Go to **MDedge.com/CHESTPhysician** for the latest news on the coronavirus pandemic.

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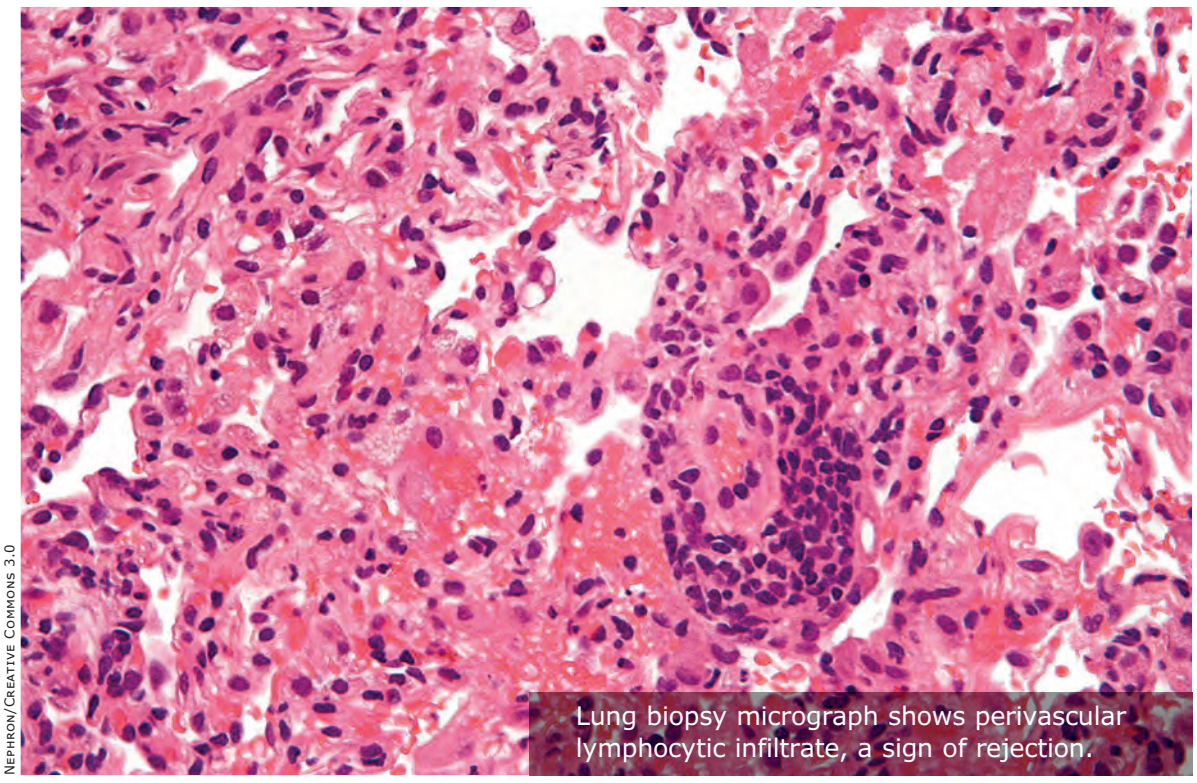
CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



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Lung biopsy micrograph shows perivascular lymphocytic infiltrate, a sign of rejection.

Lung transplantation in the era of COVID-19: New issues, paradigms

BY CHRISTINE KILGORE
MDedge News

Data are sparse thus far, but there is concern in lung transplant medicine about the long-term risk of chronic lung allograft dysfunction (CLAD) and a potentially shortened longevity of transplanted lungs in recipients who become ill with COVID-19.

"My fear is that we're potentially sitting on this iceberg worth of people who, come 6 months or a year from [the acute phase of] their COVID illness, will in fact have earlier and progressive, chronic rejection," said Cameron R. Wolfe, MBBS, MPH, associate professor of medicine in transplant infectious disease at Duke University, Durham, N.C.

Lower respiratory viral infections have long been concerning for lung transplant recipients given their propensity to cause scarring, a decline in lung function, and a heightened risk of allograft rejection. Time will tell whether lung transplant recipients who survive COVID-19 follow a similar path, or one that is worse, he said.

Short-term data

Outcomes beyond hospitalization and acute illness for lung transplant recipients affected by COVID-19 have been reported in the literature by only a few lung transplant programs. These reports – as well as anecdotal experiences being

LUNG TRANSPLANTATION // *continued on page 4*

COVID-19 pill's effectiveness appears to be less than hoped

BY BRENDA GOODMAN, MA

Merck's newly FDA-approved antiviral pill for COVID-19, molnupiravir, appears to be far less effective than early results from the clinical trial first suggested.

According to an analysis by scientists at the Food and Drug Administration, the experimental pill cut the risk of hospitalization or death from COVID-19 by about 30%, compared with a placebo, and the pill showed no benefit for people with antibodies against COVID-19 from prior infection.

The FDA's Antimicrobial Drugs Advisory Committee narrowly voted to authorize the drug, voting 13-10 to support emergency use, which requires a medication to meet a lower standard of evidence than does full approval.

Molnupiravir (brand name Lagevrio), however, was not destined to be the first FDA-authorized antiviral agent designed as a pill to treat COVID-19. The day prior to molnupiravir's Dec. 23 approval, the FDA granted emergency use authorization of Pfizer's ritonavir plus nirmatrelvir, (brand name Paxlovid), for patients age 12 and up who weigh at least 88 pounds.

COVID-19 PILL // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

Meet our new Editor in Chief and board members.

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COMMENTARY

The people's paper

BY DAVID SCHULMAN, MD, MPH, FCCP

With this issue, we usher in a new era for *CHEST Physician*, as I hand over the reins of Editor in Chief to Angel Coz, MD, FCCP.

I have had the pleasure of serving in this role over the last 4 years, and though I will still have the privilege of appearing within these pages with some frequency as I move into my new role as CHEST President, I would like to mark this milestone by passing along a few thoughts on how *CHEST Physician* has developed over the last few years. Let's reflect on the goals I set for us way back in the January 2018 issue (on page 46 of that issue, for those of you holding onto our back issues).

I've always viewed *CHEST Physician* as "the People's Paper" of CHEST. We don't feature first-run scientific manuscripts and authors aren't likely to reference our articles in other publications. But, your editorial board and our partners at Frontline aim to give our readers a broad overview of recent publications and presentations in pulmonary, critical care, and sleep medicine. This is often accompanied by expert commentary about how those developments might affect the care we provide to our patients.

I can't thank our editorial board members enough for the hours they spend selecting a small number of items to feature among all of the new medical developments each month.

One of the main goals we had established over the last few years was to create more opportunities for *CHEST Physician* to serve as the voice of the members and leaders of the American College of Chest Physicians. We achieved the latter part of this goal, with leadership penning quarterly columns on actions of the Board of Regents, developments within the annual meeting, as well as ongoing columns from our NetWorks.

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Dr. David Schulman

And, we have also provided a more reliable voice for our members, with authors of our Sleep Strategies, Critical Care Commentary, and Pulmonary Perspectives columns providing a broader and more representative sample of our membership than ever before.

One of the areas where I would love to see more progress is with reader engagement. It has been a delight to receive feedback from CHEST members, even when the author is taking issue with something we have published. *CHEST Physician* will be a better publication than it already is with your ongoing input.

Please, if you see something that we write that you particularly like (or don't!) or if there's something you'd like to see that we haven't written, please reach out to us! You can always reach us at chestphysicianews@chestnet.org.

In closing, I want to thank all of the steadfast *CHEST Physician* readers for making my 4 years as Editor in Chief enjoyable and meaningful. While I am so pleased with the current state of this publication, I cannot wait to see its ongoing evolution under the leadership of Dr. Coz and his editorial board. ■

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CHEST Physician is available at chestphysician.org.

Angel Coz, MD, FCCP, is Editor in Chief of *CHEST Physician*.

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Meet the new *CHEST Physician* Editor in Chief

Angel Coz Yataco, MD, FCCP, is a Pulmonary and Critical Care specialist at the Respiratory Institute at the Cleveland Clinic. He previously served as the Medical Director of the Intensive Care Unit at the Lexington Veterans Affairs Medical Center and was an Associate Professor of Medicine at the University of Kentucky. Dr. Coz received his medical degree from Universidad Peruana Cayetano Heredia in Lima, Peru. He completed residency training in internal medicine and did his fellowship training in pulmonary and critical care medicine at Henry Ford Hospital.

Dr. Coz was a member of the 2021 Surviving Sepsis Campaign Guidelines panel and serves on the American Board of Internal Medicine Governance – Critical Care Medicine examination board. He holds multiple leadership positions at CHEST—Chair of the Council of NetWorks; a member of the Guidelines Oversight Committee; and served as the Critical Care Section Editor for *CHEST Physician* since 2018. He has been awarded the Distinguished CHEST Educator (DCE) designation every year since its inception in 2018 and received the CHEST Presidential Citation Award in 2021.

Dr. Coz has given multiple talks on critical care, sepsis, and pulmonary topics at the national and international level. He has published several peer-reviewed articles and serves as ad hoc reviewer for *CHEST*, *Journal of Critical Care*, *Critical Care Medicine*, *Critical Connections*, *Intensive Care Medicine*, and *Annals of Pharmacotherapy*, among others. ■

COURTESY CHEST

Dr. Angel Coz

Welcome our new board members and section heads

Humayun Anjum, MD, FCCP – Board Member

Dr. Anjum is currently working as a pulmonary and critical care physician at Baylor Scott & White Medical Center-Grapevine in Dallas, Texas. He is an Adjunct Clinical Assistant Professor at University of Houston and University of North Texas. He recently moved to Dallas from Corpus Christi, TX, where he served as the core faculty for the Internal Medicine residency program and the Pulmonary Disease fellowship program. He is passionate about learning and teaching and has been very intricately involved with CHEST and the CHEST Foundation for the last few years. Currently, he serves as the chair of the Practice Operations Network steering committee. Dr. Anjum is particularly interested in medical practice management and administration and hopes to continue sharing his knowledge through various platforms to help his fellow physicians.

Dr. Anjum

Loren J. Harris, MD, FCCP – Board Member

Dr. Harris is the Chairman of the Department of Surgery and Chief of Thoracic Surgery at Richmond University Medical Center in Staten Island, NY. He has been in clinical surgical practice for more than 20 years and also has more than 20 years of experience teaching both medical students and surgical residents and fellows. In addition, he served as Program Director of the general surgery residency program at Maimonides Medical Center from 2014 to 2017. Dr. Harris has published and presented throughout his career both nationally and internationally. His main research and clinical interests are in the appropriate staging and treatment of non-small cell lung cancer. He served as the Chair of the CHEST Marketing Committee; was the editor Pulmonary Perspectives; and is a co-author on two chapters in the most recent edition of the Diagnosis and Management Guidelines for Lung Cancer published by CHEST in 2013. Dr. Harris has also received several prestigious awards including the CHEST Soffer Award for Editorial Excellence.

Dr. Harris

Aaron B. Holley, MD, FCCP – Section Editor, Pulmonary Perspectives®

Dr. Holley currently serves as the Program Director for the Pulmonary and Critical Care Medicine Fellowship at the Walter Reed National Military Medical Center. He is an Associate Professor of Medicine at the Uniformed Services University with an interest in pulmonary physiology, cardiopulmonary exercise, and lung function testing; and venous thromboembolism. Dr. Holley is a Distinguished CHEST Educator and serves the College as a member of the Pulmonary Physiology Function and Rehabilitation Network, Airways Disorders Network, Pulmonary Physiology Domain Task Force, and the Guidelines Oversight Committee.

Dr. Holley

Diego Maselli, MD, FCCP – Board Member

Dr. Maselli is an Associate Professor of Medicine in the Division of Pulmonary Diseases & Critical Care Medicine at UT Health in San Antonio. He is the director of the Severe Asthma Program at UT Health and his research focuses on severe asthma, COPD, and bronchiectasis. Dr. Maselli has been designated a Distinguished CHEST Educator since 2017 when the program was initiated. He serves on the steering committee of the Airways Network.

Dr. Maselli

Daniel R. Ouellette, MD, FCCP – Section Editor, Critical Care Commentary

Dr. Ouellette has been a clinician, teacher, and researcher in pulmonary and critical care medicine for 35 years. He is currently a Senior Staff Physician at Henry Ford Hospital in Detroit where he is the Medical Director for the Pulmonary Ward. He is also an Associate Clinical Professor of Medicine at the Wayne State University School of Medicine, and the Medical Director of the Respiratory Therapy program at Oakland Community College. Dr. Ouellette has over 20 years of military service and was the Consultant to the US Army Surgeon General for Pulmonary Medicine during the last several years of his military career. An active CHEST leader, he has chaired the Guideline Oversight Committee, the Clinical Pulmonary Network, and the Council of Governors, has been a member of the Board of Regents, and held many leadership roles with CHEST and other societies in the development of evidence-based clinical practice guidelines. Dr. Ouellette's clinical areas of interest include general pulmonary and critical care medicine and evidence-based practice.

Dr. Ouellette

Saiprakash Venkateshiah, MD, FCCP – Board Member

Dr. Venkateshiah is an Associate Professor of Medicine in the Division of Pulmonary, Allergy, Critical Care and Sleep Medicine at Emory University, Atlanta, GA. He is a clinician educator and a "general pulmonologist" practicing the entire gamut of pulmonary, critical care, and sleep medicine. Dr. Venkateshiah has been a CHEST member for close to 2 decades. He has been involved with CHEST NetWork leadership since 2012, starting as steering committee member of Clinical Pulmonary Medicine Network transitioning to Vice-Chair and Chair. He was previously a member of the Executive Committee of the Council of Networks and the Scientific Program Committee for CHEST 2019 and CHEST 2020. He is currently a steering committee member of the education committees of CHEST and American Academy of Sleep Medicine. He is also a steering committee member of the CHEST Sleep NetWork. ■

Dr. Venkateshiah

informally shared among transplant programs – have raised the specter of more severe dysfunction following the acute phase and more early CLAD, said Tathagat Narula, MD, assistant professor of medicine at the Mayo Medical School, Rochester, Minn., and a consultant in lung transplantation at the Mayo Clinic's Jacksonville, Fla., program.

"The available data cover only 3-6 months out. We don't know what will happen in the next 6 months and beyond," Dr. Narula said in an interview.

The risks of COVID-19 in already-transplanted patients and issues relating to the inadequate antibody responses to vaccination are just some of the challenges of lung transplant medicine in the era of SARS-CoV-2. "COVID-19," said Dr. Narula, "has completely changed the way we practice lung transplant medicine – the way we're looking both at our recipients and our donors."

Potential donors are being evaluated with lower respiratory SARS-CoV-2 testing and an abundance of caution. And patients with severe COVID-19 affecting their own lungs are roundly expected to drive up lung transplant volume in the near future. "The whole paradigm has changed," Dr. Narula said.

Postacute trajectories

A chart review study published in October (Transpl Infect Dis. 2021 Oct 4. doi: 10.1111/tid.13739) by the lung transplant team at the University of Texas Southwestern Medical Center, Dallas, covered 44 consecutive survivors at a median follow-up of 4.5 months from hospital discharge or acute illness (the survival rate was 83.3%). Patients had significantly impaired functional status, and 18 of the 44 (40.9%) had a significant and persistent loss of forced vital capacity or forced expiratory volume in 1 second (>10% from pre–COVID-19 baseline).

Three patients met the criteria for new CLAD after COVID-19 infection, with all three classified as restrictive allograft syndrome (RAS) phenotype.

Moreover, the majority of COVID-19 survivors who had CT chest scans (22 of 28) showed persistent parenchymal opacities – a finding that, regardless of symptomatology, suggests persistent allograft injury, said Amit Banga, MD, associate professor of medicine and medical director of the ex vivo lung perfusion program in UT Southwestern's lung transplant program.

"The implication is that there may be long-term consequences of COVID-19, perhaps related to some degree of ongoing inflammation and damage," said Dr. Banga, a coauthor of the postinfection outcomes paper.

The UT Southwestern lung transplant program, which normally performs 60-80 transplants a year, began routine CT scanning 4-5 months into the pandemic, after "stumbling into a few patients who had no symptoms indicative of COVID pneumonia and no changes on an x-ray but significant involvement on a CT," he said.

COVID-19 has proven to be far worse for lung transplant recipients than illness with other respiratory viruses, including RSV. "Patients have more frequent and greater loss of lung function, and worse debility from the acute illness."

Without routine scanning in the general population of COVID-19 patients, Dr. Banga noted, "we're limited in convincingly saying that COVID is uniquely doing this to lung transplant recipients." Nor can they conclude that SARS-CoV-2 is unique from other respiratory viruses such as respiratory syncytial virus (RSV) in this regard. (The program has added CT scanning to its protocol for lung transplant recipients afflicted with other respiratory viruses to learn more.)

However, in the big picture, COVID-19 has proven to be far worse for lung transplant recipients than illness with other respiratory viruses, including RSV. "Patients have more frequent and greater loss of lung function, and worse debility from the acute illness," Dr. Banga said.

"The cornerstones of treatment of both these viruses are very similar, but both the in-hospital course and the postdischarge outcomes are significantly different."

In an initial paper published in September 2021, Dr. Banga and colleagues compared their first 25 lung transplant patients testing positive for SARS-CoV-2 with a historical cohort of 36 patients with RSV treated during 2016-2018.

Patients with COVID-19 had significantly worse morbidity and mortality, including worse postinfection lung function loss, functional decline, and 3-month survival (J Heart Lung Transplant. 2021;40[9]:936-47).

More time, he said, will shed light on the risks of CLAD and the long-term potential for recovery of lung function. Currently, at UT Southwestern, it appears that patients who survive acute illness and the "first 3-6 months after COVID-19, when we're seeing all the postinfection morbidity, may [enter] a period of stability," Dr. Banga said.

Overall, he said, patients in their initial cohort are "holding steady" without unusual morbidity, readmissions, or "other setbacks to their allografts."

At the Mayo Clinic in Jacksonville, which normally performs 40-50 lung transplants a year, transplant physicians have similarly observed significant declines in lung function beyond the acute phase of COVID-19.

"Anecdotally, we're seeing that some patients are beginning to recover some of their lung function, while others have not," said Dr. Narula. "And we don't have predictors as to who will progress to CLAD. It's a big knowledge gap."

Dr. Narula noted that patients with restrictive allograft syndrome, such as those reported by the UT Southwestern team, "have scarring of the lung and a much worse prognosis than the obstructive type of chronic rejection." Whether there's a role for antifibrotic therapy is a question worthy of research.

In UT Southwestern's analysis, persistently lower absolute lymphocyte counts (< 600/dL) and higher ferritin levels (>150 ng/mL) at the time of hospital discharge were independently associated with significant lung function loss. This finding, reported in their October paper, has helped guide their management practices, Dr. Banga said.

"Persistently elevated ferritin may indicate ongoing inflammation at the allograft level," he said. "We now send [such patients] home on a longer course of oral corticosteroids."

At the front end of care for infected lung transplant recipients, Dr. Banga said that his team and physicians at other lung transplant programs are holding the cell-cycle inhibitor component of patients' maintenance immunosuppression therapy (commonly mycophenolate or azathioprine) once infection is diagnosed to maximize chances of a better outcome.

"There may be variation on how long [the regimens are adjusted]," he said. "We changed our duration from 4 weeks to 2 due to patients developing a rebound worsening in the third and fourth week of acute illness."

There is significant variation from institution to institution in how viral infections are managed in lung transplant recipients, he and Dr. Narula said. "Our numbers are so small in lung transplant, and we don't have standardized protocols – it's one of the biggest challenges in our field," said Dr. Narula.

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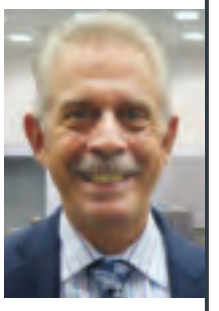

Daniel R. Oullette, MD, FCCP, comments: I am not a lung transplantation doctor. Sure, I studied immunosuppressive regimens and post-transplantation infectious complications last year when I re-certified in pulmonary medicine, but I leave the day-to-day management of these complex patients to my lung transplantation colleagues who are experts. I do refer my patients for transplantation, though. One of my patients, a man in his mid-50s with hypersensitivity pneumonitis, took me on a journey for several years through dyspnea and abnormal x-rays, lung biopsies, corticosteroids, and finally domiciliary oxygen. The robust guy who played hockey with his friends at 50 on frozen Michigan lakes a few years later couldn't walk across the room without gasping for breath. His lung transplantation gave him a new lease on life and a trip to Disneyland with his kids.

Our lung transplantation patients face a new threat from COVID-19. In addition to being at risk for acute infection and severe disease because of their immune-compromised status, we now learn that there may be insidious long-term effects from even apparently innocuous infection. Researchers are finding that patients have new and chronic changes on imaging studies and may have accelerated forms of rejection. We need to learn more about how to effectively vaccinate patients on complex immunosuppressive regimens. I hope that we surmount these problems so that our patients who have been transplanted successfully may continue to enjoy their renewed good quality of life.

Sputum biomarkers may predict COPD exacerbations

BY WALTER ALEXANDER
MDedge News

FROM THE JOURNAL *CHEST*® ▪ Examining sputum from patients with chronic obstructive pulmonary disease may help predict the course of the disease.

A mass spectrometric panel of biomarkers related to mucus hydration and inflammation examined in sputa showed elevated levels of metabolites from multiple pathways in patients with COPD. These correlated with sputum neutrophil counts and COPD exacerbations. In particular, sialic acid and hypoxanthine concentrations were strongly associated with disease severity, according to a study reported in the journal CHEST (doi: 10.1016/j.chest.2021.10.049), authored by Charles R. Esther Jr. MD, PhD, and colleagues.

Given that an improved understanding of the pathways associated with airway pathophysiology in COPD will identify new predictive biomarkers and novel therapeutic targets, Dr. Esther and colleagues posed the question: Which physiologic pathways are altered and predict exacerbations in the airways of subjects with COPD?

They noted that in persons with COPD – characterized by dominant small-airway obstruction associated with airway inflammation – multiple inflammatory pathways, as well as indices of oxidative stress (including oxidized glutathione and 8-isoprostane), are elevated in sputum. Because inflammation is a challenging therapeutic target, identification of other biologic pathways involved in COPD pathogenesis could point to novel biomarkers and therapeutic targets.

Using this approach in cystic fibrosis (CF), the authors have previously identified small-molecule metabolites correlated with airway inflammation. Findings from that research supported development of a mass spectrometric biomarker panel for simultaneous measurement of inflammatory markers coupled to biomarkers of mucus hydration. The researchers applied this technology to sputum supernatants collected through the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), which included subjects with COPD, as well as relevant smoking and nonsmoking controls.

Addressing inflammation

"Inhaled steroids are really more effective for allergic inflammation as in asthma and less so for the neutrophilic inflammation that dominates

Continued on following page

Transplantation *continued from previous page*

Vaccination issues, evaluation of donors

Whether or not immunosuppression regimens should be adjusted prior to vaccination is a controversial question, but is "an absolutely valid one" and is currently being studied in at least one National Institutes of Health–funded trial involving solid organ transplant recipients, said Dr. Wolfe.

"Some have jumped to the conclusion [based on some earlier data] that they should reduce immunosuppression regimens for everyone at the time of vaccination ... but I don't know the answer yet," he said. "Balancing staying rejection free with potentially gaining more immune response is complicated ... and it may depend on where the pandemic is going in your area and other factors."

Reductions aside, Dr. Wolfe tells lung transplant recipients that, based on his approximation of a number of different studies in solid organ transplant recipients, approximately 40%-50% of patients who are immunized with two doses of the COVID-19 mRNA vaccines will develop meaningful antibody levels – and that this rises to 50%-60% after a third dose.

It is difficult to glean from available studies the level of vaccine response for lung transplant recipients specifically. But given that their level of maintenance immunosuppression is higher than for recipients of other donor organs, "as a broad sweep, lung transplant recipients tend to be lower in the pecking order of response," he said.

Still, "there's a lot to gain," he said, pointing to a recent study from the Morbidity and Mortality Weekly Report (2021 Nov 5. doi: 10.15585/mmwr.mm7044e3) showing that effectiveness of mRNA vaccination against COVID-19–associated hospitalization was 77% among immunocompromised adults (compared with 90% in immunocompetent adults).

"This is good vindication to keep vaccinating," he said, "and perhaps speaks to how difficult it is to assess the vaccine response [through measurement of antibody only]."

Neither Duke University's transplant program, which performed 100-120 lung transplants a year pre-COVID, nor the programs at UT Southwestern or the Mayo Clinic in Jacksonville require that solid organ transplant candidates be vaccinated against SARS-CoV-2 in order to receive transplants, as some other transplant programs have done. (When asked about the issue, Dr. Banga and Dr. Narula each said that they have had no or little trouble convincing patients awaiting lung transplants of the need for COVID-19 vaccination.)

In an August statement, the American Society of Transplantation recommended vaccination for all solid organ transplant recipients, preferably prior to transplantation, and said that it "support[s] the development of institutional policies regarding pretransplant vaccination."

The Society is not tracking centers' vaccination policies. But Kaiser Health News reported in October that a growing number of transplant programs, such as UCHealth in Denver and UW Medicine in Seattle, have decided to either bar patients who refuse to be vaccinated from receiving transplants or give them lower priority on waitlists.

Potential lung donors, meanwhile, must be evaluated with lower respiratory COVID-19 testing, with results available prior to transplantation, according to policy developed by the Organ Procurement and Transplantation Network and effective in May 2021. The policy followed three published cases of donor-derived COVID-19 in lung transplant recipients, said Dr. Wolfe, who wrote about use of COVID-positive donors in an editorial published in October (Transpl Infect Dis. 2021;23[5]:e13727).

In each case, the donor had a negative COVID-19 nasopharyngeal swab at the time of organ procurement but was later found to have the virus on bronchoalveolar lavage, he said.

(The use of other organs from COVID-positive donors is appearing thus far to be safe, Dr. Wolfe noted. In the editorial, he references 13 cases of solid organ transplantation from SARS-CoV-2–infected donors into noninfected recipients; none of the 13 transplant recipients developed COVID-19).

Some questions remain, such as how many lower respiratory tests should be run, and how donors should be evaluated in cases of discordant results. Dr. Banga shared the case of a donor with one positive lower respiratory test result followed by two negative results. After internal debate, and consideration of potential false positives and other issues, the team at UT Southwestern decided to decline the donor, Dr. Banga said.

Other programs are likely making similar, appropriately cautious decisions, said Dr. Wolfe. "There's no way in real-time donor evaluation to know whether the positive test is active virus that could infect the recipient and replicate ... or whether it's [picking up] inactive or dead fragments of virus that was there several weeks ago. Our tests don't differentiate that."

Transplants in COVID-19 patients

Decision-making about lung transplant candidacy among patients with COVID-19 acute respiratory distress syndrome is complex and in need of a new paradigm.

"Some of these patients have the potential to recover, and they're going to recover way later than what we're used to," said Dr. Banga. "We can't extrapolate for COVID ARDS what we've learned for any other virus-related ARDS."

Dr. Narula also has recently seen at least one COVID-19 patient on ECMO and under evaluation for transplantation recover. "We do not want to transplant too early," he said, noting that there is consensus that lung transplant should be pursued only when the damage is deemed irreversible clinically and radiologically in the best judgment of the team. Still, "for many of these patients the only exit route will be lung transplants. For the next 12-24 months, a significant proportion of our lung transplant patients will have had post-COVID–related lung damage."

As of October 2021, 233 lung transplants had been performed in the United States in recipients whose primary diagnosis was reported as COVID related, said Anne Paschke, media relations specialist with the United Network for Organ Sharing.

Dr. Banga, Dr. Wolfe, and Dr. Narula reported that they have no relevant disclosures. ■

in COPD. The challenge is that neutrophilic inflammation is also a key response to infection, and it's really hard to find an anti-inflammatory that suppresses neutrophilic inflammation well enough to get clinical benefit but not so much that the patient becomes vulnerable to infection. Lots of clinical trials of anti-inflammatories in cystic fibrosis or COPD have been stopped because treated subjects had more trouble with infection," Dr. Esther stated in an interview,

The investigators analyzed cell-free sputum supernatants from 980 subjects, including samples from 77 healthy nonsmokers (NS), 341 ever-smokers with preserved spirometry (SPS), and 562 subjects with COPD (178 GOLD [Global Initiative for Chronic Obstructive Lung Disease]1, 303 GOLD 2, and 81 GOLD 3). Among the subjects with COPD, elevated biomarkers from multiple pathways correlated with sputum neutrophil counts.

The most significant analytes (at FDR [False Discovery Rate] 0.1) were sialic acid (a mucin marker), hypoxanthine, xanthine, methylthioadenosine, adenine, and glutathione, with sialic acid and hypoxanthine strongly associated with measures of disease severity. Elevation of sialic acid and hypoxanthine were associated with shorter time to exacerbation and improved prediction models of future exacerbations.

Study results

Sialic acid was elevated in all GOLD groups relative to NS healthy controls, with a 2.8-fold (0.44 log) increase in GOLD 2 and 3.7 fold (0.56 log) increase in GOLD 3 relative to NS. Sialic acid was also elevated in the most severe disease cohorts (GOLD 2 and GOLD 3) relative to smokers with preserved spirometry (SPS) and those with less severe disease (GOLD 1).

Within the full cohort, both sialic acid and hypoxanthine were significantly elevated in those who had multiple (two or more) pulmonary exacerbations relative to those who had none ($P = .001$). Similar, findings were observed for xanthine ($P = .01$), methylthioadenosine ($P = .01$), adenine ($P = .01$), and glutathione ($P = .01$).

Sputum tests needed

While tests still need to be developed, Dr. Esther noted in an interview that they would be based on well-established technologies commonly utilized in clinical laboratories. "Sputum biomarkers of mucus hydration and adenosine metabolism could help clinicians predict which patients with COPD are likely to experience multiple pulmonary exacerbations. Tests would be applied to patients with COPD at higher risk for exacerbations; for example, those who have low lung function or a history of prior exacerbations."

Dr. Esther noted that these biomarkers could be helpful in developing novel therapies. "Using sialic acid to assess mucus concentrations is much easier than other methods, so it could help in developing mucolytic treatments. Also, adenosine metabolism represents a novel therapeutic target in COPD. Drugs that modify adenosine metabolism that have been approved for other diseases such as gout could be tested in COPD. As with mucus hydration, the biomarkers we identified (particularly hypoxanthine) could be utilized to make sure that novel therapies are having the intended impact on airway adenosine metabolism."

The research was supported by SPIROMICS (funded by NIH and the COPD Foundation). Dr. Esther reported having no relevant disclosures. ■

COVID-19 PILL // *continued from page 1*

The Pfizer antiviral is only for people who test positive for coronavirus and who are at high risk for severe COVID-19, including hospitalization or death.

Other therapies to treat the infection are available – monoclonal antibodies and the drug remdesivir – but they are given by infusion.

The updated analysis of the Merck pill's effectiveness showed 48 hospitalizations or deaths among study participants who were randomly assigned to take the antiviral drug, compared with 68 among those who took a placebo.

Those results come from the full set of 1,433 patients who were randomized in the clinical trial, which just became available last week.

Initial results from the first 775 patients enrolled in the clinical trial, which were issued in a company news release in October, had said the drug cut the risk of hospitalization or death for patients at high risk of severe disease by about 50%.

Merck has been producing millions of doses of molnupiravir, which is the first antiviral pill to treat COVID-19 infections. The

Continued on following page

COVID-19 PILL *continued from previous page*

United Kingdom's drug regulator authorized use of the medication in early November. The company said it expected to distribute the medication globally by the end of 2021.

In October, two Indian drug companies halted late-stage clinical trials of a generic version of molnupiravir after the studies failed to find any benefit to patients with moderate COVID-19. Trials in patients with milder symptoms are still ongoing.

The medication is designed to be given as four pills taken every 12 hours for 5 days. It's most effective when taken within the first few days of new symptoms, something that requires convenient, affordable testing.

The new results seem to put molnupiravir far below the effectiveness of existing treatments. The infused monoclonal antibody cocktail REGEN-COV, which the FDA has already authorized for emergency use, is about 85% effective at preventing hospitalization or death in patients who are at risk for severe COVID-19 outcomes, and it appears to be just as effective in people who already have antibodies against COVID-19, which is why it is being given to both vaccinated and unvaccinated patients, the FDA said.

In early November, Pfizer said its experimental antiviral pill Paxlovid cut the risk of hospitalization or death by 89%.

"This was clearly a difficult decision [on molnupiravir]," said advisory committee member Michael Green, MD, a pediatric infectious disease expert at the University of Pittsburgh School of Medicine. Dr. Green said he voted yes, and that the drug's ability to prevent deaths in the study weighed heavily on his decision.

He said given uncertainties around the drug, both the company and FDA should keep a close eye on patients taking the drug going forward.

Others didn't agree that the drug should be allowed onto the market.

"I voted no," said Jennifer Le, PharmD, a professor of clinical pharmacy at the University of California. Dr. Le said the modest benefit of the medication didn't outweigh all the potential safety issues. "I think I just need more efficacy and safety data," she said.

"The efficacy of this product is not overwhelmingly good," said committee member David Hardy, MD, an infectious disease expert at Charles Drew University School of Medicine in Los Angeles.

"And I think that makes all of us a little uncomfortable about whether this is an advanced therapeutic because it's an oral medication rather than an intravenous medication," he said during the panel's deliberations.

"I think we have to be very careful about how we're going to allow people to use this," Dr. Hardy said. ■

CHEST™ Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Study: Atezolizumab plus chemo bests supportive care

BY WALTER ALEXANDER
MDedge News

The 34% reduction in disease recurrence for adjuvant atezolizumab in PD-L1 tumor cells of at least 50% stage II-IIIA patients in the IMpower010 clinical trial, may change the standard of care for early-stage non–small cell lung cancer (NSCLC), according to Enriqueta Felip, MD, the head of thoracic and head and neck cancer unit at Vall d'Hebron Institute of Oncology, Hospital, Barcelona.

IMpower010 is the first positive randomized phase 3 study to show significant disease-free survival (DFS) improvement with adjuvant cancer immunotherapy (atezolizumab, anti–programmed death–ligand 1 (PDL-1), and platinum-based chemotherapy) in this population, Dr. Felip said in a presentation at the

2021 European Society for Medical Oncology Congress on Sept. 20, 2021 (abstract LBA9).

High unmet need

Up to 60% of patients with stage I-III NSCLC still experience disease relapse despite having received treatment, Dr. Felip said. IMpower010 included 1,280 patients who received up to four cycles of chemotherapy (cisplatin with pemetrexed, gemcitabine, docetaxel, or vinorelbine) after completely resected stage IB-IIIA NSCLC. Patients were randomized to open label to atezolizumab (1,200 mg every 21 days for 16 cycles or best supportive care (BSC). The primary endpoint of investigator-assessed DFS in the stage II-IIIA population (n = 1,005) was stratified according to three groups: PD-L1 tumor cells of at least 1% (stage II-IIIA), all-randomized (stage II-IIIA) and intention-to-treat (stage IB-IIIA).

Median disease-free survival in PD-L1 tumor cells of at least 1% was not estimated in the atezolizumab group and was 35.3 months in the BSC group (95% CI, 29.0 to NE). In the all-randomized group, median DFS was 42.3 months in the atezolizumab group (95% CI, 36.0 to NE) and 35.3 months in the BSC group (95% CI, 30.4-46.4) with a stratified hazard ratio of 0.79 (95% CI, 0.64-0.96; *P* = .02). In the intent-to-treat population, median DFS was not evaluable in the

Continued on following page

atezolizumab group and 37.2 months in the BSC group (95% CI, 31.6 to NE) with a hazard ratio of 0.81 (95% CI, 0.67-0.99; *P* = .04).

DFS hazard ratio 0.43 in the tumor cells ≥50% group

Looking at DFS by PD-L1 status in the population with and without known EGFR/ALK+ disease, Dr. Felip said that the hazard ratio for the tumor cells of at least 50% group (n = 229) was 0.43 (95% CI, 0.27-0.68), as compared with 0.87 (95% CI, 0.60-1.26) for the tumor cells 1%-49% group. With EGFR/ALK+ patients excluded, the respective HRs were similar (0.43/0.82). Considering DFS events including only disease recurrence, disease incidence was 29.4% and 44.7% in the atezolizumab and BSC groups, respectively for those with PD-L1 tumor cells of at least 1%. The same pattern of atezolizumab benefit persisted in the all-randomized and intent-to-treat groups.

An assessment according to regions of relapse (locoregional only, distant only, locoregional and distant, CNS only, second primary lung) revealed no differences in the three groups. Analysis of time from randomization to relapse revealed regional differences in the PD-L1 tumor cells of at least 1% group with a median time to any relapse of 17.6 months in the atezolizumab group and 10.9 months in the BSC group. Time from randomization to relapse was generally similar for atezolizumab and best supportive care in the all randomized and intent-to-treat groups (about 11-12 months).

"The greatest magnitude of disease-free survival benefit was observed in the PD-L1 tumor cell of at least 50% population with a hazard ratio of 0.43."

"The greatest magnitude of disease-free survival benefit was observed in the PD-L1 tumor cell of at least 50% population with a hazard ratio of 0.43," Dr. Felip said. In a post hoc analysis excluding patients with known EFGR/ALK with NSCLC, she said that hazard ratios were numerically improved in most PD-L1 subgroups.

Postrelapse cancer immunotherapies were used at a higher rate in the BSC arm of the trial. "Longer-term follow-up is warranted and may reveal differences in relapse patterns and treatment options."

Playing with the immune system

Benjamin Besse, MD, director of oncology and chair of the EORTC Lung Group at Paris-Saclay University, acknowledged the disease-free survival benefit with atezolizumab in IMpower010 and underscored that adjuvant immunotherapy has been changing treatment in resected cancers across tumor types (i.e., melanoma, renal cell carcinoma, NSCLC).

He voiced some concerns, including the absence of benefit in PD-L1 less than 1%, pneumonectomy and EGFRmut/ALK+ patients, and generally the potential "when you play with the immune system for there to be a dark side too."

Dr. Besse said delayed side effects in 43.2% of patients , citing a recent report of chronic, mostly grade 1-2 immune-related adverse

Continued on following page

Apixaban outmatches rivaroxaban for VTE in study

BY WILL PASS
MDedge News

Apixaban appears to be safer and more effective than rivaroxaban for reducing risk of venous thromboembolism and bleeding, based on new research.

Recurrent venous thromboembolism (VTE) – a composite of pulmonary embolism and deep vein thrombosis – was the primary effectiveness outcome in the retrospective analysis of new-user data from almost 40,000 patients, which was published in Annals of Internal Medicine (2021 Dec 6. doi: 10.7326/M21-0717). Safety was evaluated through a composite of intracranial and gastrointestinal bleeding.

After a median follow-up of 102 days in the apixaban group and 105 days in the rivaroxaban group, apixaban demonstrated superiority for both primary outcomes. These real-world findings may guide selection of initial anticoagulant therapy, reported lead author Ghadeer K. Dawwas, PhD, MSc, MBA, of the University of Pennsylvania, Philadelphia, and colleagues.

"Randomized clinical trials comparing apixaban with rivaroxaban in patients with VTE are under way (for example, COBRRA (NCT03266783)," the investigators wrote.

"Until the results from these trials become available (The estimated completion date for COBRRA is December 2023.), observational studies that use existing data can provide evidence on the effectiveness and safety of these alternatives to inform clinical practice."

In the new research, apixaban was associated with a 23% lower rate of recurrent VTE (hazard ratio, 0.77; 95% confidence interval, 0.69-0.87), including a 15% lower rate of deep vein thrombosis and a 41% lower rate of pulmonary embolism.

Apixaban was associated with 40% fewer bleeding events (HR, 0.60; 95% CI, 0.53-0.69), including a 40% lower rate of GI bleeding and a 46% lower rate of intracranial bleeding.

The study involved 37,236 patients with VTE, all of whom were diagnosed in at least one inpatient encounter and initiated direct oral anticoagulant (DOAC) therapy within 30 days, according to Optum's deidentified Clinformatics Data Mart Database. Patients were evenly split into apixaban and rivaroxaban groups, with 18,618 individuals in each. Propensity score matching was used to minimize differences in baseline characteristics.

Apixaban was associated with an absolute reduction in recurrent VTE of 0.6% and 1.1% over 2 and 6 months, respectively, as well as reductions in bleeding of 1.1% and 1.5% over the same respective time periods.

The investigators noted that these findings were maintained in various sensitivity and subgroup analyses, including a model in which patients with VTE who had transient risk factors were compared with VTE patients exhibiting chronic risk factors.

"These findings suggest that apixaban has superior effectiveness and safety, compared with rivaroxaban and may provide guidance to clinicians and patients regarding selection of an anticoagulant for treatment of VTE," Dr. Dawwas and colleagues concluded.

Thomas Wakefield, MD, a vascular surgeon and a professor of surgery at the University of Michigan Health Frankel Cardiovascular Center, Ann Arbor, generally agreed with the investigators' conclusion, although he noted that DOAC selection may also be influenced by other considerations.

"The results of this study suggest that, when choosing an agent for an individual patient,

"Hopefully this analysis will encourage more payers to create financial incentives that facilitate the use of apixaban in more patients."

Dr. Damon E. Houghton

apixaban does appear to have an advantage over rivaroxaban related to recurrent VTE and bleeding," Dr. Wakefield said in an interview.

"One must keep in mind that these are not the only factors that are considered when choosing an agent and these are not the only two DOACs available. For example, rivaroxaban is given once per day while apixaban is given twice per day, and rivaroxaban has been shown to be successful in the treatment of other thrombotic disorders."

Dr. Wakefield also pointed out that the study may have missed some nuance in outcomes.

"The current study looked at severe outcomes that resulted in inpatient hospitalization, so the generalization to strictly outpatient treatment and less severe outcomes cannot be inferred," he said.

Damon E. Houghton, MD, of the department of medicine and a consultant in the department of vascular medicine and hematology at Mayo Clinic, Rochester, Minn., called the study a "very nice analysis," highlighting the large sample size.

"The results are not a reason to abandon rivaroxaban altogether, but do suggest that, when otherwise appropriate for a patient, apixaban should be the first choice," Dr. Houghton said in a written comment. "Hopefully this analysis will encourage more payers to create financial incentives that facilitate the use of apixaban in more patients."

Colleen Edwards, MD, of the departments of medicine, hematology, and medical oncology, at the Icahn School of Medicine at Mount Sinai, New York, had a more guarded view of the findings than Dr. Wakefield and Dr. Houghton.

"I think we really have to wait for randomized trial before we abandon our other choices."

Dr. Colleen Edwards

"[The investigators] certainly seem to be doing a lot of statistical gymnastics in this paper," Dr. Edwards said in an interview. "They used all kinds of surrogates in place of real data that you would get from a randomized trial."

For example, Dr. Edwards noted the use of prescription refills as a surrogate for medication adherence, and emphasized that inpatient observational data may not reflect outpatient therapy.

"Inpatients are constantly missing their medicines all the time," according to Dr. Edwards. "They're holding it for procedures; they're NPO; they're off the floor, so they missed their medicine. So it's just a very different patient population than the outpatient population, which is where venous thromboembolism is treated now, by and large."

Although Dr. Edwards suggested that the findings might guide treatment selection "a little bit," she noted that insurance constraints and costs play a greater role. "I think we really have to wait for randomized trial before we abandon our other choices," she said.

The investigators disclosed relationships with Merck, Celgene, UCB, and others. Dr. Houghton and Dr. Edwards reported no relevant conflicts of interest. ■

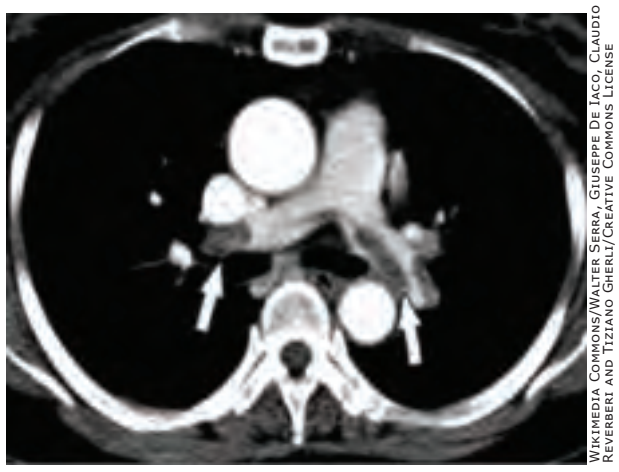

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Image shows a patient with pulmonary embolism.

CHEMO *continued from previous page*

events following (>12 weeks after discontinuation) adjuvant anti–PD-1 therapy for high-risk resected melanoma.

He mentioned, however, that the rate of second primary lung tumors in the atezolizumab group (1.4%) was lower than in the BSC group (2.6%), with generally similar rates between immuno- and nonimmunotherapies in melanoma and breast cancer trials.

"IMpower 010 is the first adjuvant study establishing immune checkpoint blockade as a new standard of care. We need to cure more, not to delay relapse," he said. The optimal population for treatment is still yet to be defined, as is the best perioperative strategy, Dr. Besse added. "If approved I would prescribe adjuvant atezolizumab ... until I see the overall survival curves."

IMpower010 was funded by F. Hoffmann–La Roche. Dr. Felip disclosed numerous financial interests, including having received financial support from F. Hoffmann–La Roche, AstraZeneca, Amgen, and Merck, among other pharmaceutical companies. ■

Poor pediatric asthma control tied to raised chance of COVID-19 hospitalization

BY HEIDI SPLETE
MDedge News

Children and adolescents with poorly controlled asthma were three to six times more likely to be hospitalized with COVID-19 infections, based on data from a national study of more than 750,000 children in Scotland.

Although the majority of COVID-19 cases in children have been mild, some children require hospitalization, wrote Ting Shi, PhD, of the University of Edinburgh and colleagues.

Vaccination policies to potentially reduce infection and hospitalization of children remain inconsistent, the researchers said. Identifying which school-age children would derive the greatest benefit from vaccination "could help to reduce the risk of infection and consequently the need for children to have time off school; and might also reduce the risk of spread of SARS-CoV-2 within schools and households."

But the potential benefits of vaccination for children with asthma in particular have not been well studied, they wrote.

The United Kingdom's Joint Commission on Vaccination and Immunisation commissioned research on the rates of hospitalization among children with poorly controlled asthma.

In a national incidence cohort study published in The Lancet Respiratory Medicine (2021 Nov 30. doi: 10.1016/S2213-2600[21]00491-4), the researchers reviewed data from all children aged 5-17 years in Scotland who were enrolled in the linked dataset of Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II).

The total number of children in the dataset was 752,867, and 63,463 (8.4%) of these had diagnosed asthma. Among the children with asthma, 4,339 (6.8%) had confirmed COVID-19 infections between March 1, 2020, and July 27, 2021. A total of 67 infected children were hospitalized. Of the 689,404 children without asthma, 40,231 (5.8%) had confirmed COVID-19 infections, and 382 (0.9%) of these children were hospitalized.

Overall, hospital admission rates for COVID-19 were significantly higher among children with asthma, compared to those without asthma (adjusted hazard ratio, 1.49), and the rates increased among children with poorly controlled asthma.

Overall, hospital admission rates for COVID-19 were significantly higher among children with asthma, compared to those without asthma, and the rates increased among children with poorly controlled asthma.

The researchers used previous hospital admission for asthma as a measure of uncontrolled asthma, and found that hospitalization was at least six times as likely for children with poorly controlled asthma, compared with those with no asthma (aHR, 6.40), although children with well-controlled asthma also had an increased risk of hospitalization, compared with those with no asthma (aHR, 1.36).

When the researchers used oral corticosteroid prescriptions as an indicator of uncontrolled asthma, the adjusted hazard ratios were 3.38, 3.53, 1.52, and 1.34 for children with prescribed corticosteroid courses of three or more, two, one, and none, respectively, compared with children with no asthma.

These hazard ratios remained significant after controlling for factors including age, sex, socioeconomic status, comorbidity, and previous hospital admission, the researchers wrote.

In an age-based analysis, results were similar for children aged 12-17 years, but in children aged 5-11 years, the hospitalization risk decreased for those with one course of corticosteroids and reached the highest rate for those with three or more courses, rather than two courses.

The study findings were limited by several factors including the relatively small numbers of COVID-19 hospitalizations, ICU admissions, and deaths in children with asthma, the researchers noted. Other limitations include potential changes in asthma control over the study period, and lack of data on certain confounders such as tobacco use, unsuitable housing, and ethnicity, they noted. However, the results were strengthened by the use of a large, national dataset, and access to electronic health records, they said.

The findings reflect data from previous studies suggesting increased risk of hospitalization for patients with respiratory illness who develop COVID-19 infections, the researchers wrote.

The results emphasize the importance of good asthma control to protect children from severe COVID-19, and careful monitoring of children with poorly controlled asthma who do become infected, they added.

"The findings from this linkage of multiple data sources have helped inform the prioritisation of school-aged children with poorly controlled asthma for vaccines," they concluded.

Findings support value of vaccination for children with asthma

"Pediatricians see many children who suffer from asthma, and although one could assume that these children would have more serious consequences from contracting COVID-19, the current study examines a large database in a way not possible in the United States to address the severity question," said Suzanne C. Boulter, MD, of the Geisel School of Medicine at Dartmouth, Hanover, N.H.

"The authors used prior hospitalization rate or two prescriptions for oral corticosteroids as markers of asthma severity prior to the onset of COVID-19 in Scotland, and they collected retrospective data for 16 months of the pandemic through July of 2021, showing a significant increase in hospitalization for those children," she said. Dr. Boulter said she was not surprised by this finding, given the impact of COVID-19 on the respiratory system.

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This month in the journal *CHEST*®

Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP
Editor in Chief

Revisiting mild asthma: current knowledge and future needs.
By Dr. A. Mohan, et al.

Treatment of *Mycobacterium abscessus* pulmonary disease.
By Dr. D. Griffith, et al.

The utility of the rapid shallow breathing index in predicting successful extubation: A systematic review and meta-analysis.
By Dr. V. Trivedi, et al.

National temporal trends in hospitalization and inpatient mortality in patients with pulmonary sarcoidosis in the United States between 2007 – 2018.
By Dr. S. Alqalyoobi, et al.

How I Do It: Considering lung transplantation for patients with COVID-19.
By Dr. C. S. King, et al.

Addressing race in pulmonary function testing by aligning intent and evidence with practice and perception.
By Dr. N. Bhakta, et al.

ASTHMA *continued from previous page*

"Pediatricians have found significant challenges from some groups of parents when discussing the indications and need for vaccination in their patients," said Dr. Boulter.

"Having this data on the increased risk of morbidity and mortality in children with asthma might help parents who are uncertain about the risk/benefit ratio of the vaccine make their decision," she said.

The results emphasize the importance of good asthma control to protect children from severe COVID-19, and careful monitoring of children with poorly controlled asthma who do become infected.

Dr. Boulter said she hoped that additional studies will yield ongoing information about hospitalization rates for COVID-19 not only about asthma, but also other diagnoses affecting children in the United States and worldwide.

"It would also be important to see a breakdown of ethnic factors and adverse childhood experiences and how they relate to hospitalization and death from COVID-19," Dr. Boulter said.

"The results of this study are not surprising, as we have known for a long time that children with severe asthma are more susceptible to severe respiratory viruses," Francis E. Rushton, MD, a pediatrician in Beaufort, S.C., said in an interview.

"But the study is still important, as it helps us determine which children are most urgently in need of protection from COVID-19 in any of its forms," he emphasized. In particular, the current study underlines the importance of vaccinating children with unstable asthma, Dr. Rushton said.

Going forward, "it would be interesting to do additional studies looking at other markers for poor asthma control that could guide our vaccine efforts so that they are focused on those most at risk," he added.

The study was supported by the UK Research and Innovation (Medical Research Council), Research and Innovation Industrial Strategy Challenge Fund, Health Data Research UK, and the Scottish Government. Lead author Dr. Shi had no financial conflicts to disclose. Dr. Rushton and Dr. Boulter had no financial conflicts to disclose. ■

Sleep disorders and cancer: It's complicated

BY RICHARD MARK KIRKNER

Sleep apnea and other types of sleep disorders appear to elevate the risk for some types of cancer, specifically prostate cancer, more so than others. But the overall risk can be highly variable, and some sleep problems were found to be associated with a lower risk for cancer and cancer-related death, an analysis of a large observational cohort study of cardiovascular patients found.

Results of the analysis were published online in the journal Cancer Epidemiology (2021 Nov 17. doi: 10.1016/j.canep.2021.102057). Investigators analyzed the presence of sleep apnea and insomnia and cancer risk in more than 8,500 patients in the Cardiovascular Health Study (CHS).

"The fact that we observed certain sleep problems, like apneas, to be associated with elevated risk of some cancers but not others reflects the fact that cancer is a heterogeneous disease," senior author Amanda Phipps, PhD, said in an interview. Dr. Phipps is an associate professor of epidemiology at the University of Washington and the Fred Hutchinson Cancer Research Center, both in Seattle.

"The fact that we observed certain sleep problems, like apneas, to be associated with elevated risk of some cancers but not others reflects the fact that cancer is a heterogeneous disease."

Variable cancer links

The researchers assessed sleep problems in two groups in the CHS: an incident cancer group of 3,930 patients and a cancer mortality group of 4,580 patients. Within those respective groups, the investigators identified 885 first-incident cancers and 804 cancer deaths with a median follow-up of 12 and 14 years. The average age of the study population was 73 years, and 57% were women.

Sleep apnea symptoms (SAS) were associated with a lower risk for incident cancers – a 16% lower baseline risk and a 24% lower time-dependent risk. The study showed no association between cancer incidence and daytime sleepiness and apneas.

However, there was a significantly elevated risk relationship between sleep problems and prostate cancer. A time-dependent analysis of apnea showed more than double the risk (hazard ratio, 2.34), and baseline snoring carried a 69% greater risk. There was also a dose-response relationship for baseline cumulative SAS, compared with not having symptoms: an HR of 1.30 for one symptom, and 2.22 for two or more symptoms.

Risks for lymphatic or hematopoietic cancers were also associated with baseline daytime sleepiness (HR, 1.81), but not with insomnia (HR, 0.54).

With regard to cancer mortality, the study found no relationship between sleep problems and cancer death. In fact, it found an overall inverse relationship with snoring (time-dependent HR, 0.73; cumulative average HR, 0.67) and baseline apnea (HR, 0.69).

Likewise, patients reporting SAS had lower risks than those having no SAS: an HR of 0.90 for one symptom and 0.75 for multiple symptoms. No relationships were found between any insomnia symptom and cancer death.

"We know the pathways that lead to prostate cancer can be very different than the pathways that lead to colorectal cancer," Dr. Phipps said. "What we don't yet understand is why these associations differ or what mechanisms are responsible for these cancer site-specific associations."

Need for sleep assessment

The findings don't change much for how clinicians should evaluate cancer risks in patients with sleep problems, Dr. Phipps said.

"Other studies have clearly demonstrated the implications that sleep apnea has for a variety of other important health conditions – such as cardiovascular disease – so there are already plenty of good reasons for clinicians to ask their patients about their sleep and to connect patients with resources for the diagnosis and treatment of sleep apnea," she added. "This study provides another possible reason."

These findings provide context for future studies of the relationship between sleep problems and cancer. "But, given that sleep is something we all do and given that sleep problems are so pervasive, it's important that we keep trying to better understand this relationship," Dr. Phipps said.

"My hope is that future cancer studies will build in more detailed, longitudinal information on sleep patterns to help us fill current gaps in knowledge."

Dr. Phipps has disclosed no relevant financial relationships. ■

Mary Jo Farmer, MD, PhD comments: Epidemiological papers are always interesting. Searching for possible associations in the dataset might set the stage for further research, whether at the bench or clinical setting.

The analysis published online in the Journal of Cancer Epidemiology uses the term "sleep problems" when identifying a significantly elevated risk relationship with prostate cancer. It is good that this term is more specifically defined as apnea, rather than baseline snoring. The presence of apnea more than doubled the cancer risk in a time-dependent analysis, while presence of baseline snoring carried a 69% greater risk of prostate cancer.

"Apnea" and "snoring" are terms that have specific meaning whereas "sleep problems" is nonspecific and harder to define, perhaps limiting the transferability of associations found in an epidemiologic analysis to further study at the bench or clinical level.

It is interesting to note that an association between prostate cancer in men and measures of intermittent hypoxia was also found in a study published in the European Respiratory Journal (https://erj.ersjournals.com/content/53/6/1900091).

This study indicated a strong relationship between a cancer diagnosis and measures of intermittent hypoxia (ODI and CT90%) rather than AHI. The most prevalent cancer in women was breast cancer (43.8%), followed by gynacological (12.3%) and thyroid (6.9%) cancer, lymphoma (5.4%), lung (4.6%) and colon (3.1%) cancer, and melanoma (3.1%). The most prevalent cancer in males was prostate cancer (33.1%), followed by lymphoma (8.3%), colon cancer (8.3%), ear, nose, and throat cancer (8.3%), lung cancer (5.9%) and melanoma (5.3%). In a sub-analysis, there was no independent influence of OSA on the prevalence of breast and prostate cancer.

A letter to the editor points to some of the issues with database studies such as these: "There is growing, but debatable evidence for the potential association between obstructive sleep apnoea (OSA) and cancer. Available studies have reached contradictory conclusions due to limited sample sizes, and poor characterization of OSA phenotypes or type of malignancies (all types or site specific)."

The letter additionally pointed out that there were several hypotheses proposed for why carcinogenesis can occur in the context of OSA, including older age, sleep deprivation, and concomitant obesity.

It discussed how intermittent hypoxia and sleep fragmentation may also play a significant role via alterations in angiogenesis, sympathetic outflow, or modulation of immune function and tumor microenvironment.

"Gender-specific differences in the association between OSA and cancer prevalence have been poorly studied," the author added (DOI:10.1183/13993003.00091-2019).

Epidemiological studies such as these identify associations that require further investigation. If multiple epidemiological studies demonstrate an association between, for example, sleep apnea and prostate cancer in males, it could set the stage for exploration of these two conditions at the biological level to understand further associations and commonalities. ■

IN AN ONGOING STUDY, KOSMOS HAS BEEN SHOWN TO PRODUCE EQUIVALENT RESULTS TO LARGE CART-BASED SYSTEMS IN A MAJOR EUROPEAN HOSPITAL—INCLUDING A REDUCED NEED FOR ORDERING MORE ECHOS.

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Staying home, staying connected

Fundraising in a virtual environment

When the United States went into a 2-week quarantine to slow the spread of the COVID-19 coronavirus in March 2020, everything changed. In the months following, social distancing, working from home, and wearing masks became the norm, and life needed to find a way to go on.

The world adapted to a virtual environment, but some of the hardest hit by this change were non-profit organizations that relied on in-person contact to encourage donations that support their worthwhile missions.

This was even more challenging for the CHEST Foundation as our donors work on the front lines of the pandemic.

"It was important for us to not only stay engaged with our donors but also to recognize what those on the front lines are dealing with," says Angela Perillo, Director, Development & Foundation Operations at the American College of Chest Physicians. "Through these events, we wanted to provide some respite from the stresses of their long days."

The CHEST Foundation is about championing lung health, and there was no greater awareness of the need than now. It was time to get creative.

Viva la vino

A well-known "secret" is CHEST CEO Bob Mussachio's love of wine, and he's not alone in his passion for the grape. Perillo put this knowledge to good use creating a wine tasting series that took people around the world one bottle at a time.

The online Viva La Vino evening gatherings serve to bring donors together for a night of good wines and good conversation. A benefit to the virtual wine nights is that no one has to travel but that it keeps the group together and keeps the Foundation at the forefront of most everyone's minds.

"I love attending the wine nights. They are so interesting, and I get to see people who don't live in New York – it's just great," says regular participant Ilene (Lenie) Rosen.

The wines are shipped directly to the participants' homes and during the online Zoom session, Mussachio guides the tasting by scrolling through a presentation on the wine's background and what to expect from the taste. As the wines are tasted, the participants have a chance to share their review.

"It's always enthralling to me how much our members know about wine. It makes for a really fun evening listening to their critiques and even learning a bit myself. These events have provided a great platform to stay engaged with our donors and enjoy an evening at home with company," says Perillo.

Doubling down on a good cause

After hosting its in-person event in March 2020, the Irv Feldman Texas Hold 'Em poker tournament shifted to a virtual environment to stay engaged with its players.

Supported by the CHEST Foundation, the Feldman Family Foundation created a series of poker tournaments through an online platform that worked with Zoom to retain the engagement offered by in-person events. Through the Zoom call, players are able to talk to each other either in the main room or in breakout rooms created for each table.

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Repositioning CHEST Networks for the future

Angel Coz, MD, FCCP, Chair, Council of Networks
Cassie Kennedy, MD, FCCP, Vice-Chair, Council of Networks
Aneesa Das, MD, FCCP, Co-Chair, Networks Task Force
David Zielinski, MD, FCCP, Co-Chair, Networks Task Force


Dr. Coz


Dr. Kennedy


Dr. Das


Dr. Zielinski

Welcome to the new year and your new Networks structure. We are excited to introduce the updated approach that will address the evolving needs of the Networks.

This transition has been more than 2 years in the making. In 2019, under the directive of former CHEST President, Dr. Stephanie Levine, the Networks Task Force was charged with guiding a redevelopment plan with the goal of better serving CHEST membership and aligning closer with curriculum categories and other CHEST priorities.

The Networks Task Force was led by Co-Chairs, Aneesa Das, MD, FCCP, and David Zielinski, MD, FCCP, along with Council of Networks Chair, Angel Coz, MD, FCCP; Jack Buckley, MD, MPH, FCCP; Christopher Carroll, MD, FCCP; De De Gardner, DrPH, RRT, FCCP; Sandhya Khurana, MD, FCCP; and David Schulman, MD, FCCP. They focused on learning what Networks aspects worked, what could be improved, and how to increase the Networks' overall influence and visibility.

The task force attentively listened to member comments and considered the insight and feedback from Network steering committee leaders. The group learned that Network priorities should include:

- Creating sustainable resources for Network members.
- Increasing digital presence.
- Generating additional leadership pathways and opportunities.

After 2 years of investigation and thoughtful strategic planning, the task force presented a plan to the Council of Networks for a new structure to achieve these objectives. The Governance Committee and College Board of Regents accepted the proposal in summer 2021.

Under the new structure, previously defined steering committees are now known as Sections. There are 22 Sections grouped under the leadership umbrella of 7 Networks. The Networks are composed of the Section chairs, vice-chairs and members-at-large. The Council of Networks still provides oversight. This layered approach is intended to help reduce silos and support improved collaboration between groups.

You might notice that many of the new Sections promote different areas of interest. These changes allow the groups to align closer to CHEST's curriculum areas. The Networks are better positioned to act as content experts in more CHEST initiatives. The new Sections each focus on a specific curriculum area of pulmonary, critical care, and sleep medicine.

You will also notice that not all of the original individual Networks mapped over into the new structure. The Task Force determined that these special interests have broad appeal across all domains and would benefit from collective curriculum integration rather than being relegated to individual Sections. The decision to dissolve these individual steering committees was neither taken lightly, nor was it easy. The intent is that these interest areas

Continued on following page

Courtesy CHEST


Courtesy CHEST
Mitch Feldman speaks at the 2020 Irv Feldman Texas Hold 'Em Annual Tournament & Casino Night.

CONNECTED *continued from previous page*

Poker player and recent winner of one of the tournaments, Kim Coles started playing professionally during the pandemic and enjoys playing in an online environment.

"I had participated in charity poker tournaments before, but it wasn't until I joined Poker Power—a group focused on teaching women how to play poker—that I really came to the table ready to compete," says Coles. "Playing in an online setting is a lot more accessible for a lot of people, especially for women. A traditional poker tournament can be intimidating to a new player, but online has a way of evening the playing field."

In an online setting, Feldman and Coles both note that buying in is a lot easier and lends itself well to fundraising.

"There is no fumbling around for your wallet or having to swipe your credit card," says Coles. "It's just the press of a button, and your credit card is already linked. It's all going to a good cause, so it makes sense to keep buying in to keep playing."

Looking into the future, while Feldman says that the virtual events have been successful, there's nothing like in-person.

"Through our virtual events, we were able to expand our network of players beyond the Chicagoland area, and these individuals have expressed their interest in attending our live events," says Feldman. "With this extended network, I am very much looking forward to being able to get together in-person again for what I expect be one of our best tournaments to date."

The 8th Annual Irv Feldman Texas Hold 'Em Annual Tournament & Casino Night will be held in early April 2022 in the Chicago suburbs, and all are welcome to attend. Visit the CHEST Foundation's website to learn more about the tournament and upcoming events at chestfoundation.org. ■

Our CHEST 2021 Award Recipients

ANNUAL AWARDS

Master FCCP
Curtis N. Sessler, MD, Master FCCP

College Medalist Award
Margaret Pisani, MD, MPH, FCCP

Distinguished Service Award
Christopher Carroll, MD, FCCP

Master Clinician Educator
Doreen Addrizzo-Harris, MD, FCCP

Early Career Clinician Educator
Matthew C. Miles, MD, FCCP

Alfred Soffer Award for Editorial Excellence
Scott Manaker, MD, PhD, FCCP

Presidential Citation
COVID-19 Task Force
Ryan Maves, MD, FCCP
Christopher Carroll, MD, FCCP
Neha Dangayach, MD
Jeffrey Dichter, MD, FCCP
Alice Gallo De Moraes, MD
James Geiling, MD, MPH, FCCP
Holly Keyt, MD, FCCP
Stephanie M. Levine, MD, FCCP
Septimu Murgu, MD, FCCP
Marcos Restrepo, MD, PhD, FCCP
Steven Q. Simpson, MD, FCCP
Angel Coz Yataco, MD, FCCP
Staff: Katlyn Froslan,
Heather Watkins, Robb Rabito,
CHCP, Lilly Rodriguez,
Karla Velilla

HONOR LECTURE AND MEMORIAL AWARDS

Distinguished Scientist Honor Lecture in Cardiopulmonary Physiology
Kenneth I. Berger, MD, FCCP
Probing the Small Airways in the Assessment of Dyspnea
The lecture is generously funded by the CHEST Foundation.

Presidential Honor Lecture
Curtis N. Sessler, MD, Master FCCP
Navigating the Road to Well-Being in the ICU

Margaret Pfrommer Endowed Memorial Lecture in Home-Based Mechanical Ventilation
Debra Weese-Mayer, MD
Artificial Ventilation, a True Life-Saver for Children with CCHS & ROHHAD
The Margaret Pfrommer Endowed Memorial Lecture in Home-Based Mechanical Ventilation is generously supported by International Ventilator Users Network of Post-Polio Health International and the CHEST Foundation.

Richard S. Irwin, MD, Master FCCP Honor Lecture
Peter J. Mazzone, MD, MPH, FCCP
Shared Decision Making in the Evaluation and Management of Early Stage Lung Cancer
The lecture is generously funded by the CHEST Foundation.

Edward C. Rosenow III, MD, Master FCCP/Master Teacher Honor Lecture
Diane E. Stover, MD, FCCP
The Many Faces of Organizing Pneumonia—What's the O(O)P With That?
The lecture is generously funded by the CHEST Foundation.

Pasquale Ciaglia Memorial Lecture in Interventional Medicine
Michael J. Simoff, MD, FCCP
Robotic Bronchoscopy: Platform to the Future?
The lecture is generously funded by the CHEST Foundation.

Roger C. Bone Memorial Lecture in Critical Care
Ognjen Gajic, MD, FCCP
Patient Comes First: Prioritizing Relevant From Irrelevant in Critical Care Medicine
The lecture is generously funded by the CHEST Foundation.

Thomas L. Petty, MD, Master FCCP Memorial Lecture
Jean Bourbeau, MD, FCCP
Pulmonary Rehabilitation and Self-Management in COPD: Understanding the Past to Build the Future
The lecture is generously funded by the CHEST Foundation.

CHEST FOUNDATION GRANT AWARDS

CHEST Foundation Research Grant in Lung Cancer
This grant is supported by the CHEST Foundation.

Daniel Ryan, MD, Royal College of Surgeons Ireland, Dublin, Ireland
Microbial Signatures Associated With Malignant Pleural Effusions in Lung Cancer

CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
This grant is jointly supported by the CHEST Foundation and RHA.
Miguel Divo, MD, Brigham and Women's Hospital, Boston, MA
Biomarker Profiles in Smokers Who Are at Risk of Developing Chronic Obstructive Pulmonary Disease (COPD)

CHEST Foundation Research Grant in Chronic Obstructive Pulmonary Disease
This grant is supported by AstraZeneca LP.

Stephen Milne, MBBS, Woolcock Institute of Medical Research, Vancouver, BC, Canada
The Oral Metagenome in COPD: Towards a Biomarker of Exacerbation Risk

CHEST Foundation Research Grant in Critical Care
This grant is supported by the CHEST Foundation.

Jacqueline Stocking, PhD, University of California, Davis, Davis, CA
University of California Critical Care Research Collaborative: Predictive Model and Risk Calculator for Early and Late Postoperative Respiratory Failure

CHEST Foundation and the Alpha-1 Foundation Research Grant in Alpha-1 Antitrypsin Deficiency
This grant is jointly supported by the CHEST Foundation and the Alpha-1 Foundation.

John Charles Rotondo, PhD, University of Ferrara, Ferrara, Italy
Alpha-1 Antitrypsin Protein as a Possible Marker of Disease Progression in COVID-19 Patients

CHEST Foundation Research Grant in Nontuberculous Mycobacteria Diseases
This grant is supported by Insmed Incorporated.

Edward Chan, MD, Rocky Mountain Regional Veterans Affairs Medical Center, Denver, CO
Visualization and Quantitation of Azithromycin, Clofazimine, and Amikacin Distribution in Surgically Removed Lung Tissues From Patients With Nontuberculous Mycobacterial Lung Disease

CHEST Foundation Research Grant in Cystic Fibrosis
This grant is supported by Vertex Pharmaceuticals Incorporated.

Shahid Sheikh, MD, FCCP, Nationwide Children's Hospital, Columbus, OH
Impact of CFTR Modulator Therapy Elexacaftor-Tezacaftor-Ivacaftor on CF- Related Chronic Sinus Disease

John R. Addrizzo, MD, FCCP Research Grant in Sarcoidosis
This grant is in honor of John R. Addrizzo, MD, FCCP and is jointly sup-

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CHEST NETWORKS *continued from previous page*

will have increased access to resources and support under the expanded structure.

We are optimistic this new structure will enhance your Network experience. As with any meaningful change, we may face some growing pains along the way. Your Network leadership is open to feedback and making adjustments to better serve the CHEST membership.

Here are your ways to stay (or get) involved with the Networks and be informed.

- Subscribe to receive the latest information on topics most important to you by joining a Network. Network membership gives you access to Network News, a bi-yearly communication from your Network chair with relevant education course offerings, key events in the CHEST community, and up-to-date information on happenings in your Network.
- Join multiple Networks, or change your affiliation any time, by logging in to your CHEST Account, and indicate your preferences on the Networks page.
- Apply for a position when the call for nominations opens. Keep an eye out soon for an announcement
- Join a Network call. Contact the Networks staff liaison for access to the call information. Call information will be available soon on the individual Network webpages.

In the meantime, please take a few minutes to become acquainted with our new structure. Visit the new Network webpages at chestnet.org/networks.

We hope you are as excited as we are with what's in store for CHEST members. ■

ported by the Addrizzo family and the CHEST Foundation.

Maneesh Bhargava, MD, PhD, FCCP, Minneapolis VA Health Care System, Minneapolis, MN
Inflammatory Protein Panel for Sarcoidosis Diagnosis and Prognosis

CHEST Foundation Research Grant in Severe Asthma
This grant is supported by the CHEST Foundation.

Felix Reyes, MD, Montefiore Medical Center, Bronx, NY
Design and Implementation of an Asthma Action Plan Generator: A Pilot Study Assessing User Satisfaction and Clinical Impact

CHEST Foundation Research Grant in Pulmonary Fibrosis
These grants are supported by an independent grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Genentech, Inc.

Marco Mura, MD, PhD, Western University, London, Ontario, Canada
Validation of the Risk Stratification Score in Idiopathic Pulmonary Fibrosis

Janelle Pugashetti, MD, University of California, Davis, Davis, CA
Determining Biomarkers of Immunosuppressant Responsiveness in Patients With CTD-ILD

CHEST Foundation Research Grant in Pulmonary Hypertension
These grants are supported by the CHEST Foundation.

Michael Lee, MD, University of California San Francisco, San Francisco, CA
Transpulmonary Metabolomic Gradients During Exercise in Systemic Sclerosis-Associated Pulmonary Hypertension

Navneet Singh, MD, Warren Alpert School of Medicine at Brown University, Providence, RI
Mitochondrial Dysfunction and Oxidative Stress in Pulmonary Hypertension

CHEST Foundation Research Grant in Sleep Medicine
These grants are funded by Jazz Pharmaceuticals, Inc.

Shahid Karim, MBChB, Mayo Clinic, Rochester, MN
Effects of OSA on Atrial and Ventricular Arrhythmia in HCM: An Incidence Study

Thomas Tolbert, MD, Mount Sinai Hospital, New York, NY
Performance Characteristics of Obstructive Sleep Apnea Physiologic Traits Measured by Phenotyping Using Polysomnography

CHEST Foundation and American Academy of Sleep Medicine Foundation Research Grant in Sleep Medicine
This grant is jointly supported by the CHEST Foundation and AASM Foundation.

Marta Kaminska, MD, McGill University Health Centre, Montreal, QC, Canada
Long-term Noninvasive Ventilation in COPD: Impact on Health Care Utilization

CHEST Foundation and APCCMPD Research Grant in Medical Education
This grant is jointly supported by the CHEST Foundation and APCCMPD.

Mark Adelman, MD, NYU School of Medicine, New York, NY
Virtual Reality Simulation Training for the Management of Tracheostomy Emergencies

CHEST Foundation Research Grant in COVID-19
These grants are supported by the CHEST Foundation.

Marlene Cano, MD, PhD, Washington University, St. Louis, MO
Circulating Mitochondrial DNA Is a Potential Biomarker for Severe Illness in COVID-19

Brandon Walsh, MD, New York University, New York, NY
How Would Existing Ventilator Allocation Guidelines Perform During the COVID-19 Pandemic: A Retrospective Observational Simulated Cohort Study

CHEST Foundation and ATS Research Grant in COVID-19 and Diversity
These grants are jointly supported by the CHEST Foundation and ATS.

Navitha Ramesh, MD, FCCP, UPMC Harrisburg, Harrisburg, PA
Improving Lung Health in the Nepali-Bhutanese Refugee Community in Harrisburg, PA

Inderjit Singh, MBBCh, Yale University, New Haven, CT
Dynamic Invasive Hemodynamic, Echocardiographic, and Plasma Biomarker Phenotyping in Post-COVID-19 Long Hauler Syndrome

CHEST Foundation Community Service Grants Honoring D. Robert McCaffree, MD, Master FCCP

Valerie Andrews, BS, The JUDAHH Project, Sacramento, CA
Asthma Mitigation Project

Chanda Holsey, DrPh, National Medical Association, Silver Spring, MD
Providing Lung Health Education to At Risk Communities

Arzu Ari, PhD, FCCP, Texas State University, San Marcos, TX
Training Future Respiratory Care Practitioners in Turkey: A Path to Successful Disease Management in Pulmonary Medicine

Panagis Galiatsatos, MD, MPH, John Hopkins University, Baltimore, MD
The Lung Health Ambassador Program: A Health Equity Initiative for Cystic Fibrosis

Patricia George, MD, National Jewish Health, Denver, CO
Development of Breathe Strong PH: An Informational Website About Pulmonary Hypertension and Related Diseases

Nishant Gupta, MD, MS, University of Cincinnati, Cincinnati, OH
Global Dissemination of the Lymphangioleiomyomatosis (LAM) Clinical Practice Guidelines

Syed Naqvi, MD, MBBS, Hoag Hospital Newport Beach, Newport Beach, CA
Asthma Managment in Rural Pakistan
These grants are supported by the CHEST Foundation.

Alfred Soffer Research Award Winners
Mathieu Saint-Pierre, MD: *Methacholine Challenge Testing: A Clinical Prediction Model Utilizing Demographic Data And Spirometry Results*

Tie:
Milind K Bhagat, MD: *High Flow Nasal Cannula Fio2 Cutoffs Identified Early In The Hospital Course Are Associated With Increased Mortality Risk In Hospitalized Patients With COVID-19*

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AWARDS *continued from previous page*

Amber J Meservey, MD: *Outcomes Of Patients Across The Spectrum Of Pulmonary Hypertension Groups Prescribed Inhaled Treprostinil*

Young Investigator Award Winners

William B. Feldman, MD: *COPD Exacerbations And Pneumonia Hospitalizations In New Users Of Combination Maintenance Inhalers: A Comparative Effectiveness And Safety Study*

Christopher Streiler, MD: *Community Pulmonologist Access To Multidisciplinary Discussion At An Academic Referral Center Leads To Changes In Management Of Interstitial Lung Disease*

Top 5 Abstract Posters

Winner: Riley Kermanian: *Management Of Coronary Artery Calcification In Patients Enrolled In A Low-Dose Computerized Tomography Lung Cancer Screening Program*

Winner: Rohit Reddy: *Outcomes Of Extracorporeal Membrane Oxygenation In ARDS Due To Covid-19: Comparison Of The First And The Second Wave*

Winner: Taylor A. Intihar, BA: *Light Patterns Of The Medical ICU: Are We Disrupting Circadian Rhythms?*

Runner up: Jason Wong, MD: *Completion Of Pulmonary Rehabilitation Is Associated With Improvement In Depression Scores And Other Quality Of Life Measures In Patients With Interstitial Lung Disease*

Runner up: Harshil Shah, MD: *Impact Of Sepsis On Outcomes Of Hospitalizations Due To COPD*

Case Report Session Winners

Remarkable Pulmonary Cases: Mena Botros, MD: *Clinical Outcomes In Lung Transplant Recipients With SARS-COV2*

Bacterial Infections: Benjamin Carmel, DO: *Cotton Swab Today, Brain Abscess Tomorrow*

Challenging Critical Care Cases: Rajaninder Sharma, MD: *Pulmonary Tumor Thrombotic Microangiopathy: The Rare And Fatal Association Of Adenocarcinoma And Right Ventricular Failure*

Diffuse Lung Diseases: Rizwana RR Rana, MBBS: *A Rare Cause Of Pulmonary Nodules*

Viruses, Fungi, and Parasites Infections: Michelle Forson, MD: *Strongyloidiasis-Related Eosinophilic Pleural Effusion: An Unexpected Differential For Post-Cardiac Injury Syndrome*

Critical Care Cases: Act Quickly: Christina Jee Ah Rhee, MD: *Airway Implications Of Cricoarytenoid Arthritis: A Report And Review Of The Literature*

Airway Issues: Benadin Varajic, MD: *An Unusual And Life-Threatening Complication Of Endotracheal Intubation*

Miscellaneous Cases 1: Shrey Shah, MD: *A Case Of Pulmonary Arterial Hypertension From Vitamin C Deficiency*

Miscellaneous Cases 2: Glenn W. Pottmeyer, DO, MPH: *Biliary Stent Migration: A Rare Cause Of Right-Sided Pulmonary Abscess*

Case Report Poster Winners

Advanced Cancer Case Report Posters: Sangita Goel, MD: *Let's Meet in the Middle: Simultaneous Endoscopic and Bronchoscopic Suture Repair to Close a Left Main-Stem Malignant Broncho-Esophageal Fistula*

Cardiovascular Case Report Posters: Marianna Weaver, DO: *Swan-Ganz And Intra-Pericardial Pressure Guided Pericardiocentesis in Scleroderma-Associated PAH*

Remarkable Cases Posters 1: Katie Capp, MD: *Humidifier-Associated Hypersensitivity Pneumonitis*

Remarkable Cases Posters 2: Sahar Samani, MD: *Artifactual Hypoxemia in Patients With Hydroxyurea-Induced Blue Lunula Fingernails*

CHEST 2021 CHEST CHALLENGE

1st Place
The Ohio State University
Sarah Cohen, MD
Gregory Eisinger, MD
Kyle Stinehart, MD
Program Director: Jennifer McCallister, MD, FCCP

2nd Place
SUNY Buffalo
Arjun Saradna, MBBS
Rajesh Kunadharaju, MD
Ahmed Munir, MBBS
Program Director: Jeffrey Mador, MD

3rd Place
Interfaith Medical Center
Tahmina Jahir, MD
Ruby Risal, MD
Binav Shrestha, MBBS
Program Director: Marie Frances Schmidt, MD, FCCP ■

SLEEP STRATEGIES

An update on the recall of PAP and HMV devices

BY SREELATHA NAIK, MD

Case 1: A 53-year-old man was newly diagnosed with atrial fibrillation (AFIB). He was started on a regimen of metoprolol tartrate and apixaban. He is planned for cardioversion by his cardiologist and referred to sleep medicine for evaluation and management of obstructive sleep apnea (OSA). A polysomnogram demonstrated an apnea hypopnea index of 32 events per hour, and continuous positive airway pressure therapy (CPAP) of 9 cm H_2O was determined to be optimal. A new CPAP device was ordered. The patient was scheduled for cardioversion the following month but is still awaiting CPAP therapy. Patients with untreated sleep apnea have higher rates of recurrent AFIB after cardioversion in comparison to treated OSA (Kanagala R, et al. Circulation 2003;107:2589-2594).

***Case 2**: A 68-year-old man with severe COPD, chronic hypoxic respiratory failure on 2 L of oxygen at rest, pulmonary hypertension, and comorbid severe OSA. He is adherent to CPAP therapy but recently learned that his device was part of a recall. Given his chronic nasal congestion and cough, he is concerned that these symptoms may be related to his recalled device and decided to discontinue treatment until the device is replaced. His device was set up 3 years ago, therefore, he is unable to receive a new one through his insurer. He registered his device with the recall website and is awaiting for repair or a replacement and had heard that it may be a year from now.*

***Case 3**: A 65-year-old woman had progressive respiratory failure due to amyotrophic lateral sclerosis. She uses the home mechanical ventilator (Trilogy 100) all night and intermittently during the daytime with improved sleep quality, fatigue, and shortness of breath. She received the recall notice and would like to know if she has alternative options, as she is dependent on the ventilator and doesn't think that she can stop therapy safely.*

While hypothetical, the cases above illustrate the challenges with patient care that medical providers are facing nationally. On June 14, 2021, Philips Respironics announced a voluntary recall of many of their positive airway pressure (PAP) therapy, noninvasive ventilation (NIV), and home mechanical ventilation (HMV) devices. This recall is related to a polyester-based polyurethane (PE-PUR) foam used for sound abatement from these devices. Philips reports on their website that 1) PE-PUR foam may degrade into particles which may enter the device's air delivery pathway and be ingested or inhaled by the user, and 2) the PE-PUR foam may off-gas certain toxic chemicals.

Dr. Naik

The foam degradation may be exacerbated by use of unapproved cleaning methods, such as ozone and off-gassing may occur during initial operation and may possibly continue throughout the device's useful life" [www.philips.com/SRC-update]. The FDA warns that "this particular foam may break down and can result in serious injury, which can be life-threatening, cause permanent impairment, and require medical intervention to prevent permanent injury to users." Potential symptoms include rhinitis and sinusitis, upper airway irritation, cough, chest pressure, headache, or dizziness.

The guidance from Philips is as follows:

1. Patients using a recalled life-sustaining home mechanical ventilator device should continue therapy until discussion with the health care provider.

2. Patients using a recalled CPAP or BiPAP device should discuss with the health care provider a suitable treatment plan.

It is estimated that between 3 and 4 million patients are impacted by this recall. Many practices across the country have been immensely challenged with finding the means to reach out to large panels of patients, while still keeping individual risk factors in mind. Commonly prescribed devices that are impacted include the Dream Station and System One devices that provide PAP therapy for OSA, Auto Servoventilation for central sleep apnea, BiPAP therapy for treatment of hypoventilation, as well as Trilogy 100 and Trilogy 200 home mechanical ventilators for chronic respiratory failure syndromes. A complete list of devices impacted can be found at www.philips.com/SRC-update. In addition to ambulatory uses in the home setting, many sleep centers utilize Philips Respironics OmniLab Advanced Plus platforms for in-laboratory titration polysomnograms. Facility-based titration studies are, therefore, heavily impacted by this recall, as well.

Patients may register for a replacement device or repair with Philips via Philips hotline or through its website; however, given the large number of patients, the replacement process plan can be prolonged and estimated up to 12 months or longer. Philips has initiated a repair and replace program whereby the PE-PUR foam would be replaced by a silicone-based foam. The FDA has initially approved this proposal. Most recently, the FDA obtained additional information regarding the silicone-based foam used in a device outside of United States, which failed a safety test due to release of certain volatile organic compounds. While similar testing provided by Philips Respironics on devices in United States provided acceptable results, the FDA requested that Philips Respironics perform additional testing with the silicone-based foam. The FDA does not recommend discontinuation of the devices in the repair and replace program at this time

It is estimated that between 3 and 4 million patients are impacted by this recall.

While patients may attempt to purchase devices unaffected by the recall at an out of pocket expense, there is a limited supply of PAP devices nationally with a back-log of 3 months or longer. This has been a challenge particularly for patients waiting to initiate treatment for newly diagnosed with sleep-disordered breathing. Availability of devices for newly-diagnosed patients, as well as patients' hesitation/unwillingness to adhere to therapy due to fear of potential risks, will impact medical providers ability to care for patients, and likely will have significant consequences to overall patient health outcomes.

It is important for the provider to have a discussion with the patient and review the following in order to best determine a course of action:

- Severity/stage of disease
- Usage/adherence
- Clinical benefits of ongoing treatment
- Alternative therapies

While it would be optimal to replace recalled devices, providers caring for patients face challenging limitations. The following are options to consider: 1) Determine if device is past 5-year mark and if patient is eligible for new device (PAP devices only); 2) For patients with chronic respiratory failure, review disease progression, adherence and device usage (eg, if usage is > 12 hours per 24-hour period, consider switching the PAP device to a home mechanical ventilator); 3) For patients on full time invasive mechanical ventilatory support, consider switching to a non-Philips home mechanical ventilator.

A patient who is using a respiratory assist device or life-sustaining home mechanical ventilator for chronic respiratory failure may not be able to stop treatment. Conversely, it may be reasonable for a patient with mild OSA who has been struggling with adherence to temporarily stop treatment. For OSA treatment, it is advisable to consider alternative options including mandibular advancement devices, sleep surgery, or new noninvasive therapies. There are medical, logistical, and ethical challenges as we navigate through this recall, and it is important to engage the patient in an informed discussion regarding risks and benefits of therapy when determining the best course of action (Owens RL, et al. *Am J Respir Crit Care Med* 2021; 204(8):887-890).

Dr. Naik is Program Director, Sleep Medicine Fellowship; Director, Sleep Medicine; and Clinical Assistant Professor, Geisinger Commonwealth School of Medicine, Wilkes-Barre, PA.

NOTE: CHEST is providing resources for its members and others with regular updates on the Philips recall. Check at chestnet.org. ■

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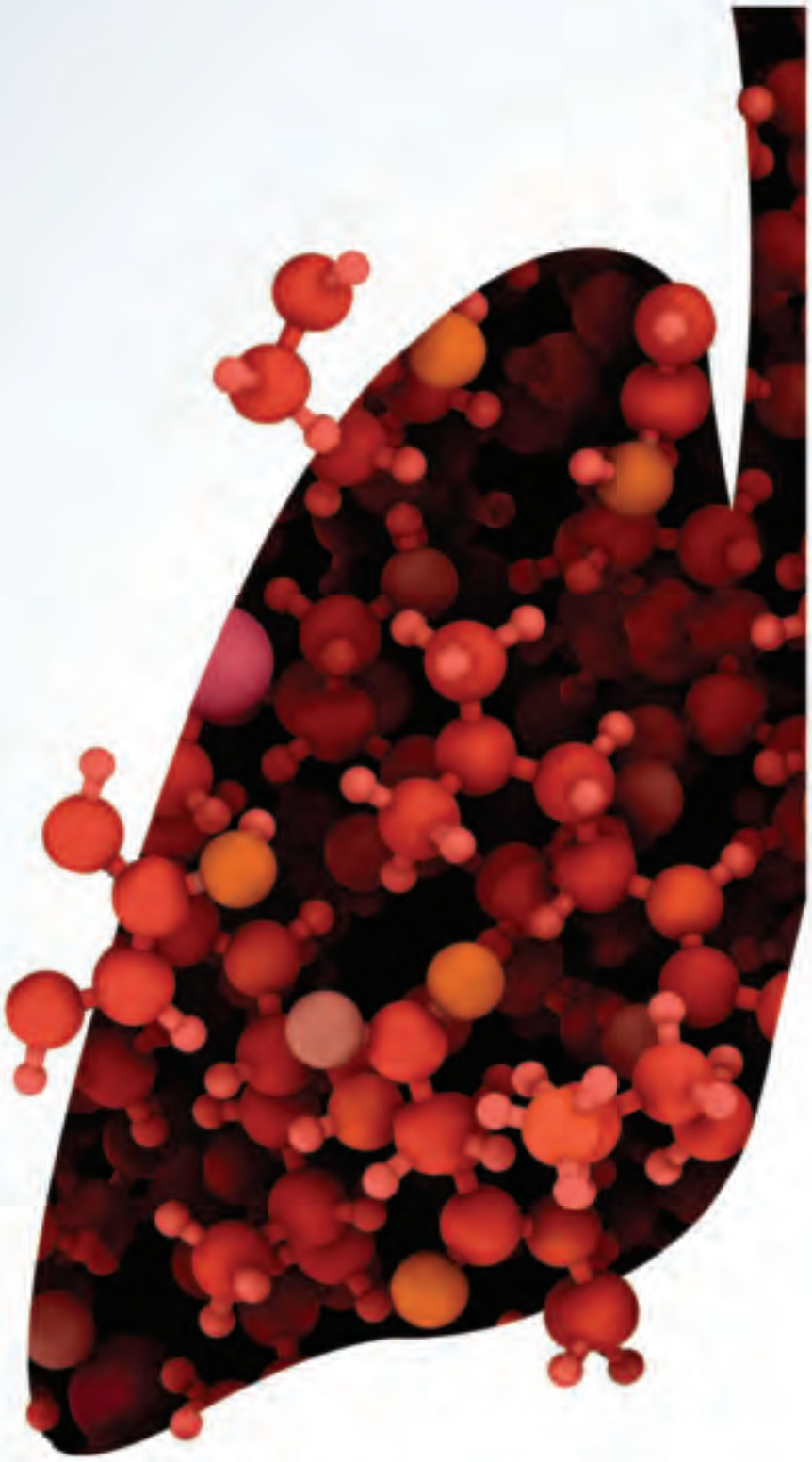

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