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Respiratory

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Review of

ATS International Conference 2023

Feature

Chronic Obstructive Pulmonary Disease at the 2023 ATS International Conference by David Mannino

Interviews

Debra Boyer, Michelle Gong, and Stacey Kassutto share their insights from the field

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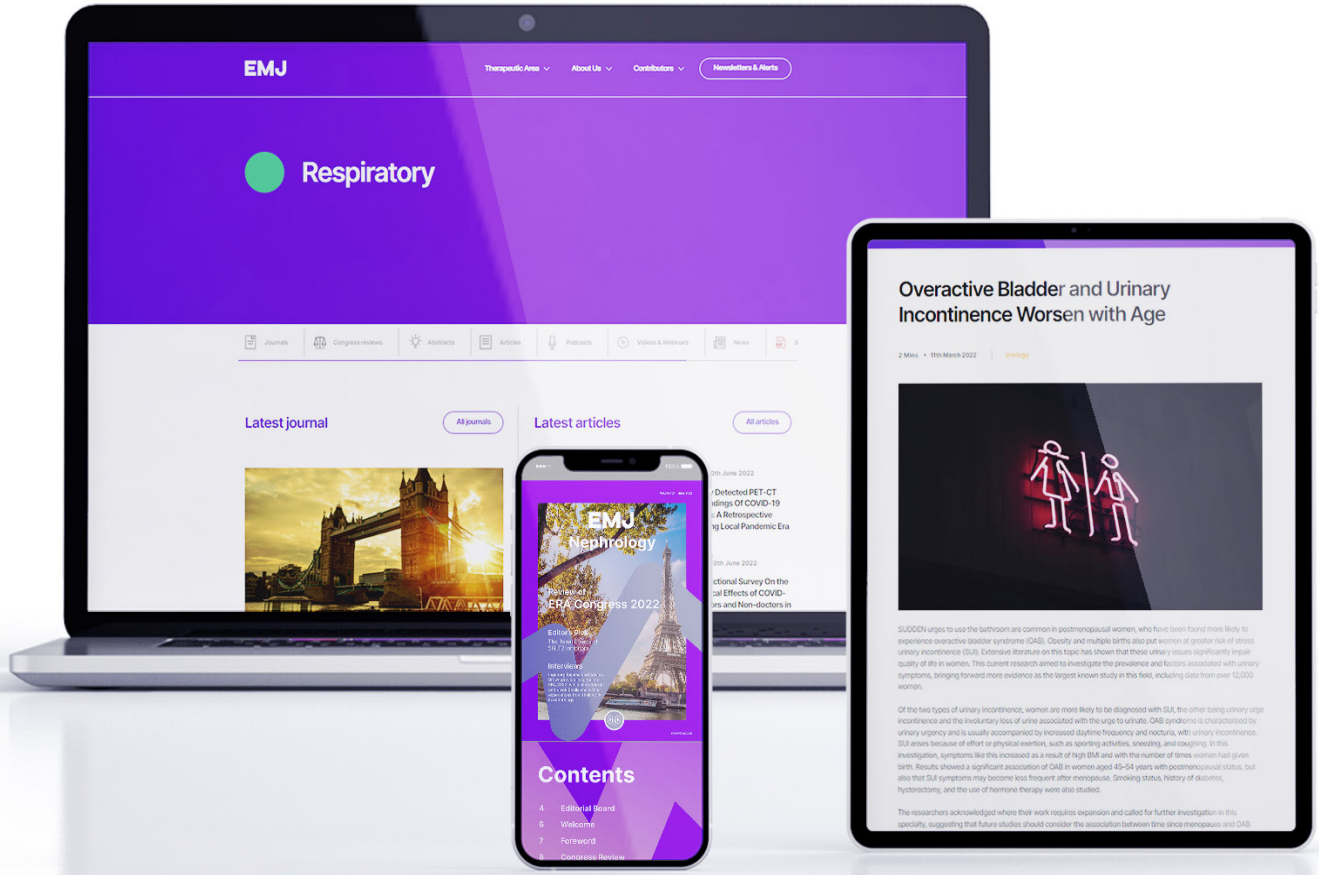

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Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to the first issue of our new American Journal focusing on respiratory medicine! We are excited to be launching this new publication, bringing you all of the latest updates from the American Thoracic Society (ATS) International Conference 2023, which this year took place in May, in Washington, D.C., USA.

Our team had the privilege of attending the ATS Conference, and we have handpicked key highlights and important findings presented there, with topics ranging from studies exploring the importance of location for asthma exacerbations in children, to the severity of obstructive sleep apnea in Black patients.

We are proud to be featuring interviews with key experts, Debra Moyer and Michelle Gong, who shared insights from the conference, and explored significant contemporary topics in the field. We also sat down with Stacey Kassuto, who dissected the role of technology and augmented reality in medical education.

Chronic obstructive pulmonary disease was among the central themes discussed at ATS. This topic was addressed in a feature by David Mannino, who delved into clinical trials, knowledge in disease progression, and advanced chronic obstructive pulmonary disease.

To bring you a taster of the research trends emerging from the conference, we are publishing selected abstracts that were presented at the congress, with topics ranging from heterogeneity of treatment effect in hospitalized veterans with COVID-19, to hypereosinophilic syndrome and bronchiectasis in pediatric patients, among others.

I would like to thank our newly-founded Editorial Board for their support and enthusiasm about this new publication. We welcome submissions of articles that span the scope of respiratory medicine, and we look forward to receiving articles from our American and global readers.

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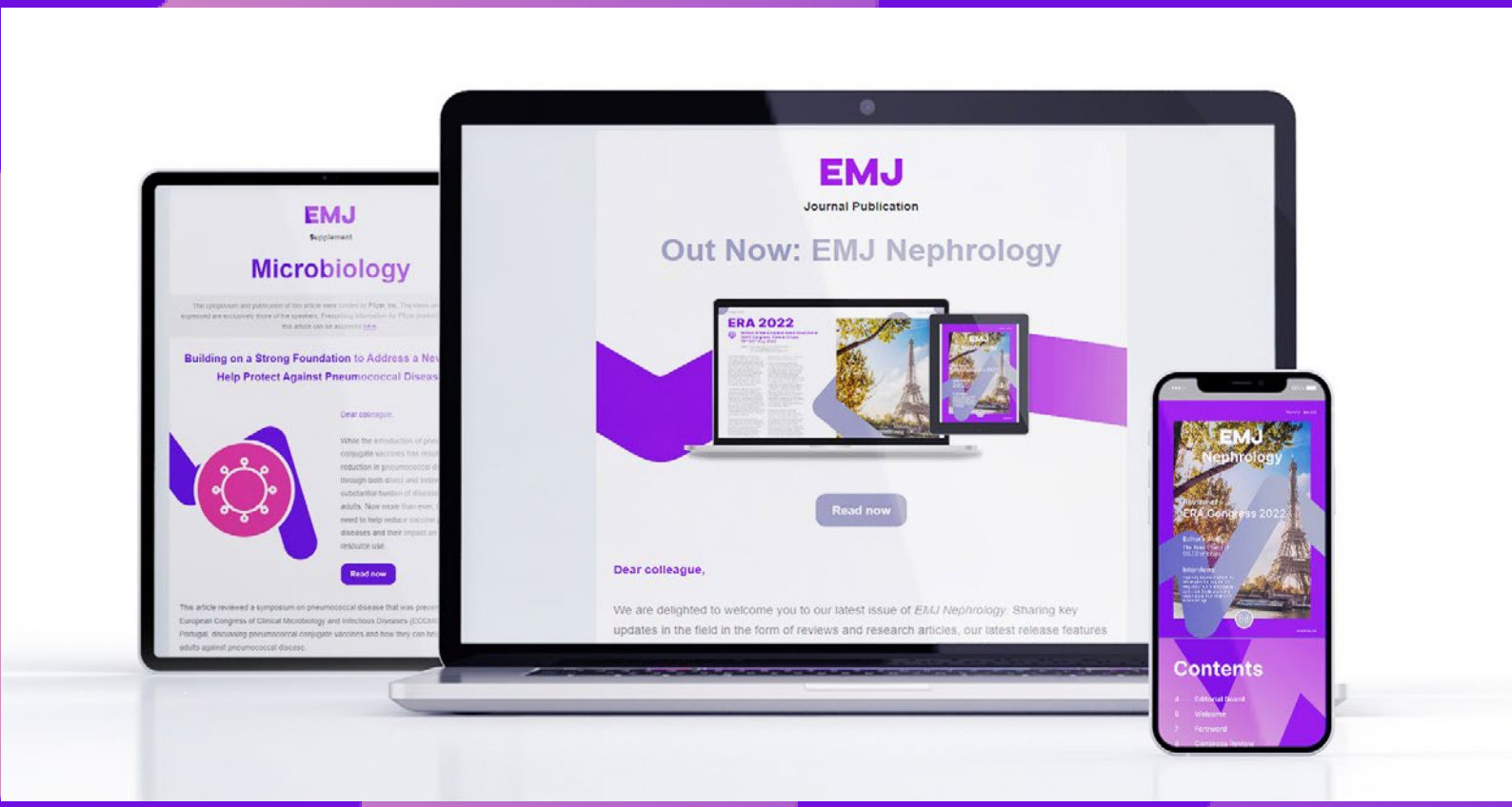

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Foreword

Dear Colleagues,

Welcome to the inaugural edition of *EMJ Respiratory The American Medical Journal*, an open access publication that covers the annual American Thoracic Society (ATS) International Conference, and provides highlights and original content as presented at the meeting. This year's meeting was held from May 19–23, in Washington, D.C., USA, and was the second in-person gathering since the onset of the COVID-19 pandemic. Attendance, especially among European and Asian-Pacific attendants, has continued to rebound, once again establishing the ATS International Conference as the premier venue for attendees and investigators to share new knowledge in pulmonary, critical care, and sleep medicine.

As is the case each year at the ATS International Conference, the results of multiple new investigations were presented. Ali Azarbarzin discussed findings of the MESA study, demonstrating that pulse oximetry measurement problems may lead to the underdiagnosis of obstructive sleep apnea in Black individuals. The finding of fever as the most common non-respiratory feature of individuals with COVID-19, something found to be higher among non-vaccinated individuals, was proposed by Shannon Cotton. Emily Skeen presented the likelihood of asthma exacerbation in children residing in urban areas, which is very much a function of lower neighborhood opportunities, as demonstrated in study performed in Denver, Colorado, USA.

The results of several new clinical trials were presented, including the ENHANCE trial, which showed the benefit of dupilumab in patients with chronic obstructive pulmonary disease who had Type 2 inflammation, as indicated by elevated blood eosinophil counts. The announcement of the revised Berlin Criteria for the Diagnosis of Acute Respiratory Distress Syndrome, which includes patients receiving heated high-flow O_2 and the inclusion of saturation to fraction of inspired O_2 criteria, was made by Michael Matthay.

While this inaugural editon of *EMJ Respiratory The American Medical Journal* provides the reader with an overview of the cutting edge information presented in Washington, in subsequent years, original content will also be included. I encourage my professional colleagues to attend next year's ATS International Conference in San Diego, California, USA, from May 17–22, 2024, and to submit their conference reviews and case reports to the journal for review, and for potential inclusion in our 2024 edition.

See you in San Diego!

Robert C. Hyzy

Professor of Medicine, Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor, USA

ATS 2023

Review of the American Thoracic Society (ATS) International Conference 2023

Location:	Washington, D.C., USA
Date:	May 21–24, 2023
Citation:	Respir AMJ. 2023;1[1]:10-16. DOI/10.33590/respiramj/10302353. https://doi.org/10.33590/respiramj/10302353.

WASHINGTON, D.C., USA, was host to the American Thoracic Society's (ATS) International Conference 2023. With over 5,500 original research projects and case reports, 400 sessions, and 900 speakers, the conference offered content for every participant's interest in adult and pediatric pulmonary, critical care, and sleep medicine.

At the opening ceremony, ATS president Greg Downey provided an update on the Society's accomplishments over the past year, and its priorities for the future. Over the last 5 years, ATS has been working on a broad strategic plan, and the past year has seen a variety of accomplishments, including implementing recommendations that will allow the international conference to evolve; implementing guidelines aiming to improve patient care; investing in infrastructure and programs to evolve the organization; providing research grants to early career investigators; increasing equity, diversity, and inclusion within the respiratory community; and pursuing climate change, air pollution, and tobacco products regulation.

Downey emphasized the threat of climate change and the role of the Society, as well as all healthcare professionals in addressing this. Following a call from the National Academy of Sciences (NAS) to improve calculations of the associated health costs of climate change, also called the social cost of carbon, ATS held a workshop with experts from different healthcare specialties, as well as economics. Results were published in 2021, and they allowed leading health economists to publish new model estimates, showing an increase in cost estimates from what was previously thought to be 51 USD per ton of CO_2 to 185 USD per ton. This new estimate can now be used by governments around the globe to formulate climate change policies and act. The workshop is a perfect example of how societies like ATS can participate in public debate and spark changes.

Another area of focus for ATS has been the progression in educational approach to year-round learning, which is led by the chair of the ATS Education Committee, Tisha Wang. Aside from providing high quality education during the 5 days of the conference, ATS wants to provide year-round materials by continuing to share congress content through a learning management system and by creating new content continuously. In December 2022, ATS launched Ed Plus, an online learning

"ATS president Greg Downey provided an update on the Society's accomplishments over the past year, and its priorities for the future. "

management system that offers people the opportunity to learn online at their own pace and in their own time, through interactive clinical cases, videos, and highlights from the conference. The Society hopes that by developing a long-term strategy that joins all their learning in one space, they can give their members the chance to engage with the Society in a way that aligns with their personal goals. The platform also allows ATS to be more adaptable, by creating content based on the needs of their members, as well as evolving trends. Through this initiative, ATS hopes to transform patient care, advance professional development, and impact global health.

Multiple awards were presented at the opening ceremony. The Public Service Award was awarded to pulmonary rehabilitation expert Christine Garvey, University of California, San Francisco, USA, whose research has been instrumental in the transition to an interdisciplinary patient-centered intervention for chronic obstructive pulmonary disease and other chronic respiratory diseases. Second, the ATS World Long Health Award was presented to Uju Ozoh, Lagos University Teaching Hospital, Nigeria. Through their innovative research approaches, Ozoh has aided the delivery of quality health services, as well as advocating for those affected by health disparities. The Jo Rae Wright Award for Outstanding Science was awarded to Lauren Ferrante, Yale School of Medicine, New Haven, Connecticut, USA, for transforming our understanding of outcomes of critically ill aged adults by integrating geriatrics and critical care research. Finally, this year's winner of the J. Randall Curtis Humanism Award was Erin Kross, University of Washington, Seattle, USA, who published more than 65 peer-reviewed articles focusing on improving delivery of palliative care to patients and their families.

EMJ was delighted to participate in this engaging conference for the first time, and the team is looking forward to participating in the next, which will take place from May 17–22, 2024 in San Diego, California, USA. Read on for scientific highlights from the congress, as well as an interview with co-chair of the International Conference Committee for ATS, Debra Boyer. ●

"The workshop is a perfect example of how societies like ATS can participate in public debate and spark changes."

Sleep Apnea May Be Underestimated in Black Patients

OBSTRUCTIVE sleep apnea (OSA) tests may underestimate severity in Black patients, according to recent research. OSA is one of the most common and serious sleep conditions, and is diagnosed through the identification of breathing pauses resulting in drops in O_2 levels.

Pulse oximeters, clips attached to the fingertip that measure blood O_2 levels, may be less accurate in Black patients compared with White patients. Ali Azarbarzin, Harvard Medical School, Boston, Massachusetts, USA, commented: "While skin pigmentation seems to affect the results of oximetry, we did not know whether the same would be true during tests for OSA," hypothesizing that "this would be the case."

Patients in intensive care units during the COVID-19 pandemic of varying ethnicities, who underwent overnight home sleep studies as part of the Multi-Ethnic Study of Atherosclerosis Exam 5, were included in the study (n=1,955). The average change in O_2 levels after each breathing pause was compared between each patient.

Results suggested that Black patients had a smaller decrease in blood O_2 levels than White patients after each breathing pause. This was after accounting for factors that may influence blood O_2 levels such as age, sex, BMI, and smoking index.

The research team concluded that their findings suggest that these differences in pulse oximeter readings may lead to an underestimation of the severity of OSA in Black patients. However, whether this underestimation of O_2 drops should alter the diagnosis and management of OSA in Black patients is unclear.

Azarbarzin concluded: "Nonetheless, these findings highlight the need to rigorously test the accuracy of oximeters across diverse populations, and also to consider whether factors other than the oximeter's characteristics could explain differences in O_2 patterns with breathing pauses." ●

"Pulse oximeters, clips attached to the fingertip that measure blood O_2 levels, may be less accurate in Black patients compared with White patients."

ICUconnect Application: Assisting Clinicians Address Unmet Palliative Care Needs

DURING the ATS 2023 International Conference, held in Washington, D.C., USA, Christopher Cox, Duke University Medical Center, North Carolina, USA, presented the results of a randomized, controlled trial. The study revealed that ICUconnect proved more effective than standard care in assisting intensive care unit (ICU) physicians in addressing the unmet palliative care needs of critically ill patients and their families.

ICUconnect is a mobile application designed to facilitate the exchange of information regarding basic palliative care principles between families and ICU clinicians. This allows the clinicians to visualize patient and family data, enabling them to provide enhanced support.

The study design included 43 clinicians and 111 pairs of patient/family members in six adult medical and surgical ICUs across academic and community hospitals in North Carolina. The clinicians were randomly assigned to either deliver standard care or utilize ICUconnect to communicate with family members and providing advice on meeting their needs.

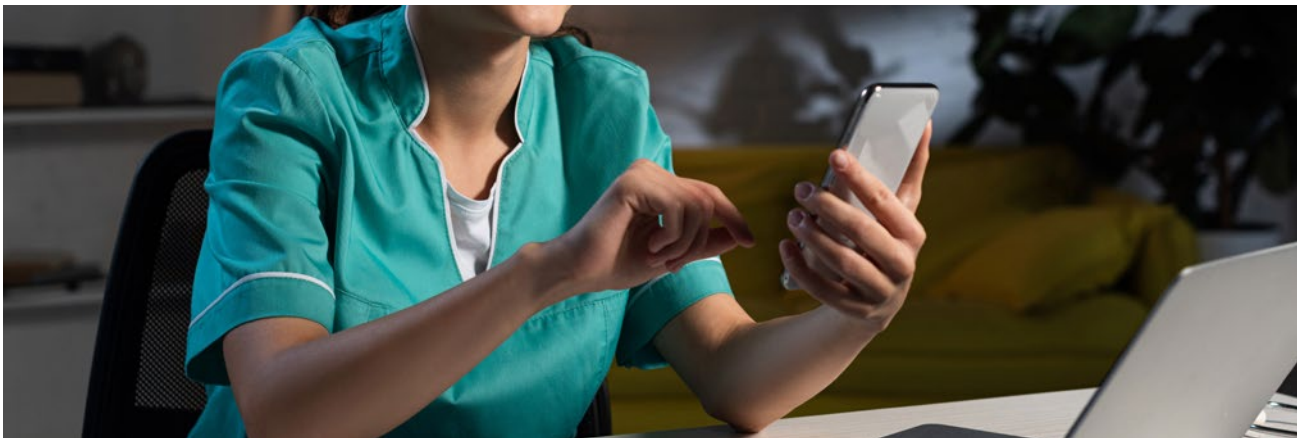
Critically ill patients who were undergoing mechanical ventilation for a minimum of 48 hours were included in the study. The participants were evenly distributed between Black and White patients, as the trial aimed to specifically address racial disparities in care.

The primary outcome of the study was patient score on the Needs at the End-of-Life Screening Tool (NEST), a patient/family member survey that assesses the patients' end-of-life care requirements, which was completed after 1 week of ICU care.

"This allows the clinicians to visualize patient and family data, enabling them to provide enhanced support."

Cox stated: "Compared to usual care, intervention participants experienced a greater improvement in unmet needs as measured by the NEST at both Day 3 and Day 7." The intervention had a significantly higher impact on improving communication with White family members compared with the usual care group. Black family members in both groups showed improvement; however, their level of improvement was similar to the pre-intervention needs of White participants.

This trial suggests strong evidence for implementing an easily reproducible 'primary palliative care' intervention to be delivered by intensivists, with a focus on person-centered outcomes. Cox concluded: "It also demonstrates that additional studies with larger sample sizes of Black and other marginalized individuals are needed to better understand potential mechanisms of and remedies for these findings, including intensivists' interactions with family members." ●



Fever Most Common Non-respiratory Symptom of COVID-19

FEVER is the most common non-respiratory symptom of COVID-19, regardless of COVID-19 variant and vaccination status, according to data presented in May 23, 2023, at the ATS 2023 International Conference. Mortality was also higher in those who were not fully vaccinated and were infected with the Delta or Omicron variants. “We determined that we would conduct this study because the scientific literature has shown that, although COVID is a respiratory disease, it affects multiple organ systems,” stated author Shannon Cotton, University of California San Diego Health, USA.

In this retrospective study, researchers analyzed data on 63,454 patients treated for COVID-19 from the University of California Health Covid Research Data Set (UC CORDS) medical records. The team investigated the relationship between non-respiratory features, vaccination status, and mortality for both the Delta and Omicron variants. Cotton explained that they aimed to determine which features and organ systems were most affected by the virus, which were likely to lead to death, and what the effects were of vaccination.

The team found that the risk of developing non-respiratory symptoms was higher in those who were not fully vaccinated for both variants. Furthermore, they noted that those who were vaccinated were at higher risk of heart disease during a period when the Omicron variant was dominant, and tachycardia with both variants. Further features of COVID-19 included diabetes and gastroesophageal reflux disease, regardless of vaccination status. Cotton concluded: “Our findings speak to the importance of vaccination as the odds of dying were significantly increased in those not fully vaccinated.” ●

"Although COVID is a respiratory disease, it affects multiple organ systems."

Asthma Exacerbations in Children: Location as a Key Factor

A STUDY has discovered that for children with asthma living in metropolitan areas, the neighborhood in which they reside is a strong predictor of asthma exacerbations. Presented at the ATS 2023 International Conference in Washington, D.C., USA, in May, the study used the Childhood Opportunity Index (COI) 2.0, which compares opportunities for children across the USA by geographical area. The index utilizes 29 measures affecting child development in three broad categories: health and environment, socioeconomic, and education. When using the index, the higher the score, the better the opportunities available. COI was used in this study as it provides the sole amalgamated measure of different neighborhood conditions which are specific to young populations.

The study population included 193 children aged 8–17 years, residing in Denver, Colorado, USA. All participants had asthma and were already participating in an observational study taking place at a tertiary care hospital, where researchers were observing rather than altering the effects of risk factors, diagnostic tests, treatments, and other interventions.

COI data included household income, parental education levels, and home address. Two statistical models were then used, which compared patients' history of asthma exacerbation with neighborhood and socioeconomic predictors. Researchers classed asthma status as asthma-null, with no exacerbations in the prior 5 years, or exacerbation-prone (n=142; median age: 11.8), with ≥1 exacerbation during the previous year.

Children who were categorized as exacerbation-prone increased by 40% where overall neighborhood-level COI scores dropped by 20 points, and by 10% with a 5,000 USD decrease in household income. Parental education was not found to be a significant factor.

Previous research has demonstrated social determinants are causal of significant health disparities in the pediatric asthma population. Corresponding study author Emily Skeen, Pediatric Pulmonary Fellow, University of Colorado at Children's Hospital Colorado, Aurora, USA, stated: "We know that these factors do not act in isolation, so we used a composite score of neighborhood-level child opportunity to determine whether it would predict exacerbation-prone asthma better than individual socioeconomic indicators. We hypothesized that having fewer opportunities would be associated with being prone to asthma exacerbations."

In future, Skeen suggests that using targeted interventions in different communities could mediate the increased risk of exacerbation-prone asthma in children. ●

"The study used the Childhood Opportunity Index (COI) 2.0, which compares opportunities for children across the USA by geographical area."

Chronic Obstructive Pulmonary Disease at the 2023 American Thoracic Society (ATS) International Conference

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THE 2023 American Thoracic Society (ATS) international conference was held in Washington, D.C., USA, from May 20–24, 2023. The conference, which was nearly back to full strength after 3 years of the COVID-19 pandemic, had over 13,000 attendees, and featured over 200 sessions that dealt with chronic obstructive pulmonary disease (COPD) in some capacity. These sessions ranged from poster presentations to mini symposia to plenary sessions, and almost every other option available at the conference. Topics ranged from basic science and mechanisms to risk factors, epidemiology, and results of important clinical trials. This review will focus on some of the more impactful presentations at the meeting.

CLINICAL TRIALS

Several key clinical trials had data presented. One was the BOREAS trial, which examined the use of dupilumab, a monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, key drivers of Type 2 inflammation in patients with eosinophilic COPD.[1] Results showed that patients who received an injection of dupilumab every 2 weeks had a significant reduction in COPD exacerbations, in addition to an improvement in their lung function and an improvement in their measures of quality of life. A second trial of this therapy is awaiting completion. If this study replicates the findings of the first trial, it will most likely result in the first biologic therapy that is approved to treat COPD in the USA (pending approval by the U.S. Food and Drug Administration [FDA]).

A second presentation looked at results from ENHANCE-1 and ENHANCE-2, studies that reported on the use of ensifentrine, a nebulized therapy used twice daily.[2] Ensifentrine is a selective dual inhibitor of the enzymes phosphodiesterase 3 and 4, combining bronchodilator and non-steroidal anti-inflammatory activities in one compound. Results of these trials showed both a significant reduction in exacerbations and an improvement in lung function. If this therapy is approved by the FDA, it will mark the first new class of therapy approved for the treatment of COPD in over 10 years.

"If this therapy is approved by the FDA, it will mark the first new class of therapy approved for the treatment of COPD in over 10 years."

INTERPRETATION OF SPIROMETRY

A current controversy in COPD and the respiratory world is how race should be used in the interpretation of spirometry. On one side of the discussion is the belief that 'race' is a term that is problematic, and may reflect factors other than ancestral ones (malnutrition, environmental factors, deprivation, etc.) that differ between racial groups, and that the best solution is to use 'race-neutral' prediction equations. The counter argument is that carefully done studies have demonstrated differences in lung function between racial groups, and that using a race-neutral approach risks categorizing people with 'normal' lung function as abnormal and vice versa, based on their race and what prediction equations are used. Although there were no definitive solutions presented, one approach may be to acknowledge the limitations of our current classification system of normal and abnormal to include an 'indeterminant' classification.

GLOBAL INITIATIVE ON CHRONIC OBSTRUCTIVE LUNG DISEASE 2023

The Global Initiative on Chronic Obstructive Lung Disease (GOLD) updated their strategy document in late 2022, and several sessions looked at the components of this update. These included the role of exacerbations in COPD therapy and how exacerbations are classified. Although the update called for implementing the new criteria for exacerbation severity based on physiologic metrics, the practicality of this approach in real-world settings has been questioned. Another important concept in the GOLD 2023 strategy is the concept of 'etiotypes', looking at sub-groups of COPD based on etiology (i.e., smoking, infections, developmental issues, genetics, etc.). The hope is that different subgroups of COPD might result in different interventions and improved outcomes.

DISEASE PROGRESSION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Another important concept discussed at several sessions relates to how COPD is diagnosed and progresses. What is important here is the reality that, by the time lung function impairment is noted, a great deal of damage has already been done. If one is to find a therapy that truly modifies disease, COPD will have to be detected much earlier in its course. For example, one session highlighted what happens to people with normal lung function but COPD risk factors, such

"If one is to find a therapy that truly modifies disease, COPD will have to be detected much earlier in its course."

as smoking and respiratory infections. Some take-away messages were that even among those with normal lung function at baseline, follow-up lung function demonstrating decline increases the likelihood of COPD development. Frequent respiratory infections increase this risk. These respiratory infections also result in a loss of the normal diversity that occurs in microorganisms found in the lung, which raises the possibility that efforts to return this diversity to a more 'normal' state may be a potential therapeutic approach.

ADVANCED CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A final topic worth noting is what happens in advanced COPD, where patients may not respond to medical therapies. Some of the advanced options being investigated include bronchial rheoplasty, which alters the epithelium of the lung in patients with chronic bronchitis that does not respond to typical therapies. Although endobronchial valves have been available for use globally for several years, many questions remain about their optimal use, including which lobes should be targeted and whether the procedure should be sequenced. Long-term data from existing trials were also presented demonstrating the safety and efficacy of endobronchial valves for COPD after 5 years of follow-up.

CONCLUSION

The above represents just a few of the COPD-related highlights presented at the 2023 ATS meeting. The ATS has provided a searchable directory of the conference presentations that can be viewed by both paid attendees and non-attendees. ●

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American Thoracic Society (ATS) Clinical Practice Guidelines: Clinical Practice on the Cutting Edge

Authors: Natasha Meunier-McVey, EMJ

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AN ENGAGING session on the newly revised American Thoracic Society (ATS) Clinical Practice Guidelines: Clinical Practice on The Cutting Edge focused on key updates to the idiopathic pulmonary fibrosis (IPF) guidelines. The session was a workshop report defining pulmonary rehabilitation, and a technical statement on the measurement of lung volumes. Presented at the Annual ATS International Conference on May 22, 2023, the session, chaired by Mark L. Metersky, Professor of Medicine and Associate Chief of Service, Department of Medicine, UConn Health, Farmington, Connecticut, USA, delved into how evidence is used to inform diagnostic and treatment recommendations.

IDIOPATHIC PULMONARY FIBROSIS AND PROGRESSIVE PULMONARY FIBROSIS IN ADULTS: A GUIDELINE UPDATE

Ganesh Raghu, Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, USA, led the highlights session of the guideline update on IPF and progressive pulmonary fibrosis (PPF) in adults from the ATS, European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Asociación Latinoamericana del Tórax (ALAT). A patient advocacy group was also involved in this update, led by esteemed professors who helped shape a rigorous methodology to ensure optimal standards of recommendation. Raghu explained how this update was beyond the scope of revised guidelines, as it took new insights into consideration following the publication of a pre-clinical milestone paper from the INBUILD Trial Investigators in October 2019, which highlighted the potential of nintedanib in progressive fibrosing interstitial lung diseases.

The primary focus of the update concerned the 2018 guidelines surrounding transbronchial lung biopsies and transbronchial cryobiopsies for patients with newly detected interstitial lung disease (ILD) of unknown cause. The panel had made no recommendations for these histopathological diagnostic procedures in the previous update due to a lack of evidence. Raghu explained that these procedures were now deemed acceptable for this patient population in the new guidelines, when the procedure is completed by a pathologist with experience in carrying out and interpreting histopathological results. Raghu reiterated that this may not be appropriate for all patients and must be considered in each case. The guidelines made no recommendation for or against genomic classifiers as an alternative diagnostic test due to insufficient evidence and a lack of accessibility.

Raghu highlighted considerations surrounding the terminology of PPF, and whether it should be termed progressive fibrosing interstitial lung disease. It was concluded that, due to the nature of the disease going beyond the scope of ILD, PPF is a more accurate term to reflect the

progressive nature of the disease. To now be classed as PPF, a patient must meet the criteria of having unexplained respiratory symptoms that are confirmed through radiological or physiological evidence within the year. The committee also found a change in the forced vital capacity to be preferable for the classification of PPF, as this forecasted poor outcomes, as well as considering the absolute change in diffusing capacity for carbon monoxide (DLCO). The absolute rather than relative change in DLCO was voted for, as it is a consistent and strong predictor of mortality; however, Raghu emphasized that it is essential to consider other factors that may contribute to a declining DLCO. The committee also decided that the timeline element of PPF monitoring will be removed from the updated guidelines and be left to the discretion of the physician.

> **"The committee also decided that the timeline element of PPF monitoring will be removed."**

Raghu shared the updated guidelines for the treatment of asymptomatic gastroesophageal reflux disease in patients with IPF. The committee's suggestion was against treating patients with antacid therapies for the purpose of reducing gastroesophageal reflux disease symptoms, as the evidence was low-quality and further essential research must be carried out before recommendations can be made. Raghu also highlighted that physicians should not refer patients for anti-reflux surgery for the purpose of improving respiratory outcomes, a factor that has never been considered in the context of clinical practice guidelines.

PULMONARY REHABILITATION

Anne E. Holland, Professor of Physiotherapy and Head of Respiratory Research, Monash University, Melbourne, Australia, took to the stage to discuss the new guidelines in approaching pulmonary rehabilitation. With there previously only being a clinical statement to pulmonary rehabilitation, this is the first set of guidelines published for this strategy that is under-utilized and under-resourced.

Holland explained that at least 5% of patients with chronic obstructive pulmonary disease (COPD) would benefit from pulmonary rehabilitation; however, several barriers exist, including geographic disparities in the availability of programs and a lack of knowledge in referrals. They went on to address the improvements in the available evidence concerning the strategy, and the fact that the need to optimize practice and policy has become evident. The guidelines were developed according to the ATS methods, and involved a multi-disciplinary panel of healthcare professionals who are involved in referral to and delivery of rehabilitation, as well as a patient advocate.

Holland began by addressing whether patients with COPD should undertake pulmonary rehabilitation. From 82 randomized controlled trials of over 4,600 participants and a predicted

"At least 5% of patients with chronic obstructive pulmonary disease would benefit from pulmonary rehabilitation."

clinical outcome of exercise capacity, researchers found an improvement of 44 m walking distance due to pulmonary rehabilitation. This result exceeded the minimal importance difference, so the researchers considered it clinically relevant. The panel strongly recommended participation in pulmonary rehabilitation based on the evidence available, which was deemed of moderate quality, and placed high value on improvements in exercise capacity, dyspnea, and health-related quality of life.

The third pathway focused on recommendations for pulmonary rehabilitation in adults with ILD. With similar results, Holland explained that the recommendation was for pulmonary rehabilitation for patients within this demographic. Using the same approach, the committee made a conditional recommendation for adults with hypertension to undertake pulmonary rehabilitation; however, the effect was not as large, and the costs noted were potentially higher. Holland noted that there was some evidence of a risk of bias in some of the trials, and some significant adverse effects were noted in uncontrolled data.

Looking at newer models of care, Holland shared results from the focus of incentivized pulmonary rehabilitation versus telerehabilitation in adults with chronic respiratory disease. There were no clinically or statistically significant differences noted between the two, but program completion was higher in telerehabilitation, reflecting the positives of ease of access. The recommendation for adults with stable chronic respiratory disease is to offer the choice of incentivized rehabilitation or telerehabilitation, which is a strong recommendation based on moderate quality evidence.

The final recommendation concerned adults with chronic respiratory disease who are on pulmonary rehabilitation maintenance programs, which is defined as a supervised exercise program following chronic rehabilitation completion. The committee found that maintenance was favored over no maintenance; however, this was not a statistically significant finding and hospitalization rates, dyspnea, and quality of life measures were not affected. A conditional recommendation was advised for adults with COPD based on high quality evidence, suggesting either supervised maintenance and rehabilitation or usual care following the initial program.

Holland concluded the session, noting that the panel also made key recommendations surrounding research needs in pulmonary rehabilitation to improve the uptake of these programs. They also highlighted the lack of data for producing models suitable for low-and-middle income countries, which must be adapted to optimize the role of pulmonary rehabilitation in these patient populations.

CONCLUSION

Key updates to the guidelines on IPF and PPF in adults, and the new guidelines on pulmonary rehabilitation, will help to optimize decision-making for physicians and healthcare professionals, contributing to improved patient care. As mentioned, the importance of ongoing research to continually improve recommendations will undoubtedly contribute to better clinical outcomes and future treatment strategies.

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Promoting Health Equity and Reducing Medical Disparities

Authors: Robin Stannard, EMJ

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IN A highly current, relevant, and consequential keynote lecture at the American Thoracic Society (ATS) International Conference 2023, Eliseo J. Pérez-Stable, National Institutes of Health (NIH), Bethesda, Maryland, USA, delved into the pervasive disparities in health equity that are seen both in the USA and across the globe. Pérez-Stable focused their lecture on the need for standardized measures and data sets to increase understanding of the socioeconomic factors that contribute to medical disparities. Using clinical examples of tobacco use behavior, asthma epidemiology, lung cancer management, and diversity of medical professionals, Pérez-Stable delved into the nuanced and significant challenge of health disparities.

INTRODUCTION

In their presentation at ATS, Pérez-Stable introduced their keynote lecture by summarizing what they understand as the underlying core concepts of the health disparities crisis. One of the key contributing factors to the crisis is a lack of diversity in those providing healthcare, which can arise from both legal and structural barriers, and remains a significant problem reflected in the proportional representation of medical school graduates. The recent COVID-19 pandemic has underlined to public health researchers that community engagement, building relationships, and understanding the motivations of the population is critical to the quality of public health research. Additionally, the health disparities research community is sorely lacking in data science expertise, and disparities in health outcomes due to ethnicity and socioeconomic class need to be measured in a standardized way. Without this data standardization, key contributing mechanisms will be missed. Implementation science also needs to be improved in the field, as interventions with efficacy need to be identified and put to best use. Pérez-Stable remarked that a significant trend observed by experts in the field is that efficacy of interventions is lacking in the most disadvantaged populations, compounding disparities in health outcomes.

Pérez-Stable also used their introduction to establish the populations and communities that researchers in the field have identified as disadvantaged in terms of health equity. These groups include racial and ethnic minorities, those of lower socioeconomic class, and women of color. In 2016, sexual and gender minorities were also added to this list. The field has embraced the notion that all these populations have social disadvantage that is due, at least in part, to social discrimination and racism, in addition to being underserved by healthcare systems. Health outcomes tend to be worse in these populations when compared with reference populations, demonstrating health inequity.

"Efficacy of interventions is lacking in the most disadvantaged populations, compounding disparities in health outcomes."

TOBACCO USE AND EDUCATIONAL ATTAINMENT

In their presentation, Pérez-Stable highlighted the importance of socioeconomic measures for understanding health disparities. By analyzing health in relation to educational attainment, comparing individuals with or without a college degree, researchers were able to summarize that the possession of a college degree is beneficial for health. Total health inequities related to premature death, lost labor hours, and other factors for those with less educational attainment than a college degree equated to almost 1 trillion USD in the USA in 2018. Significant progress has been made in recent years in terms of health equity relating to combustible tobacco consumption. Data published by the Centers for Disease Control and Prevention (CDC) in 2021 demonstrated no great difference in rates of tobacco use between different racial and ethnic groups. However, what remains is a huge educational gradient of tobacco use, with a particular stark increase in rates for those with a high school diploma compared to those with a college degree. Pérez-Stable explained that this is one possible reason why we see such significantly different health outcomes with educational attainment. On deeper analysis, data from tobacco use surveys show that the benefit of educational attainment is decreased for people of color compared to White populations. This is a trend that health disparities researchers see across the board, namely an improvement in ethnic minorities with increasing educational attainments; however, absolute benefit compared with White populations remains lower.

THE PANDEMIC AND DISPARITIES

As with many other aspects of society, the COVID-19 pandemic shone a light on healthcare systems, highlighting societal inequities and disparities in how disadvantaged groups receive medical care. Racial and ethnic disparities in COVID-19 mortality were initially ascribed to biological differences, such as higher rates of obesity and heart disease. In reality, the differences in mortality were, to a much greater degree, intrinsically interlinked with social and structural differences. In 2022, when the vaccine had been rolled out to much of the USA's population, a huge leveling of the playing field was seen between different ethnic groups in terms of mortality. Uptake for the vaccine was similar across racial and ethnic groups, resulting in an equalization of the differences, and an example of a successful and equitable intervention.

"As with many other aspects of society, the pandemic shone a light on healthcare systems, highlighting societal inequities and disparities."

The pandemic also brought with it changes in standard medical practice, the acceptance of telemedicine being just one. In 2020, insurers in the USA were disinclined to cover tele-visits, except for a minimal number of exceptional circumstances. However, as restrictions increased, telemedicine was quickly adopted. Pérez-Stable emphasized the importance of public health researchers being aware of changing practices, such as the spread of telemedicine, for monitoring how this change may impact disparities in healthcare. Evidence from the pandemic and beyond has already demonstrated that racial and ethnic minorities, older adults, and those who do not speak English are less likely to be offered telemedicine, and are less likely to accept it.

DIVERSITY WITHIN THE MEDICAL PROFESSION AND HEALTHCARE SYSTEMS

Patient communication and the doctor–patient relationship is an essential constituent part of healthcare provision; however, there is a conspicuous lack of quality research in this area focusing of disparities and equities. Only 14% of medical school graduates come from all underserved and disadvantaged populations. Pérez-Stable drew the audience's attention to data on medical school enrolment: American Indian and American Alaskan populations account for well under 1% of total enrolments. Though African-American and Latino community enrollment has now reached a proportional 7%, until recent years this rate has hovered around 3–4%, meaning that the current practicing medical profession does not have proportional ethnic and racial representation. However, Pérez-Stable highlighted that the current minority enrolment rate of approximately 14% means that the pipeline is not empty, and the medical community of the future will be far more representative and equal for minority populations.

Healthcare provision is also inextricably defined by access. The proportion of the USA's population who are uninsured has decreased over recent years with the introduction of the Affordable Care Act (ACA). Uninsured rates in the USA population are now below 10%; however, the proportion of populations that are uninsured varies between different racial, ethnic, and socio-economic groups. For example, the uninsured rate in Hispanic populations is just below 20%, significantly higher than the reference population. Patient-centered care and primary care are essential and fundamental foundations of healthcare systems. Empirical evidence shows that effective primary care saves lives; however, not enough efforts have yet been made to move healthcare in the USA in this direction. Pérez-Stable suggested to the audience that equity and equality should be made essential measures for institutions, with rewards that encourage them to take care of the most vulnerable constituent populations. The ACA is the first move towards making healthcare systems responsible for population health.

CONCLUSIONS

Pérez-Stable's presentation touched on key instances of health inequity displayed at all levels within the USA's healthcare system. Highlighting disparities from the source of healthcare with the lack of proportional representation in medical student cohorts, encompassing inequitable healthcare provision demonstrated by the telehealth and initial COVID-19 responses, and finally touching on the differences between health risk choices made by the individuals with tobacco use surveys, Pérez-Stable underlined how health disparities are currently endemic to healthcare in the USA. These examples highlight the importance in observing, understanding, and combining these data to define factors associated with, and contributing to, health inequities, as emphasized by Pérez-Stable. Additionally, recent interventions focusing on tobacco use and the COVID-19 vaccine demonstrate the value of efficacious interventions that work for all aspects of the population. ●

Host Inflammatory Response in Viral Lower Respiratory Tract Infections: Friend or Foe?

A review of an industry theater presentation session that took place at the American Thoracic Society (ATS) 2023 International Conference, held on May 23, 2023, in Washington, D.C., USA

Speakers: Pratik Sinha,[1] Nuala Meyer[2]

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Disclaimer: The purpose of the industry theater presentation was for disease state awareness and is not meant to imply efficacy or safety of any AstraZeneca products or other medications.

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Keywords: COVID-19, cytokines, dysregulated host immune response, infection, influenza, IL-33, respiratory syncytial virus (RSV), viral lower respiratory tract infections (LRTI).

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Symposium Summary

Viral lower respiratory tract infections (LRTI) are a leading cause of hospitalizations and death worldwide, placing significant pressure on healthcare systems. In this article, two pulmonary critical care specialists explored the prevalence and global burden of viral LRTIs, focusing on recent advancements in understanding the role of dysregulated host immune response and hyper-inflammation. Specifically, they focused on the relevance of alarmin cytokines and their association with adverse patient outcomes.

This article reviews the presentations delivered during an industry theater session that took place at the American Thoracic Society (ATS) 2023 International Conference, held in person in Washington, D.C., USA, in May 2023. The primary objective of this session was to provide a comprehensive overview of the impact and burden imposed by severe viral LRTIs. Pratik Sinha, an Assistant Professor in Anesthesiology at Washington University in St. Louis, Missouri, USA, provided valuable insights into the drivers behind the progression of viral LRTIs, which result in significant mortality and morbidity, imposing a considerable clinical burden with unmet needs. Nuala Meyer, an Associate Professor of Medicine at the Hospital of the University of Pennsylvania, Philadelphia, USA, shed light on the dysregulated host immune response and hyper-inflammation triggered by viral infections, which serve as key drivers of disease progression and severe patient outcomes. Sinha also discussed the potential role of alarmin cytokines, particularly IL-33, in influencing the severity and progression of respiratory viral infection. These cytokines may also serve as pleiotropic regulators of the host immune response to viral LRTIs.

Severe Viral Lower Respiratory Tract Infections Pose a Significant Burden on Patients and Healthcare Systems

Pratik Sinha

Severe viral LRTIs pose a substantial global burden, resulting in hospitalizations and death.[1-5] This burden is particularly evident in the winter months, when seasonal RTIs caused by multiple viruses such as influenza, COVID-19, respiratory syncytial virus (RSV), metapneumovirus, and parainfluenza become prevalent (Figure 1).[6] These infections continuously challenge the resilience of healthcare systems worldwide, leading to a surge in emergency hospitalizations and intensive care unit (ICU) admissions.[6-8]

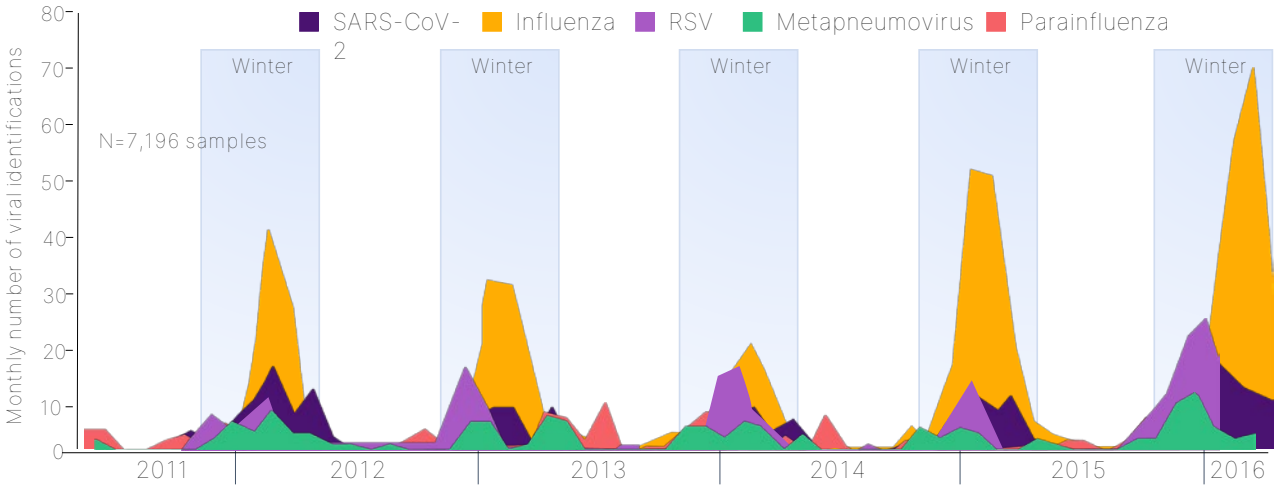
Sinha described the impact of influenza in the USA prior to the COVID-19 pandemic. In 2019–2020 there were an estimated 36 million cases of influenza, with 25,000 deaths.[1] Despite the surge in COVID-19 cases during the pandemic in 2020–2021, with around 147 million cases and 921,000 deaths,[2] the burden of influenza has continued to persist. Preliminary estimates for 2022–2023 are up to 50 million cases of influenza and up to 56,000 deaths.[3] According to Sinha, these numbers resonate with healthcare practitioners working in ICUs across the USA, highlighting the ongoing challenges posed by viral LRTIs.

The concern regarding viral LRTIs extends beyond mortality and encompasses substantial hospital admissions. Sinha emphasized that considering future burden, it is crucial to recognize that it is "not just influenza that we should be thinking about." In the USA, it is projected that up to 630,000 patients may require hospitalization for influenza-associated LRTIs in 2022–2023,[3] along with approximately 7.5 million cases of COVID-19.[2] Additionally, for respiratory syncytial virus (RSV), the estimated annual number of patients hospitalized is up to 80,000 in those <5 years old and as many as 160,000 in those aged ≥65 years.[9]

Despite the recurrent peak periods in multiple viral pathogens, including influenza, severe acute respiratory syndrome coronavirus 2, and RSV, leading to RTIs (Figure 1),[6] the timing and intensity of respiratory viral activity can vary and is not precisely determined from one season to the next.[10-12] Sinha noted that this variability makes it "tricky to predict when in the winter these peaks will occur, and how large these peaks are going to be," thus making optimal and efficient resource allocation of hospitals difficult, including staffing,[4] and contributing to the financial burden.[13] Therefore, the prevention and effective management of seasonal LRTIs is fundamental to reducing the demand on healthcare services.[4]

Sinha also emphasized the importance of considering the burden on patients. A study presented at the ATS 2023 International Conference, which summarized real-world evidence from a retrospective analysis of a USA claims database, assessed ICU admissions and outcomes associated with viral LRTI (influenza and COVID-19) before (2015–2019; n=49,317) and during (2020–2021; n=236,661) the COVID-19

Figure 1: Seasonality of lower respiratory tract infections.[6]



Adapted from Visseaux et al.[6]

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

pandemic.[14] The study showed an increased burden on an already overwhelmed healthcare system in light of the COVID-19 pandemic. It demonstrated a rise in ICU admissions, escalating from 37% pre-pandemic to 44% during the pandemic. Additionally, there has been an increase in the utilization of invasive mechanical ventilation and extracorporeal membrane oxygenation, from 12% pre-pandemic to 25% during the pandemic, and a heightened mortality, escalating from 8% pre-pandemic to 22% during the pandemic.[14] Influenza accounted for the majority of pre-pandemic cases, while COVID-19 contributed to the substantial increase in cases during the pandemic, amplifying the burden.[14] Sinha highlighted the need to understand the impact of COVID-19 on seasonal pressures in conjunction with other RTIs in the future.

Sinha also noted that viral infections are known to "smoke out" non-respiratory symptoms such as palpitations, chest pain, dyspnea on exertion, and exercise intolerance.[15] Concurrent infection with influenza has been associated with acute cerebrovascular events, such as ischemic stroke,[16] as well as cardiovascular events, including myocarditis, acute myocardial infarction, heart failure, sudden cardiac arrest, and acute coronary syndrome.[15,17-19]

The Concept of Heterogeneity in Viral Lower Respiratory Tract Infections

There is a large degree of heterogeneity in response to viral LRTIs among patients, indicating that not every patient with an infection experiences the same outcomes, with marked differences in length of stay, O_2 support, and other hospital trajectories.[20] Thus, it is important to note that not all viral infections should be managed the same way.[20] This heterogeneity may arise from multiple pathogens or host-driven responses, resulting in differing disease states, and can lead to severe complications, such as acute respiratory distress syndrome and death.[20] For example, Sinha stated the need for respiratory support can differ substantially among hospitalized patients over time for those with COVID-19 pneumonia compared with influenza pneumonia.[20] Sinha also stated that the best approach is to reduce the need for hospitalization.

Better understanding the dysregulated host immune response to viral LRTIs may present opportunities to improve patient outcomes.[21]

Treatment options for viral LRTIs are limited, and the unmet patient need is substantial. Sinha noted the need for more treatments and infection prevention programs. The COVID-19 pandemic has highlighted the potential benefits of targeting

host-response inflammation.[22] Sinha summarized that selecting the right patients at the right time with the right therapeutic approach is crucial.

Dysregulated Host Immune Response is the Driver of Disease Progression and Severe Patient Outcomes

Nuala Meyer

Appropriate host defense against viral respiratory infections is a delicate balancing act. Dysregulation of the host immune response contributes to progression and severity of the disease.[23,24] Meyer discussed the intricacies and complexities associated with a dysregulated host immune response in viral LRTI, explaining that viral infections occur along a spectrum. During the early infection phase, most individuals are asymptomatic or experience mild symptoms such as fever, cough, myalgia, fatigue, sore throat, and headaches, which may persist for several days.[23] However, clinicians encounter patients that develop infections in the lower airways, resulting in more severe symptoms of dyspnea, hypoxemia and tachypnea, which may result in pneumonia and respiratory failure necessitating hospitalization.[23] Progression of the disease is driven by dysregulated host immune response to the infection and a dysregulated local and systemic inflammation. This phase, as described by Meyer, is also defined as sepsis, and leads to lung tissue damage, respiratory failure, acute respiratory distress syndrome, shock, and multi-organ failure, often resulting in death.[23,24]

Meyer emphasized the importance of considering how viral infections enter the human body and which host tissues are targeted, as well as the inflammatory pathways that are triggered.[24] Respiratory viruses primarily target various lung epithelial cells, alveolar cells, endothelial cells, and immune cells.[24] The initial point of contact for these viruses is typically the nasal mucosa and respiratory epithelium, as the virus travels down the nasal passage. These tissues are constantly "exposed to the outside world, always surveying," and play a vigilant role in viral detection, triggering numerous inflammatory pathways (Figure 2).[24,25]

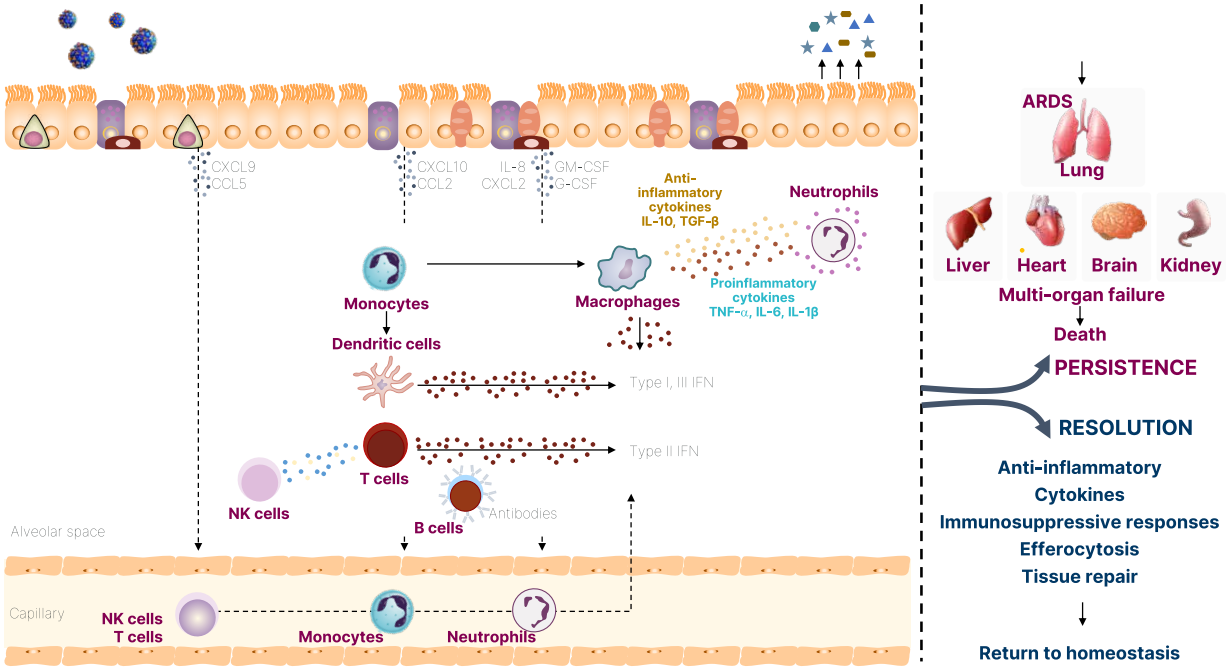
The epithelium acts as a physical barrier and mounts protective secretory responses against viral infections, including the secretion of interferons (Type I-III) and pro-inflammatory cytokines such as IL-6, TNF-α, and chemokines.[24] These cells recruit local innate immune cells such as neutrophils, monocytes, and dendritic cells, which activate the adaptive immune response involving natural killer cells, cytotoxic T cells, and B cells, inducing interferon (IFN)-γ secretion and antibody production.[24] However, there can be a dysregulated immune response that can persist in some patients, leading to multi-organ failure.[25] Meyer stated that with LRTIs, "the lungs are the most commonly affected organ," but also provided examples of fatal influenza and RSV cases, where patients developed multi-organ failure along with circulatory dysfunction.[23,25]

In the context of the lung, inflammatory injury acts as a secondary indirect inducer of tissue damage following viral infection.[26] Meyer emphasized the intricate nature of inflammation, highlighting the dysregulation that can occur in both the epithelium and endothelium. Inflammatory-driven injury increases the permeability of the epithelial barrier, allowing protein-rich edematous fluid to enter the alveolus.[26] Meyer suggested that this process may "serve some function in pathogen-host defense by recruiting inflammatory cells to the alveoli."[26] However, this response can become dysregulated, leading to alveolar edema, respiratory failure, hypoxemia, and vascular injury, resulting in hypercapnia.[26] These effects further impair the clearance of alveolar edema and can contribute to the development of acute respiratory distress syndrome.[26]

Evolutionary Paradigm: Defining, Describing, and Measuring Immune Dysregulation

Meyer emphasized the concept of innate immune dysregulation, which was traditionally viewed as a sequential process involving an initial hyper-inflammatory response characterized by excessive inflammation and elevated plasma cytokine levels, followed by a compensatory anti-inflammatory response.[27] This hyper-inflammation can cause tissue damage, while dysregulated adaptive immune suppression may place patients at risk of secondary infections.[27]

Figure 2: The inflammatory signaling pathways in lung epithelium and immunopathology during viral infections.[24,25]



Adapted from Clementi et al.,[24] and Yang et al.[25]

ARDS: acute respiratory distress syndrome; CCL: chemokine (C-C motif) ligand; CXCL: chemokine (C-X-C motif) ligand; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IFN: interferon; NK: natural killer; TGF-β: transforming growth factor β.

Meyer clarified that these processes actually occur simultaneously within the same patient, and often those who exhibit "the most hyperinflammatory response also display the most adaptive immune dysregulation." Thus, immune dysregulation manifests as a sustained inflammatory state driven by dysfunctional innate immunity and suppressed adaptive immunity, which may contribute to mortality in the long term.[27]

Meyer highlighted the need to establish markers that can aid in identifying excess inflammation and dysregulated adaptive immunity. Potential candidate markers include elevated inflammatory cytokines,[28] vascular activation,[28,29] activated neutrophils,[28] low reduced human leukocyte antigen monocytes,[27,29] endotoxin tolerance,[27] and apoptosis.[28] These markers may indicate a dysregulated host response, yet Meyer emphasized that further research is required to identify the key markers, due to patient heterogeneity. Despite this heterogeneity, there are examples of consistent patterns observed across different pathogens. Translational studies have demonstrated that elevated levels of IL-6, for instance, show strong associations with disease severity and survival in patients with LRTIs. A single-center study of patients hospitalized with COVID-19 (N=1,484) in the USA, demonstrated increased IL-6 levels in severe cases and independently predicted survival.[30] Similarly, elevated IL-6 levels were associated with disease severity in a cohort of patients hospitalized with influenza A virus subtype H1N1 infection (N=32), particularly those with acute respiratory distress syndrome (n=21).[31] In children ≤5 years old who attended the emergency department (between September 1998–May 2008) with RSV infection (N=851), elevated IL-6 levels were also associated with disease severity.[32] Similar results were observed for other pro-inflammatory cytokines, including IL-1β, IL-8, and TNF-α.[30-32]

Heterogeneity Among Severe Patients Hospitalized with COVID-19

However, heterogeneity in the host response can exist even within the same pathogen. As an example, a study profiling 125 patients hospitalized with COVID-19 compared them with healthy donors or individuals who experienced mild COVID-19 and recovered without requiring hospitalization.[33] Using a uniform manifold approximation approach, approximately 200 immune features were distilled into two dimensions, which identified three immunotypes of COVID-19 associated with clinical outcomes.[33] The findings demonstrated that patients who were severely ill clustered separately from healthy donors and those who recovered without hospitilization.[33] Among the patients with severe illness, the distribution demonstrated more heterogeneity while identifying multiple clinical features.[33] Those identified as 'immunotype 1', associated with higher severity of illness, organ failure (as measured by Acute Physiology, Age, Chronic Health Evaluation [APACHE] III scoring), and higher mortality, and corresponded with hyperactivated T cells, higher plasmablasts, and lower altered follicular helper T cells.[33] 'Immunotype 2' represented "a more balanced immune response," stated Meyer, with the emergence of memory B and T cells, while 'immunotype 3' showed little evidence of active B or T cell response, indicating the complex heterogeneity of the immune response with COVID-19.[33]

Additionally, heterogeneity has also been observed in the secreted plasma protein response to COVID-19, where a protein signature consisting of 14 plasma proteins strongly associated with severe disease (defined as illness that resulted in death, the need for high-flow nasal cannula, non-invasive or invasive positive pressure ventilation, or extracorporeal membrane oxygenation).[34] Differential upregulation of protein expression (n=145), including tenascin-C, C-C motif chemokine ligand 7, transforming growth factor-α, and IL1-receptor like-1, and downregulation (n=49) of IL12-β, TNF superfamily 11, and matrix metallopeptidase 9, were observed after correcting for multiple comparisons.[34] Meyer identified that these proteins could be integrated into a "protein severity score" that could provide information about a patient's prognosis. This proteomic score was used to evaluate heterogenous treatment effect by predict disease severity or death in an observational study involving patients hospitalized with COVID from Massachusetts General Hospital, Boston, USA.[34] The data demonstrated an effective modification in the relationship between the protein score, stratified by corticosteroid receipt, and the prediction of severe disease or mortality at 90 days, with an area under the receiver operating characteristic of 0.88 (95% confidence interval [CI]: 0.83–0.93).[34] This was validated in an external dataset, yielding an area under the receiver operating characteristic of 0.92 (95% CI: 0.87–0.95).[34] Of note, patients with a low predicted severity protein score who received corticosteroids were associated with higher mortality, suggesting a disruption of the regulated host response to the virus.[34]

Meyer summarized that in order to make progress, key features of the viral disease need to be identified, and targeted precision medicine may be used for the treatment of patients with severe LRTIs. Similar achievements have been made in other complex traits, where the identification of biomarkers has driven substantial improvements in patient care, management, and outcomes.[35-37] To facilitate this progress, Meyer identified the three major advances are needed: a better understanding of the drivers of severe outcomes and their causality;[35] quantitative traits that can be measured to indicate patients with significant of dysregulated inflammation; and the ability to promptly sort or classify patients to identify which therapy is suitable for each individual.

The Role of the Alarmin IL-33 in Viral Lower Respiratory Tract Infections

Pratik Sinha

Alarmins are a group of proteins and peptides released upon cellular injury.[38-40] They are effector molecules that trigger downstream activation of inflammation and act as a chemotactic agent, stimulating both the innate and adaptive immune system.[38] Alarmins include thymic stromal lymphopoietin, IL-25, and IL-33, which are central regulators of the immune response.[38]

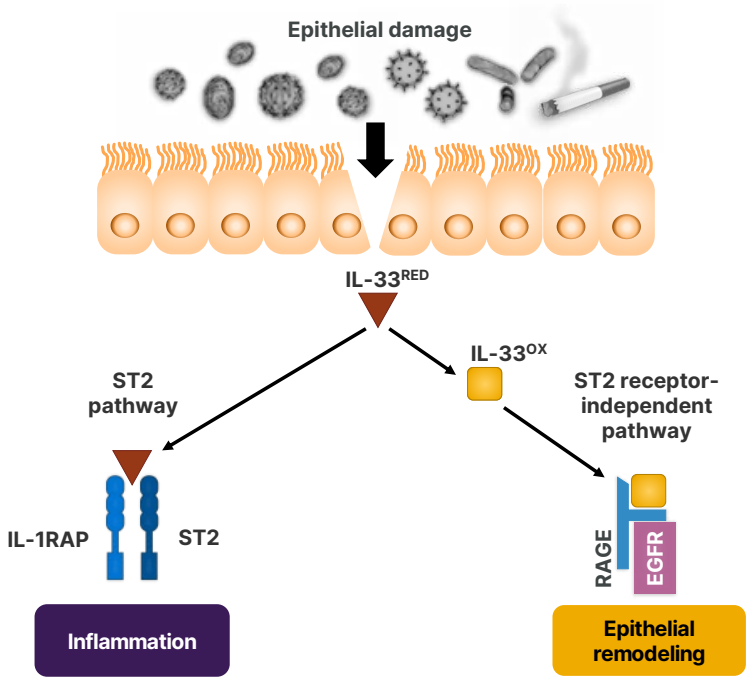
Sinha focused specifically on the role of IL-33, noting that it is part of the IL-1 superfamily and acts as a danger-associated molecular pattern protein.[40,41]

Following damage to the airway epithelium induced by several triggers, including viruses, toxins, allergens, or smoking,[41] there is a rapid release of bioactive IL-33 into the extracellular milieu as cells die.[42] Sinha stated that IL-33 acts via two distinct receptor pathways (Figure 3).[43]

In the "canonical pathway," reduced IL-33 binds to ubiquitous serum stimulated-2 (ST2) receptors, forming a ternary IL-33/ST2/IL-1 receptor accessory protein complex that induces a broad downstream inflammatory cascade.[41,42] Under the "non-canonical pathway," oxidized IL-33 is unable to bind to ST2.[42] Instead, it binds to the receptor for advanced glycation end products and epidermal growth factor receptor complex on epithelial cells, leading to epithelial repair, regeneration, and remodeling.[43] Sinha added that IL-33 is constitutively expressed in airway epithelial and endothelial cells, indicating a homeostatic role in barrier repair and maintenance. However further research is required to establish IL-33's potential as a biomarker in lung epithelial injury.[38,44-46] In addition, IL-33 is a pleiotropic amplifier of inflammation and may be an upstream regulator of host damage, leading to epithelial injury.[44,45] However, Sinha pointed out that "a better understanding of the difference between a regulated versus dysregulated response is still required."

Upon rapid release from damaged cells, the reduced IL-33 binds and signals through the ST2 receptor expressed by both innate and adaptive immune cells.[45] By binding to ST2, IL-33 activates these immune cells to produce multiple cytokines and growth factors that promote and regulate both local and systemic immunity.[45] Additionally, IL-33 expression is known to be upregulated in viral respiratory infection, and various inflammatory diseases such as asthma, where it increases airway hyperresponsiveness.[44,45]

Figure 3: The distinct receptor pathways of IL-33.[41-43]



EGFR: epidermal growth factor receptor; IL-1RAP: IL-1 receptor accessory protein; IL-33^{OX}: oxidized IL-33; IL-33^{RED}: reduced IL-33; RAGE: receptor for advanced glycation end products; ST2: serum stimulated-2.

Furthermore, Sinha added that IL-33 plays a role in the interaction with fibroblasts during epithelial airway regeneration.[45,45]

Sinha stated that IL-33 is "a molecule that is effective in homeostasis, but is involved in triggering the immune system upon damage." Sinha also mentioned that the function of IL-33 is "related to the timing and conditions under which it is found communicating with other cells." In addition, Sinha summarized that the "activation of the IL-33 pathway may be implicated in the dysregulated inflammation related to airway tissue damage, as seen in viral infections."

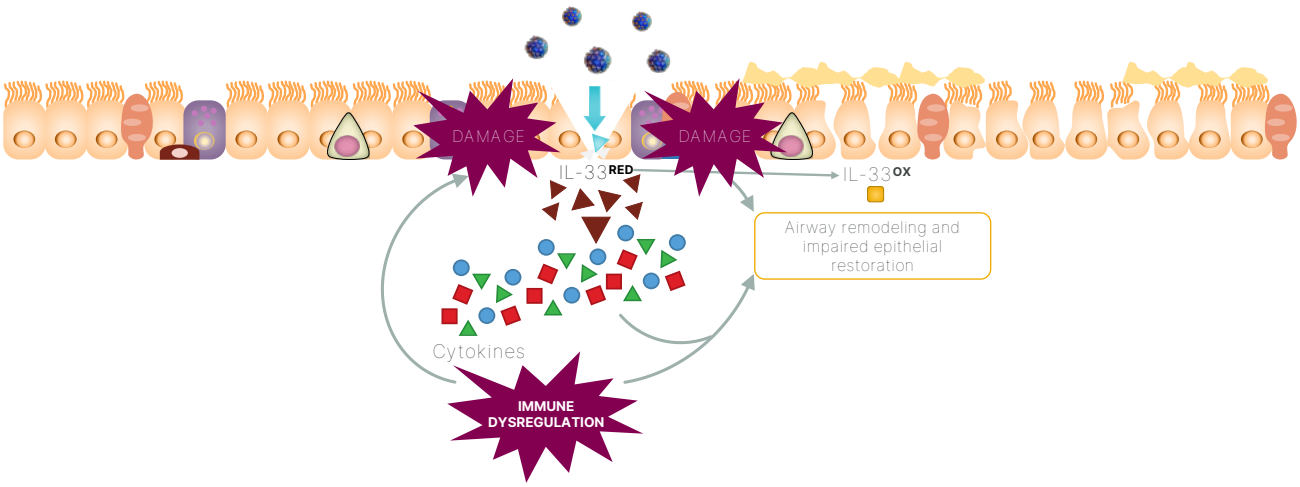
There is evidence supporting the pleiotropic effects of IL-33. In a study of natural killer T cells co-cultured with IL-33, it was demonstrated that downstream protein biomarker response of cytokines IL-4, IL13, IL5, IL2, IFN-γ, and TNF-α increased in a dose-dependent manner, demonstrating that IL-33 enhances the effector function of human invariant natural killer T cells.[47]

One hypothesis of the IL-33-mediated mechanism of injury, suggests that epithelial injury caused by a virus may lead to the rapid release of reduced IL-33, which may drive dysregulated inflammation and epithelial and endothelial dysfunction.[43,46] This, in turn, has a downstream impact on ST2 receptors, resulting in an increase in inflammatory cytokines that further signal epithelial injury (Figure 4).[43,46]

Sinha reviewed some evidence suggesting a potential role for IL-33 in viral LRTIs. In a study of human primary bronchial epithelial cells, it was determined that IL-33 release was induced by viral infections (influenza A, RSV, and rhinovirus) and this induction increased in a time-dependent manner (1–72 hours), highlighting a potential role of IL-33 across a broad range of viral RTIs.[48] Additionally, in a study of patients hospitalized with COVID-19 (N=40), peripheral blood obtained during the 30 days post symptom onset showed that serum IL-33 levels correlated with disease severity, with higher levels in moderate/severe disease compared with mild disease ($p=0.0211$).[49] Similar results were observed for IFN-α2, IL-6, and IL-10.[49] There is also evidence of pathogen-dependent host responses. In a study comparing IL-33 levels in adults with influenza A (n=24) and influenza B (n=48), serum IL-33 levels were significantly higher in patients with influenza A ($p<0.05$).[50]

IL-33 is also associated with more severe disease in infants and children with RSV infection. A study including infants <5 years with LRTIs caused by RSV (n=29) showed significantly higher

Figure 4: An IL-33 feedforward loop may drive dysregulated inflammation, as well as epithelial and endothelial dysfunction in viral infections.[43,46]



IL-33^{OX}: oxidized IL-33; IL-33^{RED}: reduced IL-33.

expression of IL-33 (p=0.029) in nasopharyngeal aspirates compared to those with upper RTIs (n=12).[51] Similar findings were observed for nasopharyngeal IL-8 levels, but not for IL-3 or thymic stromal lymphopoietin levels.[51] Similarly, another study found that IL-33 or ST2 levels in nasopharyngeal secretions were associated with the severity of acute LRTI in children <5 years (p<0.001).[52] The study also showed a higher risk of mechanical ventilation with a risk ratio of 2.89 (95% CI: 1.83–4.57) for IL-33 and a risk ratio of 4.57 (95% CI: 1.78–11.70) for soluble suppression of tumorigenicity 2.[52]

Sinha summarized the need for further investigation to establish the mechanisms involved and determine whether IL-33 is involved in dysregulated inflammation and epithelial and endothelial dysfunction pathways. Additionally, there needs to be better understanding of the kinetics of IL-33, as well as better understanding in the molecular epidemiology of viral LRTI populations.

Summary

In conclusion, LRTIs are a leading cause of hospitalizations and death globally, placing a significant burden on healthcare systems.[1–5] The dysregulation of the host immune response plays a critical role in the severity and progression of LRTIs.[23,24] Importantly, IL-33 has emerged as a potential pleiotropic regulator of dysfunctional host viral response in patients with LRTIs.[44]

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Abstract Reviews

Sharing key insights into the latest research in the respiratory field from novel abstracts presented at the American Thoracic Society (ATS)'s International Conference 2023.

The Plot Thickens When the Trachea Is Thickened

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Obstructive lung disease, pulmonary manifestations of connective tissue disease, relapsing polychondritis, tracheal disease, tracheobronchomalacia.

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BACKGROUND AND AIMS

Diffuse tracheal wall thickening is often subtle, and carries a wide differential diagnosis. Radiographic features that can narrow the differential include posterior membrane sparing and calcification.[1]

MATERIALS AND METHODS

A 61-year-old male who had never smoked, with BMI of 24, presented to clinic for 3 years of progressive dyspnea (Modified Medical Research Council [mMRC]: Grade I) and dry cough. The cough was occasionally 'barky' in quality and was steroid-responsive. Physical exam was notable for mild expiratory wheezing, and rhinoscopy showed erythematous turbinates without structural abnormality and normal vocal cords/subglottis.

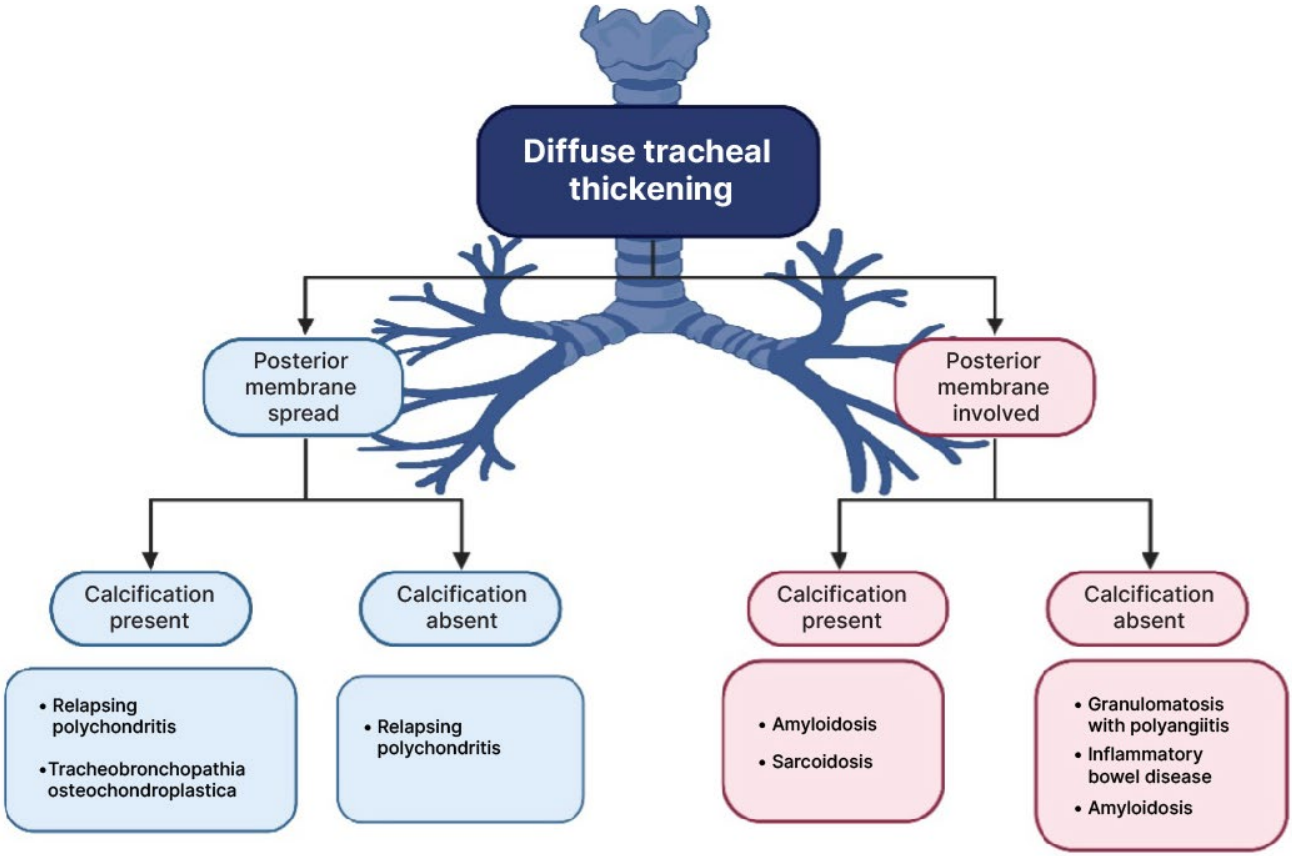
RESULTS

Pulmonary function tests demonstrated severe obstruction with forced expiratory volume in 1 second of 1.19 L (31% predicted), with positive bronchodilator response with an expiratory flow volume curve with biphasic appearance. Laboratories revealed elevation in C-reactive protein to 23.8 mg/L, with otherwise negative autoimmune and infectious testing. CT of the chest showed diffuse thickening of the anterior and lateral trachea sparing the posterior membrane with patchy calcification and tracheobronchomalacia involving the trachea to central bronchi. Further history was notable for sensorineural hearing loss that predated onset of the patient's respiratory symptoms, and had resolved on audiology re-evaluation. Bronchoscopy revealed erythematous bronchial mucosa and mild tracheobronchomalacia, thought to be consistent with the appearance of relapsing polychondritis (RP). Using the modified Damiani criteria, the patient's presentation was consistent with RP, given respiratory tract chondritis involving the trachea and bronchi on CT, sensorineural hearing loss thought likely due to RP, and steroid responsiveness.[2] The patient was started on oral prednisone, and methotrexate was initiated, resulting in gradual improvement in cough and dyspnea. The patient remains under close follow-up to monitor for treatment response, as well as airway complications.

CONCLUSION

RP often presents as a diagnostic challenge, especially in those without typical features of chondritis or arthritis on presentation.[3] Furthermore, a lack of specific serology, limitations in the role of biopsy, and lack of

Figure 1: Differential diagnosis of diffuse tracheal thickening on imaging, using posterior membrane involvement and presence/absence of calcification as two key radiographic features.



unified diagnostic criteria can complicate this diagnosis.[4] Airway involvement occurs in around 50% of patients with RP, although rarely presents with isolated tracheobronchial disease.[3,5] Several features on CT differentiate RP from other diffuse diseases in the trachea, including diffuse tracheal thickening sparing the posterior membrane, with or without patchy calcification as characterized in Figure 1.[1,5]

Patients with RP and airway involvement represent a distinct clinical subset often associated with poorer prognosis with relapsing disease, as well as airway complications, including progressive stenosis, tracheobronchomalacia, and infection.[1,6] The evidentiary basis for treatment of RP primarily based on case reports and case series, which is generally dictated the degree of organ involvement, although randomized trials are warranted.[7] Treating patients with RP and airway involvement requires oral corticosteroids and as well as considering disease modifying anti-rheumatic drugs, oftentimes is the first line agent, as a substantial proportion of those with RP progress despite initial immunosuppression.[4] In refractory cases of those with tracheobronchial disease, the use of biologics with most case series data supporting TNF-α inhibitors can be considered, although again, randomized data in this field are lacking.[7,8] Patients with RP with respiratory manifestations not only require follow-up monitoring for treatment response and complications, but also for other evidence of concurrent autoimmune disease or hematologic malignancy, which occurs in a subset of those with RP.[4,6]

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Could Malacia of the Tracheobronchial Tree Cause Bronchiectasis in Pediatric Patients?

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Keywords: Bronchiectasis, bronchomalacia, childhood, chronic cough, tracheomalacia.

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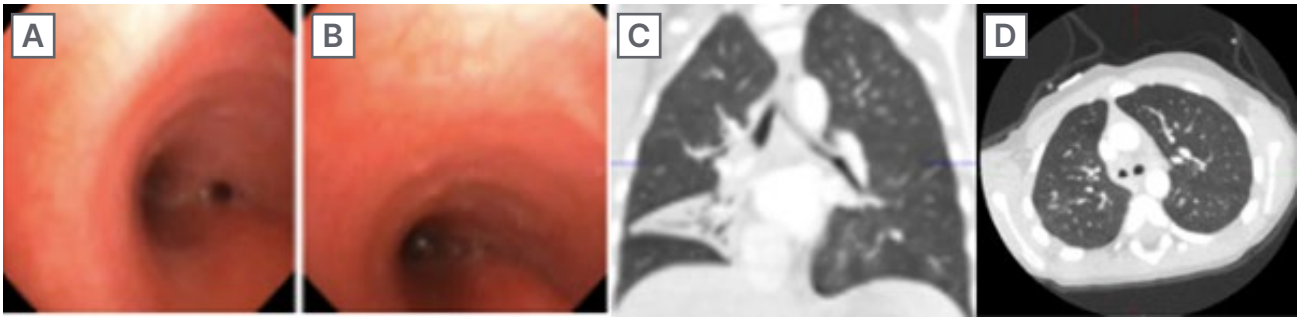
BACKGROUND

Bronchiectasis is one of the differential diagnoses in the pediatric patient with chronic wet cough.[1] Determining the etiology of the bronchiectasis is essential to initiate prompt and appropriate treatment, preventing further lung injury.[2-4] Previous studies have revealed an association of childhood bronchiectasis and the presence of tracheomalacia and/or bronchomalacia, but causality has not been proven yet.[5,6] It is hypothesized that impairment on airway clearance may lead to chronic inflammation and recurrent infections seen in these patients.[7]

CASE PRESENTATION

The authors' case is an 8-year-old female who presented to the pulmonary clinic at age 3 years with poorly controlled asthma despite appropriate treatment, chronic wet cough, and mild clubbing. Initial workup revealed normal

Figure 1: Right bronchomalacia (A and B); chest CT with right inferior and middle lobe consolidation (C); and chest CT at 1 year follow-up with right bronchiectasis (D).



immune studies and sweat test. Chest CT with contrast showed right lower and middle lobe consolidations and narrowing of the proximal portion of the right main bronchi (right bronchomalacia). Given the findings on chest CT, a flexible bronchoscopy was performed, which revealed severe right bronchomalacia and purulent mucus plugging in the right main stem. The patient was admitted for intravenous antibiotics and initiation of airway clearance with intrapulmonary percussive ventilation. They were discharged on mucolytics and an airway clearance device (oscillatory vest). A year after the diagnosis of bronchomalacia, repeat CT revealed bronchiectasis in the same areas previous involved. The patient's airway clearance regimen was intensified, establishing an outpatient sick plan with hypertonic saline, intrapulmonary percussive ventilation, and vest. Since, there has been a significant improvement on their clinical course as indicated by a decrease in airway secretions and improvement in the inflammatory pattern, as well as decreased neutrophils seen on subsequent bronchoalveolar lavage samples.

CONCLUSION

Bronchiectasis is an important cause of morbidity in pediatric patients, especially in developing countries.[8,9] Cystic fibrosis is the most common cause of bronchiectasis in the pediatric population; nevertheless, there are many other etiologies leading to bronchial dilatation.[10]

In the authors' case, a pediatric patient with chronic wet cough was diagnosed with bronchomalacia and posteriorly developed bronchiectasis. Significant improvement was noticed after initiation of airway clearance.

Further studies should be performed in order to elucidate this hypothesis. Meanwhile, healthcare professionals should have a high index of suspicion for bronchiectasis in pediatric patients with tracheobronchial malacia and symptoms suggestive of bronchiectasis.

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Melatonin: Harmless Supplement? A Case of Angioedema and Anaphylaxis

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Keywords: Anaphylaxis, angioedema, dietary supplements, melatonin.

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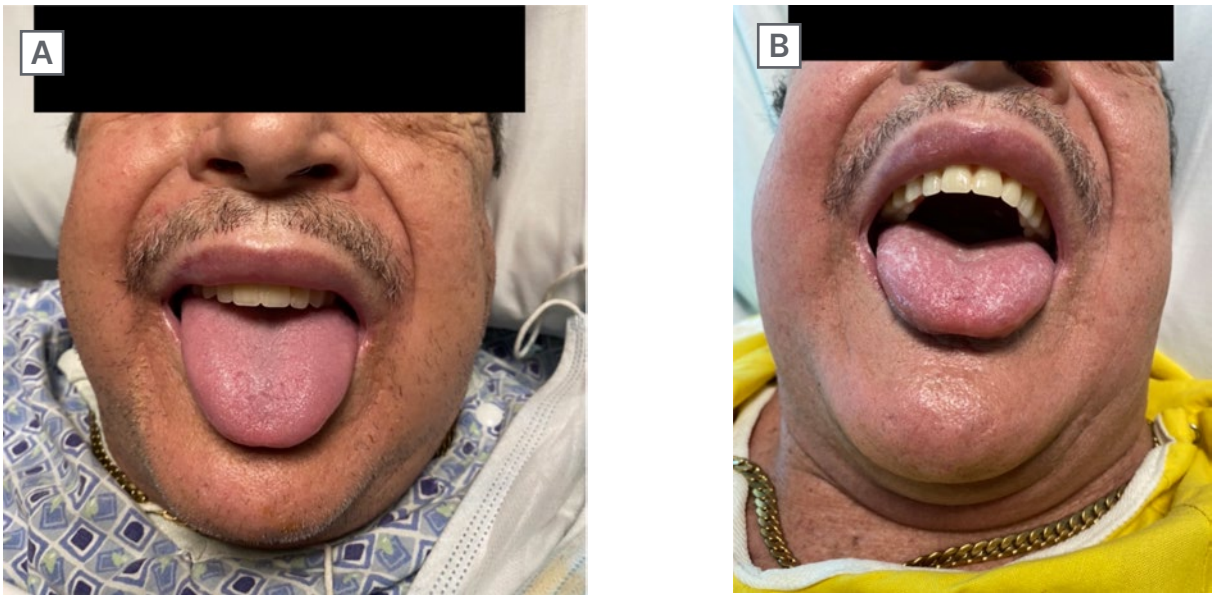
BACKGROUND AND AIMS

Angioedema can present as a benign symptom or a life-threatening emergency. Angioedema accompanied by anaphylaxis is generally caused by allergic reactions due to IgE-mediated hypersensitivity that leads to mast cell degranulation.[1] Melatonin is an unregulated supplement that providers commonly prescribe for its effect on sleep onset and maintenance.[2] Here, the authors present a patient who developed angioedema and anaphylaxis after melatonin ingestion.

MATERIALS AND METHODS

A 68-year-old male without a history of allergy, eosinophilia, or atopy administered melatonin 2 nights prior to presentation, and woke up with minor facial swelling, which resolved shortly after. They used melatonin again the following night, and quickly awoke with acute dyspnea and worsened facial swelling. They were given intramuscular diphenhydramine en route to the emergency department, but presented with hypotension and an oral cavity obstructed by glossal edema (Figure 1A).

Figure 1: Patient images of improved angioedema following medical management.



A) Patient showing facial and glossal edema. **B)** Improved angioedema following medical management.

RESULTS

Laboratory results revealed peripheral eosinophilia, while imaging did not reveal pertinent findings. They were administered intravenous methylprednisolone and intramuscular epinephrine, and subsequently admitted to a progressive care unit. Complement 4 was normal, reducing the likelihood of complement 1 esterase deficiency. The patient did not report prior melatonin, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker use, and family history of angioedema. Furthermore, a thorough medication review did not reveal any significant drug-drug interactions with melatonin. Laryngoscopy revealed no airway compromise. The following day, re-examination revealed significantly improved facial and tongue edema with increased oral cavity space (Figure 1B). The patient was at their baseline 2 days later, and was discharged with a 5-day prednisone course and an EpiPen® (Viatris, Canonsburg, Pennslyvania, USA). The patient did not complete outpatient allergy testing as they chose instead to avoid melatonin. Upon 1-year follow-up, the patient denied any further episodes of angioedema.

CONCLUSION

Although relatively well tolerated, melatonin supplements have rarely been reported to cause angioedema with symptoms of flushing, difficulty breathing, and dysphagia.[3] To the authors' knowledge, this is the first case of melatonin-induced anaphylaxis. As melatonin is a naturally produced hormone, the allergic agent in this case is likely an unregulated excipient. A previous study found that among 31 different commercial melatonin supplements, the melatonin percentage of the labelled content ranged from -83–+478%.[4] Compared with prescription drugs, dietary supplements are regulated less strictly by the U.S. Food and Drug Administration (FDA), and may contain unlabeled, potentially allergenic, inactive ingredients.[5] Therefore, a comprehensive medication review that includes over-the-counter drugs and dietary supplements is necessary to identify an etiology for new onset allergic symptoms, in this case as severe as angioedema and anaphylaxis.

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Examining Heterogeneity of Treatment Effect in Hospitalized Veterans with COVID-19

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Keywords: Corticosteroids, COVID-19, heterogeneity of treatment effect severe acute respiratory syndrome coronavirus 2, veterans.

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BACKGROUND AND AIMS

The clinical response to severe acute respiratory syndrome coronavirus 2 varies widely among patients, some of whom may progress to severe COVID-19. Frequently, patients are stratified by a single characteristic (e.g., age or use of supplemental oxygen) to determine treatment allocation and response. A more comprehensive approach using a multivariable prediction tool may help identify heterogeneous treatment effects by risk strata and help guide therapeutic interventions.

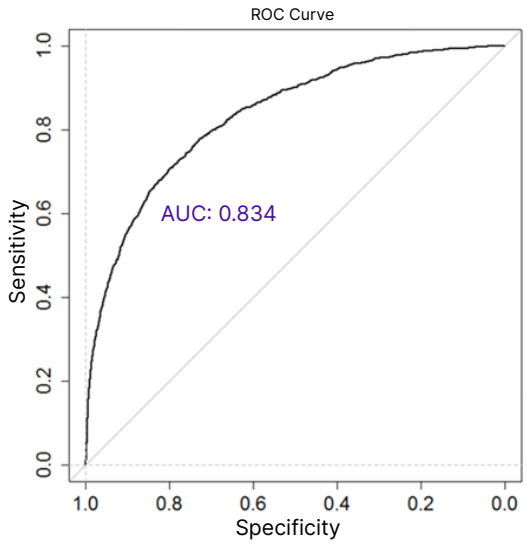
MATERIALS AND METHODS

The authors assembled a national cohort of veterans hospitalized between March 1, 2020 and February 28, 2022, with real-time PCR-confirmed severe acute respiratory syndrome coronavirus 2 infection. The authors used patient demographics, laboratory, and vital sign data in stepwise logistic regression to create a mortality risk prediction model stratified into five distinct risk categories for 60-day mortality in patients not treated with corticosteroids. They subsequently incorporated patients who were treated with steroids and estimated the differential steroid effect by risk group on 60-day mortality, by using doubly robust linear regression with inverse probability of treatment weights.

RESULTS

The authors identified 43,222 veterans hospitalized at 130 Veterans Affairs Medical Centers (median age: 71; 72% White) with COVID-19, of whom 22,436 (51.9%) received treatment with systemic steroids. The authors' final risk prediction model included 16 clinical and laboratory variables and had an area under the curve of 0.834 (Figure 1). Risk quintiles for 60-day mortality ranged from <3% (lowest) to >28% (highest). Unadjusted mortality rates in the

Figure 1: Receiver operative characteristic curve for COVID-19 mortality risk prediction model.



The authors' mortality risk prediction model incorporated 16 clinical and laboratory variables, and had an AUC of 0.834. The 60-day mortality risk quantiles ranged from <3 to >28%.

AUC: area under the curve; ROC: receiver operative characteristic.

validation set were 23.0% for patients receiving steroids, and 11.6% for those not receiving steroids. In the authors' validation cohort, steroid treatment was associated with reduced odds of death in the lowest risk group (odds ratio: 0.65; 95% confidence interval: 0.44–0.93). They also saw a trend towards increased odds of death in the highest risk group (odds ratio: 1.14; 95% confidence interval: 0.78–1.67), corresponding to an absolute risk increase of approximately 8%.

CONCLUSION

In a cohort of elderly multimorbid veterans, the authors observed evidence of decreasing mortality risk benefit due to steroids across groups with increasing baseline risk of death. These results contrast with currently published studies, but may also point to a signal of increased mortality with steroid use seen in a recent large-scale study in the RECOVERY trial group in non-mechanically ventilated patients,[1] and an increased rate of ventilator-associated pneumonia noted in patients undergoing mechanical ventilation.[2]

Future steps will include the identification of and accounting for possibly excluded confounders, including supplemental oxygen use and steroid dosing. ●

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Neuropsychiatric Problems in Primary Ciliary Dyskinesia? First, Go to Sleep

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Keywords: Neuropsychiatry, obstructive sleep apnea, primary ciliary dyskinesia (PCD), sleep disorders.

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BACKGROUND AND AIMS

Sleep disorders are characterized by the impairment of the quality, timing, and amount of sleep, which results in daytime distress and functioning. Primary ciliary dyskinesia (PCD) is a rare genetic condition characterized by oto-sino-pulmonary pathologic manifestations with multiple comorbidities, including sleep disorders. The available literature on sleep disorders and their neuropsychiatric comorbidities in PCD is limited, especially for Hispanic patients.[1,2] This pilot study aims to assess the presence of sleep disorders and neuropsychiatric comorbidities in patients with the *RSPH4A* PCD founder mutation (c.921+3_921+6delAAGT) in Puerto Rico.

The aims of this study were to identify sleep-related disorders in PCD patients with the Puerto Rican founder mutation, and assess their neuropsychiatric manifestations. The researchers also aimed to recognize the importance of early diagnosis and prevention of PCD-related obstructive sleep apnea (OSA) or other sleep-related disorders in pediatric and adult patients with PCD.[3]

MATERIALS AND METHODS

The authors performed a retrospective case series which included 15 patients with PCD (n=15; 10 pediatric and 5 adult), at the Puerto Rico PCD Foundation. Sleep questionnaire reports were obtained by the pediatric modified STOP-Bang (PM-STOP-Bang) and standardized (STOP-Bang) criteria for pediatric and adult patients, respectively.[4] These tools aid in identifying risk factors for respiratory obstruction and neuropsychiatric manifestations. A STOP-Bang Score of >3 points correlates to a moderate risk of OSA in children and adults. In addition, sleep-behavioral manifestations in the areas of cognition and mood were assessed.

RESULTS

Most pediatric patients presented with a PM-STOP-Bang >3 (90%), for a moderate-to-high risk (Figure 1). Obstructive risk factors such as snoring (70%), tonsillar hypertrophy (50%), nasal polyps (50%), and bronchiectasis (70%) were identified (Figure 2). The most common neuropsychiatric symptoms reported were poor concentration (70%), oppositional behaviors (50%), irritability (30%), and hyperactivity (20%) (Figure 1). Furthermore, the adult population showed a STOP-Bang >5 (60%), with high-risk. Obstructive risk factors included snoring (60%), BMI >35 kg/m^2 (40%), and bronchiectasis (100%; Figure 3). Neuropsychiatric presentation with tiredness (80%), poor concentration (40%), and irritability (20%) was reported (Figure 4).

CONCLUSION

Based on the data, most PCD patients with the *RSPH4A* (c.921+3_921+6delAAGT) PCD founder mutation presented with a high risk for OSA, and neuropsychiatric manifestations as seen in patients with this sleep disorder. This observation would warrant further studies, including physical examination, screening protocols, sleep studies, and neuropsychological testing. Additional

Figure 1: Most common sleep-related neuropsychiatric symptoms were reported in pediatric patients with primary ciliary dyskinesia.

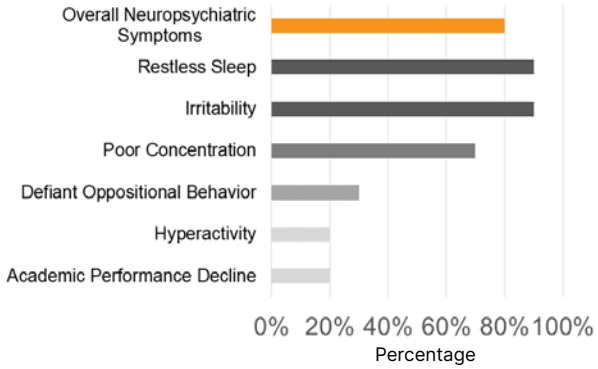


Figure 2: Risk factors related to sleep-related disorders in pediatric patients with primary ciliary dyskinesia.

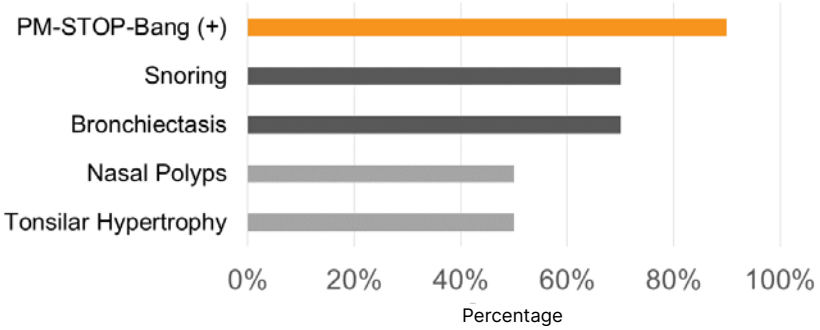


Figure 3: Most common sleep-related neuropsychiatric symptoms were reported in adult patients with primary ciliary dyskinesia.

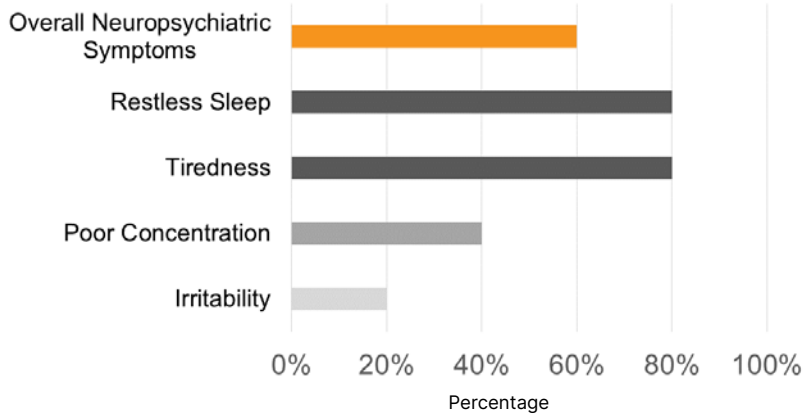
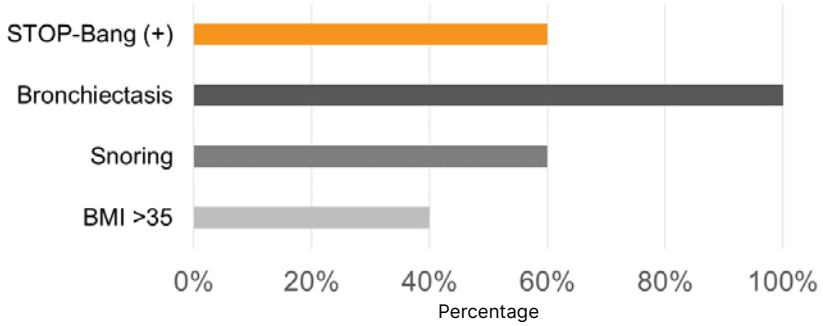


Figure 4: Risk factors related to sleep-related disorders in adult patients with primary ciliary dyskinesia.



studies are required in multicentric clinical trials to allow an understanding of whether these neuropsychiatric manifestations are related to a neurodevelopmental or neurodegenerative process due to this rare ciliopathy.[3,5,6]

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Beginning with the Ace of Spades and Ending with the Clot of Hearts: Hypereosinophilic Syndrome with a Left Ventricular Thrombus

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Keywords: Hypereosinophilic syndrome, idiopathic hyereosinophilic syndrome (IHS), left ventricular thrombus.

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BACKGROUND

Idiopathic hypereosinophilic syndrome (IHS) is characterized by persistent eosinophilia greater than 1,500 /µL for more than 6 months with organ system involvement in the absence of an explained cause.[1] The organs involved can vary, affecting systems such as the lungs, skin, and cardiovascular system. Cardiovascular complications are a major source of morbidity and mortality, and prevalent in 40–50% of cases.[1] The most characteristic cardiovascular abnormality is endomyocardial fibrosis, causing restrictive cardiomyopathy.[1] However, patients are also prone to hypercoagulability, which in rare cases can manifest as ventricular thrombi.

CASE PRESENTATION

A 65-year-old female presented to the emergency department with complaints of worsening dyspnea and cough for 2 weeks. They were recently discharged following treatment for bilateral pneumonia, at which time they were noted to have an incidental left ventricular (LV) thrombus on an echocardiogram. Their symptoms improved with antibiotics, prednisone, and apixaban, but acutely worsened following completion of their treatment. Their laboratory work was remarkable for significant eosinophilia. A CT scan of the chest revealed recurrent bilateral pulmonary infiltrates, and repeat echocardiogram revealed persistence of the LV thrombus with an obliterated apex in the shape of an ace of spades (Figure 1). Cardiac MRI confirmed the presence of a 1×2 cm LV thrombus with highly mobile components, along with diffuse subendocardial gadolinium enhancement consistent with IHS, with cardiac involvement (Figure 2). They were ultimately discharged on prednisone, mepolizumab, and warfarin with resolution of their eosinophilia. They returned a month later with multifocal embolic stroke. Repeat echocardiogram revealed the thrombus had enlarged to 3×2 cm. While on therapeutic low-molecular heparin, they developed acute right limb ischemia and underwent a right common and external iliac thrombectomy. Following embolectomy, they were ultimately discharged on dabigatran.

They returned 2 months later with recurrent stroke-like symptoms. MRI revealed new multifocal infarcts, and echocardiography showed the thrombus had grown to 3×4 cm. Their anticoagulation was changed to enoxaparin, and they were scheduled for LV thrombectomy by cardiothoracic surgery. Unfortunately, they returned a week later secondary to a fall and were found to have a subdural hematoma with midline shift. They underwent two craniotomies with poor neurological response and were given comfort care.

CONCLUSION

The cardiovascular complications in IHS typically involve a stepwise process. Initially, the eosinophils penetrate the myo- and endocardium, with subsequent eosinophilic degranulation and necrosis.[2] The resulting necrosis allows fibrin deposition, beginning the formation of a thrombus.[2] However, the thrombus in IHS is not solely comprised of platelets. A study by Leiferman et al.[2] noted that

Figure 1: Echocardiography showing four chamber view and ace of spades left ventricle (A); two chamber view with left ventricular thrombus (B); and two chamber view with left ventricular thrombus (C).

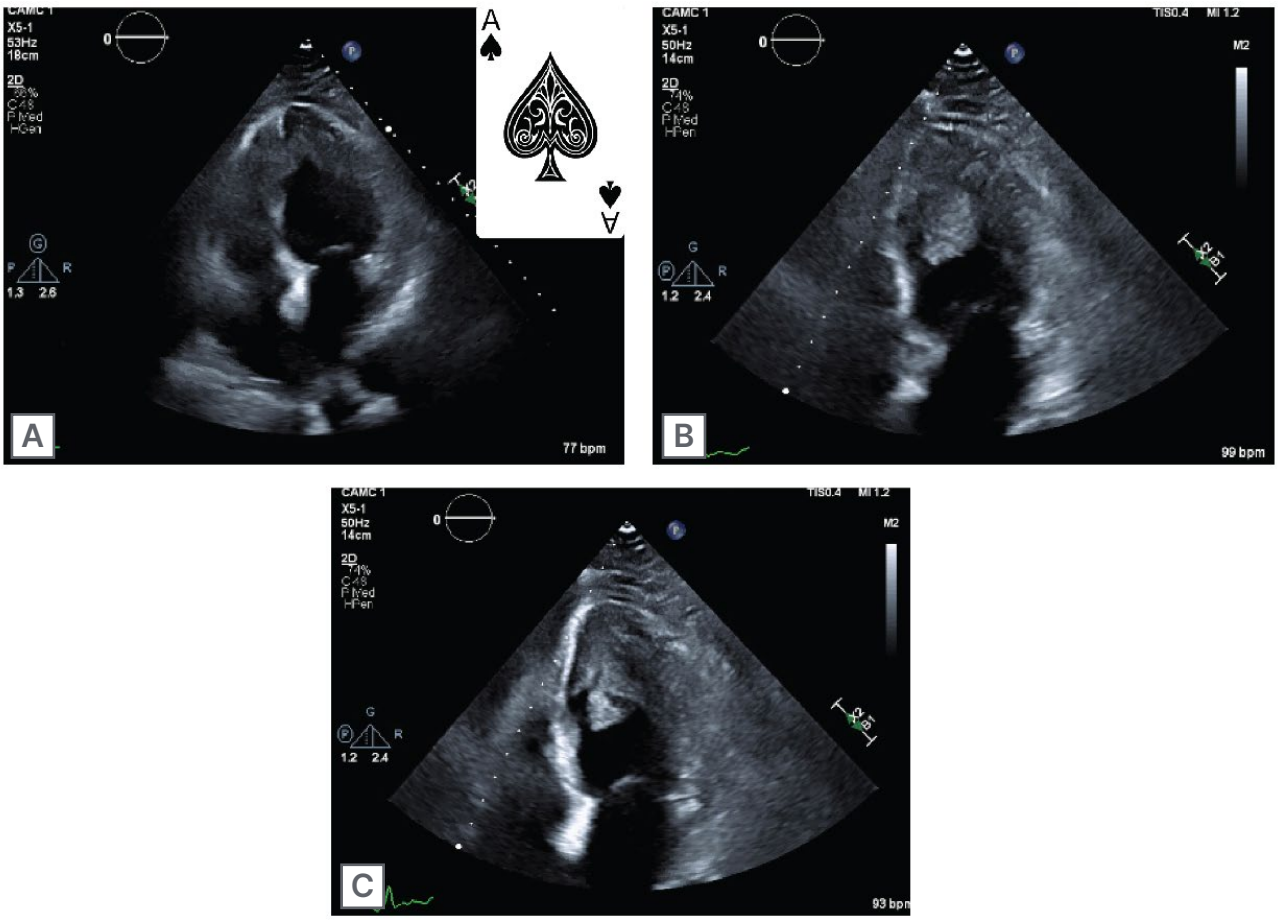
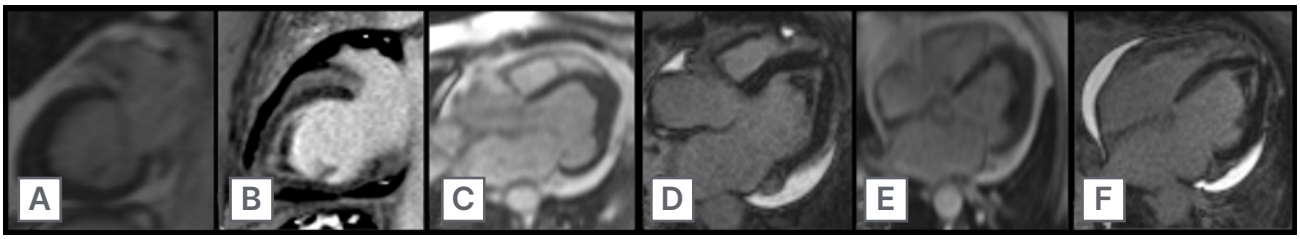


Figure 2: Cardiac MRI showing two chamber view of late gadolinium enhancement (A–C), and four chamber view of late gadolinium enhancement and left ventricular thrombus (D–F).



the thrombi are comprised of intact eosinophils and eosinophilic granulation proteins.

It is thought that eosinophilic granules have components that inhibit thrombomodulin, enhancing thrombus formation.

This raises the question as to how thrombi in IHS should be treated given its composition.

There are currently no guidelines for treatment. The authors' patient had complications of the thrombus despite being on apixaban, warfarin, and heparin. In one case report, warfarin was given with successful reduction in an LV thrombus.[3] However, there are several cases of continued thromboembolic phenomena despite adequate anticoagulation, while others report acute bleeds.[2] As a result, current treatment

should revolve around treating the underlying hypereosinophilic syndrome.[4]

First-line therapy consists of corticosteroids, with mepolizumab being considered an alternative second line option in corticosteroid sparing treatment.

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A Rare Case of Samter's Triad due to Acetaminophen

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Keywords: Acetaminophen, airway, aspirin sensitivity, hypersensitivity, nasal polyps, Samter's triad.

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BACKGROUND

Aspirin-exacerbated respiratory disease (AERD), also known as Samter's triad, is characterized by the presence of bronchial asthma, nasal polyps, and hypersensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAID). The authors present a unique case of a 54-year-old female with a history of asthma and diabetes who developed life-threatening respiratory failure requiring intubation following the administration of acetaminophen. This case highlights the potential dangers of seemingly benign medications in patients with AERD and underscores the importance of obtaining a comprehensive medical history prior to drug administration.

CASE PRESENTATION

The patient underwent an elective hysterectomy and bilateral salpingo-oophorectomy without complications. However, on post-operative Day 1, they experienced acute respiratory failure with hypoxia and hypercapnia, necessitating intubation for airway protection. Despite administration of bronchodilators, the patient exhibited air trapping and high airway resistance, making mechanical ventilation challenging and requiring manual bag–mask ventilation.

The patient subsequently experienced asystole, requiring cardiopulmonary resuscitation and vasopressor support, with return of spontaneous circulation achieved within 1 minute. On Day 3, the patient was successfully extubated after weaning off pressors, sedatives, and paralytics. Acetaminophen was identified as the trigger for respiratory failure, and a diagnosis of AERD was established based on a CT sinus scan revealing significant mucosal thickening consistent with chronic inflammatory illness. The patient's symptoms improved with appropriate management, and they were discharged on a steroid taper.

AERD is a non-IgE-mediated hypersensitivity reaction associated with aspirin or NSAIDs. The inhibition of the cyclooxygenase (COX) pathway by NSAIDs leads to reduced production of anti-inflammatory prostaglandin E2 and increased synthesis of pro-inflammatory leukotrienes. Acetaminophen, although not classified as an NSAID, exhibits weak COX-1 and COX-2 inhibition, potentially resulting in increased leukotriene production and decreased glutathione levels in alveolar macrophages.

Reduced glutathione levels can trigger acute inflammatory processes in the lungs. Importantly, up to 34% of aspirin-sensitive patients may experience dose-dependent cross-reactivity with acetaminophen, particularly at doses of 1 g or higher. This case underscores the significance of obtaining a detailed medical history when prescribing apparently innocuous medications to patients with asthma.

CONCLUSION

In conclusion, this case highlights the severe respiratory complications that can arise from acetaminophen administration in patients with AERD. Healthcare providers should be vigilant in assessing patients' medication history, particularly in those with asthma, to prevent potentially life-threatening reactions. Improved awareness and understanding of AERD and its associated risks will facilitate appropriate management strategies and optimize patient outcomes. ●

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An Unusual Case of Hymenoptera Venom-Induced Angioedema

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Angioedema, IgE, hymenoptera, venom-induced, wasp.

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INTRODUCTION

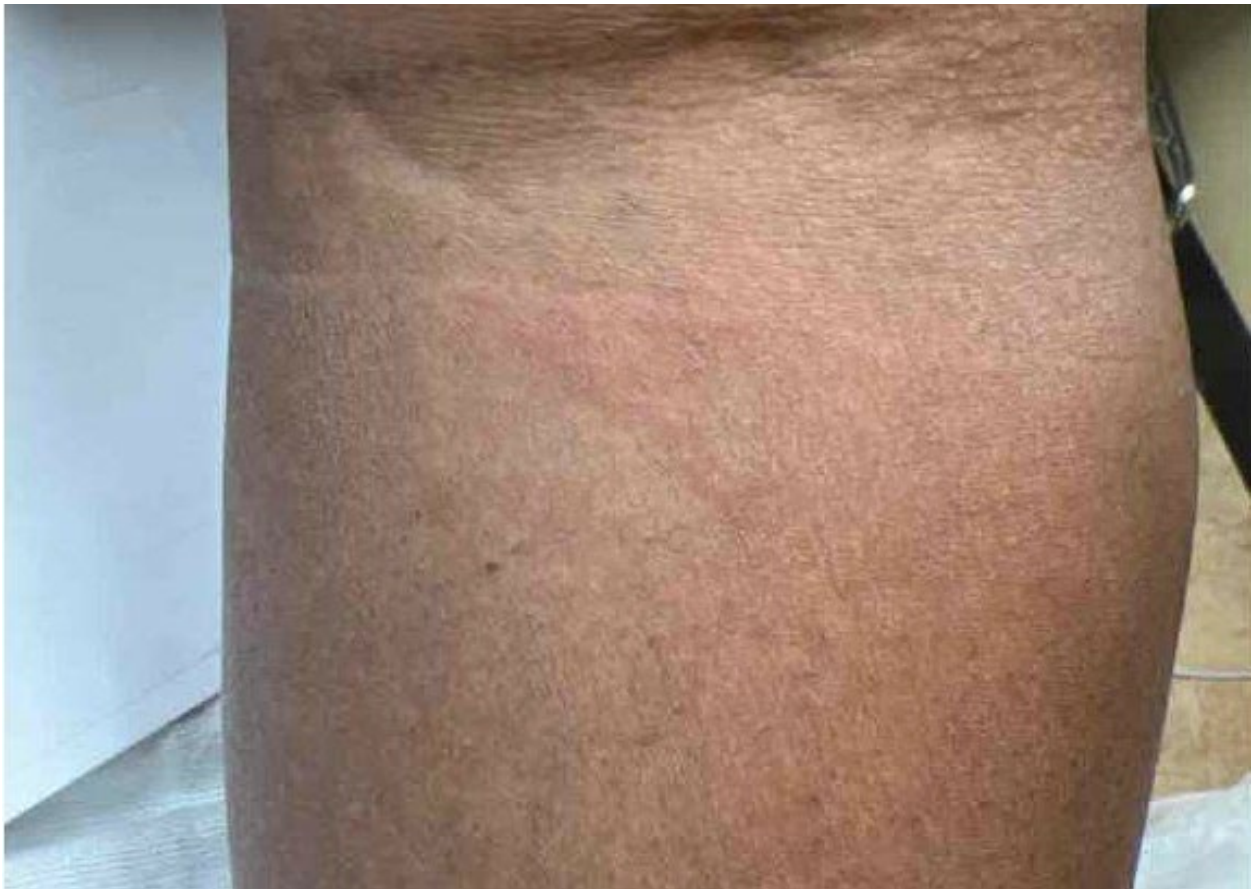
Angioedema is a localized submucosal reaction that can be part of a systemic anaphylactic response. The etiology can be difficult to diagnose, but is commonly mast-cell or bradykinin-mediated. Here the authors present a case of hymenoptera (a large order of insects) venom-induced angioedema.[1]

CASE PRESENTATION

A 58-year-old male presented with a 12-hour history of progressive oral angioedema advancing to glossitis. Their medical history included hypertension and hyperlipidemia, with reported use of lisinopril 3 years ago, which was discontinued due to coughing. Current home medications include losartan (initiated 3 months prior), aspirin, amlodipine, and rosuvastatin. The patient did not recall any enticing events, such as insect bites or stings, so there was high suspicion for losartan-induced angioedema. Upon further questioning, they reported working as an electrician and they had been underneath a house 1 hour prior to the onset of symptoms, where they did recall seeing a 'wasp'. There was also a questionable history of their mother requiring hospitalization for oral edema, raising concern for hereditary angioedema.

The patient denied any rashes, dysphagia, drooling, hoarseness, stridor, shortness of breath, or abdominal pain. Physical exam was notable for profound lip and tongue base swelling, with slight blunting of the epiglottis evidenced on flexible bronchoscopy. There was a mild area of localized, raised, non-pruritic, erythematous left forearm rash (Figure 1). They were administered intravenous (IV) methylprednisolone 125 mg, IV diphenhydramine 25 mg, and IV famotidine

Figure 1: Cutaneous eruption from wasp sting.



with improvement in symptoms. Ear, Nose, and Throat recommended monitoring for 24 hours for signs of anaphylaxis. Laboratory testing revealed normal erythrocyte sedimentation rate, C-reactive protein, and tryptase levels, with borderline elevations in complement component 3 and 4.[2] Their hospital course remained uneventful, and they were discharged home with prednisone, diphenhydramine, epinephrine auto-injectors, and an allergy/immunology follow-up for further allergen testing. Send-out laboratories returned with normal C1 esterase inhibitor antigen level and elevated wasp venom IgE >1,300 (normal <214).

DISCUSSION

Hymenoptera stings can lead to IgE-mediated effects that are more commonly localized to cutaneous or submucosal reactions, including angioedema.[3] Prompt recognition and management can prevent further progression to anaphylaxis. This case emphasizes the importance of clinical history, and highlights the lab workup to differentiate angiotensin receptor blocker angioedema versus hereditary angioedema versus venom-induced angioedema.

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Congress Interviews

We had the pleasure of speaking with Debra M. Boyer and Michelle Gong, who shared insights into their careers and the field of respiratory healthcare. The experts covered fascinating topics and highlighted key focuses of the American Thoracic Society (ATS) 2023 International Conference.

Featuring: Debra M. Boyer and Michelle Gong

Debra M. Boyer

Division of Pulmonary Medicine, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, USA; Co-chair of the International Conference Committee for the American Thoracic Society (ATS)

Citation: Respir AMJ. 2023;1[1]:51-55. DOI/10.33590/respiramj/10305111. https://doi.org/10.33590/respiramj/10305111.

Q1 Were you initially interested in pursuing a career in pediatrics? What was it about pediatric pulmonology that drew your attention?

I think a lot of us initially get inspired by individuals, and it was a particular individual for me, who I thought was phenomenal who attracted me to learn more about the field. We have remained friends, and he is a mentor and an inspiration to me to this day.

Once I started, I really enjoyed the patient population and the fact that you can establish significant longitudinal relationships with patients, whether it is a patient with cystic fibrosis (CF) or patients with lung transplants. I see these patients more often than their pediatricians and really get to know them.

I also enjoyed the ability to do procedures; however, I did not want to be a surgeon and spend all my time in the operating room. I liked doing bronchoscopies and interventions, but also seeing my patients awake and being able to talk to me. And then I just enjoyed the physiology and the fact that pulmonary medicine involves the whole body as opposed to just focusing on one organ. This is very true with CF or patients of lung transplant. While I have to know pulmonary physiology, I also have to know about infectious disease, reproduction, mental health, and gastroenterology. I like the fact that while I focus on the lungs, I also have to know a lot of medicine, which was very interesting to me.

Q2 Having specialized in lung transplantation, what do you think are some of the unique challenges associated with lung transplantation?

Lung transplantation, whether it is pediatric or in adults, is probably one of the hardest

areas to have success, aside from intestinal transplantation. Heart, kidney, and liver transplants have much better outcomes than lung transplants. Added to that is the challenge of finding donors. The good news is that there are fewer children dying and becoming donors, but the flip side of that is when you have a sick child who needs a lung transplant, there are fewer donors available. This means children often have to wait longer, and we have to find ways to keep them comfortable while waiting for a donor. Finally, it is about finding the balance between immunosuppression and allowing them to accept the organs, while not giving them so much immunosuppression that they then get infections and consequences from that. When you do a lung transplant in pediatrics, you hope a child can have as normal a life as they can. You do not want to do a lung transplant and then have them live in a bubble, unable to do anything. While we want these children to go out and live and do things, that also exposes them to risk and infections. So, it is about finding a balance to have a life, but to also be somewhat reasonable.

Q3 You co-authored a paper earlier this year entitled 'A statement on the current status and future needs of the pediatric pulmonology workforce: Pipeline Workgroup'. Can you talk about the main findings from this paper and whether workforce shortages are a particular challenge in pediatric medicine compared to other specialties?

This is an area that I, and the community of pediatricians and pediatric subspecialties, are very interested in. There are a lot of initiatives that think about this, and I have been involved with a number of them. The short answer is yes. There is a tremendous shortage both of general pediatricians and of pediatric subspecialists, including pulmonary, nephrology, and infectious diseases; however, the reason why is complicated. This paper looked at trying to understand why people choose to go into a subspecialty, and to identify areas where you can intervene. If the reason is to do with finances or the length of training, for example, you can intervene.

So, we talked with trainees as to why they were interested in pediatric pulmonology. A lot of the reasons were similar to mine: they were interested in bronchoscopy, applying pulmonary physiology, and longitudinal relationships. After looking at different literature and analyzing trainee surveys, we looked at the different reasons. Two very significant factors include exposure and mentorship.

There was also a question about whether the length of training affected people's interest in going into the field. In the USA, to do what I do, after medical school you complete 3 years of pediatrics and then 3 years of fellowship training in pediatric pulmonary, and we wondered whether that is too long. It is not really clear if that length of time negatively influences pediatric residents to choose pediatric pulmonary training.

Then there was the question of whether debt had an influence, as in the USA we accumulate a lot of debt when going to medical school.

The short answer to that is it is not clear. It might play a role, but a lot of trainees do not think about debt when they choose a field, as they choose based on what they are interested in. In pediatrics, we get paid a lot less than our adult counterparts, based on government reimbursement. This is not okay and could be another reason, but more data is needed.

The paper addressed all these different things, and really recommended the need to mentor our trainees. We need them to engage with us as pediatric pulmonologists, get them to conferences, and really show them that what we do is pretty amazing, and that it is fun to work with kids.

Q4 One of your prominent research interests is medical education. What would you most like to see optimized in medical education surrounding pediatric pulmonology?

We are doing a lot of research into what is the best way to teach. Generations are different, and the way people want to learn changes. The biggest change in medical education is probably moving towards what we call competency-based medical education. In the USA, all our training is time-based. As I mentioned before, you do 3 years of a pediatrics residency after medical school. However, there is now a question of if it should be based more on competency. I might, for example, only need 2 years to achieve competency, whereas somebody else might need 4 years. Should it really be based on length of training, or should it be based on when you achieve those metrics? A lot of people are thinking about it logistically, which is challenging. If you do not know how long trainees might be around, it makes it harder to plan a program for them and to take care of the patients under your care. So, it can get complicated, but that is one of the exciting areas in medical education, and I think is the right way to go. It is super challenging to think about how to how to do it well, and how to implement it properly and safely.

At the moment, different certifying bodies are at different stages in applying this. The American Board of Pediatrics (ABP) have developed different tools such as entrustable professional activities that are more competency-based tools. Over time, I think it will become more and more part of what we all do, but right now it is still evolving.

Q5 What are the key areas of focus for the American Thoracic Society (ATS) this year?

I can speak best about the congress in general, which I think reflects on the society. Our goal is to serve our membership and to be one of the premier, if not the premier, respiratory society in terms of research, clinical care, and advocacy for pulmonary, critical care, sleep medicine, and pediatrics. We are the ATS, but we have a pretty substantial international membership, despite taking a little hit with COVID-19.

With this conference there are a couple of goals that we are hoping to accomplish, and I think a lot of that is set by the fact that we are in Washington, D.C., USA, which is our capital. There is a particular emphasis on advocacy and how we can all participate. A lot of the sessions are focused on how scientists, clinicians, and researchers can also function as advocates and help to improve the respiratory health of people in the USA and abroad. While we have a lot of science, education, and clinical areas being presented, we are also moving into how we can also advocate for things like global health, health disparities, health inequities, climate change, and gun violence. Those are all areas that have multiple touch points during the conference, and we hope that the government folks that are in town in Washington, D.C., can participate as well.

We have three keynote sessions at the start of the first 3 days of the conference to set the tone. The first session talks about how science promotes health equity by decreasing disparity, thinking about health care disparities and health care equality. The second session touches on how climate influences health, both positively and negatively. And then the last session is something that, unfortunately, is a huge problem in the USA, which is gun violence. This will be a panel discussion about reducing gun violence through advocacy, and it will explore what we can do as individuals, but also as caregivers and researchers, to have an impact on reducing gun violence. The hope is that those keynotes will set the stage for the rest of the conference and thinking about how to put the things we have learned into action.

Q6 How does the ATS use its position to educate surgeons, nurses, and trainees about the field of thoracic medicine?

There is no one way to educate everybody, and one of the things that we take pride in at our conference is the number of people who attend. You cannot provide one way to educate all these people; therefore, we offer a large variety of sessions and session types during the conference.

I have always been impressed at the number of different things you can do at the congress. There are large plenary sessions and keynotes, which are in large rooms and where you just listen. There are smaller symposia, where it is a little more comfortable and attendees have the ability to ask questions at the end. There are sessions that present science, clinical care, cases studies, or pros and cons. We have poster sessions where you can walk up and talk to the presenter, as well as education sessions, small group sessions, and meet-the-experts sessions. We try to offer variety so that, whether you are a nurse, a surgeon, a physician, or a trainee, you can get information in the way you want. My co-chair, for example, has more of an interest in basic science research and asthma, which is not something that I am as interested in; however, there are plenty of sessions for him to go to and plenty of clinical sessions, research, and medical education sessions that are interesting to me. The benefit of being a large society, and having a large conference, is that we can offer things in many different ways. This makes every individual's conference experience really different.

> **"I have always been impressed at the number of different things you can do at the congress."**

The conference also offers an opportunity to network, and that is one of the reasons people want to go. I can give you a talk over Zoom (Zoom, San Jose, California, USA), but you cannot come up to me after my lecture to ask me a question or introduce yourself and ask me about my research. Networking is something that is very important to our members and is something that we foster. This year, we have put our Networking Centers together, so we have a super networking center, which includes individual centers for clinicians, young professionals, international participants, etc. There will be lots of different presentations there, but also just time to meet people, and to exchange information and ideas.

Q7 What were your proudest achievements in your role as chair of the Education Committee for ATS?

I was on the Education Committee for about 9 years in total, and I was chair for the last 5 years. I am very passionate about education, so being able to combine my interest in education with my clinical interests in pulmonary medicine was a blessing. One of the things we tried to do was help the rest of the Society to improve how we educate each other. This includes improving the quality of the sessions at the conference, reviewing slides, and talking about innovative ideas. We also have a series of postgraduate courses, including hands on courses teaching bronchoscopy, extracorporeal membrane oxygenation, and ultrasound, which happen pre-conference. The other thing we did in my term as education chair was offer people the opportunity to obtain certification points at the congress for their national certifications. Being chair was fun; it was one of the more exciting jobs I have gotten to do.

Q8 What does your role as co-chair of the ATS International Conference Committee entail, and can you tell us about the work you aim to do whilst in this position?

The chair, or the co-chairs, do not dictate all the sessions; rather, we work with the membership, which is represented by leaders of our different assemblies. My role is to ensure that everybody can get some of their content into the conference, ultimately so that there is something for everybody. We want there to be content of interest to the basic scientist as well as clinicians. By working as co-chair, I can ensure that we get a wide variety of material. We have some significant input into keynote sessions, but we also rely on our membership and the leaders of our assemblies to program the specific sessions. This results in tremendous variety, and I am confident that anybody who attends is going

to find something interesting to go to. In this role, I get to meet a lot of people and learn about areas that I maybe do not have expertise in.

Q9 Over the years that you have been practicing and teaching in the field of pediatric pulmonology, what are the most significant changes you have seen that have impacted clinical practice?

The easiest one is in the realm of CF. When I started my pediatric pulmonary training in 1999, not only were we just starting to formalize newborn screening, but the average lifespan was around 30 years of age. Now, with the new drugs and modulator therapies that have come out, we rarely see patients with CF in the hospital anymore. CF used to be the most common indication for lung transplant, both in adults and pediatrics; however, it is no longer the most common reason at all, because these children and adults are doing so much better, and their life span is extending. People training today do not see CF, which is good and bad as they need to learn about it. However, it is good because it means that the patients are doing better. This has been the most phenomenal change, and it is just amazing for that patient population.

> "People training today do not see CF, which is good and bad."

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

This is something that I would have to think about. I moved to Nationwide Children's Hospital, Columbus, Ohio, USA, because my role here predominately involves medical education. I probably spend 80–85% of my time teaching, and then I still do a some pulmonary and lung transplant care. I see myself moving more to thinking about education in pediatrics and the pediatric subspecialty, and my focus will be to continue to see how we can improve that. I spend a lot of my time thinking about the pediatric workforce, and how to ensure that we have enough pediatricians and pediatric subspecialists to take care of the next generation of children.

Another area that I am very interested in is thinking about pediatric physician scientists. Not only are there not enough pediatric subspecialists, but there are even fewer that become pediatrician physician scientists and do research. If we do not have people doing science, we are never going to advance in the field. If we did not have people doing research, we never would have had those advances in CF. One of the things I am very passionate about is thinking about how we can ensure that enough people are interested in pediatrics and interested in advancing our science because it is essential. ●

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Q1 Having acquired a bioengineering degree at the University of Pennsylvania, Philadelphia, USA, what inspired you to pursue a medical degree at the Yale University School of Medicine, New Haven, Connecticut, USA?

I knew I wanted to go into medicine even before college. I had switched from a major in biochemistry to engineering after my freshman year because I wanted a chance to do something different before medical school. I knew that I would still learn about biochemistry in medical school, but I was not going to get a chance to learn about engineering principles in medical school. In addition, I am a problem solver by nature. The engineering discipline is basically applied science to finding solutions to questions and problems. So, I gravitated to that approach, and that view towards research and problem-solving has guided me through medical school and my subsequent career.

Q2 With over 200 publications to your name, which do you believe to be the most impactful and why?

The publications from our clinical trials during the COVID-19 pandemic on therapeutic anticoagulation and hydroxychloroquine were impactful and personal to me. Not only did it inform how we should care for patients in a pandemic, but it was also incredibly challenging to do research during the height of the pandemic. Given the fear and urgency of the pandemic in the beginning, there was a great deal of pressure to use medications that might help rather than doing clinical trials to make sure there is evidence for benefit. We were able to rapidly conduct and publish the results of clinical trials in the midst of a pandemic, which quickly changed the standard of care and outcomes for patients.

Q3 You were recently appointed as chief of critical care medicine and chief of pulmonary medicine. Could you explain what this position entails, and what you are hoping to achieve?

I was appointed chief of critical care in 2019 and chief of pulmonary medicine in 2020. At Montefiore Medical Center and Albert Einstein College of Medicine, New York City, New York. USA, critical care and pulmonary medicine are different entities as there is a Critical Care Organization that encompasses multiple medical, surgical, and neurological intensive care units. As chief of critical care, I ensure 24/7 intensivist coverage of the intensive care units and rapid response team at three different hospitals. This includes responding to all cardiac arrests and emergent airways in the hospital. That also requires co-ordination of care, resources, expertise, and staff at the different hospitals. Quality and safety initiatives are high priorities and activities for critical care given our role in the hospital. In addition, I also run a clinical research program in acute critical illness, such as sepsis, acute respiratory failure, COVID-19, and influenza. In pulmonary, I oversee respiratory and sleep specialists who provide clinical expertise to patients with respiratory conditions and lung cancer. This includes clinical specialty programs for pulmonary hypertension, sarcoidosis and interstitial lung disease, sleep disorders, pleural

disease, interventional pulmonary, lung cancer, and bronchiectasis and *Mycobacterium avium-intracellulare* infection. As chief of critical care and chief of pulmonary, I aim to deliver high quality, state-of-the-art care to our patients, to continue to support the growth of the Montefiore Healthcare System, and to bring innovation and research to advance the field of critical care. As my division has two fellowship programs, I also hope to train the next generation of physicians with the same high standards.

Q4 How have you attained the leadership skills to perform your various roles at the Montefiore Medical Centre?

My leadership skills develop by having the opportunity and experience to lead. From leading my research group to leading multiple centers in a clinical trials network, I progressively developed skills to motivate, organize, and lead larger and larger teams. From there I also accepted leadership positions in national and international professional societies such as the American Thoracic Society (ATS) and Society of Critical Care Medicine (SCCM), which helped me develop leadership skills on a national and international level. In addition to these experiences, I was also a graduate of the Executive Leadership in Academic Medicine (ELAM) program, which provided invaluable background and experience in management, negotiation, and operations in academic medicine.

Q5 How does the ATS aim to accelerate global innovation in the advancement of respiratory health through multidisciplinary collaboration, education, and advocacy?

ATS has a broad base approach to improving respiratory health and critical illness globally. This ranges from research to professional development, generation of clinical practice guidelines, training and education, advocacy, public policy, and global and health equity.[1]

> **"ATS has a broad base approach to improving respiratory health and critical illness globally."**

Q6 As the chair of the Assembly on Critical Care for the ATS, what has been your proudest achievement so far?

After the disruption of the COVID-19 pandemic, I am most proud of helping ATS and the larger community of pulmonary and critical care return to in-person meetings. The pandemic resulted in cancellation or limited in-person meetings for 2 years, which furthered the isolation of the very physicians who were called to respond to the crisis and the financial stress faced by professional societies like ATS. The importance of meeting together to connect with our colleagues, rejuvenate our passion, and refocus our energies on improving care of our patients are vital to preventing burnout.

Q7 What would you describe as the biggest challenge for ATS in their goal to accelerate global innovation?

There are many challenges, but among the biggest is the growing disparities we see in healthcare that spread across race, gender, ethnicity, middle- and low-income countries, and socio-economic status. This was exacerbated and more delineated during the COVID-19 pandemic, but this existed even before the pandemic and is further exacerbated by political divide, climate change, income disparities, and hostility.

Q8 Could you highlight some exciting sessions in the program for ATS 2023?

There are so many that it is hard to highlight just a few. The ATS Plenary Session will be given by Todd Caulfield, bestselling author, Canadian Research Chair, and professor of health law and science policy at the University of Alberta, Edmonton, Canada. There are presentations of major publications in the past year by the authors. Within the critical care assembly, there are multiple sessions on health equity and diversity in critical care across the world, and presentations from the latest science in cardiac arrest and sepsis, to the future of clinical trials and personalized medicine in acute illness. There is original research presented from all aspects of critical care involving all organs and extending to long term outcomes. It will truly be an exciting conference.

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1. American Thoracic Society (ATS). Homepage. Available at: https://www.thoracic.org/. Last accessed: 9 June 2023.

"There are many challenges, but among the biggest is the growing disparities we see in healthcare."

Interview

Stacey M. Kassutto

Associate Professor of Clinical Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA; Director of Simulation and Technology for Undergraduate Medical Education, Co-director of Measey Learning in a Virtual Environment Curriculum; Director of Simulation for Internal Medicine Residency, Hospital of the University of Pennsylvania, USA

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Stacey M. Kassutto shared fascinating insights into the use of virtual reality and artificial intelligence in respiratory healthcare, as well as her journey into the field.

Q1 Was there a particular person or event that encouraged you to pursue a career in pulmonary medicine?

While I have wanted to be a physician since I was 3 years old, my intended specialty has shifted over the years. It was not until my intern year medical intensive care unit rotation that I first realized an interest in critical care and then, ultimately, pulmonary medicine. Although critical care is initially what piqued my interest, I later found a passion for pulmonary medicine as well. I was fortunate enough to work with a variety of amazing attendings throughout my training as a resident and later fellow, which inspired my current career path as a clinician educator. The mentorship I have received throughout my career has been invaluable in helping me to hone my skills in curriculum development, medical education research, and implementation of new educational innovations.

Q2 Your research focuses on the application of novel technologies such as virtual and augmented reality in medical education. How have these technologies changed the way education is tackled?

The application of emerging technologies in medical education is still in its infancy; however, their impact on the way we deliver educational content and interface with learners is already being realized. The ability to create standardized, scalable content that can be delivered asynchronously provides the ability to reach large groups of learners anywhere, at any time, and in any location. For example, students can engage with virtual standardized patients and perform a full history and physical exam using artificial intelligence (AI) voice recognition software from their apartment, the classroom, or during downtime on the hospital wards. These cases allow students the ability to repeat the encounter, receive immediate feedback on their performance, and try again if they feel they need more practice. In addition to the flexibility afforded by emerging technologies, they also provide learners with immersive, interactive,

"The COVID-19 pandemic caused forced disruption in the way we practice, teach, and learn in medicine."

and realistic means to interact with content that is often more engaging than standard content delivery modalities used in much of medical education currently.

Q3 In the recently published article you co-authored, entitled 'Virtual, Augmented, and Alternate Reality in Medical Education: Socially Distanced but Fully Immersed'. What was the key message you were trying to deliver?

This review article aimed to provide readers with a broad and introductory overview of various emerging technologies, their application across a variety of medical education domains, and the evidence for their use. While most data on usage is limited to small pilot trials, we wanted to share general principles regarding best use cases with a focus on strengths and limitations of each technology. In doing so, we hoped to better inform future uptake, design, and implementation of virtual, augmented, and alternate reality across the spectrum of health professions learners.

Q4 How have you seen the advent of new technologies significantly impact the field of pulmonary medicine in recent years?

The COVID-19 pandemic caused forced disruption in the way we practice, teach, and learn in medicine. As a result, we saw rapid adoption of technology-based solutions in both healthcare education and clinical care delivery. When patients were unable to come into the outpatient office, we reimagined ambulatory office visits with the use of telemedicine and teleconsultations. Although in-person learning was no longer possible in many settings, we created virtual classrooms, asynchronous online learning modules, and remote simulations. During a time of social distancing, we found a way to create connection, community, and collaboration through virtual meetings and conferences.

In addition to changes brought about by the pandemic, other developments such as the improved portability and quality of handheld ultrasound devices have facilitated increased uptake of point of care ultrasound, a key diagnostic tool in critical care. Simulation-based education has also continued to advance with the use of more sophisticated high-fidelity manikins, bronchoscopy simulators, and augmented and virtual reality-based simulation modules.

Q5 Which topics require more attention when it comes to training physicians in the respiratory field?

While a significant proportion of pulmonary and critical care fellowship training focuses on inpatient medicine, most practicing clinicians will

also care for patients in an ambulatory setting. In response to this need, I worked with faculty here at University of Pennsylvania, Philadelphia, USA, to create a standardized ambulatory curriculum for pulmonary fellowship trainees. It is now being continually revised, updated, and disseminated by the Association of Pulmonary and Critical Care Program Directors (APCCMPD) Ambulatory Curriculum Working Group. While creating a standardized ambulatory curriculum was a needed first step, more work is necessary to continue to innovate, expand, and improve upon the existing frameworks for ambulatory trainee education nationally.

Q6 As an educator, where can we expect your focus to lie in the coming years?

I have always been passionate about educational innovation and curriculum development. I expect that I will continue my efforts to expand the footprint of virtual reality-based education for medical students, residents, and fellowship trainees at the Perelman School of Medicine at the University of Pennsylvania, as well as for other interprofessional learners on the healthcare team. In addition to creating virtual reality-based pilot programs to meet targeted clinical and educational needs, I plan to focus on a more comprehensive and longitudinal approach for the integration of virtual reality-enhanced education for all health professional learners.

The goal is to create virtual reality content that is broadly integrated and designed to augment existing curricula for all learner levels across content areas. I also hope to forge partnerships with innovators at other institutions to collaborate, understand best use cases, and test the generalizability and exportability of the virtual content we are currently creating.

"AI has the potential to significantly change the way we teach and practice medicine."

Q7 Are there any innovations on the horizon in the field of pulmonary medicine that you think are particularly noteworthy?

AI has the potential to significantly change the way we teach and practice medicine. While there are already early adaptations of AI in virtual standardized patients and software designed to assist with differential diagnosis and management, it is too soon to know the full scope of this technology's influence on the field. However, given the rapid evolution, power, and potential of AI, it seems almost certain that this technology will have a profound impact on medicine in the years to come. ●

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