can be diverse, including both lung specific symptoms, such as coughing, breathing changes, chest pains, and haemoptysis, as well as systemic symptoms, such as loss of weight or appetite, and fatigue.[24] Difficulties in symptom recognition or awareness of severity can impact delays in seeking medical attention, particularly in patients who self-manage their symptoms.[25] This can lead to an increased risk of tumour progression, metastatic disease, and subsequently late-stage diagnosis.[2,24]

Early identification of lung cancer symptoms combined with medical help-seeking behaviour has the potential to prolong survival for patients with lung cancer.[26] Evidence underlines several variables that are a complex mix of individual and psychosocial factors that have the potential to influence this delay.[5] Factors such as sex, age, and socioeconomic status (SES) have previously been found to correlate with delays in reporting cancer symptoms.[27-29] Additionally, anxiety, perceived severity of symptoms, attitudes toward seeking medical help, and fears of a diagnosis emerge as important psychological factors that perhaps mediate delay and how the patient reports their symptoms on early presentation to a general practitioner (GP).[5,27,30,31] For example, abstaining from seeking medical advice in the fear that their GP will castigate those in need for 'time wasting' presents a repeated barrier to the initiation of diagnostic investigations.[3,5,32]

Awareness and interpretations of symptoms, as well as broader social factors, can delay diagnosis.[4,18,25,28,30] Out of 360 newly diagnosed lung cancer patients, of whom 4% were non-smokers, 270 (75%) reported having no understanding of symptoms, and 171 (51%) described how their first symptom(s) was not serious enough to be associated with the disease.[4] Similarly, retrospective interviews were conducted with 22 lung cancer

patients (of whom 21 were current or former smokers) to obtain a pre-diagnosis symptom history.[18] Although patients described symptoms as a continual change in health status, such as breathing changes, cough, chest pain, or profound fatigue, they did not construe them to be serious at their onset.[5,18] Instead, the most plausible reason for delay was that while symptoms are reported as new, they are often too generic, especially in the context of co-existing respiratory disease (n=11), to raise concern.[3,14,25,31] The likelihood of illness is therefore only contemplated when it is enforced upon patients as a result of the severity of their symptoms.[4,18,31] Nonetheless, the failure to use any objective validation of the presence and timing of data reported questions the validity and reliability of findings.[14]

THE PRESENCE OF COMORBIDITIES

Lung cancer is strongly associated with age and smoking, and both of these factors are associated with increased comorbidities, such as chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular disease, and previous or concurrent malignancies.[32] Statistics show that 88% of patients have a chronic condition, while 22% have ≥5 comorbid diseases.[33] The presence of comorbidities may lead to symptoms being attributed incorrectly (by the patient or doctor) resulting in diagnostic delays.[24] In a study exploring help-seeking behaviours, patients at high risk of developing cancer had greater levels of comorbidities affecting respiratory function, such as COPD.[34] This overlap makes it difficult for patients to differentiate symptoms, and potential lung cancer signs can be mistaken for existing respiratory conditions.[34] This strengthens the argument that perhaps knowledge of a symptom alone is not sufficient to tackle late diagnosis.[18,34,35]

COPD is present in 50–80% of lung cancer patients[33] and includes symptoms of coughing or breathlessness, with risk factors such as smoking.[35] Individuals with COPD have reported taking twice as long to seek medical advice following the onset of symptoms.[3] Smith et al.[4] conducted face-to-face interview surveys and revealed that patients with COPD or those who were long-term smokers had longer delays in seeking medical attention. However, some symptoms were linked to decreased patient time to presentation; for example, those who had previously undergone hospitalisation for a chest infection consulted their doctor in half the time of others.[4]

SMOKING STATUS AS A POTENTIAL BARRIER TO SYMPTOM PRESENTATION

The relationship between smoking and lung cancer is universally recognised, with 80–90% of all lung cancers resulting from tobacco smoke.[5,6,36] Nevertheless, research indicates that smokers, who are at higher risk of developing lung cancer, are less likely to seek medical advice for symptoms.[13,37] A health survey given to 4,193 individuals aged >50 years (2,042 responders) asking patients to report their help-seeking behaviour for symptoms experienced in the past 3 months, demonstrated that smoking status was significantly and independently linked with help-seeking behaviours, with smokers less prone to pursuing medical attention than non-smokers when they experienced symptoms.[13] A notable limitation of this research was the failure to gather data on whether participants pursued assistance for preceding incidents of a cough or hoarseness prior to the 3-month window.[13,38] This is an important factor given that an earlier all clear diagnosis can postpone help-seeking behaviour for continual or new symptoms.[38]

Crane et al.[39] conducted qualitative focus groups, with lay members stratified by smoking status, to explore the presumption that current smokers are more likely to delay seeking help. While symptom knowledge among this cohort was relatively high, smoking groups reported a trend towards a low perceived susceptibility of lung cancer.[39] Downplaying the risk of smoking and a lack of urgency in help-seeking for symptoms considered mild was particularly evident among those most at risk (i.e. smokers).[39] However, it should be noted that the participants were, on average, 10 years younger than most patients diagnosed with lung cancer; thus, confounding the generalisability of these findings.[39] In addition, Carter-Harris et al.[2] found that smoking status is not an independent barrier influencing time taken to present with symptoms. Moreover, a delay in symptom presentation is believed to be associated with the concealing of tobacco use or by individuals linking symptoms they experience to smoking.[40]

Research highlights the lack of knowledge relating to lung cancer risk factors among both smokers and former smokers; it is therefore important to comment that a smoker may not automatically translate risks into knowledge or awareness of typical symptoms associated with this disease.[41] Future exploration is indeed required

to fully comprehend the connection between smoking status and late presentation of lung cancer symptoms.[2]

STIGMA AS A BARRIER TO PRESENTATION TO GENERAL PRACTITIONERS

Evidence describes how many people are reluctant to seek medical advice for respiratory problems due to the stigma surrounding smoking.[1,18,29,38,39,42] Although the de-normalisation of smoking has developed into an encouraging and active pathway to tobacco control, the association between lung cancer and smoking remains strong.[39] Subsequently, both current and former smokers have expressed feelings of blame and stigmatisation by friends, family, and clinicians.[40,42] Therefore, the hesitancy in seeking medical advice can be due to the general assumption that lung cancer is a smoker's disease and, for this reason, self-imposed.[1] However, this assumption also leads to those who have never smoked and ex-smokers often experiencing the same stigmatisation.[1,40]

The relationship of perceived lung cancer stigma (LCS) and timing of medical help-seeking behaviour in symptomatic patients by smoking status was explored in a study; patients were categorised as never, former, or current smokers.[43] The impact of smoking status on perceived LCS revealed no statistically significant findings among the three smoking status groups.[43] Patients with lung cancer have therefore been found to report higher levels of self-blame and poorer self-esteem regardless of smoking status.[1,44] Drawing upon 45 narrative interviews exploring lung cancer patients' perceptions of stigma, participants reported having suffered exceptional stigma and unfair blame for their illness.[45] One participant described that although he had never smoked, he recalled negative attitudes from hospital staff and presumptions that smoking was the primary cause of his disease.[5] Likewise, in a recent qualitative study, many participants felt reprehended because of their smoking history and marked as social outcasts by their families and GP.[42] This can have negative implications for individuals' self-worth and can bring about a sense of self-responsibility and embarrassment.[5,42]

Patients have reported feeling that clinicians have a tendency to incriminate those presenting with lung cancer;[32,46] a similar view was expressed among a group of health professionals, who suggested that experts automatically assume lung cancer patients to be smokers.[46] Consequently, non-smokers experience stigma more severely since they are subconsciously thought to be responsible for their cancer.[47] It is not surprising therefore that the stigma attached to lung cancer acts as an obstruction to help-seeking behaviours and may hold many patients back from reporting distressing symptoms.[48] Indeed, future research is required to validate these findings and to understand LCS as a barrier to early presentation.[46]

THE IMPACT OF LUNG CANCER SCREENING ON EARLY DIAGNOSES

One promising approach for improving late diagnoses is to provide screening programmes for early stage disease.[49] Trials such as the Danish Lung Cancer Screening Trial (DLCST), the Dutch-Belgian (NELSON) trial, and the UK Lung Cancer Screening Trial have been undertaken to determine the efficiency of low-dose computed tomography (CT) in high-risk smokers and ex-smokers.[49-51] Although the National Lung Screening Trial (NLST) reported a 20% relative risk reduction in lung cancer mortality, the favourable prospect of lung cancer screening can only be achieved if individuals at risk participate in screening programmes.[47,49] Research has highlighted that cultural barriers, such as knowledge, fatalistic views about lung cancer or its screening process, mistrust of healthcare systems, and smoking status, may inhibit participation.[50,52]

Silvestri et al.[53] revealed that smokers were less likely to participate in screening trials than non-smokers based on four typological attitudes identified in regard to lung cancer screening: those who fear an expected diagnosis at screening; avoiders, who prefer not to know the outcome of a screening test; fatalists, who feel lung cancer is an uncontrollable disease and view screening as a drawback; and those that perceive stigma and tobacco dependence as a barrier.[49,52] Current smokers held the most negative views and have been found to report emotional barriers, such as fears or worries of what the doctor might say, and avoidance of lung cancer-related information.[52] This is a commonly reported attitude towards delays in symptomatic presentation among smokers, as well as being a clear barrier to screening uptake.[53]

Perceived smoking-related stigma is a largely reported barrier to screening uptake due to

associated feelings of humiliation and self-blame, leading to impeded medical help-seeking behaviour, low levels of patient engagement, and potentially decreased participation in cancer screening.[54] Although it has been suggested that future screening programmes should integrate smoking cessation support strategies with CT lung screening,[50] the role of perceived smoking-related stigma is an essential deterrent to screening that may lead to delays in symptom presentation.[49]

PATIENT DEMOGRAPHIC FACTORS ARE IMPORTANT CONCERN DETERRENTS

Contradictory evidence has emerged to suggest that demographical factors further influence symptom awareness, knowledge, and time taken to present with symptoms.[3,41,55] A few studies in particular established that population samples consisting of low SES and ethnic minority backgrounds have poor awareness of lung cancer symptoms; these are the same demographic groups that generally have cancer diagnosed at an advanced stage.[5,24,41] Although rates of smoking in the UK have fallen in the last decade, the pattern is much more intricate for minority ethnic populations.[56] Evidence suggests that ethnic minority groups possess relatively poor knowledge about smoking and associated diseases, such as lung cancer, and are less likely to cite smoking as a significant health risk.[56] Moreover, tobacco usage is markedly higher among low SES groups, which may account for the prevalence of smoking among some minority ethnic groups.[56,57]

In a UK public-based survey, indications of a link between low SES, lower awareness of cancer warning signs, and greater anticipated delay in seeking help were evident.[9] Inadequate knowledge and understanding of personal risk is suggested to result in late presentation and poorer access to health services.[17,19,41] Interestingly, Quaife et al.[55] recognised that people with higher education and higher SES were more likely to report that they were too busy to seek medical help for symptoms, or were particularly likely to report greater delays of presentation. This finding was further echoed in an analysis of data from the National Survey of NHS patients in the UK.[17] However, two worldwide systematic reviews found no conclusive evidence to suggest that age, sex, SES, and ethnicity influence the presentation of lung cancer symptoms.[28]

PROBLEMS WITH THE CURRENT LITERATURE

A central part of the UK government strategy to decrease cancer mortality is to shorten delays in diagnosis.[15] A significant part of this work involves efforts to reduce the prolonged gap between patients' detecting possible signs of lung cancer and seeking medical assistance.[25] Current studies are limited in size and are insufficient in terms of the reasons associated with delay.[25] This casts doubt over the generalisability of existing findings when transferring them to specific populations.[19] Additionally, most studies recruit patients following a large time lapse since diagnosis; this leads to recall and reporting bias, which has the potential to reduce accuracy of information on the factors influencing the delay in reporting symptoms.[4]

Generally, the literature reviewed highlights the heterogeneous nature of barriers that prevent or delay patients from visiting a clinician with symptoms. These include lack of knowledge,[41] stigmatisation and blame,[45] perceptions that a GP will not be receptive to symptom concerns, and misattribution of symptoms to smoking habits or comorbid conditions.[18,31] Previous research clearly underlines the complexity of smoking status as an additional factor associated with delay, as patients fail to take alarming symptoms seriously enough to warrant medical aid.[13] Nonetheless, much of this research is retrospective and requires further research to unravel the intricate relationship between these variables.[13]

SUMMARY AND RECOMMENDATIONS

In conclusion, identifying the symptoms and factors that prompt an individual to seek medical help is complicated and remains a challenge.[24,25] The initiation of further research to understand the diagnostic process and to ascertain the barriers associated with increased time to presentation is required to promote earlier diagnosis.[5,12,29] Future research should aim to determine the effect on mortality and quality of life of the prompt reporting of symptoms and timely diagnosis of lung cancer.[25] Much can be gained from public awareness campaigns related to other cancers, such as breast and bowel cancer.[25] For these diseases, a strong message that reporting symptoms early and obtaining a rapid diagnosis will inevitably improve chances of survival.[25] This message should be used as a platform for future investigative trials aimed

to ascertain more about the reasons of delayed diagnosis.[13,17] Research findings can facilitate the development of interventions to improve help-seeking behaviours and ultimately improve morbidity, mortality, and psychological outcomes through earlier stage diagnosis.[17]

REFERENCES

1. Tod AM et al. Diagnostic delay in lung cancer: A qualitative study. J Adv Nurs. 2008;61(3):336-43.

2. Carter-Harris L et al. Lung cancer stigma predicts timing of medical help-seeking behaviour. Oncol Nurs Forum. 2014;41(3):E203-10.

3. Corner J et al. Experience of health changes and reasons for delay in seeking care: A UK study of the months prior to the diagnosis of lung cancer. Soc Sci Med. 2006;62(6):1381-91.

4. Smith SM et al. Factors contributing to the time taken to consult with symptoms of lung cancer: A cross-sectional study. Thorax. 2009;64:523-31.

5. Chatwin J et al. The mediation of social influences on smoking cessation and awareness of the early signs of lung cancer. BMC Public Health. 2014;14(1): 1043-53.

6. Parsons A et al. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: Systematic review of observational studies with meta-analysis. BMJ. 2010;340:b5569.

7. Cancer research UK. Lung cancer statistics. 2016. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer. Last accessed: 18 October 2016.

8. Walters et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: A population-based study, 2004-2007. Thorax. 2013;68(6):551-64.

9. Robb K et al. Public awareness of cancer in Britain: A population-based survey of adults. Br J Cancer. 2009; 101(suppl 2):S18-23.

10. Lewis KE, Roberts R. Effect of smoking status at time of diagnosis of lung cancer. Abstract 6501. American Thoracic Society, 18–23 May, 2012.

11. Roberts RE, Lewis KE. Impact on quitting smoking following a diagnosis of Lung Cancer. Abstract 269. European Respiratory Society, 26–30 September, 2015.

12. Jensen AR et al. Impact of delay on diagnosis and treatment of primary lung cancer. Acta Oncologica. 2002;41(2): 147-52.

13. Smith CF et al. Smokers are less likely than non-smokers to seek help for a lung cancer 'alarm' symptom. Thorax. 2016; 71(7):659-61.

14. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. J Thorac Oncol. 2005;60(4):268-9.

15. Smith LK et al. Patients' help-seeking experiences and delay in cancer presentation: A qualitative synthesis. Lancet. 2005;366(6488):825-31.

16. McLachlan S et al. Symptom perceptions and help-seeing behaviour prior to lung and colorectal cancer diagnoses: A qualitative study. Family Practice. 2015;00(00):1-10.

17. Neal RD, Allgar VL. Sociodemographic factors and delays in the diagnosis of six cancers: Analysis of data from the 'National Survey of NHS Patients'. Br J Cancer. 2005;92(11):1971-5.

18. Corner J et al. Is late diagnosis of lung cancer inevitable? Interview study of patients' recollection of symptoms before diagnosis. Thorax. 2005;60(4):314-9.

19. Allgar VL, Neal RD. Delays in the diagnosis of size cancers: analysis of data from the National Survey of NHS Patients: Cancer. Br J Cancer. 2005;92(11):1959-70.

20. Neal RD et al. Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: comparison between diagnostic routes. Br J Gen Pract. 2007; 57(536):212-9.

21. Hamilton W et al. What are the clinical features of lung cancer before diagnosis is made? A population based case-control study. Thorax. 2005;60(12):1059-65.

22. Ellis PM, Vandermeer R. Delays in the diagnosis of lung cancer. J Thorac Dis. 2011;3(3):183-8.

23. Kocher F et al. Incidental diagnosis of asymptomatic non-small-cell lung cancer: A register-based analysis. Clin Lung Cancer. 2016;17(1):62-7.

24. Walter FM et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: A prospective cohort study. Br J Cancer. 2015;112(1): S6-13.

25. Tod AM, Joanne R. Overcoming delay in the diagnosis of lung cancer: A qualitative study. Nurs Stand. 2010;24(31):35-43.

26. Goldberg SW et al. An actuarial approach to comparing early stage and late stage lung cancer mortality and survival. Popul Health Manag. 2010;13(1): 33-46.

27. Dubayova T et al. The impact of the intensity of fear on patient's delay regarding health care seeking behaviour: A systematic review. Int J Public Health. 2010;55(5):459-68.

28. Macleod U et al. Risk factors for delayed presentation and referral of symptomatic cancer: Evidence for common cancers. Br J Cancer. 2009;101:S92-S101.

29. Tod AM, Craven J. Diagnostic delay in lung cancer: Barriers and Facilitators in diagnostic delay. 2006. Available at: http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@hea/documents/generalcontent/cr_043178.pdf. Last accessed: 19 September 2017.

30. Bish A et al. Understanding why women delay in seeking help for breast cancer symptoms. J Pyschosom Res. 2005;58(4):321-6.

31. Birt et al. Responding to symptoms suggestive of lung cancer: a qualitative interview study. BMJ Resp Res. 2014;1(1): e000067.

32. Lüchtenborg M et al. The effect of comorbidity on stage-specific in resected non-small cell lung cancer patients. Eur J Cancer. 2012;48(18):3386-95.

33. Tammemagi CM et al. In lung cancer patients, age, race-ethnicity, gender and smoking predict adverse comorbidity, which in turn predicts treatment and survival. J Clin Epidemiol. 2004;57(6): 597-609.

34. Wagland R et al. Promoting help-seeking in response to symptoms amongst primary care patients at high risk of lung cancer: A mixed method study. PLoS One. 2016;11(11):e0165677.

35. Shieh SH et al. Decreased survival among lung cancer patients with co-morbid tuberculosis and diabetes. BMC Cancer. 2012;12(1):174-81.

36. Gemine RE, Lewis KE. Smoking cessation with lung cancer: Not too little, never too late! EMJ Respir. 2016;4(1): 86-91.

37. Chatwin J, Sanders C. The influence of social factors on help-seeking for people with lung cancer. Eur J Cancer Care. 2013; 22(6):709-13.

38. Renzi C et al. Over-reassurance and undersupport after a 'false alarm': a systematic review of the impact on subsequent cancer symptom attribution and help seeking. BMJ. 2015; 5(2):e007002.

39. Crane M et al. Knowledge of the signs and symptoms and risk factors of lung cancer in Australia: Mixed methods study.

BMC Public Health. 2016;16(1):508-19.

40. Cataldo JK et al. Lung cancer stigma, depression, and quality of life among ever and never smokers. Eur J Oncol Nurs. 2012;16(3):264-9.

41. Simon AE et al. Knowledge of lung cancer symptoms and risk factors in the UK: development of a measure and results from a population-based survey. Thorax. 2012;67(5):426-32.

42. Murray SR et al. Reducing barriers to consulting a General Practitioner in patients at increased risk of lung cancer: A qualitative evaluation of the CHEST Australia intervention. Family Practice. 2017;00(00):1-7.

43. Carter-Harris L. Lung cancer stigma as a barrier to medical help-seeking behaviour: Practice implications. J Am Assoc Nurse Pract. 2015;27(5):240-5.

44. Bell K et al. Smoking, stigma and tobacco 'denormalization': Further reflections on the use of stigma as a public health tool. A commentary on Social Science & Medicine's stigma, prejudice, discrimination and heath special issue (67:3). Soc Sci Med. 2010;70(6):795-9.

45. Chapple A et al. Stigma, shame and blame experienced by patients with lung cancer: Qualitative study. BMJ. 2004; 328(7454):1470.

46. Cataldo JK, Brodsky JL. Lung cancer stigma, anxiety, depression and symptom severity. Oncology. 2013;85(1):33-40.

47. Dunn J et al. Barriers to lung cancer care: health professionals' perspectives. Support Care Cancer. 2017;25(2): 497-504.

48. Braybrook DE et al. Men and lung cancer: A review of the barriers and facilitators to male engagement in symptom reporting and screening. J Mens Health. 2011;8(2):93-9.

49. Quaife SL et al. Attitudes towards lung cancer screening in socioeconomically deprived and heavy smoking communities: Informing screening communication. Health Expect. 2017;20(4):563-73.

50. Brain K et al. Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK lung cancer screening trial. Thorax. 2017;72(10):912-8.

51. Jonnalagadda S et al. Beliefs and attitudes about lung cancer screening among smokers. Lung cancer. 2012; 77(3):526-31.

52. Ali N et al. Barriers to uptake among high-risk individuals declining participation in lung cancer screening: A mixed methods analysis of the UK lung cancer screening (UKLS) trial. BMJ Open. 2015;5(7):e008254.

53. Silvestri GA et al. Attitudes towards screening for lung cancer among smokers and their non-smoking counterparts. Thorax. 2007;62(2):126-30.

54. Carter-Harris L et al. Lung cancer screening: what do long-term smokers know and believe. Health Expect. 2015; 20(1):59-68.

55. Quaife SL et al. Recognition of cancer warning signs and anticipated delay in help-seeking in a population sample of adults in the UK. British Journal of Cancer. 2014;11:12-8.

56. Millward D, Karlsen S. Tobacco use among minority ethnic populations and cessation interventions. A race equality foundation briefing paper. 2011. Available at: http://www.darkredweb.net/REF-better-health/sites/default/files/briefings/downloads/health-brief22_0.pdf. Last accessed: 19 September 2017.

57. Equality and Human Rights Commission (EHRC). How fair is Britain? Equality, human rights and good relations in 2010, the first triennial review. 2010. Available at: www.equalityhumanrights.com/uploaded_files/triennial_review/how_fair_is_britain. Last accessed: 19 September 2017.

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THYMOMAS AND THYMIC CARCINOMAS: A REVIEW ON PATHOLOGY, PRESENTATION, STAGING, TREATMENT, AND NOVEL SYSTEMIC THERAPIES

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ABSTRACT

Although thymomas and thymic carcinomas only represent 0.2–1.5% of all malignancies, they are the most common tumour found in the anterior mediastinum. Recently, the World Health Organization (WHO) classification of thymic epithelial tumours was revised and a new tumour, node, and metastasis (TNM) staging system is currently being developed. Nearly a third of patients with thymoma present with paraneoplastic syndromes, most commonly myasthenia gravis. Thymic carcinomas are rarely associated with paraneoplastic syndromes, with patients often presenting with local symptoms. Recommendations for the management of these tumours are primarily based on small prospective studies, meta-analyses, and expert guidelines. The development of novel therapies to treat thymomas and thymic carcinomas is an area of robust research.

Keywords: Thymoma, thymic carcinoma, thymic epithelial tumour, Masaoka–Koga stage, thymectomy, adjuvant radiation, chemotherapy.

INTRODUCTION

The differential diagnosis of a mediastinal mass is broad, including malignant and benign aetiologies, such as lymphomas, germ cell tumours, thymic tumours, thyroid goiter, infections such as tuberculosis, and granulomatous disorders such as sarcoidosis. Although rare, thymic epithelial tumours, thymomas, and thymic carcinomas are the most common primary tumours in the anterior mediastinum.[1] While there exists some morphologic overlap between thymomas and thymic carcinomas, the two diseases differ in their clinical presentation, natural history, and recommended treatment strategies. Thymomas are chemo-sensitive and often follow an indolent course whereas thymic carcinomas are associated with a suboptimal response to conventional chemotherapy, high risk of recurrence, and inferior survival. Thymic epithelial tumours are reviewed in this paper, including a brief discussion of novel systemic therapeutic options.

EPIDEMIOLOGY

Thymomas account for about 20% of mediastinal neoplasms and about 50% of primary anterior mediastinum neoplasms.[2] Nevertheless, these are uncommon tumours, with an estimated overall incidence in the USA of 0.13 per 100,000 person-years.[3] Incidences are similar in males and females, increasing from 40 years of age and peaking at 70 years.[3] Thymomas are more common and present at an earlier age among African Americans and Asians/Pacific Islanders compared to Caucasians. Racial variations in incidences and age at diagnosis suggest a genetic contribution, though the mechanism is unclear.[2,3]

Thymic carcinomas are very rare, accounting for <20% of thymic neoplasms and <100 cases in the USA per year.[4,5] They occur predominantly in Caucasians.[5] Thymic carcinomas occur over a wide age range, including adolescence, with their peak prevalence in the sixth decade of life.[5]

Table 1: Refined diagnostic criteria of thymomas in the 2015 World Health Organization (WHO) classification.

Thymoma subtype	Obligatory criteria	Optional criteria
Type A	Occurrence of bland, spindle-shaped epithelial cells; paucity or absence of immature (TdT+) T cells throughout the tumour	Polygonal epithelial cells; CD20+ epithelial cells
Atypical Type A variant	Criteria of Type A+ comedo-type tumour necrosis, increased mitotic count; nuclear crowding	Polygonal epithelial cells; CD20+ epithelial cells
Type AB	Occurrence of bland, spindle-shaped epithelial cells; abundance of immature (TdT+) T cell focally or throughout tumour	Polygonal epithelial cells; CD20+ epithelial cells
Type B1	Thymus-like architecture and cytology abundance of immature T cells, areas of medullary differentiation; paucity of polygonal or dendritic epithelia cells without clustering	Hassall's corpuscles; perivascular spaces
Type B2	Increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells	Medullary islands; Hassall's corpuscles; perivascular spaces
Type B3	Sheets of polygonal slightly to moderately atypical epithelial cells; absent or rare intercellular bridges; paucity or absence of intermingled TdT+ T cells	Hassall's corpuscles; perivascular spaces
MNT (micronodular thymoma with lymphoid stroma)	Nodules of bland spindle or oval epithelial cells surrounded by an epithelial cell-free lymphoid stroma	Lymphoid follicles; mono-clonal B cells and/or plasma cells
Metaplastic thymoma	Biphasic tumour composed of solid areas of epithelial cells in a background of bland-looking spindle cells; absence of immature T cells	Pleomorphism of epithelial cells; actin, keratin, EMA-positive spindle cells
Rare others (Microscopic thymoma, sclerosing thymoma, lipofibroadenoma)	–	–

Adapted from Suster S, Moran CA.[7]

Given the rarity of thymomas and thymic carcinomas, the knowledge of their risk factors is limited. An association between tobacco or alcohol use and an increased risk of thymic carcinoma has not been established. Epidemiologic data do not suggest a link to occupational or environmental factors.

PATHOLOGY

There are many different classification schemes for thymic epithelial tumours. The World Health Organization (WHO) Classification[6] was published in 1999 to standardise the classification of thymic tumours (Table 1). Suster and Moran[7] also proposed a classification system in 1999 that addressed some of the perceived flaws of the WHO classification. The Suster and Moran Classification grouped thymic tumours into well-differentiated tumours (thymomas), moderately differentiated tumours (atypical thymomas), and poorly differentiated tumours (thymic carcinomas). This classification was felt to better reflect the prognosis of thymic tumours.

Despite its shortcomings, the WHO histologic classification is currently the most widely used classification system of thymic epithelial tumours and was most recently revised in 2015.[6] The latest version focusses on histologic and immunohistochemical diagnostic criteria for thymomas and the distinction between thymomas and thymic carcinomas (Table 1).[8] Immunohistochemical features are included in the diagnostic criteria of otherwise difficult-to-classify thymomas and thymic carcinomas.[7] The WHO classification system emphasises that major thymoma subtypes, regardless of stage, should no longer be considered benign, as all potentially behave aggressively.[8]

There are many different subtypes of thymic carcinomas, including squamous cell, basaloid, mucoepidermoid, sarcomatoid, adenocarcinoma, nuclear protein in testis carcinoma, and

undifferentiated carcinoma. These cancers need to be differentiated from metastatic lesions, and while immunohistochemical features can be helpful, clinical staging is very important.[6]

CLINICAL PRESENTATION

Thymic epithelial tumours present as an incidental finding on imaging studies because of local symptoms related to the bulk of the mediastinal mass, or because of a concurrently diagnosed paraneoplastic syndrome. Approximately one-third of patients diagnosed with thymoma are asymptomatic at time of presentation. With the growing use of computed tomography (CT) scans for diverse conditions, as well as screening for lung cancer, the number of asymptomatic patients diagnosed with thymomas is increasing.[9] Nearly 40% of patients present with symptoms related to the mass effect of the tumour, most commonly cough, chest pain, and dyspnoea. Cases complicated by superior vena cava syndrome are also occasionally reported.

Paraneoplastic syndromes, most frequently myasthenia gravis, are frequently associated with thymomas.[1] A rich infiltration of abnormally conditioned T cells is thought to be responsible for the strong association between paraneoplastic syndromes and thymomas.[3] Paraneoplastic syndromes may occur either before or after the diagnosis of thymoma, or even following treatment. A population-based epidemiologic study using data from the Nationwide Swedish Cancer Registry revealed that thymoma patients were more likely to have an autoimmune disease at some point in their lifetime compared with controls (32.7% versus 2.4%; p<0.001). Among autoimmune diseases, myasthenia gravis (24.5%), systemic lupus erythematosus (2.4%), pure red cell aplasia (1.2%), sarcoidosis (0.9%), and rheumatoid arthritis (0.7%) were frequently observed.[10]

Although both thymomas and thymic carcinomas originate in the epithelial tissue of the thymus, their clinical presentations are quite different.[11] Thymic carcinomas tend to behave more aggressively than thymomas, and approximately 80% of patients present with evidence of invasion of contiguous mediastinal structures. This local invasion often results in cough, chest pain, phrenic nerve palsy, or superior vena cava syndrome.[4] Furthermore, paraneoplastic syndromes such as myasthenia gravis are very rarely associated with thymic carcinoma.[5,12] If myasthenia gravis is present, the diagnosis of thymic carcinoma should be reassessed to rule out thymoma.[13]

DIAGNOSIS

The initial evaluation of a patient with a thymic tumour should include radiographic imaging with a contrast-enhanced CT scan of the chest.

Table 2: Modified Masaoka–Koga Clinical Staging of thymoma with overall survival and recurrence-free survival.

Stage	Diagnostic criteria	10-year overall survival (%)	10-year cumulative incidence of recurrence (%)	
			Thymoma	Thymic carcinoma
I	Macro and microscopically completely encapsulated (tumour invading into but not through the capsule is included)	84		25
II	A. Microscopic transcapsular invasion B. Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium	83		
III	Macroscopic invasion into neighbouring organs (i.e. pericardium, great vessels, or lung) A. Without invasion of great vessels B. With invasion of great vessels	70	29	59
IV	A. Pleura or pericardial dissemination	52	27	76
	B. Lymphogenous or haematogenous metastases	53	57	54

Adapted from Falkson et al.[11] and Girard et al.[20]

CT scans play a role in characterisation of the tumour, staging, and follow-up. Magnetic resonance imaging (MRI) scans are most helpful in cases of suspected infiltration of the heart and great vessels or to differentiate a thymic malignancy from a thymic cyst.[14-16] Fluorodeoxyglucose positron emission tomography (FDG-PET) scans show significantly higher uptake of fluorodeoxyglucose among thymic carcinomas compared to thymomas.[17] However, although using FDG-PET can be helpful in select cases, its use as a routine test has yet to be determined, and further research is awaited.[18]

Although the definitive diagnosis of a thymoma or thymic carcinoma requires a histological diagnosis, the need for biopsy prior to treatment depends on tumour resectability. Patients with tumours amenable to complete resection should undergo surgery, which will establish a definitive diagnosis as well as provide a therapeutic benefit. If the tumour cannot be completely resected, or if lymphoma is considered a likely diagnosis, then a histologic diagnosis with a core needle biopsy or an open biopsy should be performed prior to any systemic therapy or radiation.[1] As thymic carcinomas are predominantly squamous cell or undifferentiated carcinomas, they should be differentiated from primary carcinoma of the lung, which can metastasise to the thymus and have a similar histologic appearance.

STAGING

The modified Masaoka–Koga staging system is widely used for both thymomas and thymic carcinomas (Table 2). In large studies, this system has been shown to correlate well with overall survival.[5] A tumour, node, metastasis (TNM)-based staging system was proposed through collaboration of the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancy Interest Group (ITMIG) in 2014. Their intention was to develop an official and consistent staging classification system. A worldwide retrospective database was created by ITMIG, which represented the collaborative effort of 105 institutions and included 10,808 patients.[19] However, correlative clinical data based on this system is still lacking and awaited. For this review, future mention of stage will refer to the Masaoka–Koga classification.

MANAGEMENT

The treatment strategies for treatment adapted from National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines are outlined in Figure 1.[20] Given the absence of randomised data to guide management, recommendations are based primarily on retrospective data and expert opinion.

Surgery

Surgical intervention is the mainstay of treatment; thus, assessment of respectability is the first step in the treatment of thymic epithelial tumours. Total thymectomy with complete surgical excision of the tumour is crucial to achieve cure in appropriate candidates. Although a recent meta-analysis showed similar effectiveness of minimally invasive surgery compared to open thymectomy in selected patients,[21] a minimally invasive approach is not routinely recommended due to the paucity of robust clinical data confirming a benefit in long-term prognosis. Therefore, both NCCN[13] and ESMO guidelines[20] recommend consideration of minimally invasive surgery for clinical Stage I–II in limited settings, including availability of appropriately trained thoracic surgeons. Partial thymectomy is also an option for Stage I tumours in patients without myasthenia gravis.[22] Historically, lymphadenectomy was not routinely performed with thymectomy; however, lymphadenectomy should be considered for all thymic carcinomas given the higher risk for lymph node metastasis.[23]

Prior to any surgical procedure, all patients suspected to have thymomas, whether symptomatic or not, should undergo assessment of serum anti-acetylcholine receptor antibody levels. If patients have myasthenia gravis, a neurology evaluation should be obtained to avoid perioperative respiratory failure.[24]

Radiotherapy

Generally, thymic epithelial tumours are moderate to highly radiosensitive. As shown in Figure 1, radiotherapy plays a role as adjuvant or definitive therapy, either as a single agent or concurrent with chemotherapy. However, evidence supporting adjuvant radiation from multicentre, prospective trials is lacking; thus, recommendations are based on data from large cohorts and pooled analyses of retrospective studies.[20] There is no known survival benefit associated with the delivery of postoperative radiotherapy in Stage I–III thymomas

following R0–1 resection.[12,25-30] Multiple studies have demonstrated a similar rate of recurrence after complete resection regardless of postoperative radiotherapy.[26] One review of the National Cancer Institute (NCI)-sponsored SEER (Surveillance, Epidemiology, and End Results) programme database, which provides incidence and survival data from tumour registries across the USA, even suggested that adjuvant radiation for localised disease may have an adverse impact on survival.[27] Recommendations for postoperative radiotherapy are reserved for patients with a higher risk of recurrence, such as those with a complete resection of a Stage III–IVA thymoma or an incompletely resected thymoma of any stage.[5,26-28,31] Thymomas do not typically metastasise to regional lymph nodes; thus, extensive elective nodal radiotherapy is not recommended.[32]

Adjuvant radiation should also be recommended for all patients with completely or incompletely resected thymic carcinoma due to the high risk of recurrence.[33,34] A recent meta-analysis of 973 patients with thymic carcinoma concluded that adjuvant radiation therapy offers both a progression free survival (hazard ratio: 0.54; 95% confidence interval: 0.41–0.71) and overall survival benefit (hazard ratio: 0.66; 95% confidence interval: 0.54–0.80).[35]

Postoperative radiotherapy should be initiated within 3 months after surgery via three-dimensional conformal techniques or intensity-modulated radiation therapy. Although the optimal dose is not defined, a total dose of 45–50 Gy for complete (R0) resection or 54 Gy for R1 resection is recommended. Following R2 resection or for definitive radiotherapy of unresectable or inoperable disease, a total dose of 60–70 Gy should be administered.

Chemotherapy

Generally, thymomas are considered chemo-sensitive, whereas chemotherapy has only modest activity against thymic carcinomas. Chemotherapy is administered both to reduce the risk of recurrence and to palliate symptoms. Adjuvant chemotherapy has not been shown to improve survival following R0–1 resection of thymomas.[11,13,20,36] On the contrary, platinum-based postoperative chemotherapy can be considered for Stage II-IV thymic carcinomas given the high risk of recurrence, especially following incomplete resection.[11,13,20]

Induction chemotherapy to downstage the tumour prior to surgery is recommended for locally advanced, Stage III–IV thymic tumours for which upfront complete resection is deemed not achievable.[12,13,20] Usually, 2–4 cycles of platinum-based chemotherapy (e.g. cisplatin, doxorubicin, and cyclophosphamide (CAP); cisplatin and etoposide; or carboplatin and paclitaxel) are administered followed by re-imaging for evaluation of surgical resectability.[37] Cisplatin and etoposide concurrent with radiation can also be considered for unresectable localised tumours, either to downstage in anticipation of surgery or as definitive therapy.[20]

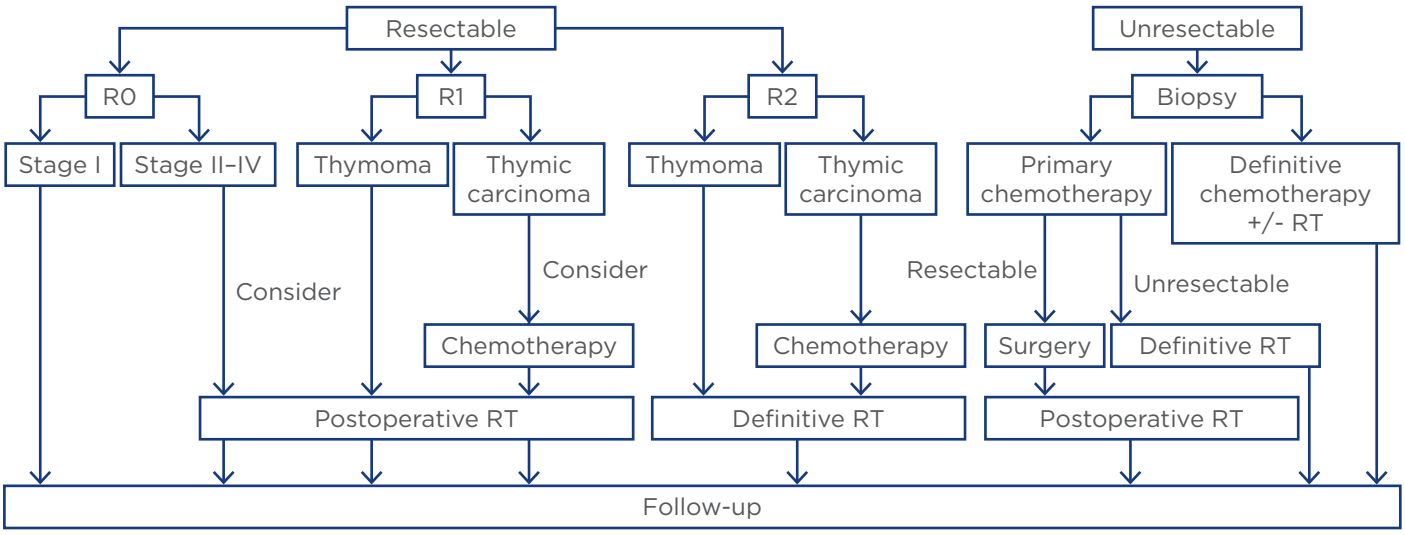

Figure 1: Treatment strategy of thymic tumours.
RT: radiation therapy.
Adapted from Ettinger et al.[13] and Girard et al.[20]

For patients with unresectable metastatic disease, palliative chemotherapy is administered to relieve tumour-related symptoms and prolong survival. Given the absence of randomised studies, broadly accepted optimal regimens and precise survival benefits are not available. Both NCCN and ESMO guidelines recommend the triplet therapy of CAP as the preferred first-line regimen for thymomas.[13,20] A study of CAP in 29 patients with thymoma and 1 with thymic carcinoma revealed a 50% response rate and 37.7-month overall survival.[38] For patients who cannot tolerate a cisplatin and anthracycline-based regimen, carboplatin and paclitaxel can be considered. A platinum-taxane regimen is also recommended as first-line treatment for patients with thymic carcinoma.[13,20,39] A Phase II study of carboplatin and paclitaxel in 46 patients demonstrated response rates of 42.9% and 21.7% for thymoma and thymic carcinoma, respectively.[40]

NOVEL SYSTEMIC THERAPIES

The limited effectiveness of cytotoxic chemotherapy in advanced thymic carcinoma, and the lack of evidence-based treatment options for relapsed or refractory thymoma, has meant that the development of novel agents has been an active area of research. Somatostatin receptors are often expressed in thymic epithelial tumours, and these tumours are detectable by octreotide scan. Octreotide administered via subcutaneous injections demonstrated modest activity (30.3% objective response rate) in a small Phase II trial.[41] Of note, none of the thymic carcinoma patients included in the trial demonstrated a response to octreotide.

Small molecule tyrosine kinase inhibitors have also been studied in previously treated thymic tumours. An analysis of thymic carcinomas demonstrated the activation of receptor tyrosine kinases, including platelet-derived growth factor receptor-beta and vascular endothelial growth factor receptor-3, both targets of sunitinib.[42] A Phase II trial of sunitinib in relapsed and refractory thymic epithelial tumours demonstrated a 26% response rate among thymic carcinomas.[43]

More recently, a study of the anti-programmed cell death (PD)-1 checkpoint inhibitor, pembrolizumab, was reported at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting. Investigators described a 22.5% objective response rate among patients with refractory thymic carcinoma. A response was detected in 6 of 9 patients with high PD-L1 expression, though a correlation between tumour mutational burden and pembrolizumab activity was not noted.[44] Immune-related adverse effects were observed at a higher than expected rate with 6 of the 40 patients experiencing Grade 3–4 immune-related adverse effects, including two noted to have myocarditis.

Beyond cytotoxic chemotherapy, a number of medications with different biological mechanisms have activity against refractory thymic epithelial tumours. Larger studies and the identification of predictive biomarkers are needed prior to moving these treatments into the armamentarium of routine clinical practice.

PROGNOSIS

As thymomas usually are indolent in nature, the extent of invasion and the completeness of resection have the greatest impact on prognosis.[45] The prognostic value of tumour histology remains controversial.[46,47] For resected Stage I and II thymomas, 10-year survival rate is excellent and >80% (Table 2).

Survival rates for thymic carcinomas, are also heavily influenced by stage and resectability. A large series of patients with thymic carcinoma in North America (N=121) showed 5-year overall survival of 100%, 81%, 51%, 24%, and 17% for Stage I, II, III, IVa, and IVb, respectively.[5]

FOLLOW-UP

There are no prospective data available to establish recommendations for post-treatment surveillance. Generally, prolonged follow-up indicated as late relapse is possible and a relapse may be potentially treated with curative-intent. NCCN guidelines recommend a chest CT every 6 months for 2 years, then annually for 5 years for thymic carcinomas, and for 10 years for thymomas.[13,48] ESMO clinical practice guidelines recommend baseline chest CT 3–4 months after surgery, followed by an annual chest CT for completely resected Stage I/II thymomas for 5 years, and then every 2 years. For Stage III/IV thymomas, thymic carcinomas, or after a R1/R2 resection, the guidelines propose chest CT every 6 months for 2 years and then annually. The recommended duration for imaging follow-up is 10–15 years.[20] Subsequent malignancies and/or late onset paraneoplastic syndrome may occur as well; however, there is no clear guidance of follow-up for these phenomena.[13,20]

REFERENCES

1. Detterbeck FC, Parsons AM. Thymic tumors. Ann Thorac Surg. 2004;77(5): 1860-9.

2. Kelly RJ et al. Thymic malignancies: from clinical management to targeted therapies. J Clin Oncol. 2011;29(36): 4820-7.

3. Engels EA. Epidemiology of thymoma and associated malignancies. J Thorac Oncol. 2010;5(10 Suppl 4):S260-5.

4. Engels EA et al. Malignant thymoma in the United States: Demographic patterns in incidence and associations with subsequent malignancies. Int J Cancer. 2003;105(4):546-51.

5. Litvak AM et al. Clinical characteristics and outcomes for patients with thymic carcinoma: Evaluation of Masaoka staging. J Thorac Oncol. 2014;9(12): 1810-5.

6. Travis WD et al. World Health Organization Classification of Tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. IARC Press. 2004:pp.145-249.

7. Suster S, Moran CA. Thymoma classification current status and future trends. Am J Clin Pathol. 2006;125(4): 542-54.

8 Marx A et al. The 2015 World Health Organization classification of tumors of the thymus. Continuity and changes. J Thorac Oncol. 2015;10(10):1383-95.

9. Henschke CI et al. CT screening for lung cancer: Prevalence and incidence of mediastinal masses. Radiology. 2006; 239(2):586-90.

10. Gadalla SM et al. A population-based assessment of mortality and morbidity patterns among patients with thymoma. Int J Cancer. 2010;128(11):2688-94.

11. Falkson CB et al.; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. The management of thymoma: A systematic review and practice guideline. J Thorac Oncol. 2009;4(7):911-19.

12. Ruffini E et al. Management of thymic tumors: A European perspective. J Thorac Dis. 2014;6 Suppl 2:S228-37.

13. Ettinger DS et al.; National Comprehensive Cancer Network. Thymomas and thymic carcinomas: Clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2013;11(5):562-76.

14. Marom EM. Advances in thymoma imaging. J Thorac Imaging. 2013;28(2): 69-83.

15. Tomiyama N et al. Anterior mediastinal tumors: Diagnostic accuracy of CT and MRI. Eur J Radiol. 2009;69(2):280-8.

16. Sadohara J et al. Thymic epithelial tumors: comparison of CT and MR imaging findings of low-risk thymomas, high-risk thymomas, and thymic carcinomas. Eur J Radiol. 2006;60(1): 70-9.

17. Thomas A et al. ^{18}F-fluorodeoxyglucose positron emission tomography in the management of patients with thymic epithelial tumors. Clin Cancer Res. 2013; 19(6):1487-93.

18. Seki N et al. ^{18}F-fluorodeoxyglucose positron emission tomography for evaluation of thymic epithelial tumors: utility for World Health Organization classification and predicting recurrence-free survival. Ann Nucl Med. 2014;28(3):257-62.

19. Detterbeck FC et al.; Staging and Prognostic Factors Committee; Members of the Advisory Boards; Participating Institutions of the Thymic Domain. The IASLC/ITMIG thymic epithelial tumors staging project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol. 2014; 9(9 Suppl 2):S65-72.

20. Girard N et al.; ESMO Guidelines Committee. Thymic epithelial tumours: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2015;26 Suppl 5:v40-55.

21. Friedant AJ et al. Minimally invasive versus open thymectomy for thymic malignancies: systematic review and meta-analysis. J Thorac Oncol. 2016;11(1): 30-8.

22. Nakagawa K et al. Does the mode of surgical resection affect the prognosis/ recurrence in patients with thymoma? J Surg Oncol. 2013;109(3):179-83.

23. Bhora FY et al.; Staging and Prognostic Factors Committee; Advisory Boards. The ITMIG/IASLC thymic epithelial tumors staging project: a proposed lymph node map for thymic epithelial tumors in the forthcoming 8th edition of the TNM classification of malignant tumors. J Thorac Oncol. 2014; 9(9 Suppl 2):S88-96.

24. Lewis JE et al. Thymoma. A clinicopathologic review. Cancer. 1987; 60(11):2727-43.

25. Utsumi T et al. Postoperative radiation therapy after complete resection of thymoma has little impact on survival. Cancer. 2009;115(23):5413-20.

26. Korst RJ et al. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. Ann Thorac Surg. 2009;87(5):1641-7.

27. Forquer JA et al. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. Int J Radiation Oncol Biol Phys. 2010;76(2):440-5.

28. Kondo K. Optimal therapy for thymoma. J Med Invest. 2008;55(1-2): 17-28.

29. Omasa M et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: The Japanese Association for Research on the thymus database study. Cancer. 2015;121:1008-16. Erratum in: Cancer. 2015; 121(12):2102.

30. Patel S et al. Evaluation of the role of radiation therapy in the management of malignant thymoma. Int J Radiation Oncol Biol Phys. 2012;82(5):1797-1801.

31. Weksler B et al. The role of adjuvant radiation therapy for resected stage III thymoma: a population-based study. Ann Thorac Surg. 2012;93(6):1822-29.

32. Masaoka A. Staging system of thymoma. J Thorac Oncol. 2010; 5(10 Suppl 4):S304-12.

33. Ruffini E et al.; European Society of Thoracic Surgeons Thymic Working Group. Thymic carcinoma: a cohort study of patients from the European Society of Thoracic Surgeons database. J Thorac Oncol. 2014;9(4):541-8.

34. Ahmad U et al. Thymic carcinoma outcomes and prognosis: results of an international analysis. J Thorac Cardiovasc Surg. 2015;149(1):95-100.

35. Hamaji M et al. A meta-analysis of postoperative radiotherapy for thymic carcinoma. Ann Thorac Surg. 2017;103(5): 1668-75.

36. Attaran S et al. Which stages of thymoma benefit from adjuvant chemotherapy post-thymectomy? Interact Cardiovasc Thorac Surg. 2012; 15(2):273-5.

37. Wright CD et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. Ann Thorac Surg. 2008;85(2):385-9.

38. Loehrer PJ Sr et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and southeastern Cancer Study Group. J Clin Oncol. 1994; 12(6):1164-8.

39. Igawa S et al. Efficacy of chemotherapy with carboplatin and paclitaxel for unresectable thymic carcinoma. Lung Cancer. 2010;67(2): 194-7.

40. Lemma GL et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. J Clin Oncol. 2011;29(15):2060-5.

41. Loehrer PJ Sr et al. Eastern Cooperative Oncology Group Phase II Trial. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: An Eastern Cooperative Oncology Group Phase II Trial. J Clin Oncol. 2004;22(2): 293-9.

42. Ströbel P et al. Sunitinib in metastatic thymic carcinomas: laboratory findings and initial clinical experience. Br J Cancer. 2010;103(2):196-200.

43. Thomas A et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol. 2015;16(2): 177-86.

44. Giaccone G et al. Pembrolizumab in patients with recurrent thymic carcinoma: Results of a phase II study. Abstract 8573. ASCO Annual Meeting, 1-5 June, 2017.

45. Zhao Y et al. Surgical treatment of thymoma: An 11-year experience with 761 patients. Eur J Cardiothorac Surg. 2016; 49(4):1144-9.

46. Jain RK et al. WHO types A and AB thymomas: not always benign. Mod Pathol. 2010;23:1641-9.

47. Kim HK et al. Type B thymoma: Is prognosis predicted only by World Health Organization classification? J Thorac Cardiovasc Surg. 2010;139(6): 1431-5.

48. Marom E. Imaging thymoma. J Thorac Oncol. 2010;5(10 Suppl 4):S296-303.

ELECTRONIC CIGARETTE USE AMONG EMERGING AND YOUNG WEST INDIAN ADULTS

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ABSTRACT

Currently, evidence concerning electronic cigarette (e-cigarette) use in the West Indies is unavailable. This study examines the prevalence and associated factors of e-cigarette use in young Trinidadian adults, 6 years after e-cigarettes were introduced in Trinidad. Young adults between the ages of 18 and 40 years were surveyed from May–June 2016. Based on the survey results, descriptive statistics and logistic regression models were used to identify correlations in e-cigarette use. The prevalence of those who had used e-cigarettes was 24.6%, and 41.9% of these people had used both e-cigarettes and tobacco cigarettes. A high proportion (16.95%) of those who had never used tobacco cigarettes had used e-cigarettes. Males were twice as likely as females to have used e-cigarettes (odds ratio [OR]: 2.60; 95% confidence interval [CI]: 1.85–3.68), and participants aged 18–25 years were more likely than those aged 36–40 years to use e-cigarettes (OR: 0.37; 95% CI: 0.14–0.81). The predictors of e-cigarette use as assessed by univariate analysis were current tobacco cigarette smoking (OR: 9.34; 95% CI: 6.14–14.39; p<0.001) and the belief that e-cigarettes are dangerous to health (OR: 0.61; 95% CI: 0.44–0.85; p=0.004). The predictors as assessed by multivariate logistic regression (adjusted OR) were ethnicity (p=0.043), education (p=0.012), and age group (p=0.007). Those who quit using tobacco cigarettes were 7.98 times more likely to use e-cigarettes (95% CI: 4.21–15.45), and those who knew that e-cigarettes contain nicotine were 2.70 times more likely to use them (95% CI: 1.53–4.86; p<0.001). Two summative scales were constructed that measured knowledge and perception. The perception scale, but not the knowledge scale (Cronbach's alpha=0.736), was a significant predictor of e-cigarette use. The number of e-cigarette users is high (24.6%) in young adults in Trinidad and in those who have never smoked tobacco (16.95%). Current smokers, as well as those who have quit smoking, are at an increased risk of e-cigarette use. This study established that young adults have a low level of knowledge regarding e-cigarettes and shows that they should be educated on e-cigarette use. Further research to examine the reasons for, and susceptibility to, e-cigarette use is necessary.

Keywords: Electronic cigarettes (e-cigarettes), prevalence, current smokers, quitters, knowledge of nicotine content, electronic nicotine delivery system (ENDS).

INTRODUCTION

Electronic cigarettes (e-cigarettes), also known as electronic nicotine delivery systems (ENDS), allow users to inhale an aerosol (vapour) containing flavoured agents, additives, and typically nicotine (though not always), by heating a solution of propylene glycol and/or glycerine. The battery-powered device becomes activated on inhalation, vapourising the liquid to form an aerosol that is then 'vaped' into the lungs via a mouthpiece. Vaping provides the same nicotine experience

as tobacco cigarettes, while the heated vapour mimics the 'throat hit' that occurs in tobacco smoking and is regarded as a vital experience for smokers. These devices are now the most common type of alternative nicotine delivery system used in several countries.[1]

E-cigarettes are being used increasingly and rapidly among the youth population and young adults.[2] Reid et al.[3] reported a high use of e-cigarettes in Canadian youth populations and young adults, and McMillen et al.[4] found that young adults were at the highest risk of using alternative tobacco products. Traditional media channels that were once used to encourage tobacco cigarette use now use the same aggressive marketing techniques to target young people, advertising e-cigarettes as smoking cessation aids[5] that provide a safe, tobacco-free, alternative smoking experience. There is limited evidence regarding the health effects of e-cigarettes. Observational data examining the long-term effects of e-cigarette use are not available and the levels of toxic constituents can vary between products. Though the majority of harmful substances found in tobacco smoke are absent in e-cigarette aerosols, evidence of decreased harm with long-term use is not available[6] and short-term e-cigarette use has been associated with adverse events, ranging from a cough, sore throat, shortness of breath, and vomiting, to serious reports of pneumonia, hypotension, and seizures.[7] The current research on e-cigarettes is complex and confounded by the wide variation in e-cigarette product composition. Despite being introduced as an aid to smoking cessation, Barrington-Trimis et al.[8] have presented data that suggested e-cigarettes may act as gateway agents to the development of a nicotine addiction. Nevertheless, it is estimated that the e-cigarette market, fuelled by the perception of a healthier alternative to smoking, will display a compound annual growth rate of 35% over the period of 2016–2021 and reach a total market size of $10.687 billion by the end of 2021.[9] Cognizant of the lack of progress made in decreasing tobacco use in adolescents and young adults, the U.S. Food and Drug Administration (FDA) banned e-cigarette use in minors (<18 years) and began regulating the manufacture, import, packaging, labelling, advertising, promotion, sales, and distribution of ENDS in August 2016.[10]

When ENDS were first used in the Anglophone Caribbean between 2010 and 2011, they had already been banned in Australia, Brazil, Canada, Israel, Mexico, Panama, and Singapore. The devices were not welcomed by the medical community in Barbados[11] and Jamaica.[12] In Trinidad and Tobago, e-cigarettes were first introduced in 2010, ironically when the Tobacco Control Act took effect, banning smoking in public places. At present, they remain untouched by regulatory controls. A 2014 report in a popular daily newspaper in the country stated that e-cigarettes were economically attractive, costing $30–90 (1 USA $=6.7 Trinidad Tobago $), and stated: "The bottles of liquids are selling like wildfire."[13] There is no information available on the prevalence and characteristics of e-cigarette users in Caribbean youth and young adults. Therefore, we examined the prevalence and associated factors of ENDS use, knowledge, and perceptions among young adults (18–25 years) in Trinidad. The findings from this study will aid the understanding of the characteristics of young adults who use e-cigarettes and will encourage the development of regulatory controls in Trinidad.

METHODS

This cross-sectional study was undertaken from May–June 2016 by convenience sampling in consenting young adults aged between 18 and 40 years. Participants were recruited from popular locations frequented by young adults across the island, including the Gulf City Mall in the south, Movie Towne at Port-of-Spain in the west, Trincity Mall in the east, and the University campuses of the West Indies and Faculty of Medical Sciences in the north-central part of the island. Validated questionnaires are not available on e-cigarette use. However, the questionnaires we used were pilot-tested using trained interviewers. Data analysis by SPSS version 24 produced descriptive statistics and a logistic regression model was used to identify correlates of e-cigarette use. Pearson's chi-squared test and the two-sample t-test were used for the univariate analyses, depending on whether the variable being studied was categorical or continuous, respectively. Variables were considered significant if the p-value was <0.05.

The following definitions were used:

- Smoking status was recorded based on self-reporting. A 'current smoker' was defined as someone who answered 'Yes' to the question: 'Have you smoked ≥100 cigarettes in your entire life?' and had smoked a cigarette in the past 28 days.
- A 'quitter', or 'former smoker', was defined as someone who had smoked >100 cigarettes

in their lifetime but had not smoked in the last 28 days.
- A 'never smoker' was defined as someone who had not smoked >100 cigarettes in their lifetime and was not a smoker at the time of study.

RESULTS

The dependent variable was binary in nature. The two categories of participants involved were those who had used e-cigarettes and those who had never used e-cigarettes. Table 1 shows the breakdown of the demographic variables and the dependent variable. Of the 911 participants approached, 777 completed the interview (response rate: 85.3%). Non-responders did not participate in the questionnaire largely because of time constraints, and few participants refused to take part. A total of 24.6% (191) of subjects had used an e-cigarette before. Most participants (70.1%) were aged 18–25 years old, 49.9% were of East Indian descent, and the female and male proportions were 50.6% and 49.4%, respectively. The African population was the least represented cohort in the sample (21.2%). The majority of participants (74.9%) had either completed, or were in, current tertiary education. Among the demographic variables, the univariate analyses showed that sex (odds ratio [OR]: 2.60; 95% confidence interval [CI]: 1.85–3.68; p<0.001), and ethnicity (p=0.002) were both significant. In addition, the odds of males having used an e-cigarette before were 2.60 (95% CI: 1.85–3.68) times more likely than females. Subjects aged 36–40 years were significantly less likely (OR: 0.37; 95% CI: 0.14–0.81) to use e-cigarettes compared with those in the 18–25 year age group (p=0.023).

Table 1: Study population profile.

Variables	Have you ever used e-cigarettes? Yes, n=191 (%)	No, n=586 (%)	Total (N=777)	OR (95% CI)	p-value
Sex					
Female	63 (33.2%)	330 (56.3%)	393	1.00	-
Male	127 (66.8%)	256 (43.7%)	383	2.60 (1.85–3.68)	0.000**
Age groups, years					0.120
18–25	139 (73.2%)	406 (69.3%)	545	1.00	-
26–30	27 (14.2%)	70 (11.9%)	97	1.13 (0.68–1.81)	0.629
31–35	18 (9.5%)	62 (10.6%)	80	0.85 (0.47–1.46)	0.563
36–40	6 (3.2%)	48 (8.2%)	54	0.37 (0.14–0.81)	0.023*
Ethnicity					0.002**
African	23 (12.0%)	142 (24.2%)	165	1.00	-
East Indian	108 (56.5%)	280 (47.8%)	388	2.38 (1.48–3.98)	0.001**
Other	60 (31.4%)	164 (28.0%)	224	2.26 (1.34–3.90)	0.003**
Education					0.280
None or unknown	1 (0.5%)	11 (1.9%)	12	1.00	-
Primary	0 (0.0%)	4 (0.7%)	4	0.00	0.999
Secondary	32 (16.8%)	78 (13.3%)	110	4.51 (0.83–0.84)	0.157
Trade or vocation	22 (11.5%)	47 (8.0%)	69	5.15 (0.91–97.06)	0.128
University	136 (71.2%)	446 (76.1%)	582	3.35 (0.64–61.6)	0.249
Employment status					0.630
Employed	57 (29.8%)	189 (32.3%)	246	1.00	-
Unemployed	14 (7.3%)	36 (6.2%)	50	1.29 (0.63–2.51)	0.467
Student	119 (62.3%)	351 (60.0%)	470	1.12 (0.79–1.62)	0.526
Other	1 (0.5%)	9 (1.5%)	10	0.36 (0.02–2.02)	0.348

*: p≤0.05; **: p≤0.01.
CI: confidence interval; OR: odds ratio.

Table 2: Univariate analysis of base characteristics to assess predictors of e-cigarette use (unadjusted odds ratios).

Variables	Have you ever used e-cigarettes? Yes, n=191 (24.6%)	No, n=586 (75.4%)	Total (N=777)	OR (95% CI)	p-value
Currently smokes tobacco cigarettes					
No	111 (58.1%)	544 (92.8%)	655	1.00	-
Yes	80 (41.9%)	42 (7.2%)	122	9.34 (6.14–14.39)	0.000***
Quit smoking tobacco cigarettes					
Never smoked	66 (60.6%)	491 (93.0%)	557	1.00	-
Yes	43 (39.4%)	37 (7.0%)	80	8.65 (5.21–14.46)	0.000***
Dangerous to health					
Disagree	116 (60.7%)	284 (48.5%)	400	1.00	-
Agree	75 (39.3%)	301 (51.5%)	376	0.61 (0.44–0.85)	0.004***
Safer than regular cigarettes					
Disagree	79 (41.4%)	378 (64.6%)	457	1.00	-
Agree	112 (58.6%)	207 (35.4%)	319	2.59 (1.86–3.62)	0.000***
Contains harmful substances					
No	119 (62.6%)	364 (62.5%)	483	1.00	-
Yes	71 (37.4%)	218 (37.5%)	289	1.00 (0.71–1.40)	0.983
Contains nicotine					
No	79 (41.6%)	334 (57.3%)	413	1.00	-
Yes	111 (58.4%)	249 (42.7%)	360	1.88 (1.35–2.63)	0.000***
Knowledge	581 (75.5%) -0.02±2.49	189 (24.5%) 0.50±2.08	770	T=2.59, df=277.89	0.010*** +
Perception	579 (75.2%) 1.84±4.39	191 (24.8%) 4.85±3.38	770	T=8.64, df= 268.11	0.000*** +

+: p-values result from Welch's, two-sample independent t-test; *: p≤0.1; **: p≤0.05; ***: p≤0.01.
CI: confidence interval; df: degrees of freedom; OR: odds ratio.

Additionally, East Indians (OR: 2.38; 95% CI: 1.48–3.98; p=0.001) and those belonging to other ethnicities (OR: 2.26; 95% CI: 1.34–3.90; p=0.003) were more likely to have tried/used e-cigarettes.

Dual use of tobacco cigarettes and e-cigarettes was observed in nearly 42% of subjects. Table 2 shows the univariate analyses among the non-demographic variables that might influence the dependent variable. The variables that were significant predictors of the use of e-cigarettes were binary variables that measured the habit of smoking tobacco, specifically whether someone smoked tobacco cigarettes at the time of study (OR: 9.34; 95% CI: 6.14–14.39; p<0.001), had quit smoking tobacco cigarettes (OR: 8.65; 95% CI: 5.21–14.46; p<0.001), whether the person thought it was dangerous to his/her health (OR: 0.61; 95% CI: 0.44–0.85; p=0.004), and whether they felt that e-cigarettes were safer than tobacco cigarettes (OR: 2.59; 95% CI: 1.86–3.62; p<0.001). Respondents who smoked tobacco cigarettes at the time of study and those who had quit smoking tobacco cigarettes were significantly more likely to have used e-cigarettes in the past. A total of 16.95% of participants who had never smoked a tobacco cigarette previously had used e-cigarettes before.

Safety variables also play a role in determining an individual's predisposition to use/try e-cigarettes. Those who agreed that e-cigarettes were dangerous to health were less likely (OR: 0.61; 95% CI: 0.44–0.85) to have tried/used the devices, while those who agreed that e-cigarettes were safer than regular tobacco cigarettes were more than twice as likely (OR: 2.59; 95% CI: 1.86–3.62) to have used/tried e-cigarettes. Respondents' knowledge of the toxic content of e-cigarettes was not a significant predictor of e-cigarette use or trial.

However, those who knew that e-cigarettes contain nicotine were almost twice as likely to have used an e-cigarette before (OR: 1.88; 95% CI: 1.35–2.63) compared to those who did not.

Two summative scales were constructed that measured knowledge and perception. The summative scale for knowledge consisted of seven questions. The questions included topics such as whether e-cigarettes are cheaper than regular tobacco cigarettes, if e-cigarettes contain nicotine or harmful substances, if users are less likely to develop a habit with e-cigarettes than regular cigarettes, and whether users of e-cigarettes are less likely to develop cancer, heart disease, or lung disease. The summative scale for perception consisted of 10 questions. These included whether e-cigarettes are perceived as dangerous to the health of users, safer than regular tobacco cigarettes, if e-cigarette use is acceptable in public, if e-cigarettes are safe to be used by pregnant women or near children, and if they should be sold to children. Other questions included whether respondents believed regulations should be instigated for e-cigarette use in public, whether a minimum age limit should be enforced for their use, and whether e-cigarettes should be openly advertised.

The reliability of these scales was examined using Cronbach's alpha.[14] A Cronbach's alpha >0.7 is a good indicator of a reliable scale. The perception scale was more reliable (Cronbach's alpha: 0.736) than the knowledge scale (Cronbach's alpha: 0.367). There were statistical differences in the mean knowledge (t=2.59; degrees of freedom: 277.89; p=0.010) and mean perception (t=8.64; degrees of freedom: 268.11; p<0.001) between those who had and those who had never used an e-cigarette.

A multivariable logistic regression with adjusted odds ratio (AOR) (Table 3) identified the variables that were significant predictors, while accounting for the presence of the other variables. The demographic variables of ethnicity (p=0.030), education (p=0.012), and age group (p=0.007) were all significant. In addition, an individual who had quit smoking tobacco cigarettes was almost eight times more likely to use e-cigarettes (OR: 7.98; 95% CI: 4.21–15.45). Those who said e-cigarettes contained nicotine were almost three times more likely to have used them before (OR: 2.70; 95% CI: 1.53–4.86). Out of the perception and knowledge scales, only the perception scale proved to be significant (OR: 0.78; 95% CI: 0.70–0.86; p<0.001). For each unit increase in the perception scale, the odds of trying/using e-cigarettes decreased by 0.78 times.

DISCUSSION

We have explored the pattern of e-cigarette use among young West Indian adults; this was the first such study to our knowledge. ENDS were introduced to Trinidad and Tobago in 2010. Six years later, close to 25% of young adults aged 18–40 years have used an e-cigarette and, of these, 41.9% (n=80) are tobacco cigarette smokers.

Table 3: Multivariable logistic regression output (adjusted odds ratios).

Variables	OR (95% CI)	p-value
Sex		
Male	1.00	-
Female	1.65 (0.99–2.78)	0.055*
Ethnicity		0.030**
African	1.00	-
East Indian	2.74 (1.34–6.02)	0.008***
Other	2.28 (1.05–5.21)	0.043**
Education		0.012*
None or unknown	1.00	-
Primary	0.00	0.991
Secondary	10.04 (1.24–223.54)	0.059*
Trade or vocation	12.50 (1.34–299.54)	0.049**
University	3.49 (0.45–75.95)	0.300
Age group, years		0.007***
18–25	1.00	-
26–30	1.36 (0.62–2.91)	0.433
31–35	0.19 (0.05–0.63)	0.011**
36–40	0.23 (0.06–0.77)	0.024**
Quit tobacco cigarettes		
No	1.00	-
Yes	7.98 (4.21–15.45)	0.000***
Safer than regular cigarettes		
Disagree	1.00	-
Agree	0.60 (0.33–1.09)	0.09*
Contains nicotine		
No	1.00	-
Yes	2.70 (1.53–4.868)	0.000***
Perception	0.78 (0.70–0.86)	0.000***

Results from two-sample independent t-tests.
*: p≤0.1; **: p≤0.05; ***: p≤0.01.
CI: confidence interval; OR: odds ratio.

Young adults aged 18–25 years and included in this study were more likely to use ENDS. For a country with a population of 1.3 million, this equates to a sizeable proportion of young adults using e-cigarettes, only 6 years after their introduction, and is worrying in the context of international reports. Gravely et al.[15] investigated 10 countries with a mix of economic levels in the International Tobacco Control Surveys for self-reported awareness, current usage, and trial of e-cigarettes, and found that e-cigarette use had rapidly increased between 2009 and 2013. In a 2014 CDC National Centre for Health Statistics report, 7 years after ENDS were introduced, 20% of people aged 18–24 years had used an e-cigarette at least once,[16] also demonstrating a high progression in e-cigarette use. The number of adults who used ENDS in the European Union (EU) increased from 7.2% to 11.6% during the period of 2012–2014.[17] In the UK the number of young people aged 11–18 years who had ever smoked an e-cigarette rose significantly, from 4.6% in 2013, to 8.2% in 2014.[18] Adult smokers perceive e-cigarettes as less harmful than tobacco cigarettes, and as an aid to help cut down on or quit smoking, without being trapped by smoke-free policies or emitting second-hand smoke; however, for young people, the market presents e-cigarettes as novel smoking devices with appealing flavours.[19]

In Trinidad, it is a concern that the prevalence of e-cigarette use has considerably increased in the last 6 years since their introduction, and could rapidly rise to a figure as high as in the UK and the USA. A further concern is that e-cigarettes may become a gateway to smoking in young adults. A longitudinal 2-year study in a cohort of American adolescents and young adults showed that e-cigarette use at baseline progressed to tobacco smoking,[20] and, in another report, e-cigarette adolescent users had >6 times the odds of starting cigarette smoking than those who had never used an e-cigarette before.[8] More recently, Spindle at al.[21] reported that American college students who had used an e-cigarette before were likely to progress to tobacco cigarette smoking after a year, and men were more likely to try these devices. Future research is necessary to monitor the patterns of use in this group to determine whether e-cigarettes provide a trajectory to regular tobacco use. Africans were less likely to try or regularly use ENDS, which may reflect their poorer representation in the study. Further research should explore the sociodemographic differences in e-cigarette use, and the possibility that this habit may be a social/cultural phenomenon favoured by East Indians. Studying the knowledge, beliefs, and health risk perceptions among Trinidad's multi-ethnic population allows an understanding of e-cigarette use and will inform future practices.

We found that e-cigarette users had higher OR of current tobacco cigarette smoking (OR: 9.34), and quitting (AOR: 7.98) compared to those who had never smoked tobacco cigarettes. Schoenborn and Gindi[16] reported that adults from the USA who were current smokers, and former smokers who had quit in the past year, were more likely to use e-cigarettes than people who had never smoked or former smokers with a history of quitting >1 year ago. The International Tobacco Control surveys in Australia and the UK reported e-cigarette use had significantly increased between 2010 and 2012 among current and former smokers in both countries.[22] Our findings showed that young adults who had never smoked tobacco cigarettes were not attracted to e-cigarettes or the experience, and this was also observed in research from the USA.[16,23] The majority of these study populations were between the ages of 18 and 44 years. In 27 EU countries, among 26,566 youth and adults, 1.2% of those who had never smoked a tobacco cigarette before had used an e-cigarette before, and smokers who had quit in the past year (AOR: 2.08; 95% CI: 1.67–2.58) had a higher likelihood of e-cigarette use.[24] This study did not assess how much time had passed since the smokers had quit their tobacco-cigarette smoking habit.

We found that a high proportion, nearly 42%, of e-cigarette smokers were dual users with tobacco cigarettes. High rates of dual use in youth populations has shown that e-cigarettes are not being used as a substitute for tobacco cigarettes.[25,26] Future studies are necessary to confirm this finding, since dual users are at high risk of resuming tobacco use.[27] E-cigarettes have not been well-studied for harm reduction or as a cessation strategy, and drug regulatory bodies have not approved them as a smoking cessation device. This study did not assess why users of e-cigarettes were deciding to use the devices, and future research should examine the reasons why Trinidadian youth and young adults choose to use e-cigarettes.

The knowledge that e-cigarettes contain nicotine and the perception that e-cigarettes are safer than tobacco cigarettes were predictors of use. It appears that users of e-cigarettes want to have the nicotine experience from the e-cigarette,

without the harmful effects associated with tobacco cigarettes. The summative knowledge scale incorporated issues on e-cigarette content, habit forming tendency, and the potential to cause cancer and heart disease. However, knowledge was not a predictor of use; therefore, this gap should be addressed to provide information and encourage awareness in young adults. We believe this finding could be due to contradictory information being readily available as a result of aggressive marketing promotions and vested interests. The perception scale items that were useful in our study delved into the underlying concepts of safety and regulatory controls for pregnant women, children, and advertising. Respondents associated e-cigarette use with harm during pregnancy and to children, and unregulated marketing made respondents less likely to use e-cigarettes. The perception that e-cigarette use is harmful will have implications for public policy and e-cigarette advertising claims.

Our study had some limitations. Being a cross-sectional study, it did not inform on causal relationships between e-cigarette use and independent variables. As all data collected were self-reported, there is the possibility that smoking behaviour was under-reported. The unexpected high rate of refusal to participate at public shopping centres meant data were largely gathered from university students aged 18–30 years, so the results cannot be generalised to all young adults in Trinidad. The study did not assess whether subjects had smoked 100 cigarettes in their lifetime; therefore, we could not use the term 'former smoker', rather they were simply called quitters. Furthermore, the study did not explore the reasons for e-cigarette use, and these factors weakened the power of the study. Despite these limitations, the current study does provide an early, valuable insight into the prevalence and correlations of e-cigarette use in young Trinidadian adults. Longitudinal studies to confirm these findings and explore practices of e-cigarette use in this population are recommended.

CONCLUSION

The prevalence of e-cigarette use in young adults in Trinidad has risen rapidly, particularly among those aged 18–25 years, reaching almost 25% 6 years after the introduction of the devices. Current smokers and quitters of tobacco cigarettes are more likely to be e-cigarette users. There are high proportions of dual users of e-cigarettes and tobacco cigarettes, as well as users of e-cigarettes who have never used tobacco cigarettes.

REFERENCES

1. Zhu SH et al. The use and perception of electronic cigarettes and snus among the U.S. population. PLoS One. 2013; 8(10):e79332.

2. McMillen RC et al. Trends in electronic cigarette use among U.S. adults: Use is increasing in both smokers and nonsmokers. Nicotine Tob Res. 2015; 17(10):1195-202.

3. Reid JL et al. Who is using e-cigarettes in Canada? Nationally representative data on the prevalence of e-cigarette use among Canadians. Prev Med. 2015;81: 180-3.

4. McMillen R et al. Use of emerging tobacco products in the United States. J Environ Public Health. 2012;2012:989474.

5. Grana RA, Ling PM. Smoking Revolution: A content analysis of electronic cigarette retail websites. Am J Prev Med. 2014;46(4):395-403.

6. Callahan-Lyon P. Electronic cigarettes: Human health effects. Tob Control. 2014; 23(Suppl 2):ii36-ii40.

7. Chen IL. FDA Summary of adverse events on electronic cigarettes. Nicotine Tob Res. 2013;15(2):615-6.

8. Barrington-Trimis JL et al. E-Cigarettes and future cigarette use. Pediatrics. 2016; 138(1):pii:e20160379.

9. Business Wire. Global e-cigarettes market worth USD 10.687 billion by 2021 - Analysis, technologies & forecasts report 2016-2021 - Key Vendors: Dash Vapes, Hubbly Bubbly, ITC - Research and Markets. 2016. Available at: http://www.businesswire.com/news/home/20160919005801/en/Global-E-cigarettes-Market-Worth-USD-10.687-Billion. Last accessed: 27 February 2017.

10. FDA U.S. Food and Drug Administration. Vaporizers, e-cigarettes, and other electronic nicotine delivery systems (ENDS). 2017. Available at: http://www.fda.gov/TobaccoProducts/Labeling/ProductsIngredientsComponents/ucm456610.htm. Last accessed: 17 March 2017.

11. Caribbean News Now. Electronic cigarettes not proven to be safe says Barbados health official. 2011. Available at: http://caribbeannewsnow.com/headline-Electronic-cigarettes-not-proven-to-be-safe-says-Barbados-health-official-4500.html. Last accessed: 26 February 2017.

12. The Gleaner Company (Media) Limited. Beware! E-cigarettes are dangerous. 2010. Available at: http://jamaica-gleaner.com/gleaner/20100825/health/health2.html. Last accessed: 2 March 2017.

13. Trinidad and Tobago NEWSDAY. The great vape debate. 2014. Available at: http://www.newsday.co.tt/sunday_special_report/0,197247.html. Last accessed: 20 February 2017.

14. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297-334.

15. Gravely S et al. Awareness, trial, and current use of electronic cigarettes in 10 countries: Findings from the ITC project. Int J Environ Res Public Health. 2014;11(11):11691-704.

16. Schoenborn CA, Gindi RM. Electronic cigarette use among adults: United States, 2014, National Center for Health Statistics (NCHS) data brief, no. 217. 2015. Available at: https://www.cdc.gov/nchs/data/databriefs/db217.pdf. Last accessed: 11 April 2017.

17. Filippidis FT et al. Two-year trends and predictors of e-cigarette use in 27 European Union member states. Tob Control. 2017;26(1):98-104.

18. Eastwood B et al. Electronic cigarette use in young people in Great Britain 2013-2014. Public Health. 2015;129(9):1150-6.

19. van Dorn A. The PATH to smoking cessation in the USA. Lancet Respir Med. 2017;5(3):170.

20. Primack BA et al. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. JAMA Pediatr. 2015;169(11):1018-23.

21. Spindle TR et al. Electronic cigarette use and uptake of cigarette smoking: A longitudinal examination of U.S. college students. Addict Behav. 2017;67:66-72.

22. Yong HH et al. Trends in e-cigarette awareness, trial, and use under the different regulatory environments of Australia and the United Kingdom. Nicotine Tob Res. 2015;17(10):1203-11.

23. Delnevo CD et al. Patterns of electronic cigarette use among adults in the United States. Nicotine Tob Res. 2016;18(5):715-9.

24. Vardavas CI et al. Determinants and prevalence of e-cigarette use throughout the European Union: a secondary analysis of 26 566 youth and adults from 27 Countries. Tob Control. 2015;24(5):442-8.

25. Lee S et al. Electronic cigarette use among Korean adolescents: a cross-sectional study of market penetration, dual use, and relationship to quit attempts and former smoking. J Adolesc Health. 2014;54(6):684-90.

26. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among U.S. adolescents: A cross-sectional study. JAMA Pediatr. 2014;168(7):610-7.

27. Dautzenberg B et al. Practical guidelines on e-cigarettes for practitioners and others health professionals. A French 2016 expert's statement. Rev Mal Respir. 2017;34(2): 155-64.

UPCOMING EVENTS

British Thoracic Society Winter Meeting 2017 (BTS)

6th–8th December 2017

London, England

Held in the Queen Elizabeth II Centre, Westminster, London, the annual winter meeting of the British Thoracic Society is a highlight on the calendar of many healthcare professionals. Last year's meeting saw the presentation of best practice awards for work that broke new ground in patient care and respiratory disease treatment and, with a packed schedule encompassing a wide range of topics, BTS 2017 promises to be an even bigger success this year.

5th International Workshop on Lung Health (IWLH)

18th–20th January 2018

Berlin, Germany

A forum dedicated to the discussion of provocative topics and cutting-edge treatments, the International Workshop on Lung Health (IWLH) regularly stimulates thought-provoking and engaging debates on the state of respiratory medicine. Focussing on asthma, chronic obstructive pulmonary disease, and personalised medicine, this year's IWLH will include abstract and poster presentations of the latest pioneering research and lectures from world renowned experts.

10th Annual Ottawa Conference: State of the Art Clinical Approaches to Smoking Cessation 2018

19th–20th January 2018

Ottawa, Canada

The 10th Annual Ottawa Conference focusses on the treatment of tobacco and smoke inhalation in patients. Held once again at The Shaw Centre at the University of Ottawa Heart Institute, Ottawa, Canada, the Annual Ottawa Conference has become a prestigious conference, attracting academics from across the world to share their expertise, present their research, and make use of the fantastic networking opportunities.

12th World Congress on COPD, Asthma and Respiratory Allergy

2nd–5th February 2018

Dubai, United Arab Emirates

Held in the striking city of Dubai, the 12th World Congress on COPD, Asthma, and Respiratory Allergy provides a broad spectrum of presentations, debates, and discussions focussing on the treatment, screening, and prevention of three diseases that continue to grow in clinical importance. Some of the key topics include a look at the genetic cause of asthma, the vital role of T cells in allergic inflammation, and the risk factors and exacerbants related to chronic obstructive pulmonary disease.

German Respiratory Society 59th Annual Meeting 2018 (DGP)

14th–17th March 2018

Dresden, Germany

The congress boasts three keynote speeches that give a medical perspective on some political hot topics, including a discussion regarding how ethics, medicine, and the economy can all fit together to achieve the best outcomes for patients. One of the key aims of the congress is to address issues in the field of pneumology, as well as to promote collaboration between respiratory specialists and their colleagues from all other areas of internal medicine.

European Lung Cancer Conference 2018 (ELCC)

11th–14th April 2018

Geneva, Switzerland

The 8th ELCC congress will focus on a collaboration between respiratory and cancer specialists to drive the treatment of lung cancers forward. The main themes of this multidisciplinary conference, suitable for both medical oncologists and pneumologists, include an analysis of the implementation of lung cancer screening strategies, the molecular background of cancers, and immunotherapy. This conference provides an invaluable opportunity to develop worldwide contacts across disciplines.

Canadian Respiratory Conference 2018 (CRC)

12th–14th April

Vancouver, Canada

CRC 2018 promises to be a memorable event, not only for its stunning setting, but also its packed and varied scientific programme, which this year includes lectures and presentations from world leading experts from throughout the field of respiratory medicine. Additionally, a host of abstracts and posters detailing the progress of ongoing research projects, destined to shape the future of respiratory medicine, are set to be presented.

European Respiratory Society International Congress 2018 (ERS)

15th–19th September 2018

Paris, France

We are very much looking forward to returning to the ERS congress, which for its 28th annual meeting will be hosted in the cosmopolitan city of Paris, France. The congress will offer outstanding opportunities for networking with academics from across the world and boasts panel discussions and presentations led by experts at the forefront of their field. Covering topics from lung cancer and sleep breathing disorders to cystic fibrosis and asthma, as well as many more, ERS 2018 cannot be missed.

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- THORASYS EUROPE UG
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