

ERS International Congress 2021

EDITOR'S PICK

SARS-CoV-2 and Cystic Fibrosis:
Expectations Versus Reality, a
Literature Review

INTERVIEWS

EMJ spoke to Sarah Walmsley and
Andres Floto, who shared insights into
their careers, the impact of COVID-19
on the respiratory field, and current
research developments.



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“This unmissable journal brings together the latest advancements in respiratory medicine. EMJ Respiratory 9.1 also offers readers a chance to hear from key players in respiratory medicine.”

Spencer Gore, CEO

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Welcome

Dear Readers,

It is my great pleasure to welcome you to the latest edition of *EMJ Respiratory*. This unmissable journal brings together the latest advancements in respiratory medicine. Prepare yourself for our content, which includes peer-reviewed articles, exclusive interviews with key opinion leaders in the therapeutic area, and research papers covering the breadth of the discipline.

The landscape of respiratory medicine has been drastically altered over the last 18 months by the emergence of the COVID-19 pandemic. These shifts in healthcare practice, research, and patient concerns were discussed and debated at the European Respiratory Society (ERS) International Congress, 5th-8th September. Alongside COVID-19 concerns, abstracts presented at the congress and included in this journal explore risk factors for asthma and chronic obstructive pulmonary disease, late-breaking research about e-cigarettes, and how changes in lung function can predict cardiac death.

The peer-reviewed and expertly written papers published in this journal explore a wide range of topics across the field, including a case study of a stroke patient with recurrent meningeal tuberculosis and HIV coinfection authored by Dilia Fontalvo-Rivera, Universidad de Cartagena,

Colombia. A literature review carried out by Anne Bantounou, University of Aberdeen, UK, which investigates the expectations of patients with cystic fibrosis and severe acute respiratory syndrome coronavirus 2 infection, is also included. This journal further features a study highlighting a case of vaccine-induced thrombotic thrombocytopenia in response to the adenoviral vector-based COVID-19 vaccine, along with many more articles and congress highlights.

This issue of *EMJ Respiratory* also offers readers a chance to hear from key players in respiratory medicine. The journal includes interviews from Sarah Walmsley, Professor of Respiratory Medicine and Honorary Consultant in Respiratory Medicine, University of Edinburgh, UK, and Andres Floto, Professor of Respiratory Biology at the University of Cambridge and Research Director of the Cambridge Centre for Lung Infection at Papworth Hospital, UK.

I would like to express my thanks to the Editorial Board, expert authors, peer reviewers, and interviewees for all the fantastic work they have put into creating this issue of *EMJ Respiratory*. Publication of this journal relies on their dedicated efforts and support. Finally, all that remains, is to thank you, the reader, for your maintained support, as EMJ continues to be the go-to place for healthcare professionals.



Spencer Gore

Spencer Gore

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Foreword

Dear Readers,

It is my pleasure to present the latest issue of *EMJ Respiratory*. The main topic is COVID-19 infections, focusing on specific clinical cases with the aim to highlight some of the difficulties clinicians may face when diagnosing respiratory syndromes amongst the COVID-19 pandemic, and also exploring the acquired skills to treat these patients.

Inside this issue, a variety of articles from respiratory experts discussing topics in disease areas other than COVID-19, such as stroke in recurrent meningeal tuberculosis, are also presented.

The European Respiratory Society (ERS) decided to hold its annual congress virtually again for this year, taking place 5th–8th September. ERS has developed an outstanding ability to organise high-quality digital conferences, allowing close interaction and discussion. The high-quality presentations, the best speakers from around the world, and to strive for greatest variety in geography, representation of specialist areas, career-stage, and gender have been selected with great care. The scientific programme included

live presentations, thousands of e-posters, and satellite symposia, a review of which is included in the following pages, which showcased key advancements in respiratory medicine, on a large variety of topics beyond the COVID-19 pandemic issue, over the last year.

The Editor's Pick for this issue is a review paper titled 'SARS-CoV-2 and Cystic Fibrosis: Expectations Versus Reality, a Literature Review'. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is expected to cause severe illness in people with cystic fibrosis. The infection prevalence and clinical outcomes of this patient cohort to SARS-CoV-2 were explored. Understanding the mechanisms and timings of response of people with cystic fibrosis to SARS-CoV-2 infection may help in evaluating the COVID-19 infection prevalence and clinical outcomes compared with the general population.

I would really like to thank you for your interest in *EMJ Respiratory* and hope that you will like the 2021 issue, which I believe to be of interest to you all.

Enjoy reading!



A handwritten signature in black ink, appearing to read 'Antonio Rossi', set against a light grey background with a subtle grid pattern.

Antonio Rossi

Senior Medical Director, Oncology Center of Excellence, Therapeutic Science and Strategy Unit, IQVIA, Milan, Italy

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Congress Review

Review of the Virtual European Respiratory Society (ERS) International Congress 2021

Location:	ERS International Congress
Date:	5 th –8 th September 2021
Citation:	EMJ Respir. 2021;9[1]:12-24. Congress Review.

THE EUROPEAN Respiratory Society (ERS) International Congress is the world's largest gathering of respiratory professionals, with over 300 speakers and more than 500 chairs. This year's congress was planned to take place in Barcelona, Spain; however, for the second year running, the ERS congress occurred virtually due to the COVID-19 pandemic. With guidelines advising against large gatherings and many respiratory professionals being frontline workers, this was the best option, and the silver lining of the virtual congress is that all sessions can be replayed by attendees until December this year.

Despite the ERS congress being virtual, the sessions were interactive and engaging, with polls throughout case studies, question and answer sessions, and breakout rooms with some of the faculty members. This allowed participants to experience the interactive and networking element of the traditional face-to-face congress. The ERS president,

Anita Simonds, discussed her aims in a welcome video clip at the start of congress: "My aim has been to advance the ERS digital respiratory health agenda, make our voice heard loud and clear on health policy issues, and celebrate our multidisciplinary teams across Europe and globally."

Simonds also shared the theme of this year's ERS congress as being digital health. Many speakers across a variety of sessions unanimously agreed that the COVID-19 pandemic helped push forward digital healthcare because physicians were forced to take a different approach to provide care for their patients, especially in countries where patients were unable to leave their homes due to strict lockdowns. In an inspiring session on the second day of the congress, patients with tuberculosis discussed their experience with accessing healthcare virtually and doctors shared obstacles they faced, such as poor internet connection and having to adapt to this new way of managing conditions virtually.



“My aim has been to advance the ERS digital respiratory health agenda, make our voice heard loud and clear on health policy issues, and celebrate our multidisciplinary teams across Europe and globally.”

The congress programme contained 320 scientific sessions, and there were plenty of standout presentations, ranging from emerging imaging biomarkers in lung disease to the latest ERS guidelines on non-continuous positive airway pressure in sleep apnoea. Additional riveting talks included the 'lungs on fire' paediatric disease session, which shared rare and fascinating case studies. Other notable sessions included using digital health to manage respiratory conditions and inspiring conversations surrounding innovative technologies to evaluate sleepiness.

There were different types of sessions, some more interactive than others. For example, 'lungs on fire', clinical cases, and the grand rounds all included polls. On top of this, there were hot topics, pro/con debates, six guidelines sessions, state-of-the-art sessions, and, for the first time ever, a skills lab. The skills lab was a new session added to the ERS congress this year and involved speakers explaining equipment and procedures used by respiratory professionals.

With an impressive 3,000 plus abstracts, a variety of research was shared at this year's virtual congress. Several of these abstract summaries are included in this year's journal, covering topics such as tracheal stenosis, asthma, chronic obstructive pulmonary disease, pneumomediastinum as a complication of COVID-19 pneumonia, and skeletal muscle afferent sensitivity in interstitial lung disease.

Next year's congress is planned to take place in early September in Barcelona, and the committee are hopeful and optimistic that this can take place in person for the first time in 2 years. Although there are a few benefits to a virtual congress, the speakers are looking forward to sharing their new respiratory research and developments in person next year, and believe that the future, post-COVID-19, is bound to look very different, with a mix of digital and in-person healthcare. The team at EMJ are excited to attend the ERS congress in 2022 in Barcelona; however, for now, please enjoy our highlights and reviews of the ERS International Congress 2021. ■

ERS 2021 REVIEWED →

Obesity Affects Steroid Medication in Asthmatic Children

"A more personalised approach should be taken to treating children with asthma who are also overweight, counteracting the current 'one size fits all' method of steroid prescription."

FASCINATING research has emerged from an international study showing that asthmatic children who are also overweight or obese are less likely to respond to inhaled steroid medication. Presented at the virtual ERS International Congress on 8th September 2021, scientists involved in this discovery have linked this to increased asthma attacks in these children, which can have fatal consequences.

The international study aimed to examine whether a poor response to inhaled corticosteroids (ICS) is linked to excess weight or environmental factors. Researchers used information on genetic variants linked to BMI to investigate this, making the study the first of its kind. Cristina Longo, Assistant Professor, University of Montreal, Canada, who carried out research in the study, explained: "Children with asthma who are overweight or obese are more likely to have worse symptoms despite being on the recommended treatment of inhaled corticosteroids, making it not only challenging to achieve a healthy weight but also to improve their quality of life." She also noted that children with asthma may exercise less due to their condition, in turn making them more susceptible to weight gain.

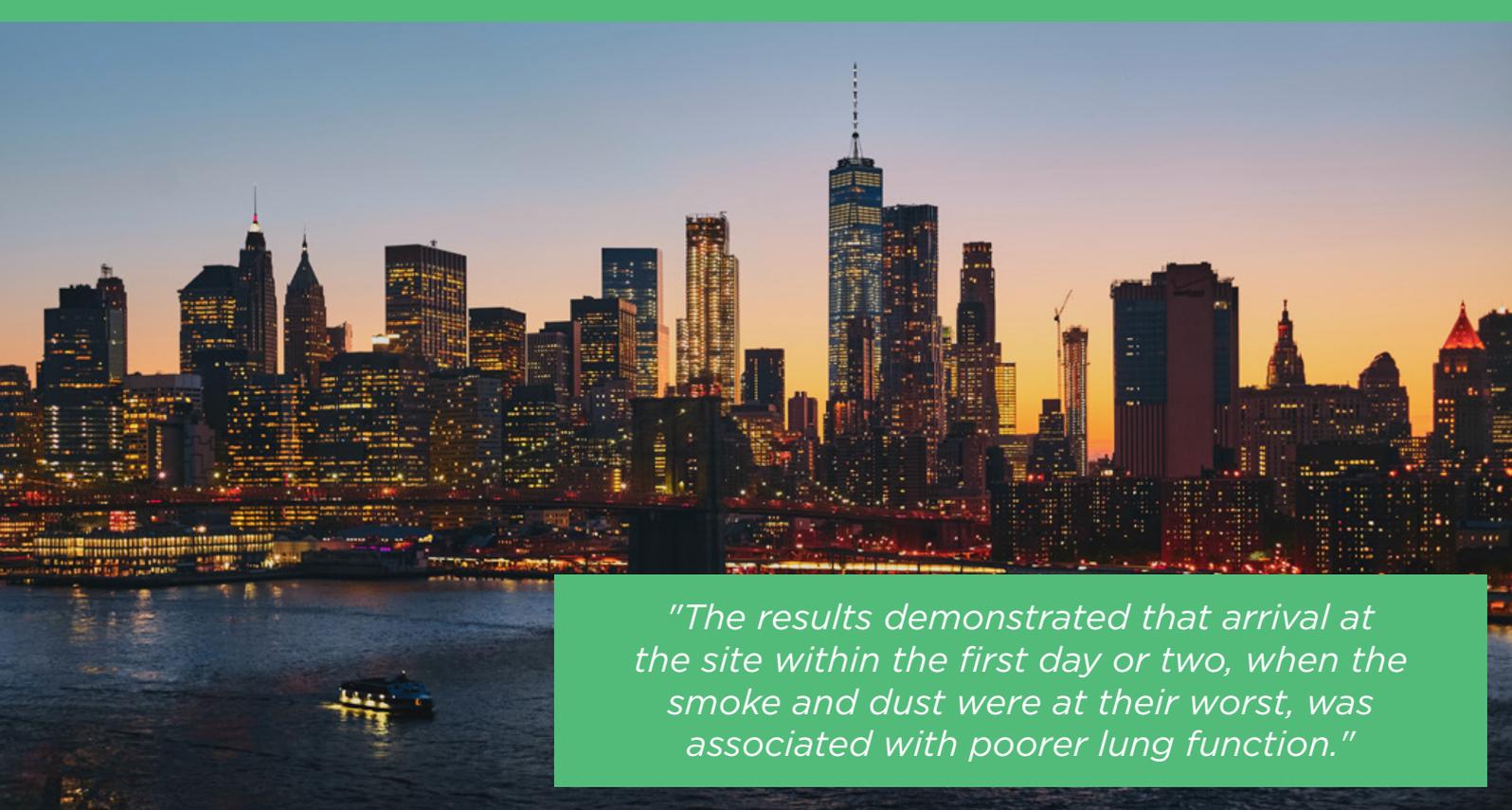
The research included data from five studies involving 1,511 children with asthma. Participants all experienced a poor response to ICS, which was characterised by one or more asthma attacks that required urgent medical care or a course of corticosteroids. Longo and colleagues collected information to create a 'risk score', which increased with the amount of BMI-linked genetic variants each child had. This score was used to

estimate fluctuation in their BMI z-score, which indicates how each child's BMI deviates from the average healthy child of the same demographic; a score of 1 indicates a risk of being overweight, 2 suggests a child is overweight, and 3 that a child is obese.

The scientists used Mendelian randomisation to assess differences in the children's responses to ICS treatment. A higher incidence of asthma attacks in children with a high BMI z-score indicated a higher prevalence of genetic variants that increased their susceptibility to being overweight. This would likely be linked to the child's BMI, rather than environmental factors. The study saw an average BMI z-score of 0.69, with 21% of participants being obese. Longo explained: "Although poor ICS response ranged from 20% to 80% between the five international studies, we consistently show that the proportion of children with poor ICS response more than doubled for each one unit increase in the BMI z-score."

The results from this study have indicated that a more personalised approach should be taken to treating children with asthma who are also overweight, counteracting the current 'one size fits all' method of steroid prescription. Although some limitations remain, this research has provided an insight into why some children may have limited responses to treatment. Longo has since continued her research, focusing on the prevalence of specific genetic variants in obese and non-obese children with asthma, and their link to a poor ICS response. ■





"The results demonstrated that arrival at the site within the first day or two, when the smoke and dust were at their worst, was associated with poorer lung function."

World Trade Centre Site Emergency Workers Chronic Obstructive Pulmonary Disease Risk

RESCUE workers and volunteers who arrived at the site of the World Trade Centre in the wake of September 11th 2001 are beginning to develop chronic obstructive pulmonary disease (COPD), according to research presented at the ERS International Congress on the 7th September 2021, 4 days before the 20-year anniversary of the attacks.

In general, COPD mainly affects older people who smoke; however, occupational and environmental exposure are increasingly being recognised as contributory risk factors. Research presented by Rafael E de la Hoz from the Icahn School of Medicine at Mount Sinai, New York City, New York, USA, examined almost 18,000 workers and volunteers and demonstrated that those who arrived at the site soon after the collapse of the Twin Towers faced the greatest risk of COPD.

The 17,996 participants were all individuals who had worked at the World Trade Centre site. Participants each took part in spirometry tests to measure lung health at least twice between 2002 and 2018. Data on the time each person arrived at the site was considered alongside

other health factors such as age, smoking status, and weight.

The results demonstrated that arrival at the site within the first day or two, when the smoke and dust were at their worst, was associated with poorer lung function. Of the study group, 586 had developed COPD so far, with those who arrived early at the site at an approximately 30% higher risk than those who arrived later. The study further showed that COPD diagnosis often followed an earlier diagnosis of asthma, and approximately 40% of those diagnosed with COPD had features of both diseases.

De la Hoz stated: "Many of these workers were non-smokers and in their early 40s in 2001, and COPD is rare in that age group."

Researchers have described this as one of the largest and most detailed prospective studies on a group of workers exposed to such high levels of dust and smoke. The findings demonstrate the importance of monitoring health workers and can contribute to understanding the best way to care for emergency workers operating in dangerous conditions. ■



Could Artificial Intelligence Improve Lung Cancer Survival Rates?

ARTIFICIAL intelligence (AI) is a surging innovation in many fields of healthcare, with new technologies transforming many aspects of patient diagnosis and care. New evidence has surfaced suggesting that the use of AI could aid diagnosis of lung cancer up to a year earlier than with current methods. Presented at the ERS International Congress on 8th September 2021, this research focuses on the use of a specific AI programme to identify signs of lung cancer on CT scans.

Being the most common cause of cancer death due to its often late-stage diagnosis, early identification of lung cancer is essential to increase the likelihood of successful treatment, and, therefore, survival. Current diagnostic strategies uses CT scans, which are examined by radiologists to identify signs of lung cancer, followed by a surgical procedure or biopsy to confirm tumour malignancy. Although effective, this strategy is time-consuming and can lead to delayed diagnosis given the volume of images each radiologist must analyse.

Benoît Audelan, a researcher of the Epione project from the Inria centre, Université Côte d'Azur, Nice, France, presented a new study, on which he collaborated with colleagues from Université Côte d'Azur, Therapixel, and the University Hospital of Nice. Audelan and colleagues used a series of CT scans from 888 patients with suspicious growths to train their AI programme. The programme was then tested on 1,179 patients involved in a lung screening trial with a 3-year follow-up, which included 177 patients that had a confirmed lung cancer diagnosis.

"Being the most common cause of cancer death due to its often late-stage diagnosis, early identification of lung cancer is essential to increase the likelihood of successful treatment, and therefore survival."

The AI program had a 97% success rate in malignant tumour detection, with the five tumours that were unidentified being at the centre of the chest, which made them more difficult to distinguish. The programme was also able to identify 152 suspicious areas from scans taken a year before cancer diagnosis in the same patient set. Although these results show promise, Audelan and colleagues explained that the programme also has a high rate of identifying false positives, an area which requires improvement before clinical use.

Audelan explained: "Screening for lung cancer would mean many more CT scans being taken and we do not have enough radiologists to review them all. That's why we need to develop computer programs that can help. Our study shows that this program can find possible signs of lung cancer up to a year earlier." He added: "The objective of our research is not to replace radiologists but to assist them by giving them a tool that can spot the earliest signs of lung cancer." Scientists involved in this exciting study intend to progress their research into developing a program to successfully differentiate between malignant and non-malignant tissue. ■

Warmer Weather Linked to Increase in COPD Exacerbations

GLOBAL average temperatures slowly but dangerously increase each year due to climate change. As the Earth gets hotter, the ice caps melt and ecosystems are disturbed; however, it is not only rising sea levels is not the only thing to worry about. Increase in temperature could also affect respiratory conditions such as chronic obstructive pulmonary disease (COPD). A unique study aimed to discover whether an increase in ambient temperatures resulted in an increase in COPD exacerbations.

The study took place in the US and involved analysing data from 1,177 individuals that were the average age of 64 years with COPD who either currently smoke or used to smoke. These participants had enrolled in studies previously namely, 'SubPopulations', and 'Intermediate Outcome Measures in COPD Study (SPIROMICS)' from as early as 2010 and had at least one COPD exacerbation.

Supaksh Gupta, pulmonary and critical care fellow, University of Washington, USA, and colleagues analysed the local ambient temperatures recorded on the day of the COPD exacerbation and the preceding week to determine whether hotter temperatures were linked to increase in COPD exacerbations.

Interestingly, the results showed that the risk and likelihood of COPD exacerbations increased with rising temperatures prior to the next 6 days. An increase in just 1 °C resulted in a 2% increase in the risk of COPD exacerbation 2 days after temperatures increased. The highest risk occurring 2 days after temperatures increased.

The findings from this study highlight how the ongoing climate crisis have a negative effect on conditions that scientists may not have even previously realised. A possible solution for patients with COPD would be to avoid hotter temperatures by staying indoors when it is too hot outside. Although this might not be ideal, it might be a preventive measure in times when temperatures soar way above normal.

To conclude, Gupta shared their teams' ambitions for the future, "I hope our research will help guide public policy recommendations and promote health precaution guidelines for people with COPD during periods of increased ambient temperature." ■

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COVID-19 Infection Does Not Affect Lung Function in Young Adults, Research Finds

“Our analysis showed similar lung function irrespective of COVID-19 history.”

LATE-BREAKING research presented at the ERS International Congress on 7th September 2021 has demonstrated that infection with COVID-19 does not appear to affect young adults’ lung function.

Ida Mogensen, Karolinska Institute, Stockholm, Sweden, led the first study presented, which demonstrated that even patients with asthma did not show a statistically significant deterioration in lung function after infection. However, there was a trend towards slightly lower measurements of forced expiratory air volume (FEV₁).

Researchers collected data from 661 adolescents and young adults, with an average age of 22 years. Data that was collected for analysis included measurements of lung function, inflammation, and eosinophils. All participants had been involved in previous study and, therefore, had data points collected pre-pandemic. Mogensen and her colleagues selected 178 individuals who had severe acute respiratory syndrome coronavirus 2 antibodies, indicating they had been infected. Measurements were taken of FEV₁, forced vital capacity, and FEV₁/forced vital capacity ratio (an indicator of narrowed airways). Changes in lung function over the pandemic were calculated and compared to participants who had not experienced COVID-19 infection.

No significant differences in lung function were identified between patients who had or had not been infected with respect to eosinophils, inflammation indicators, or allergy responses.

“Our analysis showed similar lung function irrespective of COVID-19 history,” stated Mogensen.

The second study presented at congress by Anne Schlegtendal, University Children’s Hospital, Ruhr-University of Bochum, Germany, expanded on this research by investigating children and adolescents between the ages of 5 and 18 years.

Researchers monitored lung function between 2 and 6 months following COVID-19 infection and compared results to a control group of children who had not been infected. In the follow-up, only two children were found to have presented with abnormal lung function. When the patients with COVID-19 were compared to the control group, no significant differences in frequency of abnormal lung function were found. Abnormal function occurred in 16% of the COVID-19 group and 28% of the control group.

Schlegtendal emphasised the importance of the research: “These findings should offer some reassurance to children, adolescents and their families.” ■

Electronic Nose Could Be Key to the Early Detection of Lung Transplant Failure

According to new research, presented on 7th September 2021 at the ERS International Congress, an electronic nose could ‘sniff out’ lung transplant failure. According to the current research, it could take several months to diagnose lung transplant failure known as chronic allograft dysfunction (CLAD). The study presented by Nynke Wijbenga, PhD student and Technical Physician at Erasmus University Medical Center, Rotterdam, the Netherlands, stated that an eNose could be useful in the early diagnosis of CLAD, allowing doctors to intervene and provide treatments sooner before the condition gets worse.

Wijbenga stated that approximately 50% of patients who have undergone a lung transplant are diagnosed with chronic rejection or CLAD within 5 years after the lung transplant. There is currently no treatment available to reverse chronic rejection despite the fact that it is one of greatest cause of death following lung transplantation. The innovative eNose is a device that has sensors capable of detecting chemicals called volatile organic compounds (VOCs). These VOCs vary depending on different metabolic processes occurring within the body, including the lungs. The VOCs are available in 1% of exhaled breath and, therefore, the eNose can be used to spot the VOCs pattern. The results from the eNose are analysed using machine learning algorithms and therefore could be useful in detecting several lung diseases.

The study team recruited 91 patients who had a lung transplant who visited the institution between July and November 2020. The patients were between 35 and 73 years old, with a median age since lung transplantation of 3.6 years. With one eNose measurement from each study participant, the researchers compared the data with the prior results of the diagnoses each patient received from their consultants. The results showed that in 86% of the cases, the eNose detected and distinguished that 68 patients had stable lung transplants, whilst 23 patients were diagnosed with CLAD.

“These results suggest that the eNose is a promising tool for detection of CLAD,” said Wijbenga. “However, more research is required before it can be used in the clinic. We need to assess whether repeated measurements in the same patients can provide more accurate diagnoses and even predict CLAD before it occurs. Also, we need to confirm our results in other groups of patients. Nonetheless, we aim to develop this as a technique for wide use across Europe.” ■

“Approximately 50% of patients who have undergone a lung transplant are diagnosed with chronic rejection or CLAD within 5 years after the lung transplant.”



Could E-cigarettes Containing Nicotine Cause Blood Clotting?

E-CIGARETTES were first introduced in the UK over a decade ago from China. Since then, e-cigarettes have become a worldwide trend, with almost three million

"The results showed that individuals using e-cigarettes had a 23% increase in blood clots 15 minutes after using e-cigarettes with nicotine."



people using these smoking devices in the UK alone. Many people believe that e-cigarettes are less toxic than smoking traditional cigarettes due to the lack of harmful chemicals found in tobacco smoke. Although, in recent years, new research has come to light to suggest the opposite is true and that smoking e-cigarettes with nicotine can be just as fatal.

A recent study presented at the ERS International Congress showed the effects of using e-cigarettes on the blood vessels and heart. The researchers recruited a group of 22 healthy participants aged 18–45 years old who occasionally smoked. Two tests were carried out on these individuals with a 1-week gap in between. The first test involved the participants taking 30 puffs from an e-cigarette containing nicotine and the second test involved taking 30 puffs from an e-cigarette without nicotine. Individuals' heart rate and blood pressure were measured before and after taking the 30 puffs as well as blood sample tests at the following intervals: before using an e-cigarette, 15 minutes after using an e-cigarette, and, finally, 60 minutes after use.

Further to this, the researchers used a laser to observe the ability of the blood vessels to dilate and supply blood to organs around the body before and after using e-cigarettes. The results showed that individuals using e-cigarettes had a 23% increase in blood clots 15 minutes after using e-cigarettes with nicotine, which eventually went back to normal after an hour. Other findings included an increase in heart rate by 7 beats per minute and narrower blood vessels in participants smoking e-cigarettes containing nicotine. These results suggest that the long-term effects of smoking with e-cigarettes containing nicotine could be deadly as more blood clots increases the chance of heart attacks and strokes.

The next steps could be to replicate this study on a larger scale and to make people fully aware of the dangers of smoking e-cigarettes. The speaker that presented this study, Gustaf Lyytinen, Clinician at Helsingborg Hospital and Researcher at the Karolinska Institute in Stockholm, Sweden, shared his concluding remarks: "Some people may use e-cigarettes when attempting to quit smoking because they are marketed as being safe, but this study adds to the growing evidence on the harmful effects of e-cigarettes." ■

Could Office Environments Be The Reason For Occupational Asthma?

NOVEL study, presented on 6th September 2021 at the ERS International Congress, stated that seemingly safe office environments may lead to the development of asthma in some employees. According to the study, there are several environmental triggers such as printer toners, poor ventilation, cleaning products, and even air conditioning. Furthermore, the study discovered that employees who experienced occupational asthma eventually left their jobs, especially if the employer did not resolve the issue.

The study was presented by Christopher Huntley, Birmingham Regional Occupational Lung Disease Service, University Hospitals Birmingham NHS Foundation Trust, UK. His team investigated 47 cases of office employees, reported to Birmingham Regional Occupational Lung Disease Service, UK, who had been diagnosed with occupational asthma. Using a serial peak flow monitoring, which is the fastest rate in which patients breathe air out, the majority of patients were confirmed to have asthma. The results showed that 17 patients had lungs that reacted vigorously to sensitive airways. The researchers

also recognised three main categories as the causes of occupational asthma in employees within an office environment: triggers within the office such as toners, mould, and cleaning products; triggers within the air ventilation system such as mould; and the office's surrounding environment such as paint and vehicle fumes.

Additionally, the researchers also explored a situation in which the employers adjusted to accommodate office workers with occupational asthma. The results showed that in situations where the employers did not make any adjustments, the employees were 100-times more likely to quit their jobs. According to Huntley, there were fewer referrals for new patients with occupational-related asthma during the COVID-19 pandemic restrictions and, furthermore, the currently diagnosed patients have exhibited improvements during the period of working from home. He added: "Working from home has been useful for patients in both establishing their diagnosis and as a form of non-pharmacological treatment. Allowing workers with occupational asthma to continue working from home may help keep office workers in their jobs as they require fewer sick days." ■



"Working from home has been useful for patients in both establishing their diagnosis and as a form of non-pharmacological treatment. Allowing workers with occupational asthma to continue working from home may help keep office workers in their jobs"



Exercise During Pregnancy Linked to Lung Function in Offspring

SCANDANAVIAN study has uncovered evidence that there is a link between lung function in babies and the physical activity level of their mother. Hrefna Gudmundsdottir, who presented this discovery, summarised the findings: “In our study, we found that babies born to inactive mothers were more likely to be in the group with the lowest lung function compared to babies born to active mothers.”

In total, 814 healthy babies born to women in Oslo, Norway, and Stockholm, Sweden, were included in this study, as a part of the larger Prevent ADALL study from 2014–2016, conducted at the Oslo University Hospital in Norway and Karolinska University Hospital in Stockholm. Mothers completed questionnaires at 18 weeks and 34 weeks of pregnancy about their health, lifestyle, socioeconomic factors, and nutrition. This included a report of how often they exercised, for how long, and at what intensity, to aid classification as inactive, fairly active, or very active. Lung function was measured on 3-month-old babies by assessing normal breathing in calm and awake infants, done by holding a face mask over the baby’s nose and mouth and recording the flow and volume of air inhaled and exhaled.

Of the 290 babies with inactive mothers, 8.6% (25) were in the group with lowest lung function. Moreover, 4.2% (22) of the 524 babies with active mothers were also in this group with low lung function, combining to a total of 47 babies. Overall, 5.8% of the 814 infants had low lung function, and average lung function was slightly higher among babies of active versus inactive mothers. The major measurement for this research was the ratio between time to peak

tidal expiratory flow and expiratory time (tPTEF/tE), which represents limitation to the flow of exhaled breath. Average tPTEF/tE measurement for all infants was 0.391, where 290 babies of inactive mothers exhibited the lowest average of 0.387 and 299 babies of very active mothers had the highest at 0.394. Researchers also took into account mother age, education, pre-pregnancy BMI, nicotine use during pregnancy, asthma, allergy-related illnesses in either parent, and if the mother had given birth previously.

The observation of this link is a novelty, and provokes change to the future direction of research in this field. Gudmundsdottir described the path forward expected as a result of this discovery: “Exploring factors that can be associated with lung function in infants is important. If being physically active during pregnancy could reduce the risk of impaired infant lung function, it would be a simple, low-cost way to improve the respiratory health of offspring.” Further guidance and emphasis on the usefulness and limitations of this study can be seen in Gudmundsdottir’s statement that “we observed a trend that adds to the importance of advising women of child-bearing age and pregnant women about physical activity. However, there may be factors that affect both maternal physical activity and lung function in offspring that we have not accounted for and could affect the results and so more research is needed.” The researchers will follow the babies as they grow to see how lung function progresses and how it related to development of respiratory diseases, such as asthma. ■

Lower Lung Function Could Predict Risk of Sudden Cardiac Death

SUDDEN cardiac death (SCD) is the abrupt loss of heart function, affecting approximately 20% of individuals in Europe. Risk factors for SCD include coronary heart disease, family history, and lifestyle choices such as smoking. In a study presented at this year's ERS International Congress, researchers aimed to find a way to detect individuals at risk of SCD to prevent further deaths.

The research involved 28,584 middle-aged participants from Malmö, Sweden, with no known cardiac issues. Each participant had a spirometry test, which is commonly used to assess lung function and involves blowing into a tube as hard as one can. Over the course of four decades, the researchers recorded any SCDs or non-fatal coronary events.

Fascinatingly, the results showed that the middle-aged participants who had measurably lower lung function had a 23% increase in risk of having a SCD. Further to this, those with lower lung function also had an 8% increased risk in having a non-fatal coronary event.

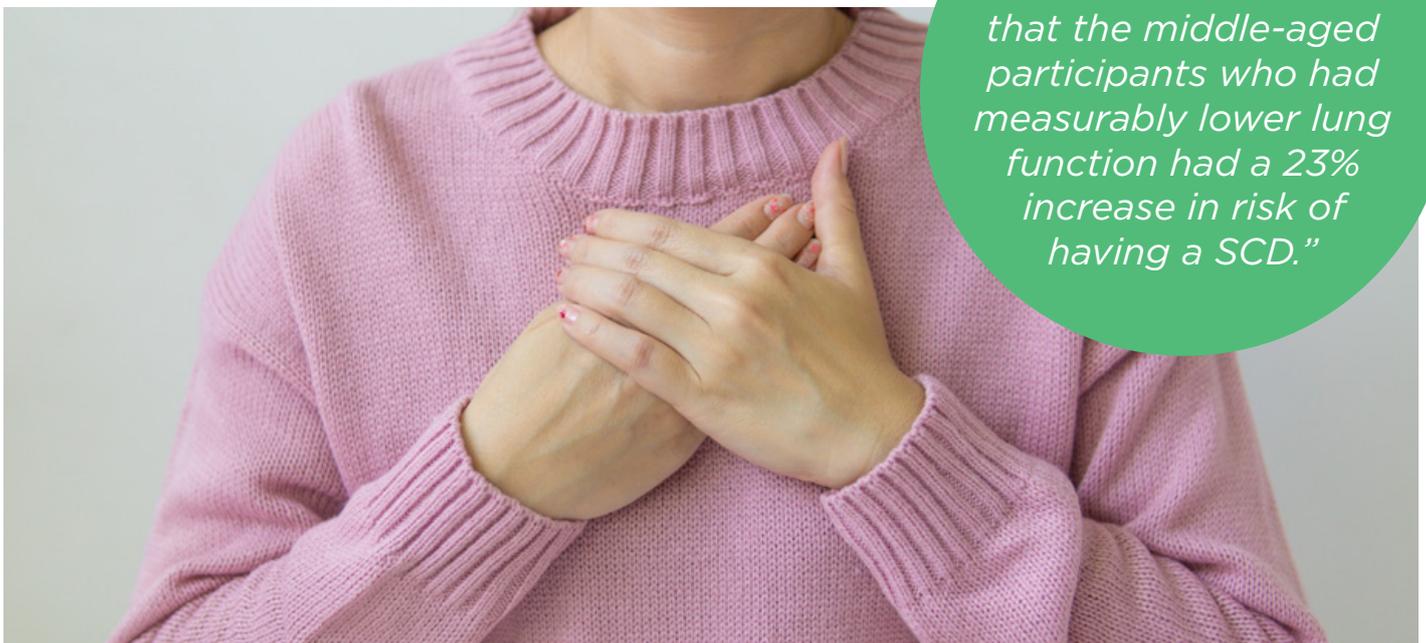
The speaker, Suneela Zaigham, a researcher from the Department of Clinical Sciences,

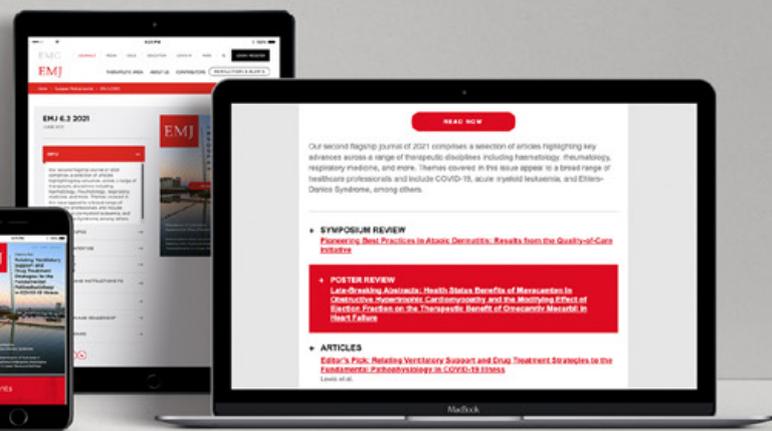
Cardiovascular Epidemiology at Lund University, Sweden, shared her thoughts about these interesting results: "We believe this is the first study to directly compare the risk of sudden cardiac death and non-fatal coronary events and their links with lung function in the general population."

The findings indicate that testing lung function of healthy middle-aged individuals might help spot individuals at risk of potentially having a SCD in the future and consequently save lives. The speakers were aware that the limiting factor of their study was that all the tests took part at the start of their study and risk factors could have changed over the 40 years.

Future work could involve testing lung function of individuals at intervals over the course of 40 years and for scientists to do more research into how lung function affects cardiac function. Understanding this link could help with early intervention, which is what the researchers from this study aim to do. Perhaps, one day in the future, measuring lung function could be used as a screening tool for SCD. ■

"Fascinatingly, the results showed that the middle-aged participants who had measurably lower lung function had a 23% increase in risk of having a SCD."





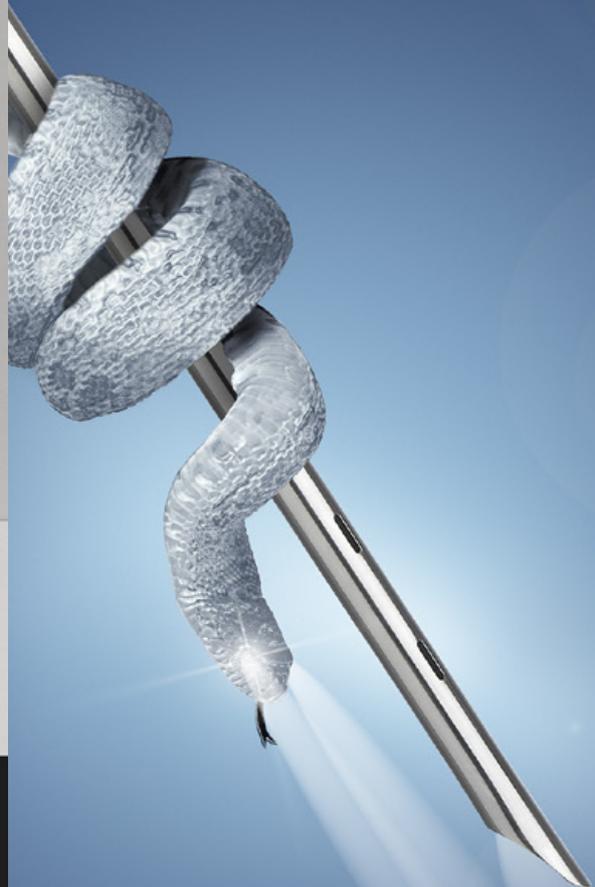
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Advances in Biomarkers for Lung Disease

Evan Kimber

Editorial Assistant

Citation: EMJ Respir. 2021;9[1]:26-27.



Bringing together a collection of the most forward-thinking approaches to lung disease, the European Respiratory Society (ERS) International Congress 2021 hosted a virtual session on imaging biomarkers. Four insightful presentations discussed the shift towards more longitudinal imaging approaches for lung disease and provided an overview of quantitative analyses with computer-trained algorithms. Alongside this was a discussion of the use of novel biomarkers such as pleuroparenchymal fibroelastosis.

QUANTITATIVE TECHNIQUES

Opening the session, James Eaden, University of Sheffield, Sheffield Teaching Hospitals, UK, began by delivering a cross-sectional summary of the current options for quantitative imaging of lung disease. Eaden emphasised the usefulness of quantitative CT analysis for diagnostic, predictive, and prognostic purposes, enabling clinicians to objectively measure disease progression on consecutive scans. Focusing on the automated texture analysis techniques, which can be applied to the study of interstitial lung disease (ILD), Eaden highlighted that some specific automated texture analysis techniques can identify features on CT that are not visually detectable by humans.

Eaden went on to contextualise several clinical case reports of MRI with difficult ILD, cystic fibrosis, and chronic obstructive pulmonary disease. According to Eaden, this field could contribute to providing diagnostic support to centres lacking expertise in thoracic imaging by stratifying patients in clinical studies. He went on to mention barriers to the research environment and limits to the software at present, including the lack of commercially available analysis software and the requirement for significant computational power to run analyses.

In his summary of a number of methods,

Eaden ran through several computer-aided techniques, which were later referenced by Joseph Jacob of University College London, UK. Jacob described Computer Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) variable analysis and pleuroparenchymal fibroelastosis in idiopathic pulmonary fibrosis (IPF). In line with Eaden's presentation, Jacob emphasised that computer scores are more sensitive than visual analysis. Adaptive multiple features method, quantitative lung fibrosis score, and functional respiratory imaging were among the methods discussed in the context of deep learning methods being used to train algorithms to classify high-resolution CT scans.

NOVEL IMAGING BIOMARKERS

The main body of the session discussed new approaches to using biomarkers for the assessment of lung disease. Eaden outlined hyperpolarised 129-xenon MRI as a quantitative biomarker of gas exchange, which is useful in producing ratio maps with a higher sensitivity to disease progression than pulmonary function tests for IPF and other fibrotic ILD subtypes. Building on this, the next speaker, Irma Mahmutovic Persson, Lund University, Sweden, reviewed recent preclinical and translational

"Jacob also outlined the existing issue with outdated radiological terminology, where scanning practice has improved but is limited by 20-year-old vocabulary."

studies by describing new biomarkers identified by imaging methods. Persson stated succinctly: "The way forward in the development of biomarkers for diagnosis, but also for follow-up monitoring of lung disease, is using imaging biomarkers."

Persson explained that this pathway will involve lung injury models and translational studies with imaging, to bridge the gap and allow crossover between preclinical and clinical studies. The speaker outlined the bleomycin model in the new perspective of implementing multimodality imaging, and also referred to preclinical imaging systems, including combining MRI and CT/PET. This multimodal approach tackles the difficulties in imaging the lungs caused by internal organ 'noise'. In her concluding remarks, Persson described lung injury models using a systematic review, which she co-authored. The review assessed lung disease and what type of pathology the respective models mimicked, and it was narrowed from over 5,000 to 182 studies, including exclusively live imaging models.

Other speakers also discussed novel imaging biomarkers; during her talk, Greetje Vande Velde, of the KU Leuven in Belgium, explained that micro-CT can be useful for producing 3D visualisation based on X-rays taken from different angles. This non-invasive and dynamic technique allows effective evaluation of disease progression, and can be performed both longitudinally and quantitatively. Vande Velde mentioned that micro-CT implements simple biomarkers to find total lung volume and density from the interaction of aerated and non-aerated lung volume. In his concluding remarks on biomarkers, Jacob discussed CALIPER variable analysis in IPF. Findings show the vessels are destroyed in areas of fibrosis, and blood is diverted to lower pressure areas to allow gas exchange to take place. This means that the vessel-related structures are subsequently enlarged and more are quantified by the computer, acting as a surrogate marker of the extent of ILD. In using pleuroparenchymal fibroelastosis to identify subtypes of IPF, Jacob remarked that there are increased areas of triangular opacity in patients, making PPF a

suitable biomarker for independently predicting both forced vital capacity decline and mortality in IPF.

LONGITUDINAL ANALYSES

A common theme throughout the session was the requirement for longitudinal design intervention. Jacob mentioned that, currently, challenges lie with the data and the low amount of longitudinal imaging. This makes a case for the requirement for standardised imaging practice. Jacob also outlined the existing issue with outdated radiological terminology, where scanning practice has improved but is limited by 20-year-old vocabulary. Jacob suggested we are blind to the potential new imaging features that come with a long-term approach, and described an inability to identify these features in current practice.

"I am a very big fan of longitudinal imaging and I think that it is the key if you are going to track disease progression," was Persson's clear supporting statement for longitudinal analyses. Vande Velde also concurred, vocalising that long-term follow-up targeting biomarkers offers a dynamic solution to provision of snapshot information. She further explained: "I really want to emphasise the additional advantage that is, if you have longitudinal time points, you can do repeated measurements, and you can do animal studies with much fewer animals and still have high statistical power in your experiments." In this way, the speakers emphasised that longitudinal input would help provide a baseline for using imaging technology for evaluating lung disease progression and therapy.

CONCLUDING REMARKS

The information delivered at this ERS session by clinicians at the forefront of the field provides an update to the analysis techniques and imaging biomarkers for lung disease. The discussions will guide future studies and hone medical practice, raising awareness for the requirement of a longitudinal approach. ■

Latest ERS Guidelines on non-CPAP Therapies in Obstructive Sleep Apnoea

Heeral Patel

Editorial Assistant

Citation: EMJ Respir. 2021;9[1]:28-30.



During the European Respiratory Society (ERS) International Congress 2021, speakers discussed the latest updates to the ERS guidelines on non-CPAP therapies in obstructive sleep apnoea. The new recommendations were drawn following a systemic review of the literature.

OBSTRUCTIVE sleep apnoea (OSA) is the most common sleep breathing disorder, affecting up to 100 million individuals around the globe. Patients with OSA have several episodes throughout the night where they struggle to breathe due to the collapse of their upper airways during sleep. Some of the most common symptoms of OSA include fatigue, daytime sleepiness, and disruptive snoring. OSA is a chronic disease with no cure and requires careful phenotyping and constant patient engagement with therapy.

Continuous positive airway pressure (CPAP) therapy is often the first line of treatment for OSA, which involves a mask or nose piece that delivers positive air pressure to the airways, forcing the airways to stay open. Although this is an effective treatment, many patients have reported discomfort sleeping with a mask. This ERS guidelines session hosted a discussion of the recent updates to the guidelines on non-CPAP therapies in OSA, determined by a systemic review of the literature.

The first speaker, Sophia E Schiza, Head of the Sleep Department, University of Crete, Greece, highlighted the gaps in OSA treatment as well as previous and current clinical practice. She explained how the refinement of techniques has led to an update on the ERS guidelines on non-CPAP therapies in OSA. Until 2012, the Chicago criteria were used to calculate the apnoea-hypopnea index (AHI), which is the number of apnoeas or hypopneas recorded per hour of sleep in a study. Despite AHI being a helpful metric in defining the presence of OSA, the speaker acknowledged that AHI has its limitations.

Firstly, the calculation of AHI assumes apnoeas and hypopneas are equal in their biological effects. Secondly, AHI does not indicate the magnitude of oxygen desaturation. In addition, AHI does not account for gender or age-related changes. In other words, two patients with OSA with similar AHI scores could have significantly different severity of OSA, depending on other factors such as age, occupation, and associated conditions. The use of AHI as a continuous exposure variable is based on the assumption that



"Schiza suggested a multicomponent grading system to determine severity would be better to help decide the appropriate treatment plan."

it represents the disease state of OSA. However, this assumption has proven to be incorrect in the literature several times. Based on this conclusion, using AHI as the primary diagnostic tool of clinically relevant OSA should be reconsidered. Schiza suggested a multicomponent grading system to determine severity would be better to help decide the appropriate treatment plan.

Following the first speaker, Johan Verbraecken, University of Antwerp, Belgium, explained the recommendations on ERS guidelines on OSA in further detail as an update to the 2011 ERS guideline on non-CPAP therapies in OSA. The updated guidelines indicate that treatment recommendations must be based on different types of evidence, clinical experience, and other relevant factors. The speaker shared the various and novel interventions available for OSA, including gastric bypass surgery, custom-made duo-block mandibular advancement devices, hypoglossal nerve stimulation, myofunctional therapy, acetazolamide, and positional therapy. To end, Verbraecken presented a case study of a 57-year-old man who did not want CPAP. Using the latest guidelines, he concluded that myofunctional therapy would be the best solution in this individual scenario.

The final speaker, Joerg Steier, Guy's and St Thomas' Hospital, London, UK, discussed a few interesting cases that he had encountered in his sleep clinic. Steier acknowledged that CPAP is an effective treatment option for patients and addressed the critical question: what is the point of discussing non-CPAP therapies? As previously mentioned, some patients do not like wearing the mask and compliance is low. In fact, compliance can be as low as 50% in younger cohorts of patients and even less in females. Therefore, it is important to discuss non-CPAP therapies. The new guideline addresses different interventions such as gastric bypass surgery, carbonic anhydrase inhibitors, and positional therapy to help patients manage their OSA.

The first case Steier presented was a 54-year-old male who was referred to the sleep centre in 2007 due to excessive daytime sleepiness. The physicians ran some tests and measured the desaturation of oxygen during sleep. The patient was diagnosed with severe OSA and, consequently, they were referred to sleep apnoea therapy. At first, CPAP controlled the problem



and the heart rate of the patient returned to normal almost immediately. However, a year later, the patient returned and asked the physician what the long-term solution was. This thought-provoking yet simple question made the team realise that while this therapy helped manage OSA, it may not be sustainable as a permanent solution. Wearing a mask every night is not ideal for everyone and in this case, the patient did not want to carry on using CPAP. For this reason, the team suggested other solutions to the patient such as alternative oral devices. After trying several different devices, they finally managed to settle on a mandibular advancement device. Further to this, during the year, the patient had lost weight, which, surprisingly, also helped reduce their symptoms. This case is a perfect example of how a multidisciplinary approach was effective in treating the patient because the combination of CPAP, the mandibular advancement device, and weight loss all helped in managing OSA.

Another case discussed involved a 57-year-old man with a high BMI whose main issue was loud snoring with features of OSA. Interestingly, they did not have the sleepiness symptom but instead had difficulty falling asleep. After the team had conducted a sleep study analysing the deep sleep cycle, rapid eye movement cycle, and polysomnography, the patient was confirmed to have OSA. The patient was given CPAP therapy; however, they continuously asked for alternatives. After a bit of weight loss, the team conducted another sleep study and found there was a slight improvement in the results compared with the first sleep study that had been conducted a year

before. Finally, the team at the clinic addressed the insomnia via cognitive behaviour therapy and found this made a significant difference. Similarly to the prior case, the best treatment plan for this patient was a combination of multiple therapies depending on the individual's symptoms.

Lastly, Steier shared his final case of an older patient, a 74-year-old male, with several symptoms, ranging from night sweats to a 5-year history of snoring. In this case, the study showed that this patient had sleep apnoea through parts of the night but not during the whole night. In this instance, the patient had CPAP and cognitive behaviour therapy and their symptoms improved. Identifying the problem in all these cases was the first step because this allowed the team to find the correct and appropriate solutions.

Steier concluded that while CPAP is effective and remains the first-line treatment for many patients with OSA, it is important to consider other non-CPAP treatments and use a combined approach while having these discussions with the patient. This approach would favour a patient-centric delivery of healthcare. These three cases discussed demonstrate the array of issues patients with OSA can encounter.

In a closing statement, Anita Simonds, President of the ERS, reinforced the purpose of the ERS guidelines. She emphasised how this guidelines session could help healthcare professionals and researchers consider in more detail the alternative treatments for patients with OSA, leading to clinical improvement, reduced healthcare costs, and potentially decreased cardiovascular morbidity. ■

Harvesting the Fruits of Pulmonary Disease Research: Learnings from the COVID-19 Pandemic

This industry symposium took place on 6th September 2021 as part of the virtual European Respiratory Society (ERS) International Congress 2021

Chairpeople: Felix Herth,¹ Daiana Stolz²

Speakers: Felix Herth, Maria Sucena,³ Ilaria Ferrarotti,⁴ Dave Singh⁵

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3. Pulmonology Department, Centro Hospitalar Universitário do Porto, Portugal
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Meeting Summary

Maria Sucena opened the symposium by emphasising the importance of establishing the priority for research into alpha 1 antitrypsin deficiency (AATD) and promoting collaboration at a national and international level. She described several projects of the European Alpha-1 Research Collaboration (EARCO), which aim to address these needs, including the creation of a pan-European AATD registry

and the identification of research priorities in AATD. Ilaria Ferrarotti followed by describing three key learnings from recent reports on current diagnostic methods. These include an unexpectedly high rate of rare mutations in the *SERPINA1* gene, which requires optimised techniques in the diagnosis of AATD, variable accuracies of published diagnostic algorithms, and findings that suggest that a low alpha 1 fraction in routine serum protein electrophoresis (SPE) should lead to a suspicion of AATD. Felix Herth then discussed the importance of maintaining AAT therapy in patients with AATD. He explained that self-administration promotes independence in suitable patients, and that it has the potential to overcome some of the challenges for AAT therapy during the COVID-19 pandemic. Lastly, Dave Singh summarised the literature on COVID-19 and pulmonary disease, explaining that, overall, data suggests that COVID-19 prevalence and outcomes are worse in patients with pulmonary disease, particularly chronic obstructive pulmonary disease (COPD). He clarified that despite confounding factors in studies that have analysed the risks associated with inhaled corticosteroid, there does not appear to be clear evidence that these medicines should be withheld.

Planning for Success: Research Priorities in Alpha 1 Antitrypsin Deficiency

Maria Sucena

Sucena emphasised that although great improvements have been made in the understanding of AATD in recent years, many questions remain unanswered. She explained that for a successful future, it is imperative to establish the priorities for research into this disease. To facilitate high quality research in a rare disease such as AATD, collaboration at a national and international level is needed.

The European Respiratory Society (ERS) established the EARCO to bring together a network of researchers, patients, and clinical experts in AATD to guide clinical and research priorities in Europe.¹ The EARCO aims to support and encourage early career researchers, and to increase the number and quality of clinical trials performed in AATD.¹

Sucena explained that the first objective of the EARCO is a pan-European AATD registry, with a quality control system ensuring high quality and completeness of data entered into the database: the EARCO registry.¹ The enrolment of patients with AATD began early in 2020 and, despite a pause in recruitment due to the COVID-19 pandemic, there are now over 40 sites currently recruiting patients across Europe, with an aim of including more than 3,000 patients in the registry in the first 3 years.² The key criteria for inclusion in the EARCO registry are AATD with an AAT serum level of <11 µM (50 mg/dL)

and/or a proteinase inhibitor genotype ZZ, SZ, or compound heterozygotes or homozygotes of other rare deficient variants. Data collected include sociodemographics, respiratory physiology, radiology, blood tests, symptoms, exacerbations, comorbidities, and treatment.²

Sucena described the results from another EARCO project: the identification of research priorities in AATD, from the perspective of patients, carers, and healthcare providers (HCPs). For this project, two surveys were developed: one for HCPs and another for patients and caregivers. The HCPs' survey was sent to AATD experts throughout Europe, with 94 respondents across 24 countries. The survey for patients and caregivers was translated into nine languages; 438 questionnaires were completed by individuals across 26 countries.³

The top five most important research questions rated by HCPs were: the causes of fast progression and poor outcome in patients with AATD; improvement of early and accurate diagnosis of AATD; time for initiation of AAT therapy; effectiveness of self-management interventions; and optimal dose regimen of AAT therapy.³

The patients and carers considered the most challenging aspects of AATD to be decreased exercise tolerance and shortness of breath, followed by not feeling fit or having the strength to do daily activities, tiredness, and fatigue. They considered the most challenging aspects for treatment to be issues with access to AAT therapy, the professional implications of the diagnosis of AATD, and the access to classes or fitness centres after rehabilitation. In terms of

research priorities for AATD, patients and carers considered the top priority to be improving the knowledge of AATD, particularly among general practitioners, with 99% of patients rating this as an important or very important area. Other important priorities included: access to AATD specialised centres; access to reliable, easy to understand information about living with AATD; being able to recognise an exacerbation; and targeted screening programmes for COPD and asthma patients.³

Figure 1 presents the collective research and disease management priorities identified by HCPs, patients, and carers.³

Sucena explained that an EARCO working group is now planning a 5-year strategy to provide evidence to address these issues. From just a few AATD researchers, HCPs, patients, and industry partners, the EARCO network has grown to include representatives from almost all European countries.

What Are the Future Plans of the Research Co-operation?

The EARCO plans to investigate the impact of COVID-19 and bronchiectasis on patients with AATD, and to gather expert opinions on the initiation of AAT therapy.

Are All Questions in the Registry Mandatory?

The EARCO registry will include patients from many different countries; therefore, only the sociodemographic data and basic information about lung and liver disease will be mandatory.

Optimising Laboratory Diagnosis of Alpha 1 Antitrypsin Deficiency

Ilaria Ferrarotti

Ferrarotti began by explaining that since AATD is a rare condition, it is logical to ask how diagnosis can be optimised.

Firstly, Ferrarotti emphasised that the *SERPINA1* gene that encodes AAT is highly polymorphic. Aside from the most common S and Z mutations, there are many other pathological alleles.⁴

Recent studies of National Registries in Ireland and Italy and have reported rare variant rates of 5.8% and 21.3%, respectively,^{5,6} and in Ferrarotti's own centre in Pavia, 43.0–44.0% of AATD cases over the last 3 years were caused by rare genotypes. Together, these data suggest that actual prevalence of AATD could be much higher than suggested by the estimates based on the ZZ-genotype.

The second issue pertaining to laboratory diagnosis of AATD is that diagnostic testing methods can vary and many algorithms utilising these methods have been proposed for the diagnosis of AATD.⁴

To compare the efficacy in detecting AATD, Ferrarotti and her team carried out a systematic literature review to select six well-described diagnostic algorithms.⁴ Each algorithm was then retrospectively applied to >5,000 samples from fully characterised patients diagnosed with AATD in Pavia. The study found that the frequency of false negatives varied between 1.9–12.9% and the rate of true positives ranged from 24.2–35.1%.⁴ Ferrarotti emphasised that the choice of diagnostic algorithm is critical for the accurate diagnosis of AATD, and that the potential for false negatives should highlight to clinicians the importance of repeating tests, or adjusting the diagnostic algorithm, if a negative result occurs in a patient with clinically suspected AATD.

Lastly, Ferrarotti discussed the findings of a study into the potential of reflex testing for AATD based on the alpha 1 protein fraction of SP.⁷ Investigators screened samples from >20,000 subjects and identified 82 cases with reduced alpha 1 globulin levels; these were then genotyped for *SERPINA1* mutation. The detection rate of the composite algorithm was 51%, whereas standard screening procedures, based on clinical profiling and AAT levels <1 g/L resulted in a detection rate of just 19%.⁷ A similar approach was used in a centre in Ireland, whereby any SPE with a low alpha 1 fraction was reflexively tested for serum AAT levels over 32 months. Over >65,000 SPE tests were analysed, of which 360 had low alpha 1 fractions and underwent testing for AAT. This approach resulted in a high diagnostic rate of 39%, compared with a diagnostic rate of 58% with standard clinically targeted testing.⁸

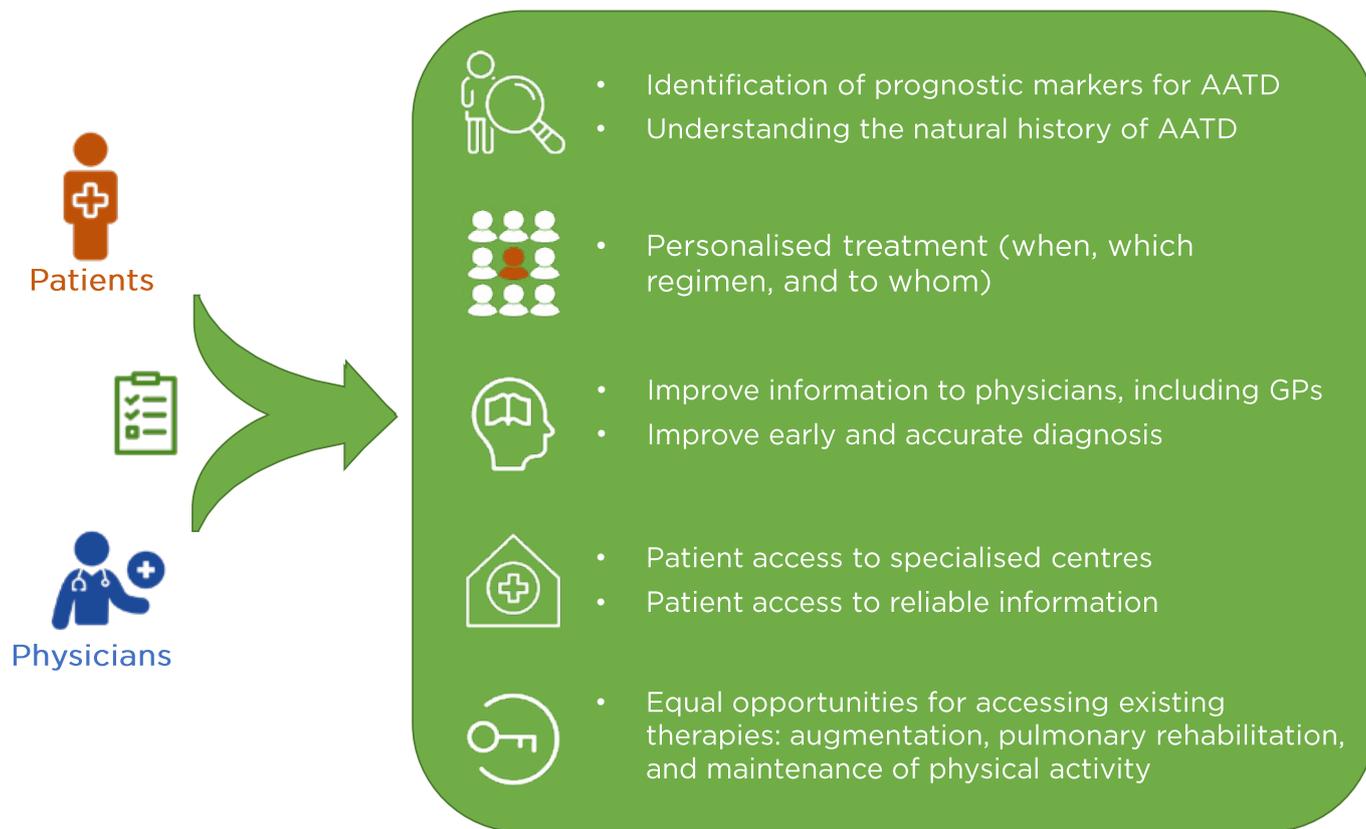


Figure 1: Top research and management priorities identified by healthcare professionals and patients in alpha 1 antitrypsin deficiency.

AATD: alpha 1 antitrypsin deficiency; GP: general practitioner.

Adapted from Barrecheguren et al.³

Ferrarotti concluded by reiterating that AATD can be caused by a rare mutation in the *SERPINA1* gene, and diagnostic approaches should take this into account; that the choice of diagnostic algorithm has a significant impact on the correct diagnosis of AATD; and that a low alpha 1 fraction in SPE should lead to a suspicion of AATD, which should be confirmed by further analysis.

How Does EARCO Help Us to Improve the Care of Patients with Alpha 1 Antitrypsin Deficiency?

EARCO activities have organised a network of seven leading laboratories across Europe. This enables the sharing of material, quality control checking, and harmonisation of the diagnostic activity of each laboratory.

Is the Measurement of the Alpha 1 Antitrypsin Level Sufficient to Diagnose Alpha 1 Antitrypsin Deficiency?

This is just the first step towards diagnosis. In most cases, it is insufficient to diagnose AATD.

Paradigm Shifts in Alpha 1 Antitrypsin Deficiency: The Impact of COVID-19 on Patient Management

Felix Herth

The benefits of AAT augmentation therapy in patients with AATD have been demonstrated in multiple clinical trials,⁹ and abrupt cessation

of AAT therapy has been shown to result in a rapid increase in the rate of exacerbations over a matter of weeks.¹⁰ Herth stressed that once AAT therapy has started, it must be continued to control exacerbation rates and, therefore, reduce the progression of the disease.

Research suggests that patients with AATD may have an increased risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and a higher risk of worse outcomes compared with the general population, due to the underlying pathophysiology of AATD and AATD-related comorbidities.¹¹ Herth explained that the risk of infection has caused patients to feel uncertain about continuing their AAT therapy because it requires contact with the healthcare system. Together with the limited access to healthcare systems at the start of the pandemic, this resulted in the abrupt cessation of treatment in some patients.

To address these challenges, clinicians have implemented additional safety measures in hospitals and clinics to mitigate the risk of SARS-CoV-2 transmission. These changes have had the additional benefit of limiting the number of exacerbations in patients with AATD. In addition, increasing numbers of patients have been referred for self-administration therapy, with virtual training sessions.

In the USA, patients who self-administer their AAT treatment consider the main benefit to be greater independence.¹² Herth posited that self-administration could potentially address some of the challenges of AAT therapy during the COVID-19 pandemic by minimising contact with HCPs and the general public. Herth suggested that intravenous infusion training sessions could be conducted virtually, and online resources and emergency contacts could be made available to patients.¹³ Although a survey of physicians in Europe suggested that the 'ideal' patient for self-administration of AAT therapy would be younger, more stable, and with less comorbidities than other patients,¹⁴ Herth feels that the older patient, with more comorbidities, may also be suitable with additional training and support. He provided an example of a 52-year-old patient from his own practice who had been undergoing AAT therapy since 2016. She discontinued therapy in March 2020 due to the COVID-19 pandemic and experienced an exacerbation 6 weeks later. After

a discussion with the patient, she was given three training sessions, and has since been successfully self-administering AAT therapy at home (Figure 2). Herth emphasised that self-administration training should continue during the pandemic, provided that patients are adequately trained, training is delivered virtually, and patients are trained between exacerbations.

In summary, Herth reiterated that it is important to ensure the continuation of AAT therapy in patients with AATD, that self-administration is an alternative means of treatment delivery that promotes independence in appropriate patients, and self-administration is a viable option for most patients during the COVID-19 pandemic.

What Do You Think Was the Most Significant Challenge to the Treatment and Care of Patients with Alpha 1 Antitrypsin Deficiency During the COVID-19 Pandemic?

In many countries, patients were concerned that they would become infected with SARS-CoV-2 if they visited their doctor. Herth explained that his clinic persuaded some of the more cautious patients to visit the clinic to learn about self-administration. Prior to COVID-19, about 10–15% of Herth's patients were using self-administration of AAT, but these figures have grown to 25–30%.

How Can You Be Sure that Self-Administration Is Working Safely and Correctly?

There is sometimes a concern that self-administration puts clinicians at risk of litigation if something goes wrong. Herth explained that, provided a suitable training regime is followed, this is not an issue. In Herth's experience, those patients who go through the training are usually very compliant in administering their treatment correctly at home.

Strategies to Prevent and Manage Severe COVID-19

Dave Singh

Singh introduced his topic by describing several large cohort studies conducted during the first

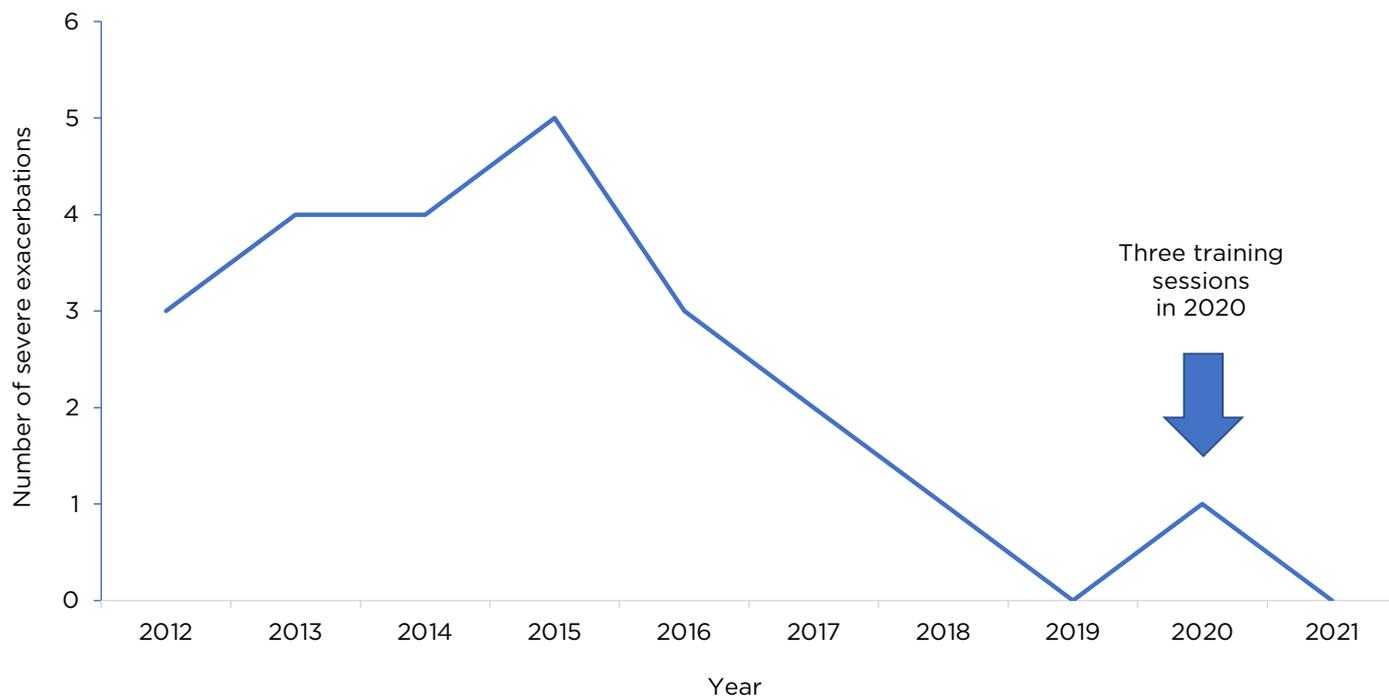


Figure 2: Exacerbations experienced by a patient with alpha 1 antitrypsin deficiency who initiated self-administration of alpha 1 antitrypsin therapy.

wave of the COVID19 pandemic. Hippisley-Cox et al. investigated the risk of severe COVID-19 disease in patients taking angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers,¹⁵ including individuals with concomitant asthma (13.0%) and COPD (2.4%). A small proportionate number of patients with asthma (14.0%) were represented in those admitted to an intensive care unit with COVID-19, suggesting that asthma did not represent a risk factor for severe COVID-19 disease. However, patients with COPD made up a disproportionate number of those admitted to an intensive care unit (3.6%), which provided one of the first indications that patients with COPD were at increased risk of severe COVID-19. In the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) World Health Organization (WHO) Clinical Characterisation Protocol (CCP)-UK study, both asthma and chronic pulmonary disease were among the most common comorbidities observed in patients admitted to hospital with COVID-19 in the UK.¹⁶ In a review of the impact of COPD on the clinical outcomes of COVID-19, most studies were found to report an increased risk for severe COVID-19 in patients with COPD.¹⁷

Singh explained that patients with COPD exhibit upregulated levels of proteins and receptors involved in the processing and uptake of the SARS-CoV-2 virus in epithelial cells compared to controls, notably ACE2, with less evidence for other proteins such as furin and transmembrane protease serine 2 precursor (TMPRSS2).¹⁷ Singh posited that patients with COPD may, therefore, be predisposed to a high viral load.

There is some debate among experts about whether corticosteroids used to treat COPD and asthma increase or decrease this susceptibility. Inhaled corticosteroids can downregulate interferon- β , thereby enhancing viral replication, and also reduce anti-bacterial defence.¹⁸ On the other hand, inhaled corticosteroids appear to downregulate ACE2 and TMPRSS2 in patients with asthma,¹⁹ which could, theoretically, reduce the ability of SARS-CoV-2 to enter epithelial cells.

Singh explained that, overall, the literature indicates that COVID-19 prevalence and outcomes are worse for pulmonary disease, particularly in COPD.²⁰⁻²³ It is difficult to determine the risks associated with inhaled corticosteroid use due to confounding factors, but there does not appear to be clear evidence that these medicines are harmful.

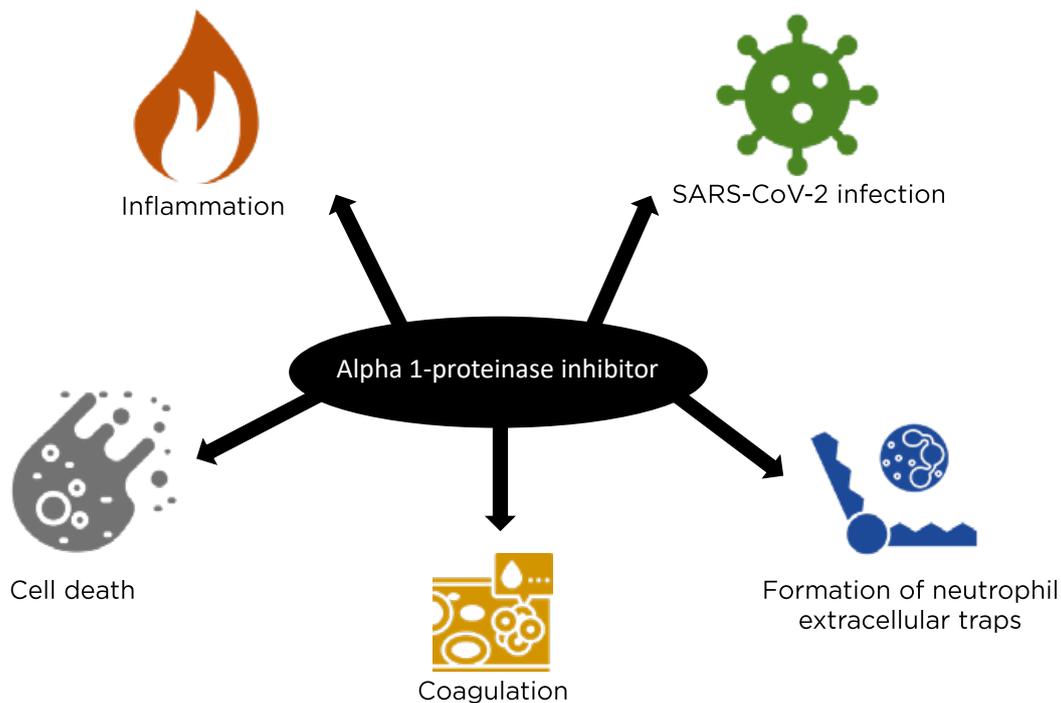


Figure 3: Alpha 1 proteinase inhibitor and COVID-19.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Adapted from Yang et al.¹⁷

In the second part of his presentation, Singh discussed interventions to manage and prevent severe COVID-19, beginning with the large randomised controlled trials that support the current management of COVID-19.

Data from the RECOVERY trial, conducted in the UK, showed that dexamethasone treatment reduced COVID-19-related 28-day mortality compared with usual care.²⁴ However, this benefit only applied to patients who were given oxygen or invasive mechanical ventilation on admission to hospital. Another analysis of the same trial showed that tocilizumab reduced 28-day mortality in a sub-group of hospitalised patients with COVID-19 who were hypoxic on room air (oxygen saturation: <92%) and had high C-reactive protein levels (≥ 75 mg/L), compared with usual care.²⁵ Lastly, a clinical trial of the oral JAK inhibitor baricitinib plus anti-viral agent remdesivir in patients hospitalised with COVID-19, analysed the patients' time to recovery. Overall, combination treatment was superior to remdesivir alone, particularly in patients who required non-invasive ventilation

or high-flow oxygen.²⁶ Other studies have suggested that remdesivir monotherapy is also associated with an improved time to recovery,²⁷ but not a reduction in overall mortality in hospitalised patients.²⁸

Singh explained that these data suggest that there is a disconnection between the clinical trial endpoints of recovery and mortality, which may suggest that anti-viral agents are more effective in the earlier stages of COVID-19 compared with the more severe, later stages. This implies that COVID-19 therapy is moving towards a more personalised, precision-medicine approach, where treatments are targeted to patients according to their clinical characteristics (including disease severity) and biomarkers (indicating the level of inflammation). For patients who are not hypoxic, Singh clarified that there are not yet treatments that can halt progression of the disease. However, in other patients there is good evidence that dexamethasone can be used, with the addition of anti-IL-6 in those with more inflammation, and these two therapies form the basis of current treatment for COVID-19. JAK

inhibitors also show promise as treatment for patients with more severe COVID-19.

Other therapeutic modalities include the tyrosine kinase inhibitor imatinib, which reduces vascular leak, and has the potential to attenuate the pulmonary oedema, which occurs during severe COVID-19. While the primary endpoint, discontinuation of ventilation and supplemental oxygen, did not reveal a beneficial effect, the mortality benefits were clear (hazard ratio: 0.52).²⁹ In a small, Phase II trial, inhaled interferon- β 1a, an antiviral therapy, improved recovery from SARS-CoV-2 infection,³⁰ and this molecule has progressed to larger, Phase III studies.³¹ Lastly, the STOIC Phase II trial of community-administered budesonide at an early stage of COVID-19 suggests that this inhaled corticosteroid improves the time to clinical recovery.³²

Singh explained that, together, the beneficial effects of dexamethasone in patients hospitalised with COVID-19, and the faster recovery from early COVID-19 induced by budesonide in the community, suggest a protective effect of corticosteroids in patients with asthma and COPD.

Finally, Singh summarised that comorbidities in patients with AATD, including hypertension, chronic kidney disease, diabetes, and COPD, are risk factors for COVID-19. Interestingly, alpha 1 proteinase inhibitors might inhibit SARS-CoV-2 uptake into cells and, along with anticoagulant and anti-inflammatory activity, this suggests that these agents could be protective against severe COVID-19, and there are several ongoing clinical trials to test this hypothesis¹¹ (Figure 3).

What Are Your Thoughts About the Relationship Between Pulmonary Fibrosis and COVID-19?

The key is to prevent the development of severe damage from COVID-19 in the first place, and this is something which is beginning to be achieved through vaccination and good therapeutics. In many individuals, COVID-19-induced lung damage does seem to resolve over time, and in those patients with significant lung tissue damage and fibrosis, the development of therapeutics for use during 'long COVID' will be important.

There Are Some Contradictory Data on the Use of Anti-IL-6 Treatment. Only the Studies that Combined these Drugs with Dexamethasone Showed Positive Results. How Do You Interpret these Findings?

In both the RECOVERY study²⁵ and the REMAP-CAP trial,³³ most patients received concomitant oral corticosteroids as per standard-of-care treatment; other studies demonstrated a benefit of anti-IL-6 in patients with COVID-19. The treatment of the SARS-CoV-2 infection has evolved to include different combinations of therapies, and any new COVID-19 treatment should be expected to be tested with, and administered on top of standard-of-care therapies, in a personalised manner.

Closing remarks

Daiana Stolz

Stolz provided a brief overview of the current understanding regarding long COVID, explaining that this represents persistent lung dysfunction after SARS-CoV-2 infection in some patients, including a deterioration in lung function diffusion capacity.³⁴ In the early stages of recovery, conditioning probably plays a major role in reduced exercise capacity, but HCPs are yet to explain the longer-term effects after SARS-CoV-2 infection. Therefore, it is important that data continue to be collected, including exercise capacity, in these patients.

Stolz concluded the symposium by clarifying that it is important to continue providing appropriate care for patients with respiratory disease during the COVID-19 pandemic. This may include the use of telemedicine, but not to the exclusion of monitoring and treating these patients. There are several initiatives in Europe that are focusing on this patient population to help HCPs to provide the best possible care. Stoltz emphasised that she was very proud to be part of a pulmonary community that has shown that it can achieve fast-paced scientific progress despite the pandemic.

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Digital Support for Wheeze Detection in Young Children

This symposium took place on the 5th September 2021, as part of the Virtual European Respiratory Society (ERS) International Congress 2021

Chairpeople:	Jonathan Grigg ¹
Speakers:	Wim van Aalderen, ² Jonathan Grigg, Stephanie Dramburg ³ <ol style="list-style-type: none">1. Centre for Genomics and Child Health, Queen Mary University of London, UK2. Department of Paediatric Respiratory Diseases, Amsterdam UMC, the Netherlands3. Department of Paediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité Universitätsmedizin Berlin, Germany
Disclosure:	Grigg reports personal fees from GlaxoSmithKline, Vifor Pharma, OM Pharma, AstraZeneca, Novartis, and OMRON Healthcare Europe BV. Dramburg reports advisory fees from OMRON Healthcare Europe BV. Van Aalderen has declared no conflicts of interest.
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Meeting Summary

Wheeze is difficult to describe and recognise, and there is a need for clear guidelines on diagnosing wheeze. Discrepancy exists between what the parent may describe as wheezing and clinician-confirmed wheeze. Wheeze detection in daily practice occurs mainly by physician confirmation using a stethoscope; however, a diagnostic difficulty arises when parents hear wheezing that is no longer present during medical consultation. Accurately assessing the presence or absence of wheeze is important for therapeutic trials and, since there is no common understanding/definition of wheeze, it is difficult to conduct studies. Current outcomes for trials in preschool wheeze are suboptimal, apart from in hospital assessment. Promising technological solutions for disease diagnosis and assessment of disease severity are on the horizon.

During this symposium, Wim van Aalderen, Jonathan Grigg, and Stephanie Dramburg reviewed the current situation with regards to wheeze detection and how to overcome the limitations of therapeutic trials on preschool wheeze. They also presented the results of a pilot study using one potential digital solution, OMRON WheezeScan (HWZ-1000T-E; OMRON Healthcare, Kyoto, Japan).

Introduction

Jonathan Grigg

Objective measures for the diagnosis of asthma are important. Grigg noted that “with preschool children we rely on parent identified symptoms, but we are entering a new era of technological solutions for disease diagnosis and assessment of disease severity and the question is whether this can be applied to the detection of wheeze.” This symposium aimed to review the current landscape with regard to wheeze detection and one potential digital solution. An audience poll showed that 36% of symposium attendees believe the main aim of digital health is to enable data-driven decisions by healthcare professionals, and 36% believe the main aim is to support blended care approaches.

Wheeze Detection in Daily Practice

Wim van Aalderen

René Laënnec, who invented the stethoscope in 1816, stated that lung sounds are “much more difficult to describe than to distinguish.” More than 200 years later, wheeze remains difficult to describe and recognise. In 2016, the European Respiratory Society (ERS) Task Force on Respiratory Sounds described wheezing as an abnormal lung sound that is musical and continuous, high-pitched with or without the stethoscope, especially heard during expiration, and indicative of airflow obstruction within the intra-thoracic airways.¹

Prevalence and Cause

Wheezing carries a significant burden as one in three children wheeze before the age of 3, and the cumulative prevalence of wheeze at six years of age is 50%.^{2,3} In addition, preschool wheeze is expensive, utilising 0.15% of the total healthcare budget in the UK.⁴ A 1995 study on the prognosis of early childhood wheeze showed that 40% of children who wheezed before the age of 3 developed persistent wheeze, which progressed to asthma.² In addition, 23% of children who did not experience wheeze before the age of 3 went on to develop late-

onset wheeze.² Asthma, however, is not the only cause of childhood wheeze. Van Aalderen described other common causes including recurrent viral upper airway infections, exposure to cigarette smoke, and recent respiratory syncytial virus (RSV) infection resulting in post-viral wheeze. Other rare conditions may also produce wheeze, for example: cystic fibrosis, *corpus alienum* (foreign body), anatomic malformation (e.g., tracheomalacia), and certain immunological diseases.

Wheeze and Asthma

In a second audience poll, 44% of symposium attendees cited improper treatment and need for scale up as the main reason children attended their practice while wheezing. Numerous studies indicate that doctor-confirmed wheeze in preschool children may be a predictor for asthma. A significantly thicker reticular basement membrane was evident in children with confirmed wheeze compared to age-matched controls and those with parent-reported wheeze.⁵ The same study also showed inflammatory characteristics (e.g., eosinophils, EG2+ cells) in confirmed wheezers, also seen in adults with allergic asthma.⁵ History, a positive family history for allergic disease, increased fractional exhaled nitric oxide, and a positive specific IgE all increase the chance of developing asthma, but there is overlap between groups. Crucially, van Aalderen emphasised that “there is at present no diagnostics available for daily practice to estimate if young children will develop asthma.” He emphasised the potential importance of recognising asthma before the age of 5 to enable adjustment of medical treatment and to prevent under- and overtreatment.

Parent- versus Clinician-Reported Wheeze

Van Aalderen reiterated that wheeze is difficult to describe and recognise and discrepancy exists between what the parent/carer may describe as wheezing and clinician-confirmed wheeze. One study found 55% disagreement between parent and physician assessment of wheeze in children, while a further study reported correct labelling of wheeze by 59% of parents.^{6,7} Importantly, lung function in children with physician-confirmed wheeze was significantly lower than lung function in children with only parent-reported wheeze,

and physicians but not parents were able to reliably judge the severity of wheeze measured objectively.^{8,9} Thus, wheeze is interpreted differently between parent/carer and healthcare provider, and is dependent upon whether it is reported retrospectively or in real-time and may be affected by environmental and cultural factors. Van Aalderen remarked that “due to the difficulty recognising wheeze, it seems logical to use computers.” An algorithm developed by Bokov et al. to detect wheezing from recorded respiratory sounds, with a smartphone placed near the mouth that showed a sensitivity of 71.4% and specificity of 88.9% for wheeze detection, likely not sufficient for use in daily practice.¹⁰

Van Aalderen concluded that “wheeze detection in daily practice occurs mainly by confirmation by the physician by stethoscope. However, a diagnostic difficulty arises when parents hear wheezing that is no longer present during medical consultation.”

Overcoming Limitations of Therapeutic Trials on Preschool Wheeze

Jonathan Grigg

Grigg opened his talk with an audience poll showing that 88% of symposium attendees correctly believe a high-pitched whistling sound made while breathing, rather than a dry cough, rattle, or noisy breathing, best describes wheeze. Grigg then went on to discuss the difficulties in conducting therapeutic trials on preschool wheeze, particularly as outcome measures are imprecise and lack objectivity. An expert meeting on paediatric asthma, convened by the European Medicines Agency (EMA) in 2010, concluded that no validated surrogate endpoints and biomarkers are available for trials in the preschool age group.¹¹ Lung function measurements could be considered as an exploratory endpoint in a subgroup of patients (e.g., 5-year-olds) in centres with experience to perform preschool lung function measurements. However, Grigg stated that the latter “is still impractical in the context of the large trials needed to demonstrate efficacy for new treatments or for repurposing existing treatments.” Experts also concluded that

standardised exercise tests to assess treatment effect cannot reliably be performed in preschool children and no validated and standardised endpoints are available to measure treatment effect in this group. However, one expert from the meeting recognised the need for novel devices for parents to use to monitor wheeze in children under the age of 6 years.

Wheeze Trials in Hospitals

Grigg stated that “hospitals provide a more controlled environment to conduct therapeutic trials in preschool wheeze, with the gold standard of clinician-diagnosed wheeze by stethoscope available, which is a good marker that the symptoms experienced are driven by airway constriction and also with response to a short-acting bronchodilator demonstrating reversibility.” A randomised controlled trial that showed no difference between oral prednisolone and placebo in preschool children hospitalised with acute virus-induced wheezing used duration of hospitalisation and interval between hospital admission and physician sign off for discharge as the primary outcome and best marker of response.¹² These were considered standard measures at the time of the study, but Grigg highlighted them as “unsatisfactory as we really want to be targeting the wheeze response.” An alternative is to use an integrated measure such as the validated Paediatric Respiratory Assessment Measure (PRAM), which uses a combination of scalene muscle contraction, suprasternal retractions, wheezing, air entry, and oxygen saturation to assess response to treatment. PRAM was included as a secondary outcome in the prednisolone trial and, again, no significant difference was seen between the groups.¹² The use of the PRAM score as an outcome measure was time-consuming and required training; however, Grigg concluded “it can be used to measure treatment effect, particularly within a hospital setting.”

Wheeze Trials in the Community

Most trials to assess the effect of certain treatments on childhood wheeze are community-based and are limited by the reliance on parent-reported outcomes. A study of intermittent montelukast or placebo administered to preschool children by parents at each wheeze episode over a 12-month period used the

number of unscheduled medical attendances for wheezing episodes as the primary outcome.¹³ However, Grigg expressed concern in “not quite knowing the reason for parents seeking medical attention.” Parents stated wheeze, however, it was not checked with clinicians whether wheeze was ever diagnosed. A small effect favouring montelukast was seen in this study; however, the difference was not significant.¹³ Grigg concluded that unscheduled need for medical attention is an outcome that has been used to assess treatment effect in trials of children with wheeze but it is imperfect, for example, as it can only be used to assess a clinically severe outcome.

Other outcome measures are required for the assessment of treatment effects in less severe wheeze or wheezing at night. A trial of azithromycin for asthma-like symptoms in young children aged 1 to 3 used diary-verified duration of episodes of “troublesome lung symptoms” after initiation of treatment as the primary outcome.¹⁴ “Troublesome lung symptoms” included cough, wheeze, or dyspnoea severely affecting the well-being of the child. Grigg explained that “this already sounds like a vague entity, and the outcome is not really addressing what we want to target with anti-asthma medication, which is airway constriction.” Azithromycin was found to be beneficial in this trial; however, the exact target is unclear. It is possible azithromycin affected some other aspect of the viral-triggered complex such as bronchitis leading to cough rather than wheeze itself. Even in older children (>6 years) parents were confused about wheeze. A study showed that parents incorrectly understood the following to mean the same as wheeze: rattly breathing, snoring, noises from the nose or throat during sleep, croup, stridor, worrying dry cough, and moist or wet cough with phlegm.¹⁵ Most parents (>80%) did also, however, correctly identify whistling or squeaky noise in the chest as wheeze. As a result, parent-reported wheeze will include children with wheeze but also those with other symptoms unrelated to reduced airflow diameter and decrease sensitivity to show a beneficial treatment effect.

Prevention Trials

Accurately assessing the presence or absence of wheeze is potentially even more important in prevention trials. A randomised controlled trial to assess the effect of a monoclonal antibody

against RSV on the development of wheeze used parent-reported wheeze in the last 12 months, use of an asthma medication, or both as the primary outcome.¹⁶ However, Grigg stated that “if the child experiences parent-reported wheezing, the physician will issue an antiasthma medication, so adding asthma medication to the outcome does not necessarily improve precision.” New options for prevention trials include the use of microbial products to alter the immune system and encourage development in a way that does not lead to T helper cell Type 2 inflammation. Bacterial lysates have shown promising results in animal studies and OM Pharma (Meyrin, Switzerland) has commercialised their use for children with recurrent chest infections as a licensed medication by the EMA. A trial of oral Broncho-Vaxom® will be conducted in the UK, focused on infants hospitalised with RSV bronchiolitis who are at increased risk of preschool wheeze and subsequent asthma. The following definition of an episode of wheezing will be used: parental report of an episode of wheezing with apparent shortness of breath, cough, or chest retraction or with any combination of these additional symptoms, which lasts at least day and for which the child receives at least one salbutamol treatment. In addition, an active wheeze diagnosis recorded by a doctor is required; however, this will be informed by parent reporting as well. Thus, limitations of this study include inaccuracy of parent-reported wheeze and inaccuracy of “active wheeze” recorded in the clinical notes as wheeze is often intermittent. Grigg stated that “we still have the same problem we had 20 years ago and what we would like is something objective to confirm that a child’s respiratory symptoms were associated with a wheezing noise emitted from the chest.” A technological solution for trials would increase certainty that the symptom complex is associated with wheeze, could be used for the primary outcome in prevention trials, and be integrated into trial itself for therapy initiation. It is important to note that even if such a device was available, further questions such as accuracy and whether the output should be blinded would need to be addressed.

Grigg concluded that current outcomes for trials in preschool wheeze are suboptimal, apart from in hospital assessment, and a new era for assessing preschool wheeze may have started but further studies need to be conducted.

Impact and Usability of a Digital Wheeze Detector in a Home Care Setting: A Pilot Study

Stephanie Dramburg

Dramburg opened her talk with an audience poll that showed that most symposium attendees felt digital technologies for wheeze detection at home were either a nice tool for most patients (55%) or absolutely the future (40%). Dramburg discussed the results of a pilot study to assess the impact and usability of the digital wheeze detector WheezeScan in a home care setting. The study aimed to assess protocol safety and feasibility, check usability, and evaluate the device in a clinical routine setting (data on file).

Methods

Patients were recruited from a paediatric respiratory care practice in Berlin in October/November 2020 and sociodemographic data were collected. An Asthma Control Test and questionnaire on Parent Asthma Management and Self-Efficacy Scale (PAMSES) were conducted at study entry and at the end of the 30-day monitoring period. A questionnaire was also administered at the final 30-day visit to assess device usability. Participating families were taught how to use WheezeScan and downloaded the WheezeMonitor app for symptom and medication recording. Parents were requested to record their child's symptoms at least twice a day (i.e., morning and evening) throughout the monitoring period and also in the event of an exacerbation. Inclusion criteria were as follows: children aged nine to 72 months who had at least one episode of doctor diagnosed wheezing and/or recurrent cough requiring treatment with beta-2-agonists in the last 12 months, sufficient comprehension of the German language, availability of a smartphone, and consensus to participate. Exclusion criteria included presence of an anatomic malformation causing chronic nasal and/or bronchial obstruction, a severe chronic disease, a contraindication for the use of beta sympathomimetic drugs, and an intention to move away from Berlin during the monitoring period. The WheezeScan device includes a noise reduction system to increase the quality of sound collection, high-definition microphone to collect breathing sounds, micron-width diaphragm to

detect wheeze at low volumes, micro-computer that uses a unique algorithm to differentiate wheeze from other breathing sounds, and protective casing to ensure durability and long-term accuracy.^{17,18}

Results

Dramburg noted that 20 participants were recruited, of which 85% were male, 25% were exposed to cigarette smoke at home, 45% had a confirmed diagnosis of atopic disease, and 55% were currently using controller medication. During the past 12 months, 90% had experienced a blocked nose, 75% a dry cough, 65% had awakened due to respiratory problems, and 30% of children had visited the Emergency Room (ER) due to respiratory distress. Overall, adherence to symptom recording was good; 81% recorded symptoms at least once per day. The PAMSES showed increased parental confidence with WheezeScan use in deciding whether to take their child to the ER or not in case of respiratory distress. Of the parents using WheezeScan, 79% reported the use of the wheeze detector to be uncomplicated, while 21% reported difficulty using WheezeScan. When asked what kind of difficulties occurred with use of device, 37% reported intolerance of the measurement in younger children and 10% reported difficulties handling the device. Most caretakers perceived benefit, were interested in future WheezeScan use, and would recommend use to other parents. There was good correlation between the results of WheezeScan and doctor diagnosis of wheeze during unscheduled visits. Using WheezeScan as the gold standard, the sensitivity of doctor diagnosis was 83.3%, while parent reporting only correlated with 15.0% of the device results. In terms of unexpected events and safety aspects, few wheezing episodes occurred, and study visits were challenging, likely due to COVID-19-related contact restrictions. One child chewed on the device's membrane, no ER visits occurred during the monitoring period, there was no excessive medication intake, and no participant was harmed (data on file).

Dramburg concluded that "the protocol is safe and feasible to conduct, the device can be used by parents who are not digital natives, and the use of the device is also feasible in a routine clinical setting."

Questions and Answers

A final audience poll showed that the major hurdles with wheezing that attendees would like to see overcome include the lack of reliable tests in children under the age of 5 years (55%) and the over/under treatment of children (45%).

What Further Evidence Regarding WheezeScan Needs to Be Generated to Convince Clinicians?

Dramburg said a larger study on the clinical use and on the accuracy in clinical practice is required. We need to ensure parents can use such a device correctly and monitor what impact the results have on parental behaviour for safety reasons (i.e., whether parents still follow doctor instructions on how to identify respiratory distress). Dramburg suggested it would be beneficial to expand the number of settings on the device to include a severity scale to enable treatment response to be monitored. Van Aalderen added that data on the effect of accurate wheeze detection on parental anxiety and treatment and whether confirmed wheeze is a strong predictor for asthma are important. Grigg emphasised a benefit of WheezeScan is the result is displayed on the device without need for an app. In addition, it may help identify children with asthma in low- and middle-income countries, many of whom remain undiagnosed. Grigg concluded that for WheezeScan “we need to build on the positive data we have to see where it fits in the complex clinical milieu.”

Is The Device Able to Distinguish Gurgling Sounds or Sounds of The Upper Airways from Wheezing?

Dramburg stated that the device in the pilot study was able to distinguish well between wheeze and other respiratory sounds.

Can Some Difficulties Associated with Device Use (i.e., Need to Be Kept on Chest For 30 Minutes) Be Overcome with Appropriate Training?

Dramburg suggested that appropriate training (e.g., presenting the device to children when they are not experiencing distress) will increase the efficacy of measurement; however, other factors (e.g., amount of activity in environment, number of siblings) will also have an influence that cannot be affected by training.

The Cost Is Going to Be Very Important and Healthcare Systems Will Evaluate the Health Economic Benefit. Can You Please Comment?

Grigg emphasised this is a commercially available product and the cost will depend on how it is being used. As a diagnostic tool, it can be used multiple times in multiple children; however, a dedicated device is probably required for management purposes. Van Aalderen quoted a cost of 149 GBP (175 EUR) for the device. Dramburg emphasised that choosing the right patient for the right intervention is important in a real-life setting and will also influence cost.

What Factors Will Improve Adherence to Recording in Apps?

Dramburg stated that if recording in apps is prescribed by the doctor and the patient understands its importance for treatment, adherence is much higher (>80%).

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Improving Asthma and Chronic Obstructive Pulmonary Disease Outcomes in 2021: Approaches to Empower Patients

This symposium took place on 6th September 2021 as part of the virtual European Respiratory Society (ERS) International Congress

Chairpeople:	Eric Bateman ¹
Speakers:	Alvar Agusti, ² Anna Murphy ³
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Disclosure:	Bateman has acted as a speaker for ALK, AstraZeneca, Chiesi Farmaceutici S.p.A., Boehringer Ingelheim, Orion Menarini, Novartis, Regeneron Pharmaceuticals, and Sanofi Aventis; and provided consultancy for ALK, AstraZeneca, Novartis, Regeneron Pharmaceuticals, and Sanofi Aventis. Murphy has received research funding, consultancy fees, or honoraria for presentations from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici S.p.A., GlaxoSmithKline (GSK), Orion, Sanofi, and Trudell Medical International. Agusti has received research grants from AstraZeneca, GSK, and Menarini Group; lectured for AstraZeneca, Chiesi Farmaceutici S.p.A., GSK, Menarini Group, and Orion; and served as member of scientific advisory board for AstraZeneca, Chiesi Farmaceutici S.p.A., GSK, Menarini Group, and Merck Sharp & Dohme (MSD).
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Meeting Summary

This symposium took place during the 2021 virtual meeting of the European Respiratory Society (ERS). It focused on improving the management of asthma and chronic obstructive pulmonary disease (COPD) by empowering patients and personalising their treatment. Alvar Agusti discussed the treatable traits of COPD and focused on use of inhaled corticosteroids (ICS). He concluded that, while ICS treatment imposes a slightly increased risk of pneumonia, it decreases all-cause mortality in patients with elevated blood eosinophils. Anna Murphy described inhaler devices and their use. Errors in device use are common and no improvement in the inhaler technique of patients has been made during the modern history of inhaler use. For successful inhaler therapy, personalised choice of the device and continuous training are paramount. Finally, Eric Bateman described the theory and practice of as-needed ICS/formoterol as a mean to empower patients to take responsibility for their asthma management. During his talk, he described the reasoning and evidence that has made as-needed ICS/formoterol the preferred treatment approach in the 2021 Global Initiative for Asthma (GINA) report.

Introduction

Bateman began the symposium by describing patient empowerment. Empowerment is a process through which people gain greater control over decisions and actions affecting their health. They become actively involved in their treatment, instead of being passive objects of medical interventions by healthcare professionals. Patient education can help patients to understand what they can do to affect their own health and promote understanding that patients can be equal partners in their healthcare decisions.

Personalised medicine implies individualised treatments that are available for every unique patient. It must not be confused with precision medicine, which seeks to create treatments that are applicable to groups of individuals who exhibit certain characteristics.

This symposium was concerned with personalised medicine and how patient empowerment and involvement can lead to better disease outcomes.

(e.g., forced expiratory volume, exacerbations, symptom perception, and comorbidities with non-linear relationships), which means that one cannot be predicted from the other. Heterogeneous means that not all these elements are present in all patients, and they may even vary over time in the same patient, either because disease improvement by treatment or disease progression.

To address this complexity and heterogeneity, a phenotypic-based strategy was proposed back in 2010.¹ However, it was later realised that this was a too simplistic approach, since patients often exhibit several so-called treatable traits (TT).²

TTs are not necessarily tied with a specific diagnostic label and can occur in the pulmonary, extra-pulmonary, and behavioural or environmental domains. TTs can be identified either by clinical examination and expertise (phenotypes), or validated biomarkers that inform on the presence of specific biologic mechanisms (endotypes). TTs can coexist and change with time, either in spontaneously or response to treatment.

The goal of treatment with ICS in COPD is to reduce the risk of exacerbations in patients who suffer from exacerbations despite appropriate treatment, with one or two long-acting bronchodilators (LABD).³ This has to be balanced against the increased risk of pneumonia. The level of circulating eosinophils (eos) is a useful biomarker, predicting the response to ICS in COPD⁴ as the risk of exacerbations increases as function of blood eos count.⁵⁻⁷ The preventive

Personalising Treatment in Chronic Obstructive Pulmonary Disease: The Case for Inhaled Corticosteroids

Alvar Agusti

COPD is a complex and heterogeneous disease. Complex means that it has several elements

Table 1: Recommendations on use of inhaled corticosteroids in chronic obstructive pulmonary disease based on blood eosinophil count.

Strong support	Consider use	Avoid use
History of hospitalisation(s) for exacerbations of COPD	1 moderate exacerbation of COPD per year	Repeated pneumonia events
≥2 moderate exacerbations of COPD per year	Blood eosinophils 100–300 cells/ μL^{-1}	Blood eosinophils <100 cells/ μL^{-1}
Blood eosinophils >300 cells/ μL^{-1}		History of mycobacterial infection
History of, or concomitant, asthma		

COPD: chronic obstructive pulmonary disease.

Selecting the Right Device for Personalised Management of Asthma and Chronic Obstructive Pulmonary Disease

Anna Murphy

effect of ICS on exacerbation is higher in patients with higher circulating blood eos, particularly above 300 eos/ μL ; below 100 eos/ μL , when ICS are no different from the use of LABD; and the risk of pneumonia increases below 100 eos/ μL .⁸ Finally, the IMPACT⁹ and ETHOS¹⁰ studies showed a significant reduction in all-cause mortality when ICS were added to LABD in patients with frequent exacerbations, despite their use.

Collectively, these observations indicate that ICS treatment in patients with COPD must be individualised. As shown below, ICS must be used thoughtfully.³ There is strong support for their use if there is history of hospitalisations for exacerbations of COPD, 2 or more moderate exacerbations of COPD per year, a blood eos count of >300 cells/ μL , or there is concomitant asthma (Table 1). The use of ICS should be considered individually if patients have between 100–300 eos/ μL or in patients with a moderate exacerbation. Finally, ICS are not recommended in patients with repeated pneumonia events and/or those with less than 100 eos/ μL .

Murphy discussed importance of optimising inhaled medication delivery, personalising the choice of delivery device, monitoring the correct inhaler technique, and the sustainability of inhaler medication. Different delivery devices can be categorised into five different groups: pressurised metered-dose inhaler (pMDI), breath-actuated pMDIs, dry powder inhalers (DPI), nebulisers, and soft mist inhalers. Each inhaler type has different attributes and the choice is determined by both the medication and patients ability and willingness to use the device (Box 1).¹¹

Studies have shown that errors in inhaler technique are common. Although studies are difficult to compare, estimates of inhaler errors

Box 1: Factors affecting the choice of inhaler type.

1. Quick and deep or slow and steady inhalation
2. Dexterity to load and use the device
3. Co-ordination for pressing and breathing in for pMDI
4. Sufficient seal on mouthpiece
5. What other devices the patient has
6. Personal preference
7. Sustainability

pMDI: pressurised metered-dose inhaler.

include up to 90% of the patients using pMDIs and up to 54% of the patients using DPIs.^{12–18} Many clinical studies have shown inhaled medication to have excellent safety and efficacy profiles but, in real life, it may be difficult to guarantee that the devices are used correctly. Sanchis et al. reviewed over 100 studies for acceptable inhaler technique and found out that only approximately 40% of patients use their devices correctly and it has remained stagnant for the 40-year history of

modern inhaler therapy.¹⁷ It is obvious that both healthcare professionals and patients need more training in the use of inhaler devices. Poor inhaler technique has significant association to clinical outcomes of asthma such as exacerbations, asthma control test (ACT) scores, or GINA symptom control measures, irrespective to the country, device type, or age of the patient.¹⁹ Poor inhaler technique also inflicts considerable economic burden. In a study conducted in UK,

Sweden, and Spain on patients using Turbuhaler® or Accuhaler®, the direct annual costs of poor inhaler technique were 2.2–7.7% of the total costs of asthma, amounting to 105 EUR across the three countries.²⁰ Both the GINA and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines stress the importance of the individual inhaler and sufficient training.

According to CRITIKAL study inhalation flow error was the most common type and was most prevalent with patients using pMDIs.²¹ With pMDIs, patients tend to inhale too forcefully, promoting oropharyngeal deposition. This will reduce the efficacy of the medication, while possibly increasing adverse effects.^{22,23} Another common error was not tilting the head correctly to straighten the airways before inhalation.²¹

With DPIs, the drug has to be detached often from lactose particles.²⁴ There is a persisting misconception that with DPI devices the airflow resistance may be too high for some patients. In fact, the devices with high internal resistance require much lower inspiratory flow rate to operate. The severity of obstruction does not limit the use of high resistance devices. This is shown by number of studies. For example, when Jögi et al. studied 100 patients with COPD and

100 healthy volunteers; practically all of the subjects were able to generate sufficient flow rate for the high resistance devices.²⁵ Haughney et al. studied 994 adult patients with asthma and 94% of the patients were able to generate sufficient flow rate with the highest resistance setting of In-Check Dial, corresponding to high resistance DPI; however, 30% of patients failed to correctly use pMDI, inhaling too fast, even after careful tutoring and guidance.²⁶ Patients, using many different kind of devices, are more prone to inhaler errors and achieve worse disease control than those using only one type of device.^{22,27-29}

Lately, there has been lively discussions on sustainability of inhaler treatment. As nearly all of the patients are able to use whichever device they like, sustainability of the inhalers has also become an important factor in the inhaler selection. Particularly, pMDIs have a high carbon footprint due to their propellants. DPIs have been suggested as an alternative when clinically feasible, as their carbon footprint is marginal compared to that of pMDIs. Favouring greener inhalers has been one of the promoted actions by the UK National Health Service (NHS) in their programme towards net zero carbon footprint of health services.

VIDEO RECORDINGS OF THE PRESENTATIONS ARE AVAILABLE FROM WEHALE.LIFE.

<https://www.wehale.life/events/>

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Abstract Reviews

Sharing insights and advancements from selected abstracts presented by experts in the field of respiratory healthcare at the European Respiratory Society (ERS) Congress 2021.

Real-World Treatment Patterns of Newly Diagnosed Patients with Asthma and/or Chronic Obstructive Pulmonary Disease

Authors: *Aniek F Markus,¹ Peter R Rijnbeek,¹ Jan A Kors,¹ Edward Burn,² Daniel Prieto-Alhambra,^{1,2} Guy GO Brusselle,^{3,4} Katia MC Verhamme^{1,5}

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Keywords: Asthma, chronic obstructive pulmonary disease (COPD), guidelines, treatment pathways.

Citation: EMJ Respir. 2021;9[1]:52-54. Abstract Review No. AR1.

BACKGROUND AND AIMS

Current guidelines provide clinical recommendations for asthma and chronic

obstructive pulmonary disease (COPD) treatment,^{1,2} but there is a lack of knowledge on how patients are treated in the real-world. The authors give an insight into treatment patterns of newly diagnosed patients with asthma, COPD, and asthma-COPD overlap (ACO) syndrome across three electronic data sources, from the Netherlands, UK, and USA.

MATERIALS AND METHODS

The study was executed in three databases, namely two electronic health record databases: Integrated Primary Care Information (IPCI), the Netherlands; Clinical Practice Research Datalink (CPRD), UK; and one claims database, IBM MarketScan® Commercial Database (CCA), USA. In each database, mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM),³ the authors created three study cohorts by identifying adult patients with a first diagnosis of asthma, COPD, or ACO, respectively. Patients needed to have at least 1 year of database observation time prior to incident diagnosis and 3-year follow-up time.

Treatment episodes were defined as continuous subscriptions from the same respiratory drug

class, with a maximum gap of 30 days between prescriptions. A prescription of another drug class was considered a switch if there were fewer than 30 days overlap, with the previous drug class and a combination therapy otherwise. Results were visualised with sunburst plots.

RESULTS

The authors identified a total of 566,168 patients with asthma, 115,971 patients with COPD, and 96,985 patients with ACO across the databases. Approximately one-third of the patients with asthma start with short-acting β -agonists followed by inhaled corticosteroids (in Europe) and systemic steroid bursts (in the USA).

In Europe, patients with COPD start more often with long-acting muscarinic antagonist than patients with asthma.

In the USA databases, treatment for asthma and COPD are comparable and systemic steroids are frequently used as first treatment. Patients with ACO most often receive treatment, and the differences are smaller between the USA and Europe. Results for one of the databases (IPCI) is presented in Figure 1.

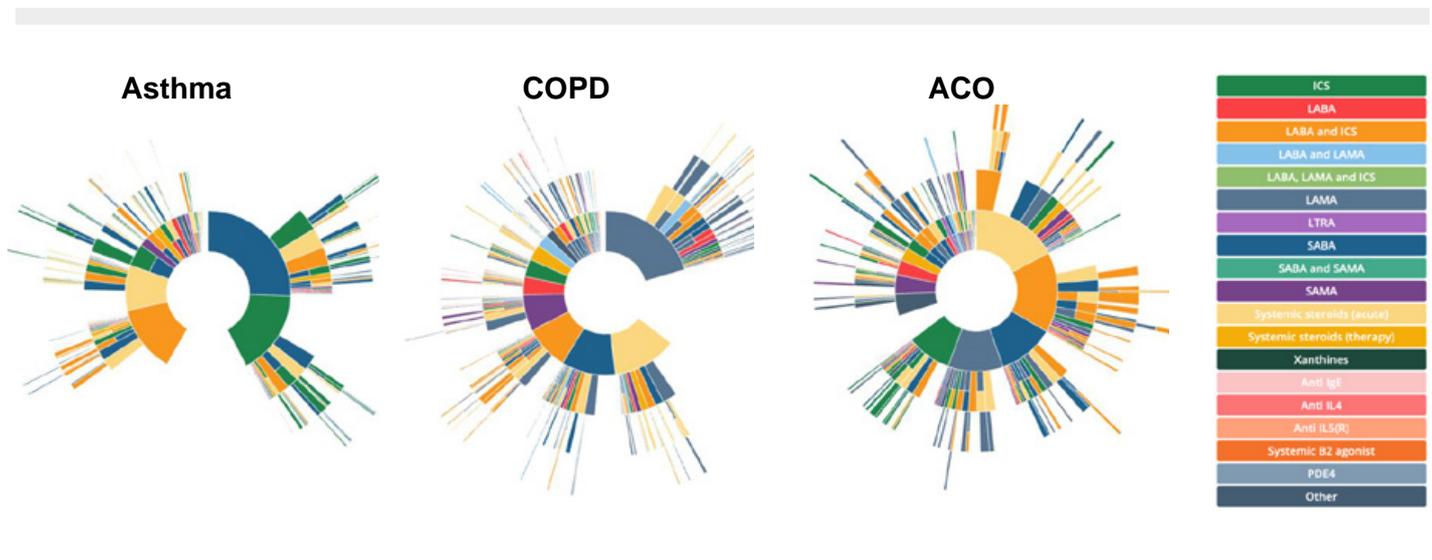


Figure 1: Sunburst plots of treatment patterns of adult patients with asthma, chronic obstructive pulmonary disease, or asthma-chronic obstructive pulmonary disease overlap, in the Netherlands (Integrated Primary Care Information database), showing the first treatment in the centre, and subsequent treatments in the surrounding outer layers. Each colour represents a drug class and a layer with multiple colours indicates a combination therapy.

ACO: asthma-chronic obstructive pulmonary disease overlap; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting β -agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonists; PDE4: phosphodiesterase-4; SABA: short-acting β -agonist; SAMA: short-acting muscarinic antagonist.

CONCLUSION

The authors conclude that treatment patterns in the real world vary across countries, with substantial differences in first treatments, suggesting deviation from global guidelines. ■

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Tracheal Stenosis: One Region Experience

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Diagnosis, stenosis, trachea, tracheostomy, treatment.

Citation: *EMJ Respir*. 2021;9[1]:54-55. Abstract Review No. AR2.

BACKGROUND AND AIM

Tracheal stenosis (TS) after long-term artificial lung ventilation remains a problem in the Russian region. In the Urals region during the last 5 years, the rate of TS after long-term artificial lung ventilation was 6.4%. The aim of the study was to find ways to reveal, prevent, and treat TS in the diagnosed patients.

MATERIALS AND METHODS

In order to reveal and treat early alterations, threatening with stenosis development, the authors examined 126 patients also subjected to tracheostomy and prolonged artificial lung ventilation (Group 1). Clinical supervision and a complex of diagnostic facilities (CT scan or MRI and laboratory investigation) were employed. Where some risk symptoms, demonstrated in the results section, were found, subsequent endoscopic treatment was performed. The endoscopic treatment consisted of cryoapplication, granulomatous tissue debridement, and bougienage of the stenotic area. The data of 150 patients with evident symptoms of TS, including emergency cases, were also reviewed (Group 2).¹ The method of treatment was chosen in accordance with the clinical variant of the stenosis.¹ In initial stages of TS, endoscopic sanation, granulations debridement, and cryotherapy were undertaken. Bougienage was performed in 124 patients. T-tube placement and subsequent reconstructive operations were necessary in 104 cases after the bougienage. In 66 patients, four from Group 1 and 62 from Group 2, circular tracheal resections were performed, including 16 patients who underwent bougienage.

RESULTS

The rate of TS appeared to be 2.5-times higher in cases where sleeve tracheostomy (Bjork tracheostomy) had been performed. The

symptoms threatening development of TS were found in Group 1 in 24 patients (19.0%), and were as follows:

- more than two rings damaged;
- intensive growth of granulation tissue;
- cartilage debris in the tracheal lumen;
- inflammation of the tracheal mucous membrane; and
- inflammation and purulent process in the neck wound around the trachea.

In 17 of the patients who had received initial alteration, endoscopic treatment was successful. Bougienage followed by T-tube placement and subsequent reconstructive operations was successful in 93 patients, and 11 are still under treatment. No complications followed these procedures. T-tube and reconstructions became necessary in three patients from Group 1, and in 90 from Group 2. Circular resection of the trachea resulted in recovery in 62 cases. Restenosis after resection developed in two cases and required repeated stenting. Erosion haemorrhage

occurred in two patients. All these complications occurred in Group 2. Overall complication and lethality rates were 9.2% and 3.1%, respectively.

CONCLUSIONS

Permanent observation of patients after prolonged tracheostomy is necessary to detect TS in early stages. Comparative data showed that T-tube placement was necessary in 90 patients from Group 2, and only three patients from Group 1. Circular resection of the trachea was performed in four patients from Group 1 and 62 patients from Group 2. Overall, constant supervision and endoscopic treatment undertaken in proper time in patients after long-term artificial lung ventilation in the vast majority results in recovery and avoids urgent situations and heavy surgical interventions. ■

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Skeletal Muscle Afferent Sensitivity in Interstitial Lung Disease: An Interim Analysis

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Keywords: Dyspnoea, exercise tolerance, interstitial lung disease, metaboreflex.

Citation: EMJ Respir. 2021;9[1]:55-56. Abstract Review No. AR3.

BACKGROUND AND AIMS

Dyspnoea and exercise intolerance are near universal symptoms in fibrotic interstitial lung disease (fILD).¹ Neither anti-fibrotic agents approved for the treatment of idiopathic pulmonary fibrosis significantly diminished exertional dyspnoea.² The physiological mechanisms of dyspnoea

and exercise intolerance in fILD are poorly understood. In other chronic diseases, such as chronic obstructive pulmonary disease and chronic heart failure, there is emerging evidence that the sensitivity of metabolically responsive skeletal muscle afferents (muscle metaboreflex) is augmented.^{3,4} This can contribute to exercise intolerance through dyspnoea, exaggerated sympathetic vasoconstriction, and hypoperfusion of the active muscle.⁵ The authors hypothesised that muscle metaboreflex sensitivity is augmented in fILD and drives dyspnoea.

MATERIALS AND METHODS

Thirteen patients with fibrotic fILD (two female; 70±13 years; forced vital capacity [FVC]: 72±19% predicted; forced expiratory volume in 1 second [FEV₁]/FVC: ≥0.7; fibrosis on high-resolution CT) and 15 healthy controls (four female; 68±7 years) were recruited. In a randomised crossover design, participants completed 2 minutes of rhythmic handgrip (50% maximal voluntary contraction) followed by either:

- i) two minutes of post-exercise circulatory occlusion (PECO trial), where a cuff placed around the upper arm was inflated to a supra-systolic pressure preventing the removal of chemical by-products of exercise, to isolate muscle metaboreflex activation; or
- ii) rested for 4 minutes (control trial).

Minute ventilation (V_E), mean arterial pressure (MAP), and heart rate (HR) were measured and analysed using two-way analysis of variance. Muscle metaboreflex sensitivity was calculated as the intra-individual difference in physiological response between the last 90 seconds of the PECO trial and the corresponding period in the control trial. Dyspnoea intensity was measured with a 0–10 Borg scale.⁶ Comparisons between the healthy and fILD groups were assessed using a Student's unpaired t-test.

RESULTS

The majority of patients with fILD had a diagnosis of idiopathic pulmonary fibrosis (n=5). Other diagnoses were connective tissue disease-associated interstitial lung disease (n=3), interstitial pneumonia with autoimmune features (n=1), organising pneumonia (n=1), unclassifiable (n=2), and asbestosis (n=1). There were no significant differences in terms of age, height, weight, or maximum voluntary contraction between the healthy and fILD groups. The fILD group had lower predicted FEV₁ (p=0.00), FVC (72±19% versus 107±8%; p=0.00), and higher FEV₁/FVC (p=0.02) compared with healthy controls. Exercise increased V_E , MAP, and HR (p<0.05) in all groups. V_E and MAP remained elevated during PECO (p<0.05) with no differences between groups. There was no difference in muscle metaboreflex sensitivity for the MAP, V_E , or HR responses between the groups (e.g., ΔV_E : fILD 0.01±1.5 L/min versus healthy 0.35±1.6 L/min; p=0.55). In the patients with fILD, PECO did not increase the mean dyspnoea rating relative to control (1.3±1.3 units versus 1.0±1.2 units; p=0.19).

CONCLUSION

These findings suggest that skeletal muscle metaboreflex sensitivity is not augmented in fILD. Metaboreflex activation did not result in increased dyspnoea. The contribution of other sensory afferents should be explored in the investigation of the mechanisms underlying dyspnoea and exercise intolerance in fILD. ■

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Pneumomediastinum as a Complication of COVID-19 Pneumonia: A Self-Experience Study

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Disclosure: The authors have declared no conflicts of interest.

Keywords: COVID-19, pneumomediastinum (PM), pneumonia.

Citation: EMJ Respir. 2021;9[1]:57-58. Abstract Review No. AR4.

BACKGROUND AND AIM

Pneumomediastinum (PM) is a rare pathological entity that is divided into two categories:

secondary, with a well-known aetiology, and spontaneous, with no clear aetiological factor.¹ At the beginning of the COVID-19 pandemic, some publications demonstrated PM as a complication of COVID-19 pneumonia.²⁻⁴ In the authors' thoracic surgery practice, they established incidences of PM in patients with COVID-19 pneumonitis. Therefore, they decided to highlight the importance of PM with its two types, secondary and spontaneous, in COVID-19 pneumonia.

RESULTS

The authors' present three patients with COVID-19 pneumonia and pneumomediastinum. A 78-year-old woman with PM diagnosed on Day 12 of mechanical ventilation. The day after establishing PM, a control chest X-ray demonstrated shifting of the mediastinal structures to the right hemithorax, with apical left-sided pneumothorax. A left-sided chest tube drain was inserted. The woman's respiratory status was progressively worsening, and she died of multiple organ dysfunction syndrome on Day 23 of intubation.

The other two patients were 58-year-old and 75-year-old men with PM as a late consequence of COVID-19 pneumonia (on Day 47 and Day 28, respectively, after diagnosis of COVID-19 infection).

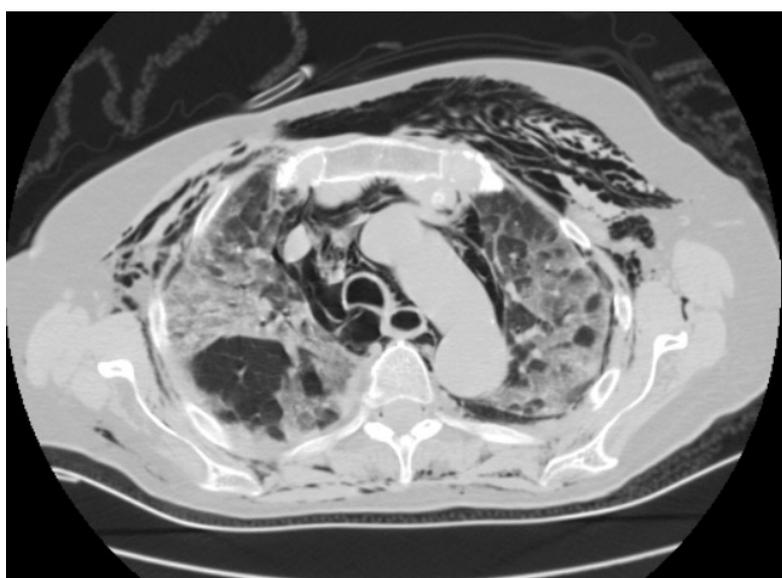


Figure 1: Chest CT of bilateral lung patchy ground-glass opacities, pneumomediastinum, left-sided pneumothorax, and significant expressed subcutaneous emphysema.

They were admitted with clinical symptoms of a dry cough, shortness of breath, chest pain, and subcutaneous neck emphysema and PM was determined by a thoracic CT. After 10 days of conservative treatment, the 75-year-old man was discharged in a good condition, with a significant reduction of PM. On the second day of hospitalisation, the 58-year-old man expressed severe dyspnoea and progression of subcutaneous emphysema to the chest, neck, face, and arms. A control chest CT determined progression of PM with left-sided apical pneumothorax (Figure 1). A chest tube drain was inserted. The patient's respiratory status continued to worsen with *exitus* on the second day after chest drain insertion.

CONCLUSION

The authors accepted the destructive viral effect on the alveoli as the main predisposing factor for spontaneous type of PM in COVID-19 pneumonia. In cases with mechanical ventilation with positive airway pressure support, the authors consider barotrauma as an aetiological factor on secondary type of PM.

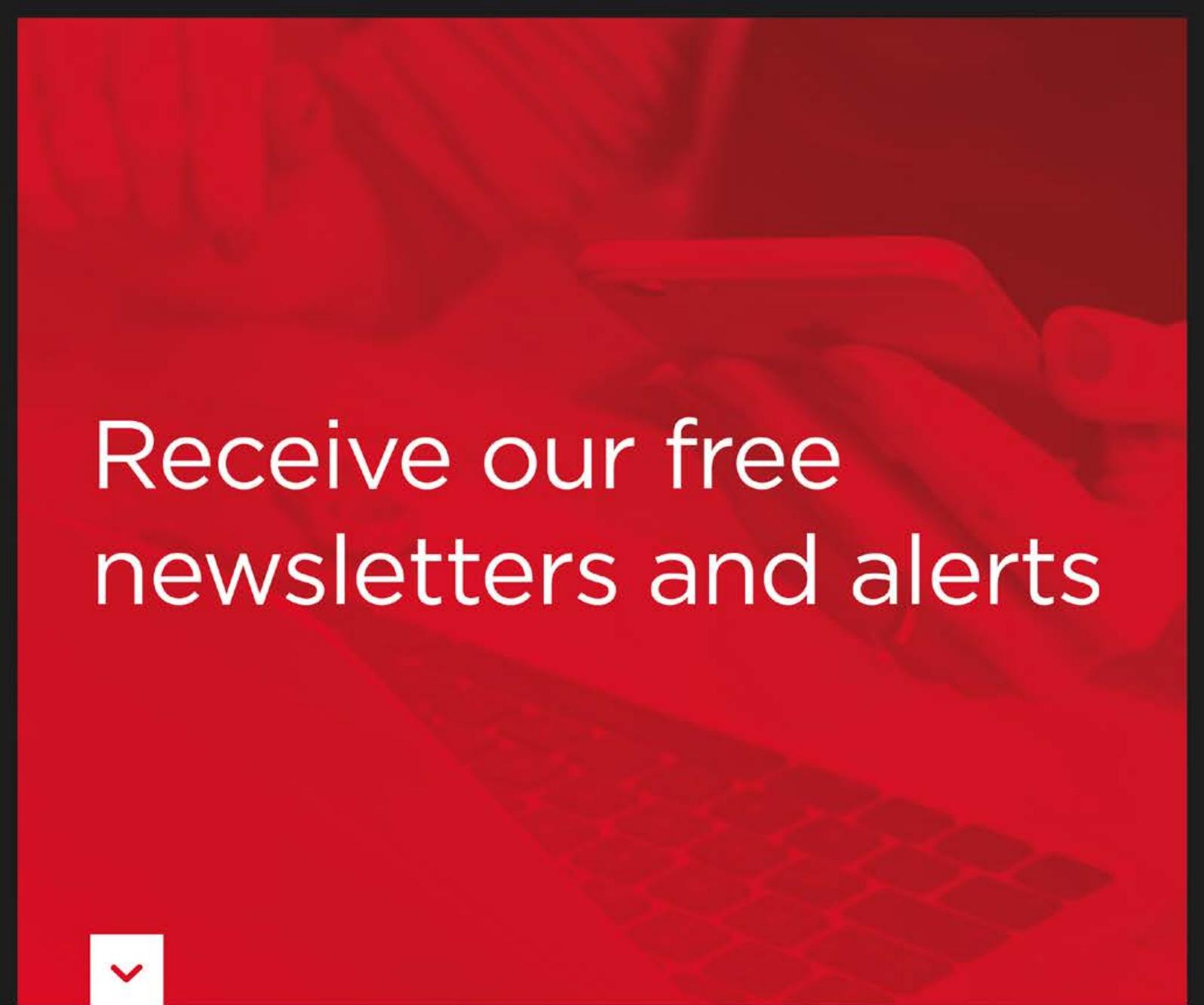
They concluded that a concomitant spontaneous pneumothorax was 'secondary' as a result of alveolar rupture, due to the viral-induced pneumonitis and/or positive pressure ventilation.

With this study, the authors highlight the PM in its two forms (secondary and spontaneous) to be a serious COVID-19 pneumonia complication, even in the post-COVID-19 period. Their study points out to be alert of PM in COVID-19 pneumonia, even in the patients with no need for mechanical ventilation. ■

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Interviews

EMJ spoke to Sarah Walmsley and Andres Floto about their career and experience in the field of respiratory, by covering topics such as their personal research interests, the impact of the COVID-19 pandemic, and the latest therapeutic and scientific advancements in the field of respiratory medicine.

Featuring: Sarah Walmsley and Andres Floto.



Sarah Walmsley

Professor of Respiratory Medicine and Honorary Consultant in Respiratory Medicine, University of Edinburgh, UK.

Q1 What initially sparked your interest to pursue a career in respiratory medicine?

As a medical student in Edinburgh, I was inspired by the opportunities in Edinburgh to combine clinical and basic science research in respiratory medicine. As I progressed through my clinical training, the need for therapies to target acute and chronic inflammatory lung diseases became more apparent, as they remain to this date.

Q2 With over 95 publications to your name for your research in the respiratory field, what do you believe to be the gaps in current literature and what topics merit greater attention?

Neutrophils are essential for host defence but widely implicated in the pathogenesis of acute lung injury and chronic inflammatory lung diseases including chronic obstructive pulmonary disease. In my opinion, there remains a huge clinical need to develop therapeutic strategies that target neutrophilic inflammation, ideally with therapies that limit or resolve tissue inflammation without compromising systemic immunity.

Q3 What has been your proudest achievement of your career as a respiratory physician?

Training and supporting clinical and non-clinical academics of the future, within respiratory medicine, across clinical specialties, veterinary medicine, and biomedical research.

Q4
Your main area of research focuses on the regulation of neutrophil apoptosis by hypoxia. Could you tell us about the current stage that this area is in and what you aim to achieve from your research?

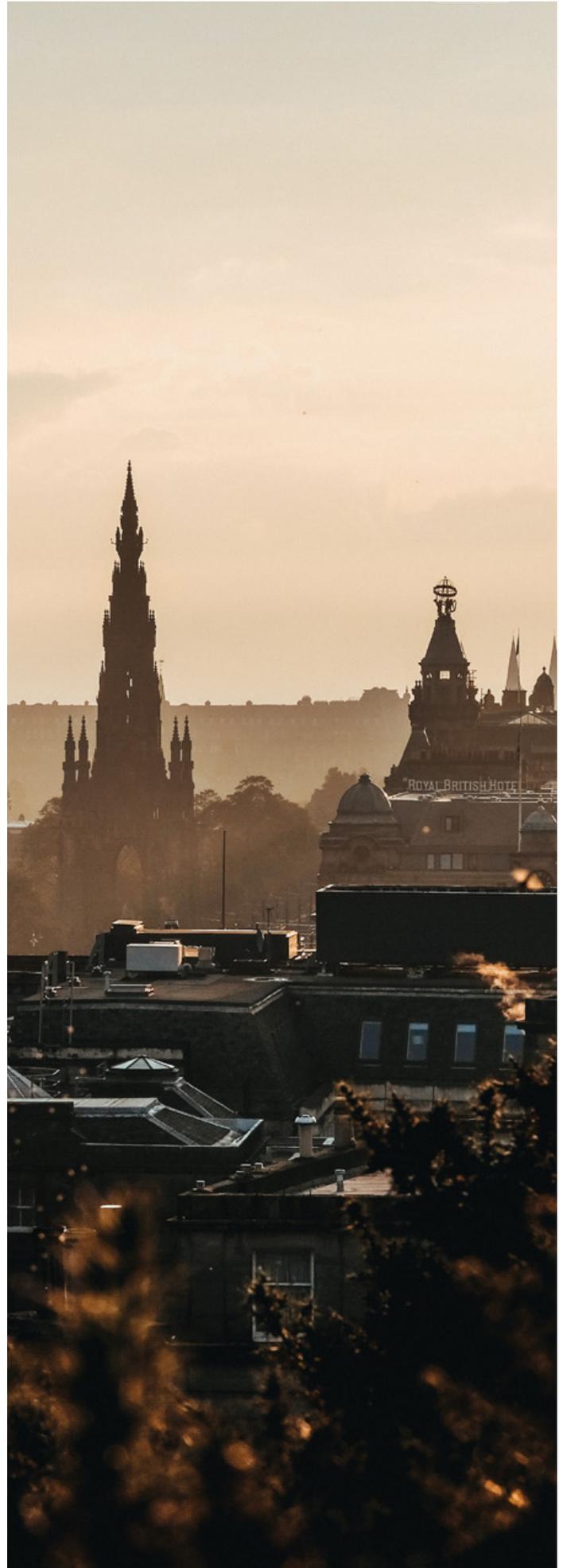
A fine balance exists between maintaining effective host pathogen responses and limiting host-mediated tissue damage. Innate responses to bacterial challenge and sterile inflammation are critically regulated by the local tissue environment. We have implicated oxygen sensing responses and metabolic adaptations of the neutrophil to be critical in regulating outcomes of the inflammatory response. More recently, we have described long-term reprogramming of neutrophils by systemic hypoxia in health and disease states, opening the possibility of therapeutic intervention.

Q5
In the midst of the current pandemic, how do you feel the field of respiratory medicine and research has been impacted by COVID-19?

I think that respiratory medicine has contributed significantly to the global research efforts targeted towards COVID-19, facilitating a greater understanding of the immunological response to severe acute respiratory syndrome coronavirus 2, identifying patient cohorts, recruiting patients to national trials, and latterly starting to define the long-term consequences of COVID-19. This work has brought together scientists and clinicians across disciplines, regions, and countries, which is a force for good. I am, however, extremely concerned of the impact COVID-19 has had on early career researchers, many of whom are having to juggle family responsibilities with increased clinical workload, and a highly competitive research and funding environment. Whilst COVID-19 has re-enforced the need for biomedical research, if we don't support these early career researchers, we won't have people to drive forward biomedical research of the future.

Q6
Over the years that you have been practising as a respiratory physician, how have you seen the field change in terms of advancements to the technology used?

I hope that I am not that old yet!





"I am, however, extremely concerned of the impact COVID-19 has had on early career researchers, many of whom are having to juggle family responsibilities with increased clinical workload."

Q7 Have you found that the public are generally receptive to new technology, or do you occasionally experience resistance?

In my experience, the public I have spoken to, ranging between school children to the more senior members of society, are incredibly engaged in new opportunities and the need for therapeutic and scientific advancements in medicine.

Q8 What are some points of emphasis you incorporate into practice to be the best respiratory physician you can be?

I am not sure I can answer this question about myself. I hope what I bring is the ability to listen and communicate; the ability to assimilate information and use that information to reach a diagnostic conclusion; the desire to understand how the innate immune response is regulated and consequences for inflammation outcomes; and, ultimately, the ability to use this information to inform new therapeutic strategies.

Q9 What advice would you give to someone interested in pursuing a career in a similar field?

It is a real privilege to be a clinical academic in respiratory medicine. I think if you love the clinical area and the opportunity to ask questions to which no-one has an answer, then go for it. I don't think people should question their own abilities to deliver it so much but pursue what they love doing. I have been incredibly fortunate in this regard. I think having a mentor who can guide you through this process is extremely important and has certainly been instrumental in my success.

Q10 As an educator, where can we expect to see your focus lie in the coming years?

I have perhaps touched upon this point above. I think that we are making it increasingly challenging for clinical academics of the future. We have increased clinical training demands, increased scientific competition to deliver world leading science, and increased competition for early and mid-career fellowships at a time when many individuals have caring responsibilities and young families. We need to be encouraging these academics of the future by not making it so difficult that they question their own abilities to succeed. This has been recently amplified by COVID-19 and it needs to be a focus in the years to come. ■



Andres Floto

Professor of Respiratory Biology at the University of Cambridge; Research Director of the Cambridge Centre for Lung Infection at Papworth Hospital, Cambridge, UK

Q1 What inspired you to become a Professor of Respiratory Biology and how did your teaching career lead you to the University of Cambridge?

I have always been incredibly interested in science and in trying to understand how things work. My first degree was in natural sciences at Cambridge, UK, where I specialised in neurobiology, and this exposed me to the beauty and rigor of basic science. During this degree, I realised that I needed to also train as a doctor to be able to translate clinically relevant scientific discoveries into impact for patients.

Following a PhD in immunology (as part of the Cambridge MB/PhD programme), and time in London combining post-doctoral research with postgraduate medical training, I returned to Cambridge in 2002 as an MRC Clinician Scientist Fellow and then Wellcome Senior Clinical Research Fellow, where I started my lab focused on understanding the interaction between bacteria and the innate immune system. My clinical interest has always focused on difficult bacterial infections (non-tuberculous mycobacteria, cystic fibrosis [CF], and non-CF bronchiectasis) and immunodeficiencies. My current role as Professor of Respiratory Biology (which I've held for 7 years) gives me the unique opportunity to align these clinical interests with my basic and translational research programmes.

Q2 From professor to research director, you have many important roles and responsibilities. Which role occupies most of your time and what do you enjoy most about it?

I am very fortunate that, despite some leadership responsibilities and management duties, I am still able to spend most of my time in the lab discussing results with my group, planning new

experiments over coffee, and helping them problem solve when things don't go to plan.

Q3 As a director of the UK Cystic Fibrosis Innovation Hub, what does your role entail and what are the biggest challenges you have seen in CF research and treatment?

The UK Cystic Fibrosis Innovation Hub is a strategic partnership between the UK Cystic Fibrosis Trust and the University of Cambridge, UK, focused on delivering precision medicine to individuals with CF and overcoming the health challenges that remain despite the introduction of highly effective CF transmembrane conductance regulator modulator therapy. We have three programmes of work based in Cambridge: drug discovery, focusing on creating new antibiotics and anti-inflammatories; stem cell research, developing induced pluripotent stem cells-derived epithelial cells to understand modifier genes and test new drugs, and (in the future) provide cellular therapy; and smart technologies, testing new home monitoring sensors and developing machine learning methods to forecast clinical outcomes. The fourth pillar of the Innovation Hub is to support UK-wide CF research through a variety of training and infrastructure projects. As part of this effort, we are very excited to have received National Institute for Health Research (NIHR) backing to try to DNA sequence the entire CF population in the UK. We hope that this genetic information will provide a huge boost to CF researchers aiming to understand pharmacogenomics and develop new treatments.

Q4 One of your current areas of clinical research involves model-based machine learning and respiratory conditions. How do you think machine learning can help predict pulmonary exacerbations in CF?

We have been applying machine learning methods to analyse daily home monitoring data from individuals with CF, originally from our multi-centre feasibility study SmartCare and now from our clinical implementation programme Project Breathe. In collaboration with Microsoft Research, we have now developed a robust predictive algorithm that can forecast the onset of an acute pulmonary exacerbation approximately 10 days earlier than we currently can. We are very pleased to have recently been awarded an NIHR Artificial Intelligence Award to evaluate this algorithm in a randomised controlled trial starting next year.

Can you tell us the story of how you started Floto Lab and the current research you and your team are working on?

I started my lab in 2008 with a small group looking at the innate immune response to bacterial infection. Over the next few years, using a combination of comparative biology and reverse genetics, we identified signalling pathways in macrophages and dendritic cells that could be exploited as host-directed therapy as well as genes that act as restriction factors for specific species of bacteria.

As the group has got bigger, we have been increasingly excited by the bacterial side of this interface and have appreciated the power of population-level pathogen sequencing and forward genetic screens in understanding how bacteria evolve during chronic infection and cause disease. Over the last 8 or 9 years, we have been developing new methods to create antibiotics through combining structure-guided chemical elaboration with machine learning and have been focusing more on the interaction of bacteria with the lung epithelium.

The Phase II clinical trial to treat chronic infection with *Mycobacterium abscessus* in patients with CF was influenced by you. What were the results of the Phase I trial and were there any limitations or gaps to the research?

M. abscessus infections are extremely hard to treat, with current guidelines-approved regimens (involving months of combination treatment with

poorly tolerated antibiotics) curing only about one in three patients. We have been working hard to find other ways to kill *M. abscessus* and have found, in pre-clinical studies, that acidified nitrite is very effective. Nebulised acidified nitrite appears safe in healthy volunteers, and we are very excited to be starting a Phase IIa study in adults with CF infected with *M. abscessus* to see the impact of 1 month of nebulised acidified nitrite on their bacterial burden. If successful, we hope to launch a multi-national study of this therapy next year.

Aside from CF, what other respiratory genetic diseases are you interested in and why?

We are really interested in uncovering the genetic susceptibility to developing idiopathic bronchiectasis, meaning bronchiectasis not caused by CF, primary ciliary dyskinesia, or immunodeficiency. We have a very exciting discovery programme of multi-omic research combining whole exome sequencing, single cell RNA sequencing, and functional validation, which is transforming our understanding of the pathophysiology of this overlooked condition.

What advice would you impart on someone who aspires to be an expert in the respiratory field?

Whether your focus is on improving clinical care or on advancing research (whether that be basic, translational, or clinical), you need to strive to understand your specialist area at a fundamental level. It's only by doing so, that you can appreciate how much of the established dogma is wrong, what areas are unknown, where opportunities lie for research and improvements in clinical care, and what learnings can potentially be applied to other conditions.

A great example is CF. You don't have to know how CF transmembrane conductance regulator works (or doesn't work) to practice as a CF physician. But you do need to understand these basics to appreciate how airway surface pH is disturbed in CF or how modulation of the epithelial sodium channel or anoctamin-1 might restore airway surface liquid. ■

SARS-CoV-2 and Cystic Fibrosis: Expectations Versus Reality, a Literature Review

**EDITOR'S
PICK**

I have selected this review as my Editor's Pick for this issue because there is a real interest in establishing the infection prevalence of people with cystic fibrosis to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the potential associated contributing factors. An important role could be played by inflammatory factors utilised by SARS-CoV-2 to penetrate cells. This review aims to explore and discuss the available clinical data concerning this topic, looking to the clinical outcomes of people with cystic fibrosis compared with the general population.

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the COVID-19 pandemic, is expected to cause severe illness in people with cystic fibrosis (CF). The infection prevalence and clinical outcomes of this patient cohort to SARS-CoV-2 were explored, alongside contributing factors to the observed response.

Search terms were entered into Medline/PubMed and Embase databases, with relevant published papers written in English chosen.

The COVID-19 trajectory in people with CF (including children) was similar to the general population. Specifically, in Veneto, Italy, the infection rate of people with CF was nearly half compared to the general population (0.19% versus 0.40%, respectively). Similarly, in Spain, the cumulative incidence of COVID-19 was lower compared to the general population: 32/10,000 and 49/10,000 respectively. Likewise, in Belgium 2.7% of patients with CF had SARS-CoV-2 antibodies compared with 4.3% of the general population. Moreover, in Europe, fewer CF-COVID-19 cases and deaths were reported compared to the general population (1.1%, 0.9%; and 3.2%, 2.3%, respectively). Overall, worse outcomes in CF were associated with poorer lung function and post-transplant status.

The encouraging response of people with CF to COVID-19 is hypothesised as due to higher levels of anti-inflammatory angiotensin-1-7 and lower levels of pro-inflammatory IL-6 and protease transmembrane

serine protease-2, utilised by SARS-CoV-2 to penetrate cells. Additionally, the use of CF medication, chiefly Dornase alfa and CF transmembrane conductance regulator modulators as well as CF cohort characteristics, predominantly younger age, and early isolation might have mitigated COVID-19 severity.

Thus, people with CF do not appear to have a higher COVID-19 infection prevalence or worse clinical outcomes compared to the general population.

INTRODUCTION

Cystic fibrosis (CF) is a chronically deteriorating lung condition that can affect multiple systems, frequently accompanied by a plethora of comorbidities.¹ Viral infections account for approximately 60% of CF exacerbations, and people with CF have increased morbidity when exposed to viruses, such as the influenza A virus (H1N1).^{2,3} This can be because of the limited antiviral response of airway epithelial cells and co-infection with other bacteria known to affect patients with CF, such as *Pseudomonas aeruginosa*.³ Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the highly contagious virus responsible for the COVID-19 pandemic, leads to worse clinical outcomes in individuals with comorbidities compared to healthy individuals.² People with CF are reported to be at a higher risk of displaying more severe COVID-19 symptoms.⁴ Infection by SARS-CoV-2 in severe cases can cause acute respiratory distress syndrome (ARDS) and even death.³

People with CF are assumed at increased risk of worse outcomes when infected by SARS-CoV-2 compared to healthy individuals. This is because of their chronically deteriorating lung function and susceptibility to viral infections, as well as the underlying pathophysiology of their condition and pro-inflammatory and respiratory nature of SARS-CoV-2.²⁻⁶ Thus, this cohort is advised to 'shield' by self-isolating.

UK guidelines currently highlight that people with CF may be at increased risk of rapid deterioration if infected by SARS-CoV-2. It is recommended that they should manage their condition as previously instructed, including pharmacological and non-pharmacological interventions, with the additional advice to contact their CF team if experiencing COVID-19 symptoms.^{4,7} However, emerging data suggest that people with CF may not be at a higher risk of SARS-CoV-2 infection or worse clinical outcomes when infected.⁷

The primary aim of this literature review was to establish the susceptibility of people with CF to SARS-CoV-2 and the prevalence and severity of COVID-19 in this patient cohort. The secondary aim was to identify potential factors that could have contributed to the observed response to SARS-CoV-2, focusing on cellular processes, medication, and cohort characteristics in people with CF.

METHODS

This literature review was undertaken from 1st November 2020 until 12th February 2021, using a combination of the following search terms: "cystic fibrosis," "SARS-CoV-2," "COVID-19," "ACE-2," "CFTR," "azithromycin," "Dornase-alfa," and "corticosteroids" on the EMBASE and MEDLINE/PubMed databases. Papers were also identified via the reference lists of examined papers. Only published papers and papers written in English were reviewed and chosen according to content relevance.

RESULTS AND DISCUSSION

Cystic Fibrosis and Severe Acute Respiratory Syndrome Coronavirus 2: Epidemiology

Even though data are still preliminary, the emerging picture is that patients with CF experience milder COVID-19 symptoms than expected. A study reported that from 100,000 people infected with COVID-19 (>100 people also having CF), approximately 90% of people with CF experienced a milder infection.⁷

Furthermore, a retrospective study of 532 people with CF in Veneto, Italy, tested 118 (22.2%) of these patients (throat and nose swab) who were symptomatic for COVID-19. They identified one patient who had mild symptoms as COVID-19 positive, resulting in an infection rate of 1/532

(0.19%). Interestingly, the infection rate for people with CF was nearly half compared with the general population. Of the 4,907,704 people in Veneto, 465,433 (9.5%) were tested, and 19,729 were COVID-19 positive, resulting in an infection rate of $19,729/4,907,704$ (0.4%).² Similarly, a COVID-19-CF observational retrospective survey was conducted by the Spanish CF Society. It demonstrated that the cumulative incidence of COVID-19 in patients with CF was lower compared to the general population: 32/10,000 (0.32%) and 49/10,000 (0.49%), respectively. From the 2,498 patients that were registered with the Spanish CF Society (data from 2018), 8/2,498 (0.3%) COVID-19-positive people were identified, and no fatalities were reported.⁵

Furthermore, a prospective study examined the Belgian SARS-CoV-2 seroprevalence in CF by recruiting 149 patients with CF. Blood tests were undertaken to establish the presence or absence of SARS-CoV-2 IgG and IgM antibodies. Positive serologies were reported in 2.7% (4/149) of patients with CF (3 patients for IgG and 1 for IgM) compared with 4.3% of the Belgian population at the time. A total of 36/149 (24%) patients had symptoms that were aligned with COVID-19. Six patients required medical attention and were PCR tested for COVID-19, five of whom were hospitalised. Only 1/6 patients tested positive for COVID-19, who paradoxically did not test positive for anti-SARS-CoV-2 antibodies.⁸

Moreover, out of 49,886 registered patients with CF⁹ (from 38 European countries), 554/49,886 (1.1%) have been COVID-19 positive, 13/49,886 (2.3%) of whom needed intensive care, and 5/49,886 (0.9%) died.¹⁰ These data align with the response of the general population in Europe. At the time of writing this review (1st January 2021), it is estimated that 747,863,079 people live in Europe. Out of the aforementioned population, 23,844,011 (3.2%) people were reported to be COVID-19 positive, including 547,196 (2.3%) people who died.^{11,12}

Likewise, a multinational study, with Australia, Canada, France, Ireland, Netherlands, New Zealand, UK, and USA being the participating countries, reported a similar trajectory of COVID-19 infection in people with CF to the general population. Specifically, 40 people with CF who tested positive with COVID-19-were

identified with a median age of 33 years (15–59 years). A total of 31/40 (77.5%) of these people were symptomatic with COVID-19, 28/40 (70%) experience recurrent bacterial infections, and 11/40 (27.5%) had received a lung transplant. Furthermore, 25/40 (62.5%) people were treated with antibiotics, 13/40 (33%) needed oxygen supplementation, 1/40 (2.5%) invasive ventilation, and 4/40 (10%) intensive care unit (ICU) admission. From the 14/40 (35%) people who were on CF transmembrane conductance regulator (CFTR) modulator therapy, one required ICU admission. No deaths were reported in this cohort.¹

Severity of the COVID-19 infection between patients with CF and the general population seemed to correlate. A study conducted by the Global Registry Harmonization Group (GRHG) recruited 181 patients with CF from 19 countries. They identified that people with CF had similar clinical outcomes to the proportion of patients who experienced a worse COVID-19 infection, with worse outcomes associated with poorer lung function and a post-transplant status. The patients' outcomes were analysed according to their transplant status; 141 patients being non-transplant and 27 were post-transplant, with relevant data missing for 13 patients. Overall, non-transplant patients had a significantly lower percentage of admissions compared to the post-transplant patients; 66/141 (66%) and 20/27 (74%), respectively. Likewise, fewer non-transplant patients (4%) were admitted to ICU compared to post-transplant patients (25%). Overall, seven patients out of the entire cohort died, four of whom were non-transplant.¹³

Similar findings have been reported in paediatric studies. An observational study conducted by the GRHG recruited 105 children with confirmed COVID-19 from 13 countries. The study dataset contained missing values, which were attributed to variability in data collection. The median age of the patient cohort was 10 years (6–15 years), with 31 patients treated with long-term azithromycin, 50 with a CFTR modulator, and 2 being post-transplant. A total of 26/89 (29%) patients had no COVID-19 symptoms. In symptomatic patients, fever (46/63, 73%) and a change in cough (38/53, 72%) were most reported. A total of 24/82 (29%) patients were admitted to hospital, with 6/21 (29%) requiring additional oxygen, 2/20 (10%) non-invasive ventilation,

and 1/20 (5%) invasive ventilation. Significantly fewer patients who were on CFTR modulator therapy required hospitalisation compared to patients who were not on such therapy; 6/40 (15%) and 34/40 (85%), respectively. No deaths in this patient cohort were attributed directly to COVID-19. One patient, however, died 6 weeks after testing positive for COVID-19, due to disease exacerbation. The authors concluded that children with CF experience a similar COVID-19 disease course compared to children without CF.¹⁴

Likewise, the expert panel from the European Respiratory Society (ERS) examined the response of children with chronic respiratory conditions to COVID-19 by collating data from 174 ERS centres. Fourteen children with CF were reported to have COVID-19. Due to the incomplete data, one child had to be excluded from the analysis. Severity of symptoms varied: 1 child presented with fever; 2 with pneumonia; 4 had a pulmonary exacerbation; and 5 presented with upper respiratory tract infection. From 7/13 (53.8%) hospitalised children, 3 were admitted to the paediatric ICU, 2 required oxygen, and 1 invasive ventilation. Additionally, 3 children required antibiotics, 3 azithromycin for COVID-19 treatment, and 1 hydroxychloroquine. No deaths were reported in this cohort. The authors of the study concluded that children with CF are at no higher risk of having worse outcomes with COVID-19 compared with the general population.¹⁵

Therefore, current epidemiological data suggest that people with CF do not have higher infection rate or suffer from worse COVID-19 clinical outcomes compared to the general population.

Cystic Fibrosis and Severe Acute Respiratory Syndrome Coronavirus 2: Cellular Level

Severe Acute Respiratory Syndrome Coronavirus 2

Coronaviridae is the viral family of SARS-CoV-2, which is one of the seven types of coronaviruses that infect humans. SARS-CoV and Middle East respiratory syndrome coronavirus also belong to the same viral family and infect the airways, causing respiratory illness. SARS-CoV-2 has a 31 kb RNA enclosed within a glycoprotein envelope. Spike proteins, Type 1 glycoproteins,

are attached and protrude from the envelope. These are broken down by host cell-membrane proteases to facilitate viral entry, chiefly angiotensin-converting enzyme-2 (ACE2) for SARS-CoV-2 because of a single mutation in the spike protein that improves the attachment to ACE2. Cathepsins human airway trypsin-like protease and transmembrane protease serine 2 (TMPRSS2) also contribute to viral entry. After host cells are infected, cytokines are released into the bloodstream causing systemic inflammation, acute lung injury, ARDS, and even death.^{3,16} However, like most human genes, the *ACE2* gene also shows polymorphism, which might affect an individual's susceptibility to SARS-CoV-2.³

Cystic Fibrosis

CF is an autosomal-recessive condition and predominantly arises due to a mutation in a gene responsible for encoding the CFTR protein.^{17,18} Although several mutation classes have been described, the most common one belongs to Class II, namely Phe508del (previously F508del).¹⁹⁻²¹ The CFTR is a protein channel whose main role involves the regulation of chloride ion balance across the cell membrane. If fully functional, water will be retained in mucus, thereby aiding the process of the mucociliary clearance. However, when the Phe508del mutation occurs, the produced CFTR protein is misfolded and therefore cannot be transported from the endoplasmic reticulum to the cell membrane.²² Additionally, the misfolded protein will be recognised and degraded by the ubiquitin-proteasome pathway in a process known as endoplasmic-reticulum-associated degradation.^{23,24} Thus, in the absence of the functional CFTR protein, chloride ions cannot be secreted into the mucus, resulting in an ion imbalance, followed by the retention of viscous mucus and increased susceptibility to infections and inflammation. Collectively, these cellular modulations will lead to typical signs and symptoms of CF.²⁵

Cystic Fibrosis and Severe Acute Respiratory Syndrome Coronavirus 2

It is hypothesised that two key proteins could be involved in pathways to decrease the severity of SARS-CoV-2 infections: ACE2 and TMPRSS2. Specifically, the former cleaves angiotensin I (ANG-1) into ANG-2, and ANG-2 to ANG-1-7.

The two enzymatic cleavages produce proteins with contradictory functions: pro-inflammatory ANG-2 and anti-inflammatory ANG-1-7.^{3,26} ACE2 also supplements the binding of SARS-CoV-2 to the epithelial cells, and TMPRSS2 completes this process, facilitating viral entry into host cells.^{27,28}

A recent study utilised previously generated gene microarray data to compare the expression of ACE2 and TMPRSS2 mRNA levels in CF and non-CF airway epithelial cells.^{29,30} In CF cells, ACE2 mRNA levels were higher, while TMPRSS2 levels were decreased. Although a higher ACE2 concentration would enhance the binding of SARS-CoV-2 to host cells, it would also enhance the cleavage rate of ANG-2 to anti-inflammatory ANG-1-7, resulting in milder severity of SARS-CoV-2 infection in people with CF. Furthermore, lower TMPRSS2 levels could contribute to the lower infection prevalence in people with CF, as viral entry to the host cells would be hindered.³

Multiple other CF-associated cellular dysregulations, such as increased autophagy⁷ and lower levels of IL-6 in the airways of people with CF, might improve their response to SARS-CoV-2. Specifically, IL-6 is one of the main cytokines involved in the cytokine storm induced by SARS-CoV-2 and has been associated with worse clinical outcomes. Therefore, lower levels of IL-6 may reduce COVID-19 infection severity.³¹

Further studies are needed to determine whether ACE2, TMPRSS2, and IL-6 levels can be used as clinically useful biomarkers for infection severity or drug targets for COVID-19.

Cystic Fibrosis Drugs and Severe Acute Respiratory Syndrome Coronavirus 2

The drugs commonly prescribed to people with CF might mitigate the severity of COVID-19 and, indeed, some have been repurposed and are currently in clinical trials to determine their effectiveness against the disease.^{32,33}

Corticosteroids

Low-dose corticosteroids are often prescribed as adjuvant treatment for patients with CF who have not responded to maintenance treatment with oral azithromycin.³⁴ Corticosteroids, normally secreted by the adrenal cortex, are shown to be effective in severe COVID-19.³²

They are not directly antiviral but downregulate pro-inflammatory genes such as *NFκB* and thus dampen immune and inflammatory response.³⁵

In the randomised clinical trial RECOVERY, 6 mg dexamethasone was administered once daily for up to 10 days to >2,000 hospitalised patients with COVID-19. Patients on respiratory support had a reduced 28-day mortality, as well as the need for mechanical ventilation and hospitalisation compared to the usual care group.³⁶ Other studies also support the protective effect of low-dose or pulsed corticosteroid administration in severe COVID-19,^{37,38} which is reflected by the recommendation of corticosteroid treatment (including dexamethasone, methylprednisolone,³⁹ prednisolone, and hydrocortisone) for severe COVID-19 by the World Health Organization (WHO), European Medicines Agency (EMA), National Institutes of Health (NIH), Italian Medicines Agency (AIFA), and Infectious Diseases Society of America (IDSA).³²

Nevertheless, one systematic review suggested that time for viral clearance, from 8–24 days (standard care group) to 10–29 days (corticosteroid group), infection rate, and antibiotic use are increased with corticosteroid administration. This did not, however, impact length of hospitalisation or mortality.⁴⁰ In contrast, a separate systematic review concluded that corticosteroid treatment was associated with a lengthier hospitalisation. Nonetheless, the corticosteroids were administered to more unwell patients.³⁵ Finally, a literature review highlighted that corticosteroids did not improve outcomes in patients with milder COVID-19 infection severity.³⁸

Thus, since patients with CF seem to have a milder form of COVID-19, corticosteroids might not offer them any further benefit, as they seem to work best in severe COVID-19 infection.

Dornase Alfa

The abnormally thick mucus and reduced mucociliary clearance in CF can cause bacteria and noxious particles to get trapped in the airways, leading to infections and chronic inflammation. Neutrophils invade the airways, degranulate and undergo cellular lysis, releasing their DNA, thickening the mucus further, and forming traps for particles and bacteria: the neutrophil extracellular traps (NETs). Dornase

alfa, a human recombinant DNase I enzyme used in CF, breaks down NETs, reducing mucus viscosity and improving lung function.⁴¹

Elevated neutrophil count and NET are also a feature of COVID-19 and a marker for severe respiratory disease. In one study, Dornase alfa (additional to usual care) was administered to three patients with COVID-19, with clinical benefit. This was indicated by the patients' improved oxygen saturation and respiratory rate, as well as reduced coughing, dyspnoea, NET formation, and viral load. Dornase alfa was also shown to lower neutrophil and cytokine levels in blood samples of patients with COVID-19 *in vitro*, reduce sepsis markers in a septic mouse model *in vivo*⁴² and even have antiviral properties *in vitro* in four cell lines infected by SARS-CoV-2.⁴³

Due to the similarities of COVID-19 and CF in neutrophil, cytokine, and NET production, promising preclinical findings, and encouraging case series,⁴⁴ there is a clinical trial investigating aerosolised intratracheal Dornase alfa as a treatment for SARS-CoV-2-induced ARDS.³³ Therefore, Dornase alfa, which is regularly administered in CF,³⁴ could mitigate COVID-19 severity in these patients.

Azithromycin

Azithromycin, a macrolide antibiotic, is commonly prescribed in CF as antibacterial prophylaxis.³⁴ Macrolides inhibit bacterial protein synthesis, neutrophil activation and chemotaxis, and reduce the expression of cell-surface adhesion molecules and pro-inflammatory cytokines. They also increase macrophage activity in the lung alveoli and thus modulate the immune system and inflammatory response.³²

Additionally, azithromycin has anti-inflammatory and potentially antiviral properties, particularly against respiratory syncytial, influenza, Zika, and Ebola viruses.^{3,45} Its antiviral mechanism is possibly associated with interferon pathways and reduced airway mucus. Alternative hypotheses include prevention of SARS-CoV-2 cellular entry by inhibiting the binding of the COVID-19 spike proteins to ACE2⁴⁵ or inhibition of the autophagy process by increasing the pH of key organelles such as endosomes and lysosomes.³

The use of azithromycin as a COVID-19 treatment is controversial.⁴⁶ Two French observational

clinical studies tested the combination of azithromycin and hydroxychloroquine in patients with COVID-19 and one observational Brazilian clinical study in unconfirmed, symptomatic patients with COVID-19. These studies found that patients treated with the two drugs were rapidly discharged, had significantly more negative nasopharyngeal swabs, and reduced hospitalisations.⁴⁵ Therefore, azithromycin treatment in people with CF may be associated with an improved response against SARS-CoV-2.

Conversely, a prospective study recruited 11 hospitalised patients with severe COVID-19 to evaluate azithromycin and hydroxychloroquine treatment. No clinical benefit of the aforementioned combination was found; one patient died, two required ICU transfer, and one experienced QT interval prolongation within 5 days of treatment. Overall, 8/10 patients were still positive for SARS-CoV-2 on Days 5-6 post-treatment.⁴⁷ Similarly, a retrospective study evaluated 807 patients hospitalised with COVID-19. Hydroxychloroquine monotherapy or combined with azithromycin did not decrease the risk of death or ventilation and was associated with prolonged hospital admissions.⁴⁸

Furthermore, azithromycin has been associated with cardiac complications, particularly QTc prolongation.^{32,49} A study retrospectively reviewed 81 patients treated with hydroxychloroquine and azithromycin and found that 7/81 (8.6%) had QTc prolongation (≥ 500 ms), with no patients developing ventricular tachycardia.⁵⁰

Therefore, the AIFA, EMA, U.S. Food and Drug Administration (FDA), and WHO do not recommend azithromycin or macrolide antibiotics for the treatment of COVID-19 without an underlying bacterial infection.³²

Cystic Fibrosis Transmembrane Conductance Regulators

CFTR is critical for bronchodilation and effective mucociliary clearance. In its absence, as in CF, a highly viscous mucus is produced, which triggers an inflammatory response. CFTR modulators repair dysregulated CF cellular processes, increasing airway fluid production, reducing oxidative stress and pro-inflammatory cytokines.⁷

The COVID-19 inflammatory response, particularly when TNF-mediated, reduces the presence of

the CFTR protein, primarily in the lungs and brain. This leads to dysregulation of the immune system and physiological changes similar to CF. Specifically, it leads to the activation of cytokines, neutrophils, and macrophages; impediment of mucus clearance and antigen destruction; and promotion of local inflammation and bronchial-wall thickening.

Therefore, due to the COVID-19 and CF pathophysiology overlap, there is a rationale for the mechanism of action of CFTR modulators in COVID-19,⁵¹ which could also explain the advantageous response of people with CF to COVID-19.

Severe Acute Respiratory Syndrome Coronavirus 2 and Cystic Fibrosis Cohort Characteristics

Finally, patients with CF might be responding better than expected to SARS-CoV-2 because of cohort characteristics, particularly age and habits. People with CF are younger, with the median age in Europe being 18.4 years and in the UK being 21 years,^{52,53} while COVID-19 severity worsens with increasing age.^{1,54} Furthermore, people with CF were instructed to 'shield' earlier in most countries than the general population and for a prolonged time, limiting their exposure to

SARS-CoV-2. Finally, people with CF have learned to live with a chronic deteriorating respiratory illness and may have better learned behaviours than the general population regarding personal hygiene and distancing, reducing their risk of infection.¹

CONCLUSION

The emerging trend is that people with CF have not had worse clinical outcomes nor a higher infection rate with COVID-19. Multiple hypotheses to explain this exist, including dysregulation of CF cellular processes, certain CF medications, and cohort characteristics of patients with CF. Thus, it would be prudent to collect and analyse up-to-date CF data and update UK guidelines, if appropriate. Other areas of interest for future research are whether Dornase alfa, CFTR modulators, or azithromycin mitigate SARS-CoV-2 infection severity. Additionally, the cellular interplay between CF and SARS-CoV-2 could be investigated further and used to determine an individual's susceptibility to the virus. Lastly, exploration of ACE2, TMPRSS2, and IL-6 can be undertaken to evaluate if the aforementioned proteins can exist as drug targets or clinically useful biomarkers to predict SARS-CoV-2 infection severity.

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Post-COVID-19 Pulmonary Fibrosis: Report of Two Cases

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Abstract

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 has led to a pandemic situation worldwide. However, remarkable progress has been made in evolving policies, strengthening healthcare efforts, and pharmacotherapy. As more patients are recovering from COVID-19, clearer concepts about possible short- and long-term complications are emerging. Respiratory failure is the most common morbidity in hospitalised patients, and post-COVID-19 pulmonary fibrosis is the most common respiratory complication after recovery. The authors report two cases of COVID-19 pneumonia with respiratory failure who were cured but developed pulmonary fibrosis with restrictive lung disease in the follow-up period.

INTRODUCTION

COVID-19 is defined as an illness caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 pneumonia has unique features and comprises co-occurrence of viral pneumonia and acute respiratory distress syndrome.¹ The authors describe the cases of two patients with COVID-19 pneumonia who were hospitalised with respiratory failure and subsequently developed pulmonary fibrosis. To the best of the authors' knowledge, this case report is the index publication from their country describing two cases of post-COVID-19 pulmonary fibrosis, in which a restrictive pattern was demonstrated on spirometry. The authors seek to draw the

attention of clinicians towards understanding the natural course of COVID-19 in patients and to identify and treat sequelae.

CASE REPORT

Case One

A non-smoking, 52-year-old male presented with cough on and off and myalgia associated with fever and dyspnoea for 5 days. Nasopharyngeal and throat swab sampling for real-time reverse transcription (RT)-PCR assay for the detection of SARS-CoV-2 was advised by a local practitioner, which was positive, and was referred to the authors' institution. On admission, the patient had a high fever. Clinical findings and vitals at the time of presentation are provided in [Table 1](#).

Table 1: Clinical and laboratory parameters of both cases.

	Case One	Case Two
Oxygen saturation in room air at time of presentation	91%	93%
Auscultatory findings	Fine crepitation in bilateral infra-scapular and infra-axillary lung fields	Fine crepitation in right scapular, bilateral infra-scapular, and infra-axillary lung fields
Inflammatory markers		
ESR (0–30 mm/hr)	65	52
CRP (0–5 mg/L)	195	131
Ferritin (22–322 ng/mL)	1,366	721
LDH (230–460 U/L)	1,903	1,408
D-dimer (<0.2 mg/L)	>20.00	2.79
Procalcitonin (<0.50 ng/mL)	0.15	0.05

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase.

All routine blood investigations and inflammatory markers were performed and repeated as per clinical requirements (Table 1). Bedside chest X-ray revealed peripheral haziness.

The patient was started on moist O₂ along with intravenous injection of 6 mg dexamethasone, twice daily subcutaneous injection of 60 mg enoxaparin, and injection of 200 mg remdesivir on the initial day, followed by 100 mg administered intravenously for 5 days. On Day 12, his oxygen saturation (SpO₂) dropped to 85% on 15 L/min supplied via a non-rebreathing mask. Consequently, he was started on non-invasive ventilation using a mechanical ventilator with 100% fraction of inspired oxygen. The patient was also treated with intravenous injection of 1 mg/kg body weight methylprednisolone in two divided doses. Intravenous injection of 8 mg/kg body weight tocilizumab was administered on Day 14, as per institutional protocol. He was on non-invasive ventilation intermittently until Day 21, followed by a gradual decrease in fraction of inspired oxygen, and was later changed to non-rebreathing mask support. CT pulmonary

angiography with high-resolution CT (HRCT) thorax on Day 25 revealed multiple confluent areas of consolidation and ground-glass opacities (GGO) with posterobasal predominance and peribronchial distribution. Traction bronchiectasis with no evidence of pulmonary embolism was also visible (Figure 1A). His O₂ requirement gradually reduced. Repeat nasopharyngeal and throat swab testing by RT-PCR assay for SARS-CoV-2 was performed after 3 weeks and was negative. A screening HRCT thorax after 6 weeks of admission showed multiple patchy areas of perilobular and subpleural consolidation and GGOs with interstitial thickening and fibrotic changes, including traction bronchiectasis and subpleural bands (Figure 1B). Spirometry using the EasyOne® spirometer (NDD Medizintechnik AG, Zurich, Switzerland) was performed after 6 weeks of onset of illness, revealing moderate restriction. He was discharged on long-term oxygen therapy, a course of oral steroids (prednisolone 10 mg once daily) and antifibrotics (pirfenidone 600 mg three times daily), and called for review at a future date.

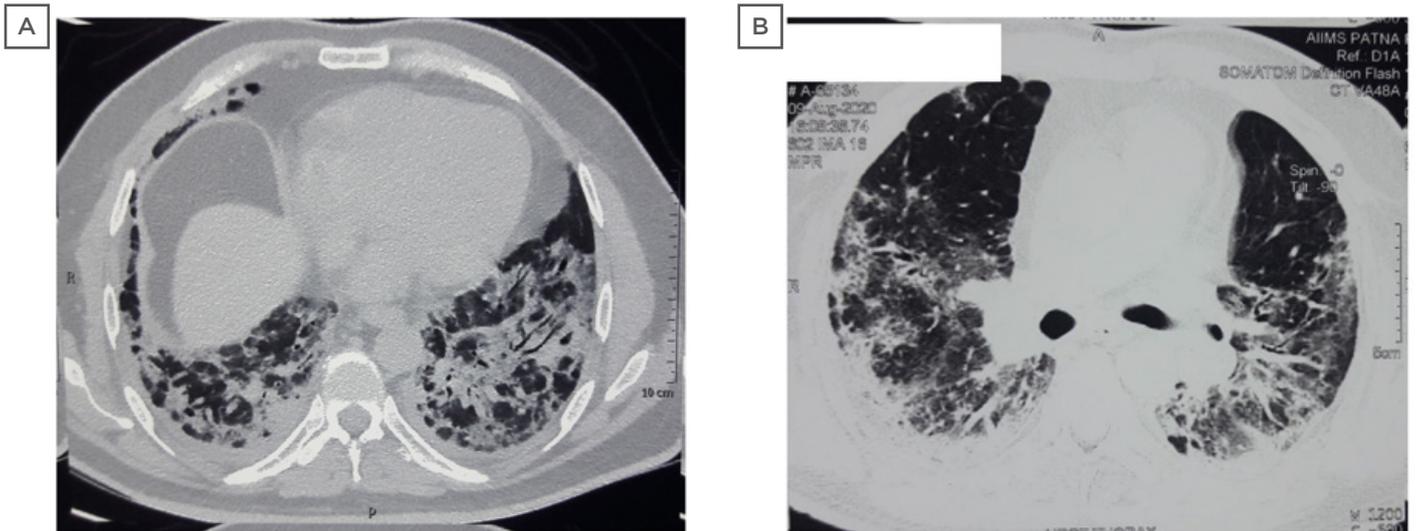


Figure 1: Pre- and post-COVID-19 high-resolution CT images: Case One.

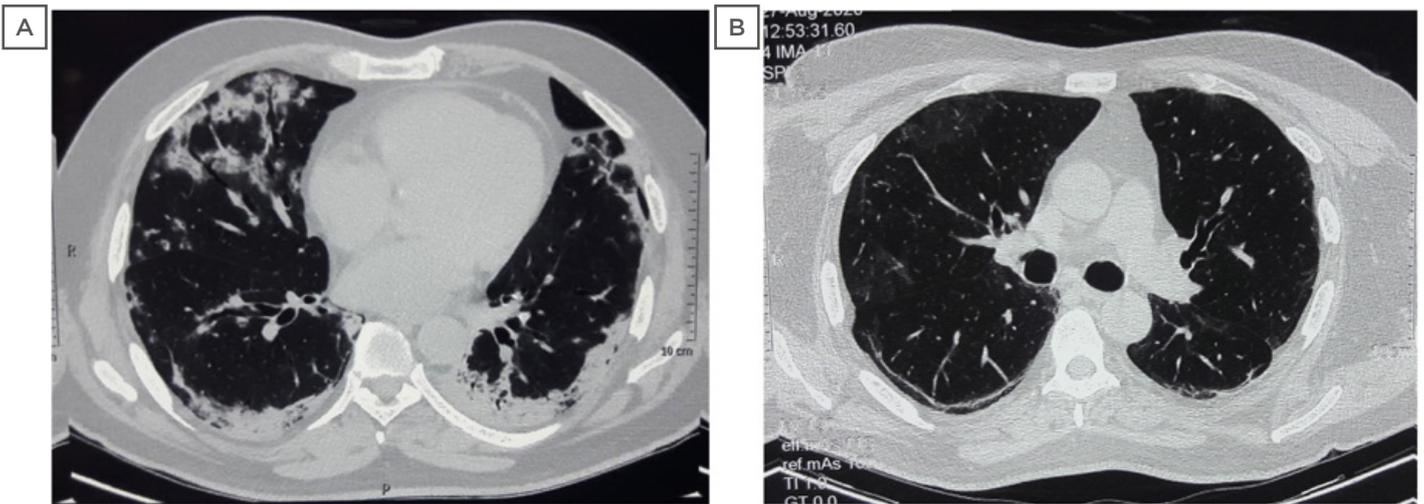


Figure 2: Pre- and post-COVID-19 high-resolution CT images: Case Two.

Case Two

A 57-year-old male with no history of smoking and a history of hypertension on telmisartan presented with cough on and off for 7 days and fever for 1 day. A RT-PCR assay of SARS-CoV-2 was performed, which was positive, and was referred to the authors' institution. On admission, clinical examination and vitals were recorded as shown in [Table 1](#).

The patient was started on dexamethasone and enoxaparin injections. After 3 days of admission, his room-air SpO₂ fell to 89% and moist O₂ was

given at 5 L/min by venturi mask. Injection of remdesivir was administered for 5 days. After 7 days of admission, his room-air SpO₂ was 84% and O₂ at 12 L/min was delivered using a non-rebreathing mask. Injection of dexamethasone was stopped after 10 days. After 14 days of admission, his room-air SpO₂ improved to 90%, followed by 94% after 21 days. CT pulmonary angiography with HRCT thorax was performed on Day 21, which showed areas of consolidation and GGOs predominantly in the posterobasal lobes with subpleural sparing, areas of bronchiectasis and bronchiolectasis, and minimal areas of early honeycombing in the basal areas. There was no

evidence of pulmonary embolism (Figure 2A). Repeat nasopharyngeal and throat swab testing by RT-PCR assay for SARS-CoV-2 was negative.

The patient was discharged on Day 28 of admission, with a room-air SpO₂ of 96% and on oral steroids (prednisolone 10 mg once daily) and antifibrotics (pirfenidone 600 mg tablets three times daily). He was reviewed in the outpatient department, 3 weeks after discharge, and a repeat HRCT thorax (Figure 2B) and spirometry was done, which showed mild restriction. His treatment was continued and he was called for review at a future date.

DISCUSSION

Coronaviruses are a group of related RNA viruses that cause diseases in mammals and birds. In humans, they cause respiratory tract infections that can range from mild to lethal. Lethal varieties can cause SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and COVID-19.

Presentations of COVID-19 are categorised as asymptomatic, mild-to-moderate (81.0%), severe (14.0%), critically ill (5.0%), and fatal (overall 2.3%).²

Fibrotic abnormalities of the lung have been detected after 3 weeks of onset of symptoms in mild, moderate, and severe disease.³ Restriction, reduced diffusion capacity, and small airways obstruction have been identified at discharge and 2 weeks later.³ The impairments are mainly restrictive in nature, with a predominance of abnormalities in diffusing capacity of the lungs for carbon monoxide, vital capacity, and total lung capacity, compared to forced expiratory volume in 1 second.⁵ Lung function abnormalities are more common among elderly patients and patients with severe COVID-19 and high levels of inflammatory markers. These individuals show evidence of pulmonary fibrosis, such as interstitial thickening, coarse reticular patterns, and parenchymal bands.⁴ A meta-analysis by Ahmed et al.⁵ showed that in SARS-CoV and MERS-CoV (coronavirus outbreaks similar to the current COVID-19 pandemic), although lung function improves over time, reduction in diffusing capacity of the lungs for carbon monoxide may still be present in 11–45% of survivors at 12 months.

Under normal circumstances, the wound healing response is downregulated after injury is repaired. Infection with SARS-CoV in mouse models and humans causes severe damage to epithelial cells lining the airways. When the infectious burden overwhelms the system, the wound healing response can become dysregulated, resulting in scarring and fibrosis.⁶ Epidermal growth factor receptor (EGFR) signalling is one of the key regulators of the wound healing process. Studies of SARS-CoV in mouse models have shown that EGFR ligands are expressed at the onset of wound healing (Day 2 post-infection) and return to baseline after the resolution of injury (Day 9 post-infection), coinciding with the expression of wound healing genes at Day 2 and downregulation of these genes by Day 9. In mouse models with constitutively active EGFR, SARS-CoV infection causes enhanced lung disease and the EGFR ligands amphiregulin and heparin-binding EGF-like growth factor are upregulated. Exogenous addition of these ligands during infection leads to enhanced lung disease and altered wound healing dynamics. Dysregulation in the initial activation or the eventual downregulation of this pathway disrupts the wound healing process, resulting in unchecked fibrosis.⁷ The combined effect of the virus-induced cell injury and inflammatory mediators may be responsible for the lung damage that occurs in COVID-19.⁸

Predictors of pulmonary fibrosis are advanced age, illness severity, length of intensive care unit (ICU) stay and mechanical ventilation, smoking, and chronic alcohol use.⁹ Older people are more likely to have severe symptoms and be more susceptible to both SARS-CoV-2 and its complication of lung fibrosis.¹⁰ Experimental studies using mouse models have reported increased lung fibrosis in older animals compared to younger ones.¹¹ Additionally, there is an increased resistance of fibroblasts and myofibroblasts to apoptosis in older mouse models.¹² Illness severity is correlated with inflammatory markers, including lactate dehydrogenase (LDH) levels following acute lung injuries, and is also an indicator of pulmonary tissue destruction.¹³ Concomitantly, the extent of lung injury and inflammatory response correlates with the extent of fibroblastic response.^{14,15} A high LDH level was found to significantly correlate with the risk of pulmonary fibrosis following MERS-CoV infection.¹⁶ One follow-up study at

6 months in patients with SARS-CoV showed a significant relationship between elevated levels of LDH during acute illness and an increased risk of developing pulmonary fibrosis.¹³ Higher disease severity is closely related to the prolonged length of ICU stay and mechanical ventilation, and leads to possible ventilator-induced lung injury. In ventilator-induced lung injury, there occurs a release of pro-inflammatory modulators, worsening acute lung injury, and increased mortality or pulmonary fibrosis in survivors.¹⁷ Smoking is associated with chronic oxidative stress, increased expression of inflammatory cytokines, and interstitial lung fibrosis, with the risk continuing even after cessation.^{18,19} Smokers are more likely to have severe symptoms, need ICU admission and mechanical ventilation, or die compared to non-smokers.²⁰ Chronic alcohol use is a predisposing factor for severe respiratory infections and acute respiratory distress syndrome.^{21,22} Chronic alcohol use causes glutathione depletion, chronic oxidative stress, inflammation, and induction of TGF- β in the lungs, thereby increasing the risk of acute lung injury and pulmonary fibrosis.²² TGF- β is a potent fibroproliferative cytokine.

Tocilizumab appears to be an effective treatment option in patients with COVID-19 and a risk of cytokine storms.²³ Pirfenidone could inhibit apoptosis, downregulate expression of angiotensin-converting enzyme 2 receptors, decrease inflammation by several mechanisms, and ameliorate oxidative stress, thus protecting pneumocytes and other cells from COVID-19 invasion and cytokine storm simultaneously.²⁴

Both patients with COVID-19 pneumonia had high inflammatory markers and progressed to respiratory failure, with Case One needing non-invasive ventilation, and Case Two needing

supplemental O₂ with pharmacotherapy. Repeat RT-PCR became negative, signifying viral clearance and resolution of COVID-19. Signs of resolution in CT thorax begin approximately 2 weeks after the onset of initial symptoms.²⁵ Pulmonary fibrosis develops in most patients with SARS-CoV-2 after 5 weeks.²⁶ In the present cases, screening with HRCT thorax showed radiological signs of fibrosis and spirometry as well as a finding of restriction after 6 weeks, leading to the hypothesis of post-COVID-19 pulmonary fibrosis. Optimal time for follow-up imaging to assess for radiological clearance is, as yet, unknown.²⁷

Post-COVID-19 pulmonary fibrosis is a predictable and serious complication of COVID-19 pneumonia that requires early recognition and comprehensive management. Future research should attempt to address the issues of prevalence and significance of post-COVID-19 pulmonary fibrosis.

LIMITATIONS

Clinical investigations were performed in a public sector institution and therefore, under government regulations during the pandemic period, investigations beyond spirometry and CT chest were prohibited for patients. The 6-minute walk distance test could not be performed; however, it is part of a future original research article in patients with post-COVID-19 fibrosis. Although follow-up was until 6 weeks, fibrosis was evident by the radiographic findings on repeat CT scan and restrictive findings on spirometry, after repeat RT-PCR testing was negative for SARS-CoV-2, suggesting viral clearance. Although a longer follow-up would be advantageous, the authors believe that the short-term follow-up findings would be a beneficial addition to the relevant literature on post-COVID-19 fibrosis.

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Pulmonary Embolism in Vaccine-Induced Thrombotic Thrombocytopenia: Under-Reported?

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Abstract

Vaccine-induced thrombotic thrombocytopenia (VITT) is a rare, newly described syndrome characterised by thrombocytopenia and thrombosis 5–24 days after administration of an adenoviral vector-based COVID-19 vaccine. It resembles heparin-induced thrombocytopenia and, therefore, diagnostics and treatment are similar. Early recognition is essential to avoid potentially fatal outcomes. This article describes a case of VITT with symptomatic cerebral venous-sinus thrombosis and splanchnic vein thrombosis, as well as asymptomatic pulmonary embolism in a 49-year-old male. The authors discuss VITT, focusing on the possibility of pulmonary embolism being under-reported, diagnostic criteria, differential diagnosis, and treatment.

INTRODUCTION

Vaccination is currently the most powerful tool for controlling the COVID-19 pandemic.¹ In large randomised controlled trials, the approved vaccines have shown good efficacy and safety.² However, there is increasing concern about the safety of the adenovirus-based COVID-19 vaccines of AstraZeneca (ChAdOx1 nCoV-19) and Janssen (Ad26.COV2.S). This concern is based on multiple reports of thrombocytopenia in combination with thrombosis at unusual sites (mainly cerebral venous sinus thrombosis [CVST] and splanchnic vein thrombosis [SVT]) 5–24 days after administration of the adenovirus-based COVID-19 vaccine. Many of these cases were fatal.^{3,4} This article describes a case of a 49-year-old male with this rare, so-called vaccine-induced

immune thrombotic thrombocytopenia (VITT), with both symptomatic CVST and SVT and asymptomatic pulmonary embolism (PE), 1 week after receiving the ChAdOx1 nCoV-19 vaccine, with a favourable outcome after treatment. Further, the authors discuss the possibility of under-reporting of PE in VITT.

CASE PRESENTATION

Initial Presentation

A 49-year-old white male, with a history of fibromyalgia and nephrolithiasis, presented at the emergency department with fever, vomiting, and abdominal pain radiating to the back. Seven days earlier, he had received his first dose of the ChAdOx1 nCoV-19 vaccine. The day after

vaccination, he experienced low-grade fever, myalgia, and fatigue for 48 hours. On Day 6 after vaccination, vague pressing lower abdominal pain and vomiting occurred during the night but symptoms had disappeared by the next morning. However, in the evening, abdominal pain recurred and became gradually worse. There were no other complaints. No other family members were ill. He did not take any medications. There were no predisposing factors for thrombosis.

On examination, his temperature was 37.5 °C, blood pressure was 165/95 mmHg, pulse 70 beats/min, respiratory rate 13 breaths/min, and oxygen saturation was 98% while the patient was breathing ambient air. He appeared unwell and sweaty, but there was no abdominal tenderness nor other remarkable findings. His weight was 80 kg.

Laboratory results are shown in **Table 1**. C-reactive protein (CRP) was very high and platelet count was 46,000 cells/mm³. Severe acute respiratory syndrome coronavirus 2 reverse-transcriptase PCR assay of a nasopharyngeal swab was negative. Urine sediment examination showed no haematuria or pyuria.

An additional CT scan with intravenous contrast of the abdomen was performed, which did not show any abnormalities.

The patient was admitted to the ward and was given broad-spectrum antibiotics, intravenous fluids, and painkillers. Despite the low platelet count, there was no immediate suspicion for VITT.

Inpatient Stay

On Day 1 after admission, there were no new complaints, but the abdominal pain was still

Table 1: Blood results.

Laboratory analysis	Day 0	Day 2	Day 4	Day 6	Day 9	Reference value
Haemoglobin (g/dL)	14.9	15.1	13.0	12.9	13.8	13.5-16.9
Platelet count (x10 ³ /µL)	46,000	21,000	44,000	117,000	268,000	166-308
Leukocytes (x10 ³ /µL)	7,570	4,890	11,690	8,570	7,860	3,450-9,760
Activated partial thromboplastin time (sec)	37.3	44.6	34.0	N/A	N/A	29.0-38.1
International normalised ratio	1.19	1.27	1.35	N/A	N/A	<1.20
Fibrinogen (mg/dL)	N/A	3.01	1.20	N/A	N/A	2.00-4.00
D-dimer (µg/mL)	N/A	>4.00	>4.00	N/A	N/A	<0.50
AST (U/L)	31	54	82	82	49	<40
ALT (U/L)	29	41	101	132	116	<41
GGT (U/L)	52	65	54	100	110	40-129
LDH (U/L)	365	331	278	266	250	<250
CRP (mg/L)	184.0	131.0	29.2	12.6	7.8	<5.0
cTnT (ng/L)	N/A	N/A	197	284	106	<14

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; cTnT; cardiac troponin T; GGT: γ-glutamyltransferase; LDH: lactate dehydrogenase.

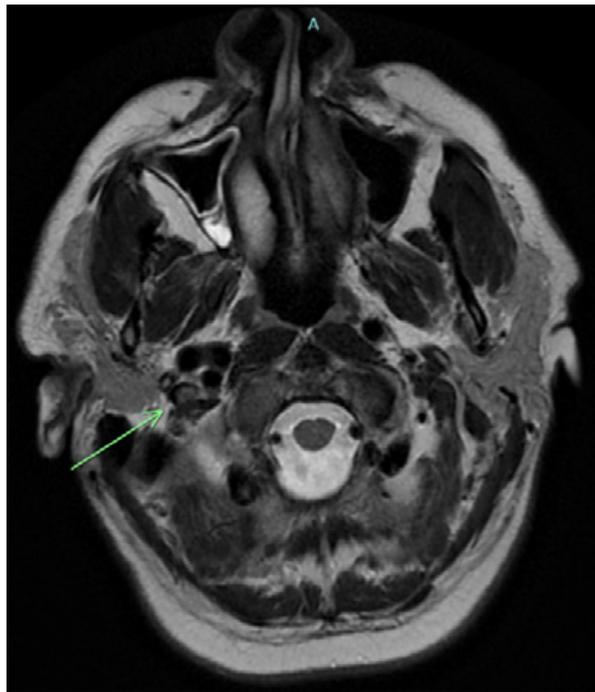


Figure 1: MRI T2-weighted imaging showing a thrombus in the right internal jugular vein.

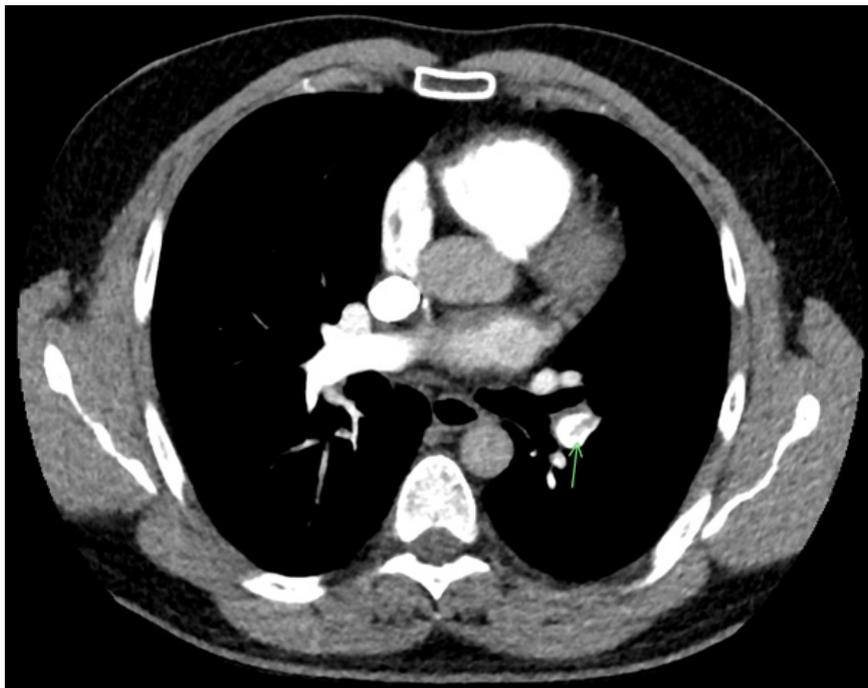


Figure 2: CT pulmonary angiography showing pulmonary embolism in the left lower segmental pulmonary artery.

present. The platelet count had dropped further to 30,000 cells/mm³, while CRP diminished. There was a slight elevation of the aminotransferases. The coagulation parameters became impaired, with an elevated international normalised ratio, a

prolonged activated partial thromboplastin time, and high D-dimer level. The diagnosis of VITT was suspected and the patient was started on a prophylactic dose (2.5 mg once daily) of the non-heparin anticoagulant fondaparinux.

DISCUSSION

On Day 2 after admission, the patient complained of mild frontal headache. The platelet count decreased to 21,000 cells/mm³. An urgent magnetic resonance scan of the brain showed a thrombosis of the right sinus transversus and right bulbus jugularis (Figure 1). The patient was transferred to the intensive care unit for further observation and treatment with intravenous Ig (IVIg) at a dose of 1 g/kg bodyweight for 2 days, methylprednisolone at a dose of 1 mg/kg bodyweight for 5 days, and fondaparinux at therapeutic dose (7.5 mg once daily).

On Day 3 after admission, mild abdominal pain and headache still existed. Platelet count stabilised, but coagulation abnormalities worsened, with decreased fibrinogen too. A new CT scan of the abdomen was performed, this time with intravenous contrast in the venous phase. It revealed thrombosis of the superior mesenteric vein as well as thrombosis of several intrahepatic veins, causative for the patient's abdominal pain and liver function abnormalities.

On Day 4 after admission, the patient was discharged from intensive care as symptoms diminished and platelet count started to rise. A transthoracic echocardiogram was performed because of an abnormal ECG (new T-wave inversion, inferolateral) taken on admission at the intensive care unit, with mildly elevated troponins. The echocardiogram showed mild pulmonary hypertension, for which a subsequent CT pulmonary angiography was done on Day 6 after admission, which revealed PE in the left lower segmental pulmonary artery (Figure 2). There were no symptoms suggestive for PE.

On Day 7 after admission, the anticoagulant was switched from fondaparinux to the direct oral anticoagulant rivaroxaban. Antibiotics were given for 5 days. On Day 9 after admission, symptoms disappeared completely, platelet count fully recovered, and the patient was discharged from the hospital with rivaroxaban therapy for 3 months.

There was no administration of heparin before or during hospitalisation. On Day 2 after admission, an ELISA for heparin-induced thrombocytopenia (HIT) was requested. The test turned out to be positive by Day 5 and, therefore, confirmed the authors' diagnosis of VITT.

VITT is a rare, newly described syndrome characterised by the development of antibodies that activate platelet factor 4 (PF4) via the crosslinking of the FcγRIIA receptor, with subsequent thrombosis and thrombocytopenia 5–24 days after the administration of an adenoviral vector-based COVID-19 vaccine.⁴ It resembles HIT, where antibody formation is induced by heparin exposure. The estimated incidence of VITT is approximately 1 in 150,000 for the ChAdOx1 nCoV-19 vaccine and approximately 1 in 470,000 for the Ad26.COV2.S vaccine, although the incidence rates vary by age group and sex.⁵ VITT is not seen in the mRNA-based COVID-19 vaccines, or other adenoviral vector-based vaccines for COVID-19 (e.g., the Sputnik V [Gam-COVID-Vac]) and Ebola (e.g., the Ad26.ZEBOV-GP, recombinant vaccine).^{6–9}

Rapid recognition to prevent a fatal outcome is important. Symptoms vary depending on the site of thrombosis. CVST is the most common site of thrombosis in VITT, followed by SVT (which includes mesenteric, portal, hepatic, and splenic veins) and PE.^{3,4,10} Therefore, the main presenting symptoms are headache, photophobia, abdominal pain, nausea and vomiting, and dyspnoea.¹¹ It is well known that patients often have more than one site of thrombosis, although the presence of thrombosis in three different sites, as in the described case, is rare. In two recent case series of 11 and 23 patients, only 2 (18%) and 1 (4.8%) had all three (CVST, SVT, and PE, respectively).¹²

In the authors' case, the patient had no symptoms of PE, and the diagnosis was only made in response to a routinely taken ECG showing repolarisation abnormalities. More cases of asymptomatic PE have been reported in VITT. For example, in a case series of 12 patients with VITT with CVST, 3 also had asymptomatic PE.¹³ Garnier et al.¹⁴ described a case of a 26-year-old female with VITT, with both symptomatic proximal left middle cerebral artery occlusion and asymptomatic SVT and PE after receiving the ChAdOx1 nCoV-19 vaccine. Moreover, the patient used as an index case in Greinacher et al.'s case series had peripheral PE without respiratory symptoms.¹⁵ Therefore, PE is likely to be under-reported in VITT. The clinical relevance of this

phenomenon is still unknown. In patients with proven VITT and thrombosis in other sites, there seem to be no direct therapeutic consequences, but follow-up may be different since PE can have long-term complications.

VITT should be suspected in patients developing signs or symptoms of thrombocytopenia or thrombosis during an appropriate time-frame following the COVID-19 vaccination. According to the American Society of Hematology (ASH), five criteria must be met to make a definitive diagnosis of VITT:

1. administration of a COVID-19 vaccine 4–42 days prior to symptom onset;
2. any venous or arterial thrombosis;
3. thrombocytopenia (platelet count $<150 \times 10^9/L$);
4. markedly elevated D-dimer (>4 times upper limit of normal); and
5. positive PF4 ELISA.¹⁶

Although a positive PF4 ELISA is necessary to confirm diagnosis, no single ELISA method detects all VITT cases. In a large prospective study, 2.7% of patients meeting all other diagnostic VITT criteria had a negative PF4 ELISA result. These cases were considered 'probable VITT' and received regular VITT therapy.¹⁷ A second ELISA should be considered if there is a strong clinical suspicion of VITT.¹⁸ Other types of PF4 antibody tests, such as the serotonin release assay or rapid HIT assays, are not reliable enough to exclude or confirm the diagnose of VITT.¹² To reduce the chance of false negative results, it is important to collect all blood samples for VITT testing before the administration of any treatment (especially IVIg).⁶

In patients with suspected VITT, alternative diagnoses should be considered too. **Table 2** provides a non-exhaustive list of differential diagnoses.^{6,17} VITT belongs to a spectrum of platelet-activating anti-PF4 disorders. This spectrum also includes HIT, in which the production of PF4 antibodies follows heparin exposure. A clinical history is usually sufficient to distinguish between VITT and HIT. An even rarer condition is spontaneous HIT, where there is no known preceding heparin exposure. VITT could be seen as a form of spontaneous HIT

triggered by vaccination. The combination of thrombocytopenia and thrombosis is also seen in haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, paroxysmal nocturnal haematuria, and haematologic malignancies.⁶ Moreover, a COVID-19 infection itself carries a high risk of thrombosis, often in combination with thrombocytopenia.¹⁹ Thrombocytopenia without thrombosis is seen in a lot of diseases. Vaccine-associated immune thrombocytopenic purpura is mainly seen after vaccination for measles, mumps, and rubella, but is also described after vaccination for COVID-19.^{20–23} A lot of infections can induce thrombocytopenia, but VITT cannot be ruled out based on the presence of highly elevated CRP. As in the authors' case, VITT is sometimes associated with high levels of CRP.^{1,24}

The treatment of VITT is similar to that of HIT and is based on high-dose IVIg and anticoagulation. The therapy should be initiated when there is high clinical suspicion for VITT (confirmed thrombosis and thrombocytopenia after recent vaccination) before the results of the anti-PF4 antibody testing is known. Urgent administration of IVIg in a dose of 1 mg/kg of ideal bodyweight for 2 days is recommended. Although there is no evidence, the use of heparin may be harmful and, therefore, non-heparin anticoagulants are preferred. The choice of anticoagulant is based on preferred route of administration, availability, duration of action (no long-acting anticoagulants when high bleeding risk or there is need for invasive procedures), availability of antidotes (especially with a high bleeding risk), price, and reimbursement criteria. Options are direct parenteral (argatroban, bivalirudin) or oral (dabigatran) thrombin inhibitors, direct oral anti-Xa inhibitors (edoxaban, apixaban, rivaroxaban), low-molecular-weight heparinoid devoid of heparin (danaparoid), and selective factor-Xa inhibitor (fondaparinux). The authors' patient was started on fondaparinux, but after confirmation of the diagnosis of PE, they could switch to rivaroxaban because it is reimbursed for this indication in Belgium. Both the British Society of Haematology (BSH) and ASH recommend continuing systemic anticoagulation for a minimum of 3 months in patients with documented thrombosis.⁶

Table 2: Differential diagnosis of vaccine-induced thrombotic thrombocytopenia.

Thrombosis	Thrombocytopenia
• COVID-19 infection	• Drug-/toxin-induced thrombocytopenia
• Hereditary thrombophilia	• Thrombocytopenia reactive to an acute medical condition (sepsis, viral infection, etc.)
• Acquired thrombophilia	• ITP, inclusive post-vaccine ITP
• Antiphospholipid syndrome	• Hypersplenism, e.g., secondary to portal hypertension in liver cirrhosis
• Chronic DIC	• Vitamin deficiencies
• Idiopathic with possible risk factors, such as malignancy, smoking, female gender, oestrogen therapy or pregnancy, immobilisation	
Thrombosis and thrombocytopenia	
• COVID-19 infection	
• HIT	
• TTP	
• HUS and aHUS	
• PNH	
• Malignant haematologic disorders	

aHUS: atypical haemolytic uraemic syndrome; DIC: disseminated intravascular coagulation; HIT: heparin-induced thrombocytopenia; HUS: haemolytic uraemic syndrome; ITP: immune thrombocytopenic purpura; PNH: paroxysmal nocturnal haematuria; TTP: thrombotic thrombocytopenic purpura.

The described patient was also given corticosteroids, which is not recommended in the current guidelines. Platelet transfusions should be avoided as they can worsen thrombus formation. They should be only considered when there is life-threatening bleeding.^{5,6} Further, close monitoring and supportive therapy (painkillers when there is pain, oxygen when there is hypoxia, antiemetics when vomiting, thrombectomy in exceptional circumstances, etc.) are indicated. Finally, adenoviral vector-based COVID-19 vaccines should be avoided in patients with confirmed VITT, but mRNA-based COVID-19 vaccines are considered safe as they are not associated with VITT.⁶ The ideal interval between the diagnosis of VITT and administration of an mRNA-based COVID-19 vaccine is not known.⁵

CONCLUSION

VITT is a rare but potentially fatal complication of adenoviral vector-based COVID-19 vaccines. CVST is the most common site of thrombosis in VITT, followed by SVT and PE. The authors reported a case of VITT in a 49-year-old male, with both symptomatic CVST and SVT and also asymptomatic PE. Based on existing literature, asymptomatic PE is not uncommon in VITT. Therefore, PE seems to be under-reported in VITT. The clinical relevance of this phenomenon is yet undetermined, but clinical awareness is needed. The authors suggest performing a CT scan of the chest with pulmonary angiography in every patient with a proven VITT to rule out PE.

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Massive Alveolar Haemorrhage Presenting During the COVID-19 Pandemic

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Abstract

The coronavirus disease (COVID-19) pandemic has challenged healthcare systems and has resulted in complex diagnostic processes for patients with non-COVID-19 pathology. Here, we demonstrate a case of massive alveolar haemorrhage secondary to antineutrophil cytoplasmic antibody-positive vasculitis, presented to a district general hospital in the UK during the first wave of the global pandemic. This case highlights some of the difficulties clinicians may face when diagnosing life-threatening antineutrophil cytoplasmic antibody-positive vasculitis amidst the COVID-19 pandemic. The authors place emphasis on the careful interpretation of chemical biomarkers such as troponin and D-dimer when assessing patients with acute respiratory distress. They also aim to highlight the importance of CT thorax imaging when seeking an alternate diagnosis to COVID-19.

BACKGROUND

The coronavirus disease (COVID-19) pandemic has challenged healthcare systems and has resulted in complex diagnostic processes for patients with non-COVID-19 pathologies. Recent data have shown that elevated troponins in patients with COVID-19 are related to cardiac injury and poor prognosis.^{1,2} However, it is not clear whether these biological markers are secondary to the respiratory distress associated with COVID-19 or to the primary acute cardiac disease.³

The authors demonstrate a case of massive alveolar haemorrhage secondary to antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis, which presented to a district general hospital during the COVID-19 pandemic. The patient was treated successfully with plasma exchange and immunosuppressive therapy after exclusion of COVID-19. The case highlights the difficulty in diagnosing and treating patients with non-COVID-19 pathology during the pandemic, with emphasis on radiological imaging.

CASE PRESENTATION

A 61-year-old male presented with acute dyspnoea, cough, and haemoptysis. The patient had a history of Type 2 diabetes mellitus with retinopathy, hypertension, previous deep vein thrombosis, and hypercholesterolaemia. He was no longer taking anticoagulants. He also reported haematuria 2 weeks prior to admission.

An initial chest radiograph raised concern of possible COVID-19, showing centrally diffuse bilateral ground-glass opacifications. Admission biochemistry revealed: haemoglobin 70 g/L; eosinophils $0.36 \times 10^9/L$; troponin 2,385 ng/L; D-dimer 0.65 ug/mL; and erythrocyte sedimentation rate of 45 mm/hour. An ECG was suggestive of left ventricular hypertrophy and dynamic ST segment changes in V1-V3. He was transfused two units of packed red cells and proceeded to a CT scan of the thorax. This confirmed central opacification and bilateral ground-glass shadowing in the lungs without evidence of pulmonary embolus (Figure 1A). The report suggested the possibility of COVID-19 or vasculitis as a differential; therefore, the patient remained in respiratory isolation until two COVID-19 nasopharyngeal swabs were negative and further biochemical testing was performed.

Vasculitis screening soon confirmed ANCA positivity ($>1/320$) with positive

myeloperoxidase levels (>8.0 apolipoprotein). The patient was urgently reviewed by the rheumatology team and started on induction immunosuppressive therapy: cyclophosphamide with pulsed methylprednisolone. Thereafter, the patient continued a maintenance dose of prednisolone at 60 mg daily. One week following cyclophosphamide, the patient experienced increasing episodes of chest pain associated with dyspnoea, tachycardia, and fever. He was treated with empirical antibiotics for suspected hospital-acquired pneumonia and transferred back to the respiratory isolation ward, while COVID-19 infection was further excluded.

He was transfusion dependent to maintain a haemoglobin level of >70 g/L and continued to experience large-volume haemoptysis with persisting hypoxia. His renal function deteriorated with a 30% rise in creatinine (163 mmol/L). Repeat ECG showed further ischaemic changes in V1-V3. His case was discussed with the cardiology department who advised on further cardiac imaging and management of a Type 2 myocardial infarction secondary to ongoing pulmonary haemorrhage.

Cardiac MRI revealed severe left ventricular impairment without late gadolinium enhancement. Repeat CT thorax demonstrated new areas of ground-glass density and consolidation, consistent with progressive alveolar haemorrhage (Figure 1B).

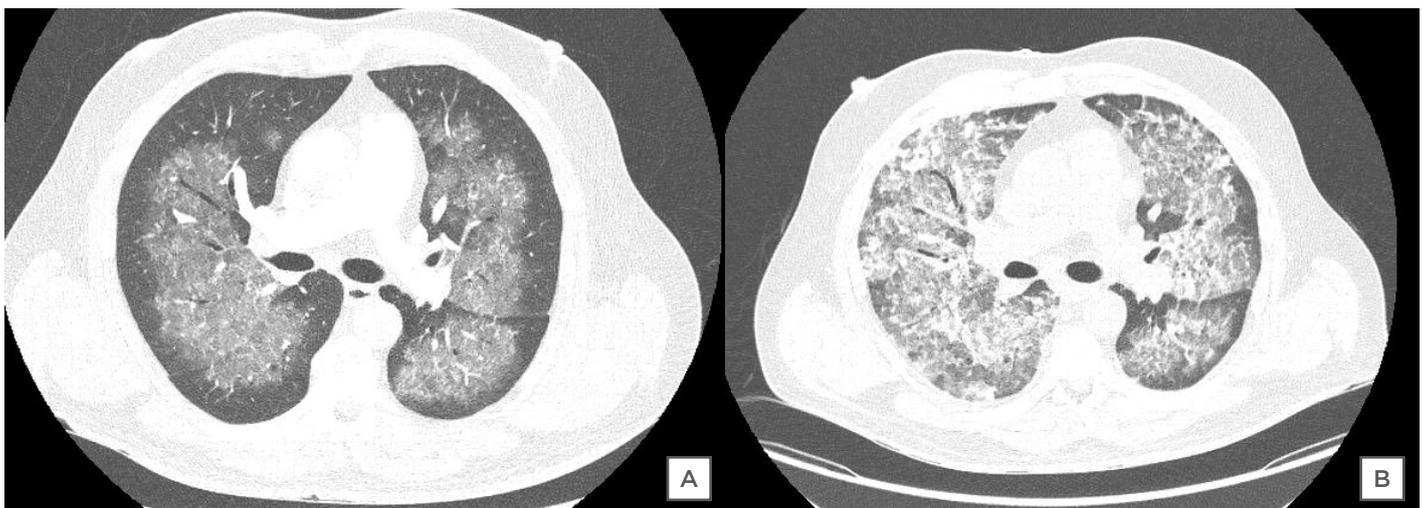


Figure 1: A) CT thorax image confirming central opacification and ground-glass shadowing in the lungs bilaterally; **B)** comparative CT thorax image at Day 24 confirming new areas of ground-glass density and consolidation consistent with progressive alveolar haemorrhage.

Following further discussion with the rheumatologists, the patient was transferred to the high dependency unit for seven cycles of plasma exchange. The patient clinically improved throughout his plasma exchange without further need for blood transfusion or oxygen therapy. He denied any further episodes of chest pain and was successfully discharged after 39 days in the hospital.

Outcome and Follow-up

The patient subsequently received invasive angiography for non-ST-elevation myocardial infarction. The left anterior descending artery had severe, mid-vessel disease, which was successfully stented during his induction therapy. A follow-up chest radiograph confirmed resolution of the initial pulmonary haemorrhage. After discussion with the cardiology, rheumatology, and respiratory medicine departments, the patient remains on dual antiplatelet therapy. He awaits a decision regarding coronary artery bypass grafting following completion of his sixth cycle of cyclophosphamide infusions.

DISCUSSION

The authors have demonstrated a case of massive pulmonary haemorrhage secondary to ANCA-positive vasculitis that presented to a district general hospital during the COVID-19 pandemic. The clinical picture was typical of vasculitis given the patient's history of haematuria, haemoptysis, and associated hypoxaemia. However, initial diagnosis was challenging for two reasons: firstly, there were diagnostic algorithms implemented in response to the global pandemic to ensure appropriate levels of patient safety; secondly, the prodromal overlap and patient characteristics between ANCA-positive vasculitis and COVID-19 further complicated the diagnosis.^{4,5}

ANCA-positive vasculitides are the most common small-vessel vasculitides and include microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg–Strauss Syndrome), and granulomatosis with polyangiitis (Wegener's granulomatosis). They are frequently missed or delayed in their diagnosis due to their nonspecific symptoms. Clinicians may further attribute specific disease symptoms to more prevalent conditions such as viral pneumonia

and asthma.^{6–8} The most commonly reported prodromal symptoms of ANCA-positive vasculitides and COVID-19 were dyspnoea, fever, and cough.^{4,9} In one study, the median delay from initial symptom onset to a diagnosis of ANCA-positive vasculitis (or relapse) was significantly longer during the pandemic than previous cohorts.⁴ A key distinguishing feature between ANCA-positive vasculitis and COVID-19 infection is the presence of haemoptysis. The literature suggests that haemoptysis is uncommon in COVID-19 and has a symptom prevalence of 2%.^{10,11} Therefore, the presence of haemoptysis is likely to indicate an alternate respiratory pathology rather than COVID-19 infection.

Although ANCA-positive vasculitis remains a rare cause for haemoptysis in the UK, both granulomatosis with polyangiitis and microscopic polyangiitis can present with large-volume haemoptysis because of the associated alveolar haemorrhage.^{12,13} It is essential that clinicians consider these vasculitides in their differential diagnosis due to an untreated mortality of almost 90% at 2 years.¹⁴ The triad of haemoptysis, acute hypoxic respiratory failure, and diffuse lung infiltrates should further point towards the possibility of diffuse alveolar haemorrhage. This is a life-threatening manifestation of ANCA-positive vasculitis and requires prompt induction immunosuppressive therapy. However, there is substantial debate as to whether treatment with plasma exchange leads to better patient outcomes.^{15,16}

Early bronchoalveolar lavage (BAL) is the diagnostic test needed to confirm diffuse alveolar haemorrhage.¹⁷ It is also needed to exclude both infection (i.e., pneumocystis) and malignancy from the differential. The sequential rise in red blood cells or haemosiderin-laden macrophages on repeat BAL is considered a diagnostic marker. However, BAL was not performed in this case for several reasons. Firstly, the patient's clinical deterioration meant that it was not safe to perform bronchoscopy. Secondly, the procedure is highly aerosol-generating, and current guidance suggests it should only be performed in the most necessary of cases to minimise the potential risk of COVID-19 transmission.¹⁸ Thirdly, BAL has limited value in determining the specific aetiology of diffuse alveolar haemorrhage. The clinical presentation, positive biochemistry results, and multidisciplinary team approach

within this case provided consensus that the radiological imaging represented diffuse alveolar haemorrhage rather than COVID-19 or any other pathology.

Individuals with myeloperoxidase ANCA-positive vasculitis have a mean age of 59 years at diagnosis (± 17.6 years standard deviation) and a slight male predominance.¹⁹ From the hospital's COVID-19 database (April 2020), the mean age of patients testing positive for the virus was 68 years and almost two-thirds were male ($n=63/105$).²⁰ Moreover, COVID-19 and ANCA-positive vasculitis patients have similar pre-existing comorbidities; hypertension, diabetes, cardiovascular disease, and obesity are frequently reported comorbidities associated with COVID-19-related death.^{1,2,9} Similarly, there is a significantly increased risk of cardiovascular mortality in patients with myeloperoxidase ANCA-positive vasculitis.²¹ This is in part due to disease activity as well as some of the side effects caused by immunosuppressive therapy. It is proposed that risk factors for cardiovascular disease are monitored closely and that medications for hypertension, diabetes, and hypercholesterolaemia are optimised in ANCA-positive patients.^{21,22}

The pandemic has placed great importance on triaging patients with symptoms of acute respiratory distress syndrome and isolating them in dedicated wards while awaiting nasopharyngeal test results. The use of reverse-transcriptase (RT)-PCR for nucleic acid detection of COVID-19 is currently considered to be the gold-standard diagnostic test. However, RT-PCR testing is not without its shortcomings; one study suggested that up to 54% of patients may produce an initial false-negative test for COVID-19 infection with RT-PCR.²³ If there is strong clinical suspicion for COVID-19, the patient should undergo repeat nasopharyngeal RT-PCR testing and remain in respiratory isolation due to the risks associated with false-negative results.²⁴ Therefore, the patient received two nasopharyngeal RT-PCR tests and remained in respiratory isolation until further biochemical and radiological information was available.

The pandemic has also placed emphasis on the early evaluation of poor prognostic markers in suspected patients with COVID-19 using cardiac biomarkers and D-dimer.¹⁻³ High D-dimer

results are shown to correlate with disease severity and mortality in COVID-19.²⁵ However, these biomarkers are nonspecific and have an unknown role in the management of COVID-19. The use of D-dimer also raises considerable questions relating to coagulopathy and venous-thromboembolic disease in COVID-19. Expert guidance advises against the use of D-dimer in the diagnostic evaluation for venous-thromboembolic disease of suspected patients with COVID-19.²⁶ It is pertinent to remember that these positive biomarkers may relate to other serious disease processes such as acute myocardial infarction, pulmonary embolism, and diffuse alveolar haemorrhage.

The chest radiograph findings in diffuse alveolar haemorrhage and COVID-19 are nonspecific and require further characterisation with CT thorax. The classic cross-sectional imaging findings in COVID-19 and diffuse alveolar haemorrhage include ground-glass opacities (GGO) with or without consolidation.^{9,27} However, it is the pattern of disease that helps clinicians differentiate between the two diagnoses. The GGO and consolidation seen in ANCA-associated diffuse alveolar haemorrhage are usually widespread and bilateral with a perihilar predominance. Typically, the mid and lower zones of the lung are affected, with subpleural and apical sparing.^{28,29} Dense consolidation typically represents complete filling of the alveoli with acute blood.³⁰ This leads to interlobular septal thickening with GGO creating a 'crazy-paving' pattern. These changes may resolve within 10-14 days or progress to interstitial fibrosis with repeated haemorrhage.^{12,13,27,30} The repeat CT imaging (**Figure 1B**) in this case clearly demonstrates consolidation of varying density, which suggests repeated and progressive alveolar haemorrhage.

When assessing CT imaging of the chest in COVID-19 it is not just the pattern of GGO and consolidation that differs but its temporal relationship with symptom onset. CT thorax in the presymptomatic and early disease phase (0-2 days) may be normal. Therefore, CT imaging is not a reliable standalone investigation to exclude early COVID-19.³¹ Most patients with COVID-19 will typically develop bilateral, multilobar lung involvement with a diffuse, peripheral and subpleural distribution. These radiological changes are predominately GGO during the first

week of COVID-19 presentation and progress to mixed GGO with dense consolidation in a reverse halo sign over the next 2 weeks.³² Patients with COVID-19 further develop a fibrotic picture with reticulation and irregular interlobular septal thickening. However, it is currently unknown whether this is fully reversible. The distinction between the pattern of the two diseases combined with the patient's negative RT-PCR test was fundamental in seeking an alternate diagnosis to COVID-19.

CONCLUSION

This case demonstrates the added complexity of diagnosing rarer causes of diffuse alveolar haemorrhage during the global pandemic. Haemoptysis is an uncommon symptom in

COVID-19 and should prompt clinicians to consider other diagnoses for acute respiratory distress. CT thorax imaging was fundamental in seeking an alternate diagnosis to COVID-19. The authors hope this case report highlights the difference in patterns of GGO and consolidation between COVID-19 and pulmonary manifestations of ANCA-positive vasculitis. Although the use of plasma exchange in ANCA-positive vasculitis is debatable, the authors feel that the repeat imaging supported a diagnosis of possible induction treatment failure and expedited the need for plasma exchange. This case also highlights the pertinence of cautious interpretation of biochemistry results, particularly with reference to troponin and D-dimer in the context of acute respiratory distress.

Patient consent for publication: Obtained.

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Stroke in a Patient with Recurrent Meningeal Tuberculosis and HIV Coinfection

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Abstract

Recurrent tuberculous meningitis can have a non-specific clinical presentation when it presents as a co-infection with HIV and can resemble other causes of subacute and chronic meningitis, leading to unwanted outcomes; for this reason, timely diagnoses are required. The most widely used microbiological diagnostic methods can be of low sensitivity or have delayed results.

The aim of this article is to present a clinical case of recurrent tuberculous meningitis with a clinical presentation of stroke due to a basal cistern ischaemic lesion in a patient co-infected with HIV, who had a microbiological confirmation and a drug sensitivity study with phenotypic and molecular tests.

INTRODUCTION

The World Health Organization (WHO) has reported that an estimated 10.0 million people (range: 8.9–11.0 million) became ill with tuberculosis (TB) in 2019. There were an estimated 1.2 million TB deaths (range: 1.1–1.3 million) among people who were HIV-negative in 2019 and an additional 208,000 deaths (range: 177,000–242,000) among people who were HIV-positive.¹ This group of patients have a high risk of developing TB that is directly related to the degree of immunosuppression. The spread of TB that leads to extrapulmonary TB may be present in 66% of cases, with TB in the central nervous system being the most serious type.^{1–3} In particular, meningeal TB can result in significant sequelae and is the cause of death in 30–50% of patients co-infected with HIV.³

It has been observed that patients who have high or normal CD4 counts have manifestations that are typical of tuberculous meningitis (MTB), whereas those patients with low CD4 cell counts tend to have subtle and non-specific clinical manifestations. Specifically, these patients exhibit presentations with later onsets and present with severe forms of the disease, such as cerebrovascular accidents (CVA) that can be haemorrhagic or ischaemic.^{4–6} Likewise, it has been described that the majority of cerebral infarcts that are associated with MTB are multiple, bilateral, symmetrical, and are located in the basal ganglia, the anterior thalamus, or the forelimb or knee areas of the internal capsule.^{7,8}

TB is the major cause of recurrent meningitis (40–60%).⁹ According to the current criteria, recurrent meningitis is defined as that type which appears within 3–4 weeks after the end

of treatment or when a second episode occurs due to a different micro-organism after complete remission.¹⁰ Recurrent meningitis is more common in patients with immunosuppression, chronic renal failure, cystic fibrosis, head trauma, congenital malformations, and TB.^{11,12} Neuropathic manifestations are due to inflammatory deposits that are generated in the cerebrospinal fluid (CSF), which are located around the brainstem, cranial nerves, and the temporal and frontal lobes.^{10,13}

The diagnosis of MTB is based on the findings of clinical examinations, imaging, and laboratory studies. CSF studies include Ziehl-Neelsen (ZN) staining, cultures for *Mycobacterium tuberculosis*, and molecular biology tests.¹⁴⁻¹⁶

Herein, the authors present a clinical case of recurrent MTB, with a clinical presentation of stroke due to infarction in the basal cisterns in a patient co-infected with HIV. The patient had a microbiological confirmation and a drug sensitivity study with phenotypic and molecular tests.

CASE REPORT

A 40-year-old male patient, with a history of HIV infection in the AIDS phase, was receiving treatment with bicitgravir, emtricitabine, tenofovir disoproxil, and cobicistat. Upon admission, he complained of a global progressive headache, decreased visual acuity, and 3-week retrograde partial amnesia. He presented with allopsychic disorientation, visual and auditory hallucinations, and decreased co-ordination when standing and moving. His case evolved with an increase in the severity of his symptoms.

On the date of the consultation, he presented with a continuous fever; in addition, he presented with tonic-clonic movements. He also presented with weight loss, losing 10 kg in a 3-month period (18% of his weight). At the time of physical examination: tachypnoea (respiratory rate: 55 breaths/min), tachycardia (heart rate: 110 beats/min), fever (temperature: 38 °C), and normal blood pressure were found, with sulfur dioxide at 95% under oxygen by the tracheostomy tent. His weight was 44 kg (BMI: 15.2 kg/m²), which classified him as having Grade III malnutrition. He presented with drowsiness (with a Glasgow coma score of 8/15), cranial

nerve involvement (mydriasis and limitation in external eye movement in the right eye), stiff neck, hemiparesis, hypotonia and hypoesthesia in the right hemibody, and continuous tonic movements initiated in the right upper extremity with secondary generalisation were found.

Twelve months prior to his admission, a diagnosis of bacterial meningitis was made, due to the clinical and cytochemical characteristics of the CSF, although the isolation of the causative agent was not achieved. Two weeks prior to the current admission, he had a second case of meningitis, where *M. tuberculosis* was isolated as the aetiological agent.

Laboratory studies upon admission showed normal blood counts, serum electrolytes, coagulation, and for liver and kidney tests. The serology results for hepatitis B virus and *Treponema pallidum* were negative. The study of orotracheal secretions did not show positivity in the cultures for aerobes and anaerobes, and the ZN stain was negative. The viral load for HIV during the hospital stay was <40 copies/mL, and the CD4 count was 314/mm³. A clear CSF was obtained with a cytochemical analysis that was compatible with hypoglycorrhachia (45 g/dL with glycaemia at 92 g/dL), protein values of 95 mg/dL and pleocytosis (polymorphonuclear: 64%; lymphocytes: 36%), and adenosine deaminase (ADA) at 9 IU/L, with negative KOH, India ink, and ZN stains (Table 1). Serological tests for Herpes I and II, as well as for John Cunningham virus, were negative. PCR results for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* were negative in the CSF. The initial chest radiograph was normal. In both simple and contrasted brain CTs, communicating hydrocephalus was found, with discrete transependymal CSF resorption. A left basal ganglion atrophic injury was observed, as well as sequelae indicative of a vascular event. Secular images were bilaterally observed in the thalamus, without enhancement. Due to a suspicion of fungal invasion in the digestive tract, endoscopy of the upper digestive tract was performed, where changes that were suggestive of oesophageal candidiasis were observed.

Table 1: Laboratory results of the clinical case.

CSF at admission
Clear appearance
Glucose: 45 g/dL (glycaemia: 92 g/dL)
Proteins: 95 mg/dL
Cells: 150 / μ L
64% PMN
Lymphocytes: 36%
ADA: 9 IU/L (reference: <7 IU/L)
KOH,* India ink, and Ziehl-Neelsen stains were negative
PCR for <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , and <i>Neisseria meningitidis</i> were negative
Second CSF
Clear appearance
Glucose: 38 g/dL (glycaemia: 88 g/dL)
Cells: 315 / μ L
Proteins: 851 mg/dL
PMN: 66%
Lymphocytes: 34%
ADA: 17 IU/L (reference: <7 IU/L)
KOH, India ink, and Ziehl-Neelsen results stains were negative
Positive CSF culture for <i>Mycobacterium tuberculosis</i> ; negative for other micro-organisms

*Direct examination with KOH for fungal structures.

ADA: adenosine deaminase; CSF: cerebrospinal fluid; KOH: potassium hydroxide; PMN: polymorphonuclear leukocytes.

The patient was managed with supplemental oxygen via a tracheostomy tent in combination with isonatremic intravenous fluids, nutritional support, phenytoin (125 mg/8 hours), fluconazole (200 mg/day), levetiracetam (500 mg/8 hours), and acyclovir (500 mg/8 hours).

Eleven days after admission to the intensive care unit, the patient presented with greater respiratory and neurological deterioration; thus, mechanical ventilation was required. The control chest radiograph showed an image of pulmonary consolidation in the paracardiac area, with basal interstitial infiltrates in the right lung region. Finally, treatment with cefepime (2 g/8 hours, intravenously) was indicated.

Three days later, the patient showed neurological, respiratory, and haemodynamic deterioration. Maintenance adjustments of metabolic, electrolyte, and mechanical ventilation parameters were performed. Brain MRI scans revealed an intense left basal ganglia lacunar infarction in the simple sequence (Figure 1A); for the post-contrast measurement, the meningeal enhancement in the peritoneal cisterns was compatible with meningitis, predominantly in the cisternae of the base, which was suggestive of a TB origin (Figure 1B). Based on a previous report, CVA was considered secondary to MTB.

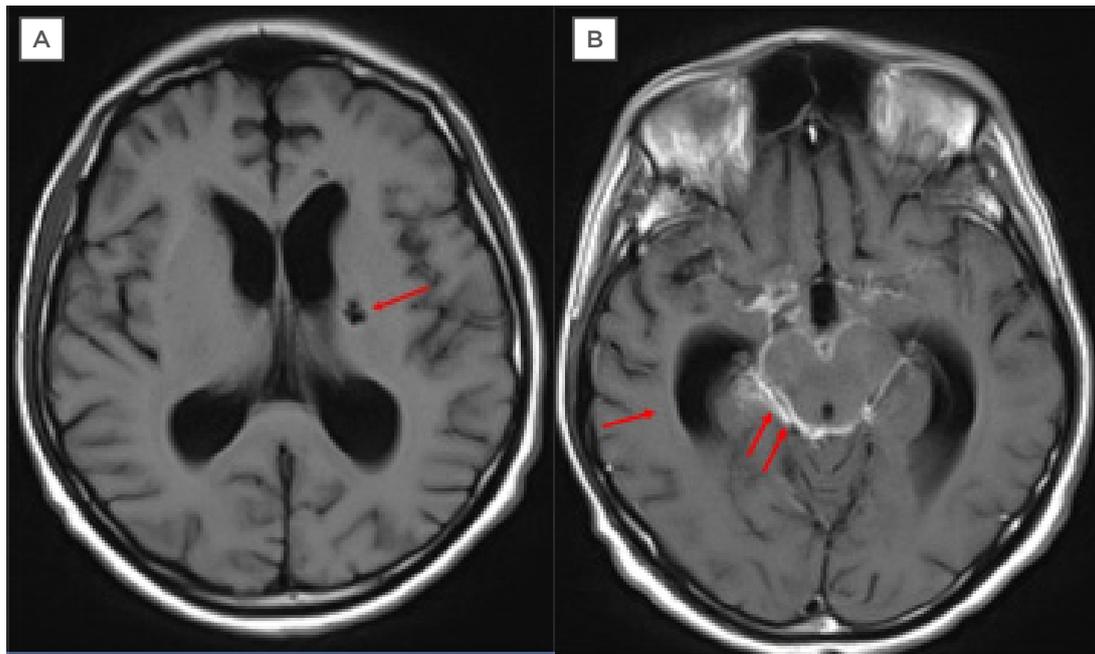


Figure 1: In meningeal tuberculosis, exudates in the basal cisterns may not be detected in simple T1 sequences. Contrast increases the signal that is usually observed in these cisterns, as occurred in this case.

A) Axial T1 sequence. Left ganglionic infarction (arrow). **B)** Post-gadolinium T1 sequence axial section. Dilatation of the ventricular system by communication hydrocephalus (arrow). High signal of the perimesencephalic cisterns, suprasellar due to meningeal enhancement (double arrow).

A second CSF study showed an increase in the protein and ADA levels, negative ZN (Table 1), and endpoint PCR results for the insertion fragment 6110 positive for *M. tuberculosis*. Two weeks later, mycobacteria in the first CSF sample were grown by using an Ogawa Kudoh culture medium.

Management with dexamethasone (16 mg/12 hours) and a fixed-dose anti-tuberculous therapy combined with rifampicin (450 mg/day), isoniazid (225 mg/day), pyrazinamide (1,200 mg/day), and ethambutol (825 mg/day) were initiated. The patient evolved towards instability without a response to new metabolic, respiratory, and therapeutic adjustments. After 33 days of his stay in the intensive care unit, he died.

DISCUSSION

The patient in the reported clinical case had risk factors for developing extrapulmonary TB, which included HIV infection, a CD4 T lymphocyte count $<200/\text{mm}^3$, and a state of severe malnutrition. The insidious clinical manifestations and microbiological characteristics of

M. tuberculosis may have contributed to the late confirmatory diagnosis of the disease. In this patient, an initial request for a ZN stain was made, but it was negative because this test requires a minimum number of bacteria to be detected, and patients with HIV infections are usually paucibacillary (the presence of <10 bacteria in the sample). Manifestations, including the predominance of cranial nerve involvement, compromising of the state of consciousness (with alterations in the development of thought), and deficits in muscular strength suggested a complicated neuroinfection.

Patients with HIV may have a miscellaneous chance of harbouring micro-organisms that may cause infectious meningitis. The patient described in this report presented with previous episodes of meningitis due to *M. tuberculosis*, which was attributed to the dissemination of pulmonary TB by reactivation. The CSF showed lymphocytic pleocytosis with increased protein and decreased glucose levels (which may be present in meningitis due to viruses), gram-positive and gram-negative micro-organisms, and mycobacteria. Molecular tests were negative

in the different biological samples except for *M. tuberculosis*.

Within the diagnostic standards of TB is the determination of clinical, radiological, and epidemiological criteria, as well as a tuberculin skin test and a direct sputum examination, which detects only 50–80% of TB cases. Due to the increases in incident cases and TB resistance, detections with faster and less complex methods are necessary in diagnosing the disease.^{16,17} PCR is capable of demonstrating the presence of mycobacterial DNA fragments in the biological samples of patients with a clinical suspicion of TB, as well as in samples with a negative result to ZN stains or in culture, which is particularly useful in infections of paucibacillary patients.¹⁸

Studies have shown that the genetic diversity of *M. tuberculosis* can have important clinical consequences.¹⁹ Epidemiological studies have found that some genotypes of *M. tuberculosis* may be associated with extrapulmonary TB, such as polymorphisms in the mycobacterial gene *PCID* (phospholipase C) in strains of the Beijing genotype; however, this association has not occurred in all of the studied patients.⁷

There are studies that have linked radiological involvement with the mycobacterial genotype.¹⁹ Lung consolidation images have been observed more frequently in the Euro-American genotype.²⁰ Additionally, caverns and fibrosis have been more closely related to the East Asian/Beijing lineage.^{19,20} In this clinical case, a radiological

image of pulmonary consolidation and findings in neuroimaging studies of neurological dissemination were found, with these findings due to the presence of left basal ganglia lacunar infarctions and exudates in peribronchial cisterns, which can lead to complications and death. Despite the medical history of MTB, the patient was not treated empirically with antituberculosis drugs because initial laboratory studies did not confirm the presence of *M. tuberculosis*. Poor adherence to treatment, co-morbidity with HIV, and difficulty in early diagnosis may have influenced the outcome of the patient.

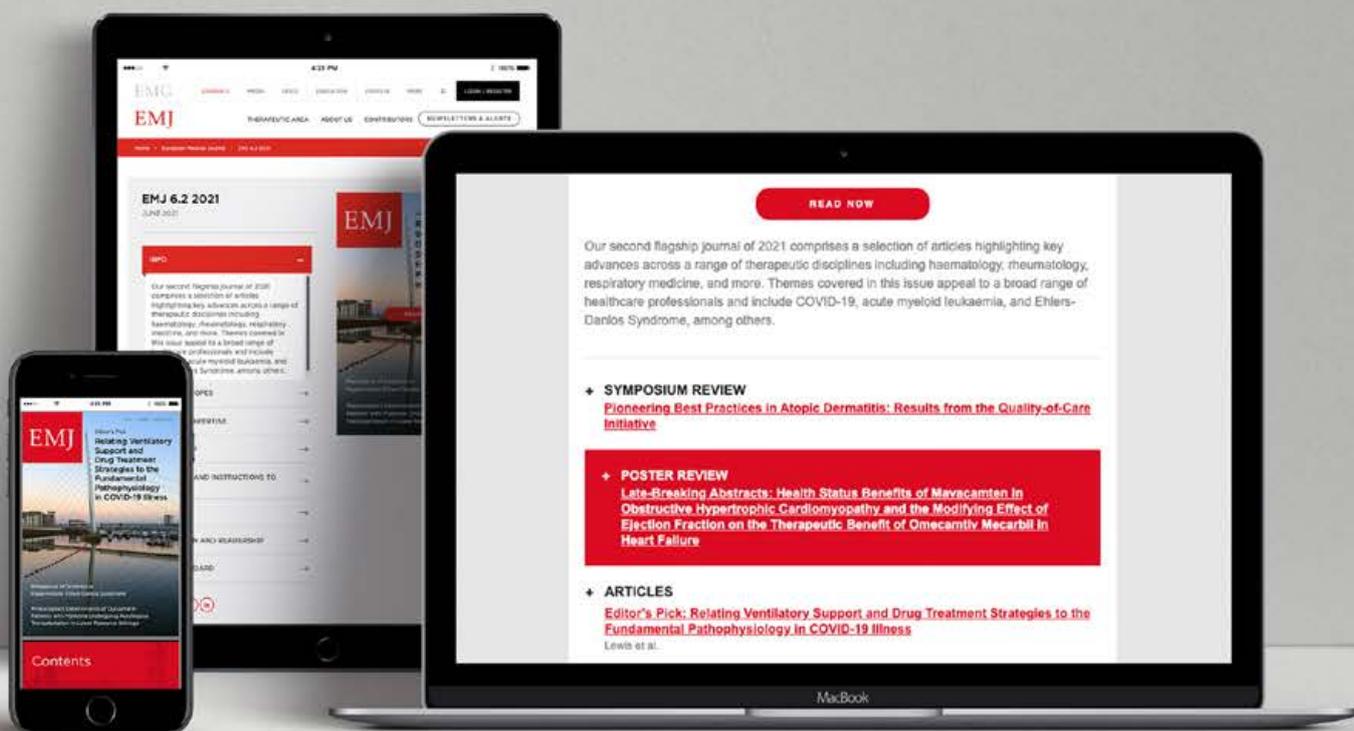
CONCLUSION

The patient in the clinical case had a history of HIV infection. The patient presented with three episodes of meningitis with a confirmed aetiological finding of *M. tuberculosis* on two occasions and CVA manifestations. The aetiological demonstration was potentially late, and support from the molecular biology tests helped to clarify the cause. MTB can occur in pathologies that are considered to be comorbid in TB, which includes HIV infection, thus becoming a risk factor for developing stroke. This condition can depend on viraemic conditions and CD4 counts for clinical characterisation and severity. In patients with high viral loads and low CD4 counts, an atypical clinical picture may present, which deviates the timely diagnosis of the disease and can lead to fatal outcomes or significant sequelae.

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