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# Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS



## E-cigarettes don't help smokers quit, suggests new research

BY HEIDI SPLETE

MDedge News

Use of e-cigarettes was not more effective than other methods at helping cigarette smokers quit, authors of new research found.

From 2013 to 2017, e-cigarette sales in the United States nearly doubled, driven by a rapid uptake of use by adolescents, wrote Riufeng Chen, MD, of the University of California, San Diego, and colleagues, in their paper published in *Tobacco Control* (2022 Feb 7. doi: 10.1136/tobaccocontrol-2021-056901).

However, the subsequent effect of increased e-cigarette use on smoking cessation has

not been examined, they said.

In their study, Dr. Chen and colleagues analyzed data from 3,578 previous-year smokers with a recent quit attempt and 1,323 recent former smokers who were part of the PATH cohort in 2017. The participants reported using e-cigarettes or other products to quit cigarette smoking. The primary outcomes were at least 12 months of cigarette abstinence and tobacco abstinence in 2019.

In 2017, 32.8% of established smokers reported trying to quit. Of these, 12.6% used e-cigarettes to help them quit. Cigarette abstinence for at least 12 months for these individuals was 9.9%, which was lower than for those who

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## PAH care turns corner with new therapies, intensified monitoring

BY CHRISTINE KILGORE

MDedge News

Aggressive up-front combination therapy, more lofty treatment goals, and earlier and more frequent reassessments to guide treatment are improving care of patients with pulmonary arterial hypertension (PAH) while at the same time making it more complex.

A larger number of oral and generic treatment options have in some respects ushered in more management ease. But overall, "I don't know if management of these patients has ever been more complicated, given the treatment options and strategies," said Murali M. Chakinala, MD, professor of medicine at Washington University, St. Louis. "We're always thinking through approaches."

Diagnosis continues to be challenging given the rarity of PAH and its nonspecific presentation – and in some cases it's now harder. Experts such as Dr. Chakinala are seeing increasing number of aging patients with left

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used either nicotine replacement therapy or a pharmaceutical aid only (15.2%), and about half of the 18.6% abstinence in those who used no products to help them quit.

"In our study, e-cigarettes resulted in seven fewer successful quitters than those who used pharmaceutical aids," emphasized corresponding author, John P. Pierce, PhD, of the University of California, San Diego.

Among smokers attempting to quit, the adjusted risk difference for cigarette abstinence for a least 12 months with e-cigarettes vs. pharmaceutical aids was -7.3%, and -7.7% for e-cigarettes vs. other smoking cessation methods.

"Among recent former smokers who had switched to daily use of e-cigarettes in 2017, 43.2% had successfully quit cigarette smoking by 2019, which was similar to those who used e-cigarettes on a nondaily basis (34.6%) or to those who switched to another tobacco product, whether daily (43.6%) or nondaily (44.7%)," the researchers wrote.

The rapid growth in e-cigarette use between 2014 and 2017 has been attributed in part to aggressive marketing of high-nicotine e-cigarettes, they said. "The high-nicotine JUUL e-cigarette has been noted as the closest match to cigarettes in both nicotine delivery and user satisfaction, which should make it one of the best candidates as a product to which smokers could switch in order to maintain their nicotine habit," they said in their discussion of the findings.

## More research needed

The researchers acknowledged the need to review more recent data.

"When we looked ahead to 2019, recent former smokers had started using high-nicotine e-cigarettes. The effectiveness of high-nicotine e-cigarettes at preventing relapse will require another follow-up PATH survey," they said.

Among recent former smokers, 2.2% reported switching to a high-nicotine e-cigarette. Although individuals who switched to e-cigarettes showed a higher rate of relapse to cigarettes than those who did not switch to other tobacco or e-cigarette products, this difference was not significant.

The study findings were limited by several factors including the observational design and inability to control for all potential confounding factors, the researchers noted. However, the results were strengthened by the use of a large and representa-

tive study population, and the inclusion of biological samples to validate self-reported smoking, they said.

## Several findings surprised study author

Dr. Pierce said he was surprised by several aspects of the study findings.

"First of all, contrary to what we expected, there was a 25% decline in using e-cigarettes to quit, compared to the previous year (not the 40% increase that was expected from the increase in e-cigarette sales) and almost no smokers were using high-nicotine JUUL products to help them quit," he said. "In this study, e-cigarettes were much less helpful (7 less successful quitters per 100) than pharmaceutical cessation aids in helping people quit," he added.

"The fact that the proportion of smokers using e-cigarettes for cessation dropped from 17% to 12% was unexpected, and it suggests that the belief that they are a cessation aid is declining," he said.

The implication for clinical practice is that e-cigarettes are not a useful tool for smoking cessation, Dr. Pierce said. "We are not finding any evidence in this very large nationally representative study that smokers who switch to getting their nicotine from e-cigarettes are less likely to relapse back to cigarette smoking," he said.

"We don't know about the high-nicotine versions," he added.

## New review advises against e-cigarettes for cessation

A recent review article published in JAMA (2022 Feb 8. doi: 10.1001/jama.2022.0395) supported the use of pharmacotherapy and behavioral support for smokers wanting to quit. In the review, Nancy A. Rigotti, MD, of Massachusetts General Hospital, Boston, and colleagues summarized the evidence for managing tobacco smoking in clinical practice.

"The health risk from cigarette smoking is primarily due to chemicals produced by the burning of tobacco and not to nicotine," they noted. However, the physical dependence on nicotine makes quitting a challenge, but it is one worth pursuing, the authors said.

The authors of this review identified 30 reviews, 12 randomized clinical trials, and 7 recent guidelines and evidence reviews. Their key message: Pharmacotherapy and behavioral support are effective when used alone, but even more effective when combined. Pharma-

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heart disease, chronic kidney disease, and other comorbidities who have significant precapillary pulmonary hypertension and who exhibit hemodynamics consistent with PAH, or group 1 PH.



Dr. Chakinala

The question experts face is, do such patients have “true PAH,” as do a reported 25-50 people per million, or do they have another type of PH in the classification schema – or a mixture?

Deciding which patients “really fit into group 1 and should be managed like group 1,” Dr. Chakinala said, requires clinical acumen and has important implications, as patients with PAH are the main beneficiaries of vasodilator therapy. Most other patients with PH will not respond to or tolerate such treatment.

“These older patients may be get-

ting PAH through different mechanisms than our younger patients, but because we define PAH through hemodynamic criteria and by ruling out other obvious explanations, they all get lumped together,” said Dr. Chakinala. “We need to parse these patients out better in the future, much like our oncology colleagues are doing.”

Personalized medicine hopefully is the next horizon for this condition, characterized by severe remodeling of the distal pulmonary arteries. Researchers are pushing to achieve deep phenotyping, identify biomarkers, and improve risk assessment tools. And with 80 or so centers now accredited by the Pulmonary Hypertension Association (PHA) as Pulmonary Hypertension Care Centers, referred patients are accessing clinical trials of new nonvasodilatory drugs.

Currently available therapies improve hemodynamics and symptoms, and can slow disease progression, but are not truly dis-

ease modifying, sources say.

“The endothelin, nitric oxide, and prostacyclin pathways have been exhaustively studied, and we now have great drugs for those pathways,” said Dr. Chakinala, who leads the PHA’s scientific leadership council. But “we’re not going to put a greater dent into this disease until we have new drugs that work on different biologic pathways.”

### Diagnostic challenges

The diagnosis of PAH – a remarkably heterogeneous condition that encompasses heritable forms and idiopathic forms, and that comprises a broad mix of predisposing conditions and exposures, from scleroderma to methamphetamine use – is still too often missed or delayed. Delayed diagnoses and misdiagnoses of PAH and other types of PH have been reported in up to 85% of at-risk patients, according to a 2016 literature review (JAMA Cardiol. 2016;1[9]:1056-65).

Being able to pivot from thinking

about common pulmonary ailments or heart failure to considering PAH is a key part of earlier diagnosis and better treatment outcomes. “If someone has unexplained dyspnea or if they’re treated for other lung diseases and are not improving, think about a screening echocar-

diogram,” said

Timothy L. Williamson, MD, vice president of quality and safety and a pulmonary physician at the University of Kansas Health Center, Kansas City.



Dr. Williamson

One of the most common reasons Dr. Chakinala sees for missed diagnoses are right heart catheterizations that are incomplete or misinterpreted. (Right heart catheterizations are required to confirm the diagnosis.) “One can’t simply

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### E-CIGARETTES continued from page 2

cotherapy helps reduce the symptoms of nicotine withdrawal, while behavioral intervention tackles the challenge of changing learned behaviors associated with smoking, the researchers said.

Although combining medications, such as varenicline and nicotine replacement therapy or bupropion might improve successful quit rates, these combinations have not been well studied, they noted.



VCAL/GETTY IMAGES

With regard to e-cigarettes, the researchers cited a 2021 Cochrane review of 16,759 individuals who used e-cigarettes for smoking cessation, which found no evidence of harm, but insufficient evidence to assess the balance of risks vs. benefits.

In addition to the lack of randomized trials, “the FDA regulates e-cigarettes as tobacco products, not as medical products and has not evaluated any e-cigarette for medical use as a cessation aid,” the authors of the new review noted.

The review was limited by several factors, including the lack of quality assessment for the selected studies and the exclusion of pharmacotherapy not licensed in the United States.

Commenting on the JAMA paper, Dr. Pierce

said, “This review looks like a number of Cochrane Reports that have been published recently. Of course, it only considers randomized trials and not population evidence.”

“If public health had limited itself to this form of evidence, then we still would not know that smoking caused cancer,” he noted. “Randomized trials are very important for testing new drugs; they use selected populations and provide considerable support that is not available in the real world. Sometimes they do not generalize to the population.”

### Findings may guide patient conversations

The Tobacco Control study was important, because few studies on e-cigarettes have been conducted, said Linda Girgis, MD, a family physician in private practice in South River, N.J., in an interview.

“As clinicians, we do not have a lot of data available in order to make clinical decisions that are evidence based. Also, getting patients to quit smoking is often very difficult, and having more tools available is a great benefit; however, we need to have the evidence that these tools are effective,” she said.

Dr. Girgis also said she was not surprised by the findings.

“Patients still have the same concerns from e-cigarettes regarding nicotine exposure, but just to a lesser degree; and we still don’t know the long-term effects of e-cigarette use, she said. Based on these studies, recommending e-cigarettes for smokers looking to quit may not be the best method, she noted.

“While it may seem reasonable that exposing lungs to lower doses of nicotine will reduce harm, we need to see actual evidence of this. Also, we also need to study the additives that are frequently used in e-cigs, such as artificial

flavorings, to see what harms they may pose, she emphasized.

With regard to the JAMA review, Dr. Girgis said she agreed with the recommendations for pharmacotherapy and behavior therapy as first-line treatments for smoking cessation. “There is evidence regarding the efficacy and safety of these methods, and they have been used for decades,” she said.

### Harm reduction, not safety

Dr. Girgis added that there is a role for e-cigarettes in smoking cessation strategies as a method of harm reduction, but pointed out the problem of many people thinking these products are safe and not understanding the hazards they pose.

“They think they can replace smoking with e-cigarettes and be safe from the health risks associated with smoking. I think if the plan were to switch to e-cigarettes for a short period and then quit, there would be a role,” according to Dr. Girgis. “However, replacing one risk for another may reduce harm, but doesn’t eliminate it.”

“To continue to use e-cigarettes indefinitely should not be the goal,” she added.

The Tobacco Control study was funded by the National Institutes of Health and the Tobacco-Related Disease Research Program of the University of California. The researchers had no financial conflicts to disclose.

The JAMA study was funded in part by a grant from the National Institute for Health Research, via Cochrane Infrastructure funds to the Cochrane Tobacco Addiction Group.

Lead author Dr. Rigotti disclosed funding from the National Heart, Lung, and Blood Institute and Achieve Life Sciences and personal fees from UpToDate and Achieve Life Sciences. Dr. Girgis had no financial conflicts to disclose. ■



measure pressures and stop,” he said. “We need the full hemodynamic profile to know that it’s truly precapillary PAH ... and we need proper interpretation of [elements like] the waveforms.”

The 2019 World Symposium on Pulmonary Hypertension shifted the definition of PH from an arbitrarily defined mean pulmonary arterial pressure of at least 25 mm Hg at rest (as measured by right heart catheterization) to a more scientifically determined mPAP of at least 20 mm Hg (Eur Respir J. 2019;53:1801913).

The classification document also requires pulmonary vascular resistance (PVR) of at least 3 Wood units in the definition of all forms of precapillary PH. PAH specifically is defined as the presence of mPAP of at least 20 mm Hg, PVR of at least 3 Wood units, and pulmonary arterial wedge pressure 15 mm Hg or less.

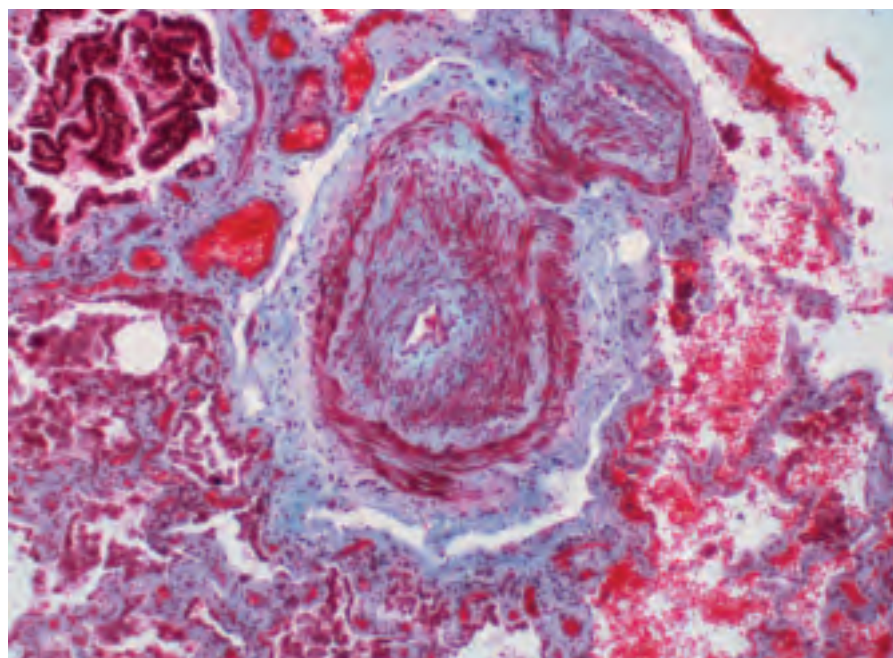
### Trends in treatment

The value of initial combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 (PDE5) inhibitor in treatment-naïve PAH was cemented in 2015 by the AMBITION trial (N Engl J Med 2015;373:834-44). The primary endpoint (death, PAH hospitalization, or unsatisfactory clinical response) occurred in 18%, 34%, and 28% of patients who were randomized, respectively, to combination therapy, monotherapy with the ERA ambrisentan, or monotherapy with the PDE-5 inhibitor tadalafil – and in 31% of the two monotherapy groups combined.

The trial reported a 50% reduction in the primary endpoint in the combination-therapy group versus the pooled monotherapy group, as well as greater reductions in N-terminal of the prohormone brain natriuretic peptide levels, more satisfactory clinical response and greater improvement in 6-minute walking distance.

In practice, a minority of patients – typically older patients with multiple comorbidities – still receive initial monotherapy with sequential add-on therapies based on tolerance, but “for the most part PAH patients will start on combination therapy, most commonly with a ERA and PDE5 inhibitor,” Dr. Chakinala said.

For patients who are not improving on the ERA-PDE5 inhibitor approach – typically those who remain in the intermediate-risk category for intermediate-term mortality – substitution of the PDE5 inhibitor with the soluble guanylate cyclase stimulator riociguat may be



**This pulmonary artery shows marked intimal thickening and adventitial thickening. The red-staining cells in the intima are probably myofibroblasts.**

considered, he and Dr. Williamson said. Clinical improvement with this substitution was demonstrated in the REPLACE trial (Lancet Respir Med. 2021;9[6]:573-84).

Experts at PH care centers are also utilizing triple therapy for patients who do not improve to low-risk status after 2-4 months of dual combination therapy. The availability of oral prostacyclin analogues (selexipag and treprostinil) makes it easier to consider adding these agents early on, Dr. Chakinala and Dr. Richardson said.

Patients who fall into the high-risk category, at any point, are still best managed with parenteral prostacyclin analogues, Dr. Chakinala said.

In general, said Dr. Williamson, who also directs the University of Kansas Pulmonary Hypertension Comprehensive Care Center, “the PH community tends to be fairly aggressive up front, and with a low threshold for using prostacyclin analogues.”

The agents are “always part of the picture for someone who is really ill, in functional class IV, or has really impaired right ventricular function,” he said. “And we’re finding increased roles in patients who are not as ill but still have decompensated right ventricular dysfunction. It’s something we now consider.”

Recently published research on up-front oral triple therapy suggests possible benefit for some patients – but it’s far from conclusive, said Dr. Chakinala. The TRITON study randomized treatment-naïve patients to the traditional ERA-PDE5 combination and either oral selexipag (a selective prostacyclin receptor agonist) or placebo as a third agent (J Am Coll Cardiol. 2021;78:1393-403). It found no significant difference in reduction in

PVR, the primary outcome, at week 26. However, the authors reported a “possible signal” for improved long-term outcomes with triple therapy.

“Based on this best evidence from a randomized clinical trial, I think it’s unfair to say that all patients should be on triple combination therapy right out of the gate,” he said. “Having said that, more recent [European] data showed that two drugs fell short of the mark in some patients, with high rates of clinical progression. And even in AMBITION, there were a number of patients in the combination arm who didn’t have a robust response.”

A 2021 retrospective analysis from the French Pulmonary Hypertension Registry – one of the European studies – assessed survival with monotherapy, dual therapy, or triple-combination therapy (two orals with a parenteral prostacyclin), and found no difference between monotherapy and dual therapy in high-risk patients (J Respir Crit Care Med. 2021;204[7]:842-54).

Experts have been upping the ante, therefore, on early assessment and frequent reassessment of treatment response. Not long ago, patients were typically reassessed 6-12 months after the initiation of treatment. Now, experts at the PH care centers want to assess patients at 3-4 months and adjust or intensify treatment regimens for those who don’t yet qualify as low risk using a multidimensional risk calculator.

The REVEAL (Registry to Evaluate Early and Long-Term PAH Management) risk score calculator, for instance, predicts the probability of 1-year survival and assigns patients to a strata of risk level based on either 12 or 6 variables (for the full or “lite” versions).

Even better monitoring and risk

assessment is needed, however, to “help sift out which patients are not improving enough on initial therapy or who are starting to fall off after being on a regimen for a period of time,” Dr. Chakinala said.

Today, with a network of accredited centers of expertise and a desire and need for many patients to remain close to home, Dr.

Chakinala encourages finding a balance. Well-resourced clinicians can strive for early diagnosis and management – potentially initiating ERA-PDE-5 inhibitor combination therapy – but still should collaborate with PH experts.

“It’s a good idea to comanage these patients and let the experts see them periodically to help you determine when your patient may be declining,” he said. “The timetable for reassessment, the complexity of the reassessment, and the need to escalate to more advanced therapies has never been more important.”

### Research highlights

Therapies that target inflammation and altered metabolism – including metformin – are among those being investigated for PAH. So are therapies targeting dysfunctional bone morphogenetic protein pathway signaling, which has been shown to be associated with hereditary, idiopathic, and likely other forms of

PAH; one such drug, called sotatercept, is currently at the phase 3 trial stage.

Most promising for PAH may be research efforts involving deep phenotyping, said



**Dr. Sweatt**

Andrew J. Sweatt, MD, of Stanford (Calif.) University and the Vera Moulton Wall Center for Pulmonary Vascular Disease.

“It’s where a lot of research is headed – deep phenotyping to deconstruct the molecular and clinical heterogeneity that exists within PAH ... to detect distinct subphenotypes of patients who would respond to particular therapies,” said Dr. Sweatt, who led a review of PH clinical research presented at the 2020 American Thoracic Society International Conference (Circulation. 2021 May 25;143[21]:2061-73).

“Right now, we largely treat all patients the same [while] we know that patients have a wide response to therapies and there’s a lot of clinical heterogeneity in how their disease

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# SCAI refines cardiogenic shock classification system

BY MEGAN BROOKS

**T**he Society for Cardiovascular Angiography and Interventions (SCAI) has refined its cardiogenic shock (CS) classification system based on the literature and clinician feedback from real-world experience.

"In the 2 years since publication in 2019, the initial definition has been broadly accepted and eagerly appreciated, allowing a very intuitive way to stage these patients for better communication, triage, and treatment," Srihari S. Naidu, MD, professor of medicine, New York Medical College, Valhalla, said in an interview.

"But the initial definition was based on consensus opinion, with a lack of real fundamental data on segregating patients into different stages. Now we have a lot more data utilizing the definition, and it became very clear that there were a couple of limitations in the initial definition," Dr. Naidu explained.

The refined CS classification system – authored by Dr. Naidu and a multidisciplinary panel of experts from specialties that included cardiac critical care, interventional cardiology, surgery, nursing, emergency medicine, and heart failure – was published online Jan. 31 in the *Journal of the Society for Cardiovascular Angiography and Interventions* (2022. doi: 10.1016/j.jscai.2021.100008), with simultaneous publication in the *Journal of the American College of Cardiology*.

It maintains the five-stage pyramid of CS, starting with "at risk" and moving through "beginning," "classic," "deteriorating," and "extremis" but now includes gradations of severity within each stage and pathways by which patients progress or recover.

"Progression across the SCAI shock stage continuum is a dynamic process, incorporating new information as available, and patient trajectories are important both for communication among clinicians and for decisionmaking regarding the next level of care and therapeutics," the panel writes.

*"The initial definition was based on consensus opinion, with a lack of real fundamental data on segregating patients into different stages. Now we have a lot more data utilizing the definition."*

The second iteration adds a streamlined table incorporating commonly seen variables, based on lessons learned from validation studies and clinician experience.

"While keeping the same initial framework of looking at the three components of staging – the physical exam, the biochemical markers, and hemodynamics – we've made it very clear that there are some factors in each of these that are most typically seen. And then there are other factors

that are consistent with that stage but don't necessarily have to be seen, ... are not typically seen in that stage, or [are] not always present at that stage," Dr. Naidu told this news organization.

The refined CS classification system provides more granularity on cardiac arrest as a risk modifier, which now excludes very brief episodes with rapid response to defibrillation and comprises only those patients

who have impaired mental status with unknown neurologic recovery status after cardiopulmonary resuscitation.

Lactate level and thresholds have been highlighted to detect hypoperfusion but may be dissociated from hemodynamics in cases such as chronic heart failure.

In addition, patients may have other manifestations of end-organ hypoperfusion with a normal lactate level, and there are also important causes of an elevated lactate level other than shock.

The revision proposes a three-axis model of CS evaluation and prognostication that integrates shock severity, clinical phenotype, and risk modifiers as distinct elements that should be applied to individualize patient management.

The revision also places more emphasis on the trajectory of the patient with CS through hospitalization, including a "hub and spoke" model for transfer of higher-risk patients, including those with a deteriorating SCAI shock stage.

"It is our desire and belief that the revised SCAI SHOCK stage classification system will enhance both clinical care and CS research trial design," the panel writes.

This statement has been endorsed by the

**David L. Bowton, MD, FCCP, comments:** The original SCAI classification scheme was developed to provide a rapid mechanism to standardize the classification of patients with CS with respect to severity and estimated mortality risk. A key element was the applicability to accurately classify patients retrospectively within registries or other databases using commonly available clinical and laboratory data. The scheme has now been modified utilizing information from more than 25,000 patients from multiple studies validating its utility.



One such modification is the application of the "A" modifier only to cardiac arrest patients who have suffered apparent neurologic injury (i.e., coma following cardiac arrest). This is an effort to discount the impact of brief cardiac arrests such as due to a rapidly reversed arrhythmia, but does raise questions of how to account for the potential impact of cardiac arrest on other organ dysfunctions. The clinical and laboratory criteria for each class are more specific and a new 3-axis framework for evaluation and prognostication of cardiogenic shock is proposed. Applying the new scheme should further enhance communication among providers by standardizing the risk status of patients and permitting more rapid and appropriate triage of patients to a higher level of care.

American College of Cardiology, American College of Emergency Physicians, American Heart Association, European Society of Cardiology Association for Acute Cardiovascular Care, International Society for Heart and Lung Transplantation, Society of Critical Care Medicine, and Society of Thoracic Surgeons.

This research had no commercial funding. Dr. Naidu has disclosed no relevant financial relationships. ■

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evolves over time," he said.

Data from a large National Institutes of Health-funded multicenter phenotyping study of PH is being analyzed and should yield findings and publications starting this year, said Anna R. Hemnes, MD, associate professor of medicine at Vanderbilt University Medical Center, Nashville, Tenn., and an investigator with the initiative, coined "Redefining Pulmonary Hypertension through Pulmonary Disease Phenomics (PVDOMICS)."

Patients have undergone advanced imaging (for example, echocardiog-

raphy, cardiac MRI, chest CT, ventilation/perfusion scans), ad-



Dr. Hemnes

vanced testing through right heart catheterization, body composition testing, quality of life questionnaires, and blood draws that have been analyzed for DNA and RNA expression, proteomics, and metabolomics, said Dr. Hemnes, assistant director of Vanderbilt's

Pulmonary Vascular Center.

The initiative aims to refine the classification of all kinds of PH and "to bring precision medicine to the field so we're no longer characterizing somebody [based on imaging] and right heart catheterization, but we also incorporating molecular pieces and biomarkers into the diagnostic evaluation," she said.

In the short term, results of deep phenotyping should "allow us to be more effective with our therapy recommendations," Dr. Hemnes said.

"Then hopefully in the longer term, [identified biomarkers] will help us to develop new, more

effective therapies."

Dr. Sweatt and Dr. Williamson reported that they have no relevant financial disclosures. Dr. Hemnes reported that she holds stock in Tenax (which is studying a tyrosine kinase inhibitor for PAH) and serves as a consultant for several biotech and pharmaceutical companies. She also receives research funding from Imara. Dr. Chakinala reported that he is an investigator on clinical trials for a number of pharmaceutical companies. He serves on advisory boards for Phase Bio, Liquidia/Rare Gen, Bayer, Janssen, Trio Health Analytics, and Aerovate. ■

# Black patients now central to lung cancer screening guidelines

BY M. ALEXANDER OTTO

MDedge News

**A** 2021 update to the U.S. Preventive Services Task Force (USPSTF) lung cancer screening guidelines eliminated racial disparities prevalent in the group's 2013 guidance, according to a report in JAMA Oncology (2022 Jan 13. doi: 10.1001/jamaoncol.2021.6720).

Fewer Black people qualified for screening in the earlier guideline of which the majority of participants in the trials assessed were White. In response, the group changed the screening eligibility age from 55 to 50 years and lowered the smoking pack by year requirement from 30 to 20 years.

The changes showed that Black smokers tend to develop lung cancer earlier and with fewer pack-years than White smokers.

## The study details

To gauge the impact, investigators from Wayne State University, Detroit, reviewed 912 patients with lung cancer and 1,457 controls without lung cancer to see who would have qualified for screening under the 2013 and 2021 criteria.

They were participants in the Detroit-area INHALE (Inflammation, Health, Ancestry, and Lung Epidemiology) study from 2012 to 2018. Over 30% were Black.

"Lowering the age and smoking criteria successfully bridged the gap in racial disparity," said investigators led by Chan Yeu Pu, MD, a lung cancer specialist at Wayne State University.

With the 2021 criteria, 65% of White patients and 63% of Black patients with lung cancer would have been eligible for screening. Under the 2013 guidance, 52% of White patients were eligible for screening, but only 42% of Black patients were.

The update also eliminated racial disparities among controls. The new guidance excluded 48% of White controls without lung cancer from screening and 50% of Black controls.

The 2013 criteria excluded fewer White controls (61%) than Black control subjects (70%).

"As expected, broader inclusion criteria increased sensitivity, but at the cost of decreased specificity," the investigators wrote.

## Why is screening important?

The hope of screening is to catch lung cancer early, when curative surgical resection is still possible,

the team wrote, but although screening has increased over the years, uptake remains dismal, just 5% in 2018, for instance.

In an editorial (JAMA Oncol. 2022 Jan 13. doi: 10.1001/jamaoncol.2021.6708), Philadelphia-area thoracic surgeons

Jonathan Nitz, MD, and Cherie Erkmén, MD, wrote that "multiple and changing criteria" and "nebulous payment plans" have made "for a confusing message. ... We need standardized" guidelines to deliver "a clear message about lung cancer screening."

The fact that nearly two-thirds of lung cancer patients wouldn't have qualified for screening under current guidelines also needs to be addressed.

"We need standardized practice guidelines based on evidence from diverse populations and policies to ensure equitable access for high-risk individuals. Although this study demonstrates improved, calculated sensitivity of the 2021 USPSTF guidelines to detect lung cancer, these refinements of criteria do not address the nearly two-thirds of patients with diagnosed lung cancer who are not eligible for screening.

"There is a pressing need to redefine screening criteria," Dr. Nitz and Dr. Erkmén wrote.

Both the 2013 and 2021 guidelines were outperformed in the study by the 2012 modification of the model from the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCOm2012 criteria) (J Thorac Oncol. 2020 Nov;15[11]:1738-47); however, this was only marginally so in the case of USPSTF's 2021 guidance.

PLCOm2012 screening eligibility,

**A. Christine Argento, MD, FCCP, comments:** This paper is vitally important. Like other advances in lung cancer, in order to decrease disparities, we need to identify inclusive risk factors. These changes took the first step with a more inclusive age and smoking history range. Ultimately, I foresee that we will need to look beyond smoking to make a bigger difference. The other important point is that so few eligible patients actually undergo lung cancer screening. Ideally this will also improve in the near future so that we can make some real headway with this deadly cancer.

however, are based on a complicated risk factor assessments that include race but also education level and other factors which might not be readily available in electronic records. USPSTF's criteria "are much more straightforward to use in a clinical setting," the investigators noted.

Study subjects were 21-89 years old and were in their early 60s, on average. Just over half were women. The analysis excluded lung cancer patients and controls who had never smoked.

The authors noted some limitations, including the retrospective

nature of the study, plus, few lung cancers were diagnosed among the control group, which were not only small, but they did not include follow-ups with CT scans.

The work was funded by the National Institutes of Health and the Herrick Foundation. Dr. Pu didn't have any commercial disclosures. One investigator disclosed personal fees from Takeda, Astra-Zeneca, Genentech/Roche, Pfizer, and other companies. Dr. Erkmén reported an American Cancer Society-Pfizer Award to address disparities. ■



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# New PET tracer detects more metastases in patients

BY M. ALEXANDER OTTO, MMS, PA

**A** new tracer for use in PET imaging can detect more metastases in patients with cancer than the standard tracer, leading to predictions of a “paradigm shift” in this field.

The new tracer, 68Ga-FAPI (fibroblast activation protein inhibitor), detected more metastases in patients with lung cancer than the standard tracer, 18F-FDG (fluorodeoxyglucose), which has been in use for years.

The study by Chinese researchers was published in *Radiology* (2022 Jan 4. doi: 10.1148/radiol.211424).

The team imaged 34 lung cancer patients with both 68Ga-FAPI and 18F-FDG. Performance was similar for primary tumors and for lung, liver, and adrenal gland metastases. However, FAPI imaging detected more metastases in the lymph nodes (356 vs. 320), brain (23 vs. 10), bone (109 vs. 91), and pleura (66 vs. 35). However, neither modality outperformed MRI for brain metastases, the researchers note.

An accompanying editorial (2022 Jan 4. doi: 10.1148/radiol.212884) concluded that

68Ga-FAPI PET/CT scanning marks “an important paradigm shift to more specific identification and characterization of a variety of cancers.”

“This may also mark the arrival of a new era in nuclear medicine where molecular imaging helps visualize and characterize the entire tumor burden in one setting,” write editorialists Francine Jacobson, MD, and Annick Van den Abbeele, MD, from Harvard University and Brigham and Women’s Hospital and the Dana-Farber Cancer Center, in Boston.

This study was the one of the latest in a fast-growing body of literature reporting that tracers targeting FAP with a small-molecule inhibitor (FAPI) outperform FDG tracers, not just in lung cancer but across a broad range of cancers, including breast, hepatic, gastrointestinal, head-neck, gynecologic, and many other tumor types.

The possibilities aren’t limited to imaging, either. Several companies are planning trials to target FAP with radiopharmaceuticals.

FAP is associated with wound repair and is highly expressed by the fibroblasts tightly packed in with cancer cells, particularly in stroma-dense tumors. FAP is rarely expressed by healthy tissue.

The underlying idea is to deliver a radionuclide to cancer-associated fibroblasts, using either a positron emitter, such as gallium-68 (68Ga), for PET imaging or a beta particle or other short-radiation emitter to kill nearby cancer cells as part of treatment.

Targeting FAP holds the promise of PET imaging that is more selective for cancer than FDG. FDG resolution depends on glucose uptake, which is high in active tumors but is also

high in inflamed tissues as well as in the brain, gastrointestinal tract, and other areas. Uptake by background tissue can make it difficult to distinguish tumors from their surroundings. FDG uptake can also be lower in small and indolent tumors.

On the therapy side, there’s hope that FAP targeting will lead to radiopharmaceuticals that work across tumor types, not just in specific cancers.

## High interest in FAP

Overall, FAP “is a target of high interest for the whole medical oncology community. The preliminary data are good, but this will take a while” to get to market, said Jeremie Calais, MD, a nuclear medicine specialist and FAP researcher at the University of California, Los Angeles.

Interest in FAP as a radiopharmaceutical target is being driven by the success of two agents that have served as a kind of proof of concept, Dr. Calais said.

The first is Novartis’s 177Lu-PSMA-617, which was granted priority review by the U.S. Food and Drug Administration in September 2021 following phase 3 results that showed a progression-free survival benefit

of about 5 months when added to standard of care for metastatic castration-resistant prostate cancer, as well as an overall survival benefit of 4 months.

PSMA-617 binds prostate cancer cells that express prostate-specific membrane antigen. The lutetium-177 (177Lu) bombards them with beta particles and gamma radiation.

FAP researchers are also encouraged by the success of 177Lu dotatate (Lutathera), from Advanced Accelerator Applications, which delivers the radionuclide to gastroenteropancreatic neuroendocrine tumors that express somatostatin receptors.

The FDA approved this agent in 2018 in part on the basis of phase 3 results that found a 20-month progression-free survival of 65.2% when Lutathera was added to octreotide for metastatic disease vs. 10.8% when it wasn’t.

Novartis is now looking into developing FAP-targeted radiopharmaceuticals, along with Clovis and Point Biopharma, among others.

“That’s the key goal” of industry research, “more so than FAP as a diagnostic tool,” Dr. Calais commented to this news organization. There’s “huge potential” if it works out, he said, in part because it won’t be limited to one tumor type.

Clovis recently launched a phase 1/2 trial of its candidate, 177Lu-FAP-2286, for advanced/metastatic solid tumors.

In the company’s “luMIERE” trial, subjects will be infused with 68Ga-FAP-2286 to image the tumor. Once uptake is confirmed, they’ll be infused with 177Lu-FAP-2286 for treatment.

The two-step process – uptake confirmation, then treatment – is dubbed “theranostics” and is

## A. Christine Argento, MD, FCCP, comments:

A new fibroblast activation protein (FAP) tracer that specifically targets cancer cells will be a big step forward in cancer detection and identification using non-invasive imaging. Even more exciting will be if FAP can play a double role in detection and therapy by delivering radiopharmaceuticals that can act on various tumor types; then it will be a home-run. The early evidence is encouraging and I will be following this closely as new data emerge.

the standard approach for radiopharmaceutical therapy, Dr. Calais said.

His own team is working to confirm that imaging accurately reflects FAP expression in tumors by comparing preoperative imaging results with FAP expression on surgical specimens. So far, his team has found that they are strongly correlated.

FAPI PET imaging research is much farther along than therapeutic applications, with almost 200 research articles listed on PubMed in 2021, up from just 3 in 2018. One 2019 paper reported “remarkably high uptake and image contrast” across 28 cancers in 80 patients, including breast, esophagus, lung, pancreatic, head-neck, and colorectal tumors.

Imaging studies so far have tended to be small, with many currently focused on identifying the optimal molecule for targeting FAP and the best positron emitter to combine with it.

FAPI tracers are not available yet commercially, so researchers are creating them themselves. One team recently reported its recipe for automated synthesis using commercially available synthesis modules.

Sofie, a maker of FDG and other tracers, hopes to change that and is working to bring FAP tracers to market. The company announced in November 2021 a phase 2 study of 68Ga FAPI-46 to image pancreatic ductal adenocarcinoma. It’s the first step in a broader development program for oncologic and nononcologic indications, Sofie said in a press release.

Dr. Calais sees potential for indications where FAPI has already outperformed FDG in the literature, particularly for gastrointestinal cancers. He doesn’t think it will ever replace FDG for indications such as lymphoma, where it “works perfectly well.”

“On the other hand, you have lesions located in a tissue that has some background level” of FDG uptake. “These things are okay with FDG, but I think maybe FAP can help” because of the improved signal-to-noise ratio, Dr. Calais commented. Unlike FDG, “you mostly never see background uptake with FAP-imaging agents,” he said.

Other pluses include quicker distribution throughout the body than FDG, so scan times are shorter, and also patients do not need to fast beforehand.

Dr. Calais predicts that FAPI tracers will reach the market within 5 years. ■

*“This may also mark the arrival of a new era in nuclear medicine where molecular imaging helps visualize and characterize the entire tumor burden in one setting.”*



# ILD upped risk of checkpoint-inhibitor pneumonitis

BY PAM HARRISON

**I**mmune checkpoint inhibitors (ICIs) are at least as effective in patients with advanced non-small cell lung cancer (NSCLC) and mild preexisting interstitial lung disease as in those without ILD. However, the risk of checkpoint inhibitor pneumonitis (CIP) is higher in patients with the dual diagnoses and they need careful monitoring when introducing an ICI, a systematic review and meta-analysis indicated.

“Patients with preexisting ILD, especially symptomatic ILD, are frequently excluded from clinical trials so almost all the patients [we analyzed] were diagnosed with mild preexisting ILD,” said Yuan Cheng, MD, Peking University First Hospital, Beijing, China.

“At this stage, we think that mild ILD is not a contraindication to the use of anti-programmed death-1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) treatment for patients with NSCLC but whether ICIs can be used in patients with moderate to severe ILD needs further study,” she added.

The study was published online Jan. 10 in the journal *CHEST* (doi: 10.1016/j.chest.2021.12.656).

A total of 179 patients from 10 studies were included in the review and meta-analysis. Preexisting ILD was diagnosed by use of CT or high-resolution CT. The mean age of patients was 71 years (range, 33-85 years), 87% were male, and 96% of the cohort had a history of smoking. Approximately one-quarter of patients with ILD had usual interstitial pneumonitis (UIP); about the same percentage had possible UIP; one-third were diagnosed with inconsistent UIP; 14% had nonspecific interstitial pneumonia (NSIP); and 6% had indeterminate UIP.

Patients received ICIs either as first-, second-, or third-line or higher therapy and all were treated with ICI monotherapy by way of either nivolumab (Opdivo), pembrolizumab (Keytruda), or atezolizumab (Tecentriq). About 10% of patients had a PD-L1 tumor proportion score (TPS) of less than 1%, one-quarter had a PD-L1 TPS of 1%-49%, and approximately two-thirds had a TPS of 50% or greater.

Some 35% of patients with both NSCLC and preexisting ILD achieved an objective response rate (ORR) to ICI therapy and almost two-thirds of patients achieved disease control. However, there was considerable

heterogeneity in ORRs between the studies where it ranged from 5.9% to 70%, the authors cautioned.

On meta-analysis, the pooled ORR was 34% (95% confidence interval, 20%-47%) but again, with significant heterogeneity ( $I^2 = 75.9\%$ ). However, on meta-analysis of eligible studies, patients with NSCLC who had preexisting ILD were 99% more likely to achieve an ORR compared to those without ILD (odds ratio, 1.99; 95% CI, 1.31-3.00), the investigators pointed out.

The disease control rate (DCR) also varied considerably between studies from a low of 33.3% to a high of 100%, they added. On meta-analysis, the pooled DCR was 66% (95% CI, 56%-75%). “Meanwhile, in patients without preexisting ILD, the crude ORR and pooled ORR were 24.3% and 24% (95% CI, 17%-31%), respectively” – again with significant heterogeneity between studies ( $I^2 = 87.4\%$ ).

In contrast to the ORR, there was no difference in the DCR between the two groups, with no evidence of heterogeneity. There were no significant differences between the two groups in either median progression-free survival (PFS) or overall survival (OS). In patients with NSCLC and preexisting ILD, median PFS ranged from 1.4 to 8 months whereas median OS ranged from 15.6 to 27.8 months.

For those without preexisting ILD, the median PFS ranged from 2.3 to 8.1 months while median OS ranged from 17.4 to 25.5 months.

## ICI safety

In patients with NSCLC and preexisting ILD, the incidence of immune-related adverse events (irAes) of any grade was 56.7%, whereas the incidence of irAes grade 3 and higher was 27.7%. “Among the 179 patients included in the studies, 45 developed any grade of CIP, corresponding to a crude incidence of 25.1%,” the authors noted – very similar to the pooled incidence of 27% on meta-analysis.

The pooled incidence of grade 3 and higher CIP in the same group of patients was 15%. The median time from initiation of ICIs to the development of CIP ranged from 31 to 74 days, but 88% of patients who developed CIP improved with appropriate treatment. In patients with NSCLC who did not have ILD, the pooled incidence of CIP was 10% (95% CI, 6%-13%), again with significant heterogeneity between

**A. Christine Argento, MD, FCCP, comments:** This is an important study demonstrating that patients with ILD improve in overall response and disease control rates, but at the cost of higher incidence of adverse events. ILD is a heterogeneous category of lung disease and each patient should be considered individually with risk/benefit analysis for treatment with ICI. Those patients with stable ILD and high exercise tolerance will likely benefit from ICI and shouldn't be denied this NSCLC therapy, but those who have progressive ILD and have a more tenuous respiratory status may want to consider other treatment options.



studies ( $I^2 = 78.8\%$ ). “Generally, CIP can be managed through ICI discontinuation with or without steroid administration,” the authors noted.

However, even if most CIP can be easily managed, “the incidence of severe CIP is higher [in NSCLC patients with preexisting ILD] than in other populations,” Dr. Cheng observed. “So patients with preexisting ILD should be closely monitored during ICI therapy,” she added.

Indeed, compared with patients without preexisting ILD, grade 3 or higher CIP in patients with the dual diagnosis was significantly higher at an OR of 3.23 (95%, 2.06-5.06), the investigators emphasized.

Asked to comment on the review, Karthik Suresh, MD, associate professor of medicine, Johns Hopkins University, Baltimore, pointed out that ILD is really an “umbrella” diagnosis that a few hundred diseases fit under, so the first question he and members of his multidisciplinary team ask is: What is the nature of the ILD in this patient? What is the actual underlying etiology?

It could, for example, be that the patient has undergone prior chemotherapy or radiation therapy and has developed ILD as a result, as Dr. Suresh and his coauthor, Jarushka Naidoo, MD, Sidney Kimmel Comprehensive Cancer Center, Baltimore, pointed out in their paper on how to approach patients with preexisting lung disease to avoid ICI toxicities (Oncologist. 2020 Nov;25[11]:e1589-92).

“We'll go back to their prior CT scans and can see the ILD has been there for years – it's stable and the patient's lung function is not changing,” Dr. Suresh related to this news organization.

“That's a very different story from [patients for] whom there are new interstitial changes, who are progressing and who are symptomatic,” he noted. Essentially, what Dr. Suresh and his team members want to know is: What is the specific sub-

diagnosis of this disease, how severe is it, and is it progressing? Then they need to take the tumor itself into consideration.

“Some tumors have high PD-L1 expression, others have low PD-L1 expression so response to immunotherapy is usually very different based on tumor histology,” Dr. Suresh pointed out. Thus, the next question that needs to be addressed is: What is the expected response of the tumor to ICI therapy? If a tumor is exquisitely sensitive to immunotherapy, “that changes the game,” Dr. Suresh said, “whereas with other tumors, the oncologist might say there may be some benefit but it won't be dramatic.”

The third risk factor for ICI toxicity that needs to be evaluated is the patient's general cardiopulmonary status – for example, if a patient has mild, even moderate, ILD but is still walking 3 miles a day, has no heart problems, and is doing fine. Another patient with the same severity of disease in turn may have mild heart failure, be relatively debilitated, and sedentary: “Performance status also plays a big role in determining treatment,” Dr. Suresh emphasized.

The presence of other pulmonary conditions such as chronic obstructive pulmonary disease – common in patients with NSCLC – has to be taken into account, too. Lastly, clinicians need to ask themselves if there are any alternative therapies that might work just as well if not better than ICI therapy for this particular patient. If the patient has had genomic testing, results might indicate that the tumor has a mutation that may respond well to targeted therapies. “We put all these factors out on the table,” Dr. Suresh said. “And you obviously have to involve the patient, too, so they understand the risks of ICI therapy and together we decide.” The study had no specific funding. The study authors and Dr. Suresh have disclosed no relevant financial relationships. ■

# Omalizumab curbs airway inflammation in severe asthma

BY HEIDI SPLETE

MDedge News

**P**atients with severe asthma who were new to omalizumab showed significant clinical improvement after 2 weeks of treatment, according to data from a pilot study of 26 adults.

Although omalizumab is approved for severe allergic asthma, not all patients respond well, and are considered nonresponders in the absence of clinical benefits within 16 weeks of starting treatment, wrote Todor A. Popov, MD, of the University Hospital St. Ivan Rilski, Sofia, Bulgaria, and colleagues.

“Since airway inflammation is a cardinal feature of asthma, we reasoned that early changes in its level may determine the subsequent course of the disease,” they said.

In a study published in *Annals of Allergy, Asthma & Immunology* (2022 Jan 23. doi: 10.1016/j.anai.2022.01.020), the researchers recruited 26 adults with severe asthma who were new to biologic therapy and eligible for omalizum-

ab. The patients ranged in age from 22 to 70 years, and 13 were men. Patients received omalizumab doses between 150 mg and 375 mg every 2–4 weeks based on body weight and pretreatment serum IgE levels, and they were assessed at baseline and followed for a total of 18 weeks (2-week run-in and 16 weeks of treatment).

Patients rated their overall discomfort from asthma on a 100-mm visual analogue scale (VAS). Asthma control was assessed via the asthma control questionnaire (ACQ), and disease-related quality of life was assessed via the Asthma Quality of Life Questionnaires (AQLQ). All patients reported significant improvement across all three measures after 2 weeks and through the study period after the first administration of omalizumab at week 0 ( $P < .001$ ).

Clinical response was based on quantitative indicators of airway and systemic eosinophilic inflammation: fractional exhaled nitric oxide (FeNO), eosinophil cationic peptide (ECP), and the

temperature of the exhaled air (EBT, exhaled breath temperature). The researchers also measured fractional EBT (FrEBT) by measuring the EBT of central and peripheral airways at the beginning and end of the

expiration.

Overall, EBT decreased significantly after 2 weeks, and the decrease lasted until week 16. FrEBT decreased significantly after 4 weeks. ECP reached statistical significance at week 16 ( $P = .029$ ). FeNO showed a downward trend, but the decrease did not reach statistical significance, the researchers wrote.

These results might suggest that “after blocking IgE, the eosinophilic

inflammation is not suppressed well and fast enough,” the researchers noted. “Consequently, indicators of eosinophilic inflammation may not be suited for early predictors of success of omalizumab treatment,” they added. The drop in EBT after the first dose of omalizumab may predict effectiveness for a particular patient, while the FrEBT results “may mean that it takes longer to suppress the inflammatory process in the vast basin of the small airways,” they noted.

A key limitation of the findings was the small sample size, although the study was designed as a proof-of-concept on which to base sample size calculation for larger trials with EBT as a predictive marker, the researchers said.

However, the EBT and FrEBT signals reached statistical significance, and the results warrant confirmation in larger trials; such confirmation may spare patients from expensive and ineffective treatments, they concluded.

The study was funded by Novartis. The researchers had no financial conflicts to disclose. ■

*“Indicators of eosinophilic inflammation may not be suited for early predictors of success of omalizumab treatment.”*

## Chronic respiratory conditions occur more often in RSV vs. flu

BY HEIDI SPLETE

MDedge News

**FROM CHEST** ■ Hospitalized intensive care patients with respiratory syncytial virus (RSV) were significantly more likely to be immunocompromised and to have chronic respiratory conditions than those with influenza infections, but in-hospital mortality rates were similar, based on data from 618 adults.

RSV is common in adults, but characteristics of RSV patients requiring ICU care have not been explored, despite routine testing for RSV in critically ill patients in many institutions, Julien Coussement, PhD, of Université Libre de Bruxelles, Brussels, and colleagues wrote.

“Influenza is another respiratory virus routinely tested for in ICU patients with respiratory symptoms because of its well-known morbidity and mortality, but there are no data specifically comparing RSV and influenza infections in adult ICU patients,” they noted.

In a retrospective, multicenter study published in the journal *CHEST* (2022 Jan 18. doi: 10.1016/j.chest.2021.12.670), the researchers analyzed data from 309 adult ICU patients with

RSV infection and 309 with influenza infection between November 2011 and April 2018 from 17 sites in France and Belgium. Each RSV patient was matched to a flu patient according to institution and date of diagnosis.

The primary objective was a comparison of in-hospital mortality between the groups, defined as death from any cause during an index hospital stay in acute care. Secondary objectives were comparisons of the clinical and biological characteristics of patients with RSV versus flu.

Overall, in-hospital mortality was not significantly different between the RSV and influenza groups (23.9% vs. 25.6%,  $P = .63$ ).

However, patients with RSV infection were significantly more likely than those with flu to have an underlying chronic respiratory condition (60.2% vs. 40.1%,  $P < .001$ ) and to be immunocompromised (35% vs. 26.2%,  $P = .02$ ). Very few of the patients overall (39 patients, 6.3%) were considered young and healthy prior to hospitalization; and significantly fewer of these were in the RSV group than in the influenza group (9 patients and 30 patients, respectively).

Airway obstruction at the time of diagnosis

RSV continued on following page

*Patients with RSV infection were significantly more likely than those with flu to have an underlying chronic respiratory condition and to be immunocompromised.*

**Sachin Gupta, MD, FCCP, comments:** With COVID-19 heightening our awareness of the impact respiratory viruses have on outcomes, this study is certainly eye-catching and important. Like in the case of COVID vs. influenza comparative outcomes analyses, there is much to be aware of when evaluating such comparisons.

On the eye-ball test, I cannot recollect seeing comparable mortality rates in my practice between influenza and RSV, though of course RSV testing is rare at our institution. Diagnosis patterns matter and the “denominator” of RSV+ patients is likely to be larger than influenza+ patients should all hospitalized patients been tested. Lastly, the impact of influenza vaccination and treatment with oseltamivir on outcomes should be considered. As a whole these findings are hypothesis generating, though I am not convinced at this stage that the findings merit a practice pattern change (such as greater RSV testing) given this study’s limitations.





# Community-acquired pneumonia in children: 5 days of antibiotics better than 10 days

BY PAM HARRISON

**T**he evidence is in: Less is more when it comes to treating uncomplicated community-acquired pneumonia (CAP) in young children. Five days of antibiotic therapy resulted in a superior clinical response compared to 10 days of treatment and had the added benefit of a lower risk of inducing antibiotic resistance, according to the randomized, controlled SCOUT-CAP trial.

“Several studies have shown shorter antibiotic courses to be non-inferior to the standard treatment strategy, but in our study, we show that a shortened 5-day course of therapy was superior to standard therapy because the short course achieved similar outcomes with fewer days of antibiotics,” Derek Williams, MD, MPH, Vanderbilt University Medical Center, Nashville, Tenn., said in an email.

“These data are immediately applicable to frontline clinicians, and we hope this study will shift the paradigm towards more judicious treatment approaches for childhood pneumonia, resulting in care that is safer and more effective,” he added.

The study was published online Jan. 18 in JAMA Pediatrics (2022. doi: 10.1001/jamapediatrics.2021.5547).

## Uncomplicated CAP

The study enrolled children aged 6 months to 71 months diagnosed with uncomplicated CAP who demonstrated early clinical improvement in response to 5 days of antibiotic treatment. Participants were prescribed either amoxicillin, amoxicillin and clavulanate, or cefdinir according to standard of care and were randomized on day 6 to another 5 days of their initially prescribed antibiotic course or to placebo.

“Those assessed on day 6 were eligible only if they had not yet received a dose of antibiotic therapy on that day,” the authors write. The primary endpoint was end-of-treatment response, adjusted for the duration of antibiotic risk as assessed by RADAR. As the authors explain,

*“In our study, we show that a shortened 5-day course of therapy was superior to standard therapy because the short course achieved similar outcomes with fewer days of antibiotics.”*

RADAR is a composite endpoint that ranks each child’s clinical response, resolution of symptoms, and antibiotic-associated adverse effects (AEs) in an ordinal desirability of outcome ranking, or DOOR.

“There were no differences between strategies in the DOOR or in its individual components,” Dr. Williams and colleagues point out. A total of 380 children took part in the study. The mean age of participants was 35.7 months, and half were male.

Over 90% of children randomized to active therapy were prescribed amoxicillin. “Fewer than 10% of children in either strategy had an inadequate clinical response,” the authors report.

However, the 5-day antibiotic strategy had a 69% (95% CI, 63%-75%) probability of children achieving a more desirable RADAR outcome compared with the standard, 10-day

course, as assessed either on days 6 to 10 at outcome assessment visit one (OAV1) or at OAV2 on days 19 to 25.

There were also no significant differences between the two groups in the percentage of participants with persistent symptoms at either assessment point, they note. At assessment visit one, 40% of children assigned to the short-course strategy and 37% of children assigned to the 10-day strategy reported an antibiotic-related AE, most of which were mild.

## Resistome analysis

Some 171 children were included in a resistome analysis in which throat swabs were collected between study days 19 and 25 to quantify antibiotic resistance genes in oropharyngeal flora. The total number of resistance genes per prokaryotic cell (RGPC) was significantly lower in children treated with antibiotics for 5 days compared with children who were treated for 10 days.

Specifically, the median number of total RGPC was 1.17 (95% CI, 0.35-2.43) for the short-course strategy and 1.33 (95% CI, 0.46-11.08) for the standard-course strategy ( $P = .01$ ). Similarly, the median number of  $\beta$ -lactamase RGPC was 0.55 (0.18-1.24) for the short-course

**Brandon M. Seay, MD, MPH, comments:** Consideration of antibiotic resistance should always be at the front of our minds when treating pediatric pneumonia. As commented in the article, there have not been studies that prove 10 days of antibiotics is essential. This study brings up an important point that a shorter course of antibiotics can be as effective as the typical 10-day treatment.

Also important, the impact of treatment length significantly impacts patients actually finishing the course of treatment.



strategy and 0.60 (0.21-2.45) for the standard-course strategy ( $P = .03$ ).

“Providing the shortest duration of antibiotics necessary to effectively treat an infection is a central tenet of antimicrobial stewardship and a convenient and cost-effective strategy for caregivers,” the authors observe. For example, reducing treatment from 10 to 5 days for outpatient CAP could reduce the number of days spent on antibiotics by up to 7.5 million days in the U.S. each year.

“If we can safely reduce antibiotic exposure, we can minimize antibiotic side effects while also helping to slow antibiotic resistance,” Dr. Williams pointed out.

Fewer days of having to give their child repeated doses of antibiotics is also more convenient for families, he added.

Asked to comment on the study, David Greenberg, MD, professor of pediatrics and infectious diseases, Ben Gurion University of the Negev, Israel, explained that the length of antibiotic therapy as recommended by various guidelines is more or less arbitrary, some infections being excepted.

“There have been no studies evaluating the recommendation for a 100-day treatment course, and it’s kind of a joke because if you look at the treatment of just about any infection, it’s either for 7 days or 14 days or even 20 days because it’s

ANTIBIOTICS continued on following page

RSV continued from previous page

was significantly more common in the RSV patients than in influenza patients (49.5% vs. 39.5%,  $P = .01$ ), but influenza patients were significantly more likely to have acute respiratory distress syndrome at the time of diagnosis (21.7% vs. 14.6%,  $P = .02$ ). Rates of coinfections were similar between the groups, and approximately 60% of coinfecting patients received at least 72 hours of therapeutic antibiotics. Overall

length of hospital stay, ICU stay, and duration of mechanical ventilation were similar between the groups.

The results show that severe RSV occurs mainly in older patients with comorbidities, and these results reflect data from previous studies, the researchers wrote in their discussion. In addition, “patients with influenza infection were significantly more likely to have fever, myalgia, increased CPK level, thrombocytopenia, and transami-

nitis at diagnosis than were those with RSV infection. Whether these differences may be used to guide patient management remains to be determined.”

The study findings were limited by several factors including the retrospective design, and testing for respiratory viruses on symptomatic patients only, rather than all ICU patients, the researchers noted. Other limitations include the inability to show a causal link between viral

infections and patient outcomes and the heterogeneous management of patients among different centers.

However, the results were strengthened by the large sample size and multivariate analysis, and support the need for interventions to prevent and treat severe RSV, they concluded.

The study received no outside funding. Dr. Coussement disclosed serving on an advisory board for Sanofi. ■

# Future respiratory infection risk raised by virus exposure in the early days after birth

BY ROB HICKS, MBBS

**M**any factors influence a child's subsequent susceptibility to respiratory tract infection (RTI), including breastfeeding, crowded conditions, and exposure to environmental tobacco. Now researchers have found that asymptomatic viral infection in the first days of a baby's life are linked to a greater risk of respiratory infections in later life.

The new research, published in *Nature Microbiology* (2022 Jan 20. doi: 10.1038/s41564-021-01043-2), was conducted as part of the Microbiome Utrecht Infant Study (MUIS), a healthy infant birth cohort study that's been running for 6 years.

In their study, the authors explained how the respiratory tract is "populated by a specialized microbial ecosystem, which is seeded during and directly following birth," adding that, "despite recognition of many host and environmental factors known to modulate RTI susceptibility, the mechanism by which a child develops recurrent or severe RTIs, while others remain healthy, remains largely unknown".

Researchers from the University of Edinburgh and University Medical Centre Utrecht (the Netherlands) examined nasal mucosa samples of 114 babies at various times from birth until 12 months of age. They then analyzed the gene activity of the babies' nasal mucosa, the microbes present in the lining of the nose, and any viruses that infected the children.

## Interferon-related mucosal gene activity

The researchers described how the microbiome – the community of microbes in the body – of a new-

born baby can be influenced by many things, including delivery method, breastfeeding, antibiotics, and the hospital environment. They highlighted how viruses were found to interact with a newborn's immune system and microbiome in a way that affected both a child's risk, and number, of subsequent infections.

They explained how when a viral infection was detected in the first days after birth, which they said largely occurred asymptotically, specific mucosal genes were activated – genes involved with interferons – coinciding with a change in the composition of the microbiome, promoting the growth of potentially harmful microbes.

"The interferon-related gene activity caused by an early first viral infection is thought to create a proinflammatory environment that makes babies susceptible to future infections," they said, adding that in their study they have demonstrated that "first asymptomatic viral encounters were associated with increased interferon signaling, and preceded the development of disadvantageous respiratory microbiota profiles and clinical RTIs."

## Proinflammatory and microbiologically perturbed environment

Debby Bogaert, PhD, chair of paediatric medicine at the University of Edinburgh, said: "We were surprised to see viral infections occur so early in life, and go mostly unnoticed, probably because the infant's immune system is in what is known as a state of tolerance after birth. Despite this, these infections seem to affect a normal immune development, which is important to know."

The authors wrote that their data

**Brandon M. Seay, MD, MPH, comments:** The age-old debate on the "hygiene hypothesis" continues to be discussed. The findings of this study run contrary to the thought of infections at a younger age help the immune system to develop as it may be that early infections (although asymptomatic) actually may set off an inflammatory cascade that puts infants at increased risk of future infection. Looks like the debate shall continue.

supports the hypothesis that first viral encounters trigger an interferon-associated proinflammatory environment, which then further drives airway inflammation and symptomatology into a "self-enforcing positive feedback loop". They said that this "proinflammatory and microbiologically perturbed environment in turn renders an individual more vulnerable to recurrent viral-induced RTIs."

Wouter de Steenhuijsen, PhD, postdoctoral investigator at University Medical Centre Utrecht, said: "Although further work will be needed to confirm the causality of our findings, the data from this

study indicate that early-life encounters with respiratory viruses – especially during the first days of life – may set the tone for subsequent non-beneficial host-microbe interactions, which are related to an infection risk and possibly long term respiratory health."

Dr. Bogaert added: "Only from birth onwards will an infant start to develop its microbiome. Limiting the number of viral encounters in those first days to weeks of life might be essential for a healthy immune and microbiome development, and consequently long term respiratory health." ■



PEJO29/THINKSTOCKPHOTOS

## ANTIBIOTICS *continued from previous page*

easy to calculate – it's not that anybody proved that treatment of whatever infection it is should last this long," he told this news organization.

Moreover, adherence to a shorter antibiotic course is much better than it is to a longer course. If, for example, physicians tell a mother to take two bottles of antibiotics for a treatment course of 10 days, she'll finish the first bottle which is good for 5 days and, because the child is fine, "she forgets about the second bottle," Dr. Greenberg said.

In one of the first studies to compare a short versus long course of antibiotic therapy in

uncomplicated CAP in young children, Dr. Greenberg and colleagues initially compared a 3-day course of high-dose amoxicillin to a 10-day course of the same treatment, but the 3-day course was associated with an unacceptable failure rate. (At the time, the World Health Organization was recommending a 3-day course of antibiotics for the treatment of uncomplicated CAP in children.)

They stopped the study and then initiated a second study in which they compared a 5-day course of the same antibiotic to a 10-day course and found the 5-day course was comparable to the 10-day course in terms of clinical cure rates.

As a result of his study, Dr. Greenberg has long since prescribed a 5-day course of antibiotics for his own patients.

"Five days is good," he affirmed. "And if patients start a 10-day course of an antibiotic for, say, a urinary tract infection and a subsequent culture comes back negative, they don't have to finish the antibiotics either." Dr. Greenberg said.

Dr. Williams said he has no financial ties to industry. Dr. Greenberg said he has served as a consultant for Pfizer, Merck, Johnson & Johnson, and AstraZeneca. He is also a founder of the company Beyond Air. ■



# Infant bronchiolitis subtype may predict asthma risk

BY RICHARD MARK KIRKNER

**B**ronchiolitis is the leading cause of infant hospitalizations in the United States and Europe, and almost one-third of these patients go on to develop asthma later in childhood.

But a multinational team of researchers has presented evidence that could avoid that outcome. They identified four different subtypes of bronchiolitis along with a decision tree that can

*Researchers identified four different subtypes of bronchiolitis along with a decision tree that can determine which infants are most likely to develop asthma as they get older.*

determine which infants are most likely to develop asthma as they get older.

Reporting in the journal *eClinical Medicine*, Michimasa Fujiogi, MD, of Massachusetts General Hospital and Harvard University, Boston, and colleagues analyzed three multicenter prospective cohort studies that included a combined 3,081 infants hospitalized with severe bronchiolitis.

“This study added a base for the early identification of high-risk patients during early in-

fancy,” Dr. Fujiogi said in an interview. “Using the prediction rule of this study, it is possible to identify groups at high risk of asthma during a critical period of airway development – early infancy.”

The researchers identified four clinically distinct and reproducible profiles of infants hospitalized for bronchiolitis:

- A:** characterized by a history of breathing problems and eczema, rhinovirus infection, and low prevalence of respiratory syncytial virus (RSV) infection.
- B:** characterized by the classic symptoms of wheezing and cough at presentation, a low prevalence of previous breathing problems and rhinovirus infection, and a high likelihood of RSV infection.
- C:** the most severe group, characterized by inadequate oral intake, severe retraction at presentation, and longer hospital stays.
- D:** the least ill group, with little history of breathing problems but inadequate oral intake with no or mild retraction.

Infants with profile A had the highest risk for developing asthma – more than 250% greater than with typical bronchiolitis. They were also older and were more likely to have parents who had asthma – and none had solo-RSV infection. In the overall analysis, the risk for developing asthma by age 6 or 7 was 23%.

The researchers stated that the decision tree

**Brandon M. Seay, MD, MPH, comments:** This research adds to the current practice of using the Asthma Predictive Index to identify patients who may be at higher risk for asthma. The criteria of a history of eczema also is present in the API, but this study adds the added criteria to consider rhinovirus infection. It could prove helpful to identifying patients who may benefit from starting preventive therapies (inhaled corticosteroids) earlier and preventing severe exacerbations/hospitalization.

accurately predicts the high-risk profile with high degrees of sensitivity and specificity. The decision tree used four predictors that together defined infants with profile A: RSV infection status, previous breathing problems, eczema, and parental asthma.

“Our data would facilitate the development of profile-specific prevention strategies for asthma – for example, modification of host response, prophylaxis for severe viral infection – by identifying asthma risk groups early in infancy,” Dr. Fujiogi said.

The study received funding from the National Institutes of Health. Dr. Fujiogi and coauthors have disclosed no relevant financial relationships. ■



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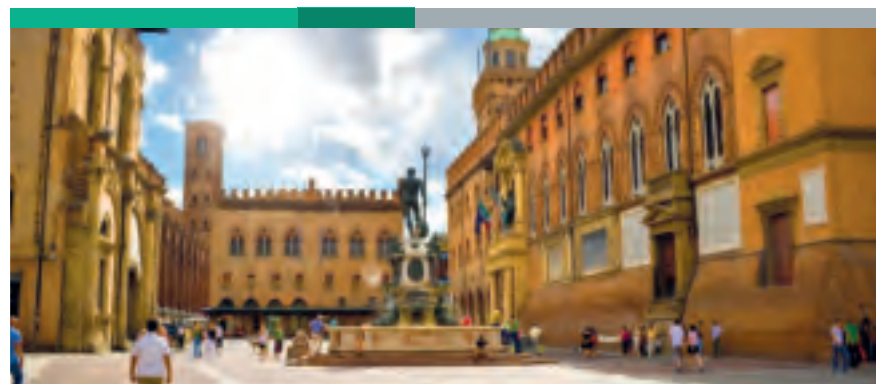
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# Seniors face higher risk of developing other medical conditions after infection

BY ADAM LEITENBERGER

MDedge News

**N**early one-third of adults over age 65 developed one or more new medical conditions in the weeks following a COVID-19 infection, according to new research.

The findings of the observational study, which were published in the *BMJ* (2022 Feb 9. doi: 10.1136/bmj-2021-068414), show the risk of a new condition being triggered by COVID is more than twice as high in seniors, compared with younger patients. Plus, the researchers observed an even higher risk among those who were hospitalized, with nearly half (46%) of patients having developed new conditions after the acute COVID-19 infection period.

Respiratory failure with shortness of breath was the most common postacute sequela, but a wide range of heart, kidney, lung, liver, cognitive, mental health, and other conditions were diagnosed at least 3 weeks after initial infection and persisted beyond 30 days.

This is one of the first studies to specifically describe the incidence and severity of new conditions triggered by COVID-19 infection in a general sample of older adults, said study author Ken Cohen, MD, FACP, executive director of translational research at Optum Labs and national senior medical director at Optum Care.

"Much of what has been published on the postacute sequelae of

COVID-19 has been predominantly from a younger population, and many of the patients had been hospitalized," Dr. Cohen noted. "This was the first study to focus on a large population of seniors, most of whom did not require hospitalization."

Dr. Cohen and colleagues reviewed the health insurance records of more than 133,000 Medicare beneficiaries aged 65 or older who were diagnosed with COVID-19 before April 2020. They also matched individuals by age, race, sex, hospitalization status, and other factors to comparison groups without COVID-19 (one from 2020 and one from 2019), and to a group diagnosed with other lower respiratory tract viral infections before the pandemic.

## Risk higher in hospitalized

After acute COVID-19 infection, 32% of seniors sought medical care for at least one new medical condition in 2020, compared with 21% of uninfected people in the same year.

The most commonly observed conditions included:

- Respiratory failure (7.55% higher risk).
- Fatigue (5.66% higher risk).
- High blood pressure (4.43% higher risk).
- Memory problems (2.63% higher risk).
- Kidney injury (2.59% higher risk).
- Mental health diagnoses (2.5% higher risk).

- Blood-clotting disorders (1.47% higher risk).
- Heart rhythm disorders (2.9% higher risk).

The risk of developing new conditions was even higher among those 23,486 who were hospitalized in 2020. Those individuals showed a 23.6% higher risk for developing at least one new condition, compared with uninfected seniors in the same year. Also, patients older than 75 had a higher risk for neurological disorders, including dementia, encephalopathy, and memory problems. The researchers also found that respiratory failure and kidney injury were significantly more likely to affect men and Black patients.

When those who had COVID, were compared with the group with other lower respiratory viral infections before the pandemic, only the risks of respiratory failure (2.39% higher), dementia (0.71% higher), and fatigue (0.18% higher) were higher.

Primary care providers can learn from these data to better evaluate and manage their geriatric patients with COVID-19 infection, said Amit Shah, MD, a geriatrician with the Mayo Clinic in Phoenix, in an interview. "We must assess older patients who have had COVID-19 for more than just improvement from the respiratory symptoms of COVID-19 in post-COVID follow-up visits," he said. "Older individuals with frailty have vulnerability to subsequent complications from severe illnesses

and it is common to see post-illness diagnoses, such as new diagnosis of delirium; dementia; or renal, respiratory, or cardiac issues that is precipitated by the original illness. This study confirms that this is likely the case with COVID-19 as well.

"Primary care physicians should be vigilant for these complications, including attention to the rehabilitation needs of older patients with longer-term postviral fatigue from COVID-19," Dr. Shah added.

## Data predate 'Omicron wave'

It remains uncertain whether sequelae will differ with the Omicron variant, but the findings remain applicable, Dr. Cohen said.

"We know that illness from the Omicron variant is on average less severe in those that have been vaccinated. However, throughout the Omicron wave, individuals who have not been vaccinated continue to have significant rates of serious illness and hospitalization," he said.

"Our findings showed that serious illness with hospitalization was associated with a higher rate of sequelae. It can therefore be inferred that the rates of sequelae seen in our study would continue to occur in unvaccinated individuals who contract Omicron, but might occur less frequently in vaccinated individuals who contract Omicron and have less severe illness."

Dr. Cohen serves as a consultant for Pfizer. Dr. Shah has disclosed no relevant financial relationships. ■

# Promising leads to crack long COVID discovered

BY DAMIAN MCNAMARA, MA

**I**t's a story of promise at a time of urgent need. Scientists are optimistic about new evidence into what is causing long COVID, a panel of research experts brought together by the New York State Department of Health said.

They proposed many theories on what might be driving long COVID. A role for a virus "cryptic reservoir" that could reactivate at any time, "viral remnants" that trigger chronic inflammation, and action by "autoimmune antibodies" that cause ongoing symptoms are possibilities.

In fact, it's likely that research will show long COVID is a condition with more than one cause, the experts said during a recent webinar.

People might experience post-infection problems, including organ damage that takes time to heal after initial COVID-19 illness. Or they may be living with post-immune factors, including

ongoing immune system responses triggered by autoantibodies.

Determining the cause or causes of long COVID is essential for treatment. For example, if one person's symptoms persist because of an overactive immune system, "we need to provide immunosuppressant therapies," Akiko Iwasaki, PhD, said. "But we don't want to give that to someone who has a persistent virus reservoir," meaning remnants of the virus remain in their bodies.

Interestingly, a study preprint, which has not been peer reviewed, found dogs were accurate more than half the time in sniffing out long COVID, said Dr. Iwasaki, professor of immunobiology and developmental biology at Yale University, New Haven, Conn.

The dogs were tasked with identifying 45 people with long COVID versus 188 people without it. The findings suggest the presence of a

unique chemical in the sweat of people with long COVID that could someday lead to a diagnostic test.

## Viral persistence possible

If one of the main theories holds, it could be that the coronavirus somehow remains in the body in some form for some people after COVID-19.

Mady Hornig, MD, agreed this is a possibility that needs to be investigated further.

"A weakened immune response to an infection may mean that you have cryptic reservoirs of virus that are continuing to cause symptoms," she said during the briefing. Dr. Hornig is a doctor-scientist specializing in epidemiology at Columbia University, New York.

"That may explain why some patients with long COVID feel better after vaccination," because the vaccine creates a strong antibody response to

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# 'Substantial' CVD risks up to a year after infection

BY PATRICE WENDLING

**P**eople who have had COVID-19 have an increased risk for, and 12-month burden of, cardiovascular disease (CVD) that is substantial and spans an array of cardiovascular disorders, a deep dive into federal data suggests.

"I went into this thinking that this is most likely happening in people to start with who have a higher risk of cardiovascular disorders, smokers, people with high BMI, diabetes, but what we found is something different," Ziyad Al-Aly, MD, said in an interview. "It's evident in people at high risk, but it was also as clear as the sun even in people who have no cardiovascular risk whatsoever."

Rates were increased in younger adults, never smokers, White and Black people, and males and females, he said. "So the risk confirmed by the SARS-CoV-2 virus seems to spare almost no one."

Although cardiovascular outcomes increased with the severity of the acute infection, the excess risks and burdens were also evident in those who never required hospitalization, a group that represents the majority of people with COVID-19, observed Dr. Al-Aly, who directs the Clinical Epidemiology Center at the Veterans Affairs St. Louis Health Care System.

"This study is very important because it underscores not just the acute cardiovascular risk associated with COVID but the increased risk of chronic cardiovascular outcomes as well," cardiologist C. Michael Gibson, MD, professor of medicine, Harvard Medical School, Boston, said in an interview. "Given the number of patients in the U.S. who have been infected with COVID, this could represent a significant chronic burden on the health care system, particularly as health care professionals leave the profession."

For the study, the investigators used national VA databases to build a cohort of 153,760 veterans who were alive 30 days after testing positive for COVID-19 between March 1, 2020, and January 2021. They were compared with

a contemporary cohort of 5.6 million veterans with no evidence of SARS-CoV-2 infection and a historical cohort of 5.8 million veterans using the system in 2017 prior to the pandemic. Median follow-up was 347, 348, and 347 days, respectively.

As reported in *Nature Medicine* (2022 Feb 7. doi: 10.1038/s41591-022-01689-3), the risk for a major adverse cardiovascular event, a composite of myocardial infarction, stroke, and all-cause mortality, was 4% higher in people who had been infected with COVID-19 than in those who had not.

"People say 4% is small, but actually it's really, really big if you think about it in the context of the huge number of people who have had COVID-19 in the United States, and also globally," Dr. Al-Aly said.

Compared with the contemporary control group, people who had COVID-19 had an increased risk (hazard ratio [HR]) and burden per

1,000 people at 1 year for the following cardiovascular outcomes:

- Stroke: HR, 1.52; burden, 4.03
- Transient ischemic attack: HR, 1.49; burden, 1.84
- Dysrhythmias: HR, 1.69; burden, 19.86
- Ischemic heart disease: HR, 1.66; burden, 7.28
- Heart failure: HR, 1.72; burden, 11.61
- Nonischemic cardiomyopathy: HR, 1.62; burden, 3.56
- Pulmonary embolism: HR, 2.93; burden, 5.47
- Deep vein thrombosis: HR, 2.09; burden, 4.18
- Pericarditis: HR, 1.85; burden, 0.98
- Myocarditis: HR, 5.38; burden, 0.31

Recent reports have raised concerns about an association between COVID-19 vaccines and myocarditis and pericarditis, particularly in young males. Although very few of the participants were vaccinated prior to becoming infected, as vaccines were not yet widely available, the researchers performed two analyses censoring participants at the time of the first dose of any COVID-19 vaccine and adjusting for vaccination

as a time-varying covariate.

The absolute numbers of myocarditis and pericarditis were still higher than the contemporary and historical cohorts. These numbers are much larger than those reported for myocarditis after vaccines, which are generally around 40 cases per 1 million people, observed Dr. Al-Aly.

The overall results were also consistent when compared with the historical control subjects.

"What we're seeing in our report and others is that SARS-CoV-2 can leave a sort of scar or imprint on people, and some of these conditions are likely chronic conditions," Dr. Al-Aly said. "So you're going to have a generation of people who will bear the scar of COVID for their lifetime and I think that requires recognition and attention, so we're aware of the magnitude of the problem and prepared to deal with it."

With more than 76 million COVID-19 cases in the United States, that effort will likely have to be at the federal level, similar to President Joe Biden's recent relaunch of the "Cancer Moonshot," he added. "We need a greater and broader recognition at the federal level to try and recognize that when you have an earthquake, you don't just deal with the earthquake when the earth is shaking, but you also need to deal with the aftermath."

Dr. Gibson pointed out that this was a study of predominantly males and, thus, it's unclear if the results can be extended to females. Nevertheless, he added, "long COVID may include outcomes beyond the central nervous system and we should educate patients about the risk of late cardiovascular outcomes."

The authors noted the largely White, male cohort may limit generalizability of the findings. Other limitations include the possibility that some people may have had COVID-19 but were not tested, the datasets lack information on cause of death, and possible residual confounding.

The research was funded by the U.S. Department of Veterans Affairs and two American Society of Nephrology and Kidney Cure fellowship awards. The authors declared no competing interests. Dr. Gibson reports having no relevant conflicts of interest. ■



Dr. Al-Aly

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fight COVID-19, Dr. Iwasaki said.

Researchers are unearthing additional potential factors contributing to long COVID.

Viral persistence could also reactivate other dormant viruses in the body, such as Epstein-Barr virus (EBV), said Lawrence Purpura, MD, MPH, an infectious disease specialist at New York Presbyterian/Columbia University. Reactivation of Epstein-Barr is one of four identifying signs of long COVID revealed in a Jan. 25 study published in the journal *Cell* (2022. doi: 10.1016/j.cell.2022.01.014).

For other individuals who have long COVID, it's not the virus sticking around but rather the

body's reaction that's the issue.

Investigators suggest autoimmunity plays a role, and they point to the presence of autoantibodies, for example.

When these autoantibodies persist, they can cause tissue and organ damage over time.

Other investigators are proposing "immune exhaustion" in long COVID because of similarities to chronic fatigue syndrome, Dr. Hornig said.

"It should be 'all hands on deck' for research into long COVID," she said. "The number of disabled individuals who will likely qualify for a diagnosis of [chronic fatigue syndrome] is growing by the second."

## Forging ahead research

It's clear there is more work to do. There are investigators working on banking tissue samples from people with long COVID to learn more, for example.

Also, finding a biomarker unique to long COVID could vastly improve the precision of diagnosing long COVID, especially if the dog sniffing option does not pan out.

Of the thousands of biomarker possibilities, Dr. Hornig said, "maybe that's one or two that ultimately make a real impact on patient care. So it's going to be critical to find those quickly, translate them, and make them available."

In the meantime, some answers might come from a large study

sponsored by the National Institutes of Health. The NIH is funding the "Researching COVID to Enhance Recovery" project using \$470 million from the American Rescue Plan. Investigators at NYU Langone Health are leading the effort and plan to share the wealth by funding more than 100 researchers at more than 30 institutions to create a "metacohort" to study long COVID. More information is available at [recovercovid.org](https://recovercovid.org).

"Fortunately, through the global research effort, we are now really starting to expand our understanding of how long COVID manifests, how common it is, and what the underlying mechanisms may be," Dr. Purpura said. ■

# Long-COVID symptoms linked to effects on vagus nerve

BY CAROLYN CRIST

Several long-COVID symptoms could be linked to the effects of the coronavirus on a vital central nerve, according to new research being released in the spring.

The vagus nerve, which runs from the brain into the body, connects to the heart, lungs, intestines, and several muscles involved with swallowing. It plays a role in several body functions that control heart rate, speech, the gag reflex, sweating, and digestion.

Those with long COVID and vagus nerve problems could face long-term issues with their voice, a hard time swallowing, dizziness, a high heart rate, low blood pressure, and diarrhea, the study authors found. Their findings will be presented at the 2022 European Congress of Clinical Microbiology and Infectious Diseases in late April.

“Most long COVID subjects with vagus nerve dysfunction symptoms had a range of significant, clinically relevant, structural and/or functional alterations in their vagus nerve, including nerve thickening, trouble swallowing, and symptoms of im-

paired breathing,” the study authors wrote. “Our findings so far thus point at vagus nerve dysfunction as a central pathophysiological feature of long COVID.”

Researchers from the University Hospital Germans Trias i Pujol in

*“The study appears to add to a growing collection of data suggesting at least some of the symptoms of long COVID are mediated through a direct impact on the nervous system.”*

Barcelona performed a study to look at vagus nerve functioning in long COVID patients. Among 348 patients, about 66% had at least one symptom that suggested vagus nerve dysfunction. The researchers did a broad evaluation with imaging and functional tests for 22 patients in the university’s Long COVID Clinic from March to June 2021.

Of the 22 patients, 20 were women, and the median age was 44. The most frequent symptoms related to vagus nerve dysfunction were diar-

rhea (73%), high heart rates (59%), dizziness (45%), swallowing problems (45%), voice problems (45%), and low blood pressure (14%).

Almost all (19 of 22 patients) had three or more symptoms related to vagus nerve dysfunction.

Of 22 patients, 6 had a change in the vagus nerve in the neck, which the researchers observed by ultrasound. They had a thickening of the vagus nerve and increased “echogenicity,” which suggests inflammation.

What’s more, 10 of 22 patients had flattened “diaphragmatic curves” during a thoracic ultrasound, which means the diaphragm doesn’t move as well as it should during breathing, and abnormal breathing. In another assessment, 10 of 16 patients had lower maximum inspiration pressures, suggesting a weakness in breathing muscles.

Eating and digestion were also impaired in some patients, with 13 reporting trouble with swallowing. During a gastric and bowel function assessment, eight patients couldn’t move food from the esophagus to the stomach as well as they should, while nine patients had acid reflux. Three patients had a hiatal hernia,

which happens when the upper part of the stomach bulges through the diaphragm into the chest cavity.

The voices of some patients changed as well. Eight patients had an abnormal voice handicap index 30 test. Among those, seven patients had dysphonia, or persistent voice problems.

The study is ongoing, and the research team is continuing to recruit patients to study the links between long COVID and the vagus nerve.

At press time, the full paper wasn’t yet available, and the research hadn’t yet been peer reviewed.

“The study appears to add to a growing collection of data suggesting at least some of the symptoms of long COVID are mediated through a direct impact on the nervous system,” David Strain, MD, at the University of Exeter (England), told the Science Media Centre.

“Establishing vagal nerve damage is useful information, as there are recognized, albeit not perfect, treatments for other causes of vagal nerve dysfunction that may be extrapolated to be beneficial for people with this type of long COVID,” he said. ■

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# Ivermectin does not stop progression to severe COVID: randomized trial

BY MARCIA FRELICK

**I**vermectin treatment given to high-risk patients with mild-to-moderate COVID-19 during the first week of illness did not prevent progression to severe disease. “The study findings do not support the use of ivermectin for patients with COVID-19,” researchers conclude in the paper published online in *JAMA Internal Medicine* (2022 Feb 18. doi: 10.1001/jamainternmed.2022.0189).

The open-label randomized clinical trial was conducted at 20 public hospitals and a COVID-19 quarantine center in Malaysia between May 31 and Oct. 25, 2021. It was led by Steven Chee Loon Lim, MRCP, department of medicine, Raja Permaisuri Bainun Hospital, Perak, Malaysia.

Among 490 patients in the primary analysis, 52 of 241 patients (21.6%) in the ivermectin group and 43 of 249 patients (17.3%) in the control group progressed to severe disease (relative

risk, 1.25; 95% confidence interval, 0.87-1.80;  $P = .25$ ). All major ethnic groups in Malaysia were well represented, the researchers write.

Participants (average age 62.5 and 54.5% women) were randomly assigned 1:1 to receive either a 5-day course of oral ivermectin (0.4 mg/kg body weight daily for 5 days) plus standard of care ( $n = 241$ ) or standard of care alone ( $n = 249$ ).

Standard of care included symptomatic therapy and monitoring for early deterioration based on clinical findings, laboratory tests, and chest imaging. Secondary outcomes included rates of mechanical ventilation, ICU admission, 28-day in-hospital mortality, and side effects. Among secondary outcomes, there were no significant differences.

Mechanical ventilation occurred in 4 patients on the ivermectin protocol (1.7%) versus 10 patients in the control group (4.0%) (RR, 0.41; 95% CI, 0.13-1.30;  $P = .17$ ); ICU admission occurred in 6 (2.4%) versus 8 (3.2%) (RR, 0.78; 95% CI, 0.27-

2.20;  $P = .79$ ); and 28-day in-hospital death occurred in three (1.2%) versus 10 (4.0%) (RR, 0.31; 95% CI, 0.09-1.11;  $P = .09$ ).

The most common adverse event was diarrhea, reported by 5.8% in the ivermectin group and 1.6% in the control group.

The researchers conducted a subgroup analysis to evaluate any differences in whether participants were vaccinated. They said that analysis was “unremarkable.” Just more than half of participants (51.8%) were fully vaccinated, with two doses of COVID-19 vaccines. Among the fully vaccinated patients, 17.7% in the ivermectin group and 9.2% in the control group developed severe disease (RR, 1.92; 95% CI, 0.99-3.71;  $P = .06$ ).

Ivermectin, an inexpensive and widely available antiparasitic drug, is prescribed to treat COVID-19 but has not been approved by the U.S. Food and Drug Administration for that purpose. Evidence-based data for or against use has been sparse.

The authors write that “although

some early clinical studies suggested the potential efficacy of ivermectin in the treatment and prevention of COVID-19, these studies had methodologic weaknesses.”

Dr. Lim and colleagues point out that their findings are consistent with those of the IVERCOR-COVID19 trial, which found ivermectin ineffective in reducing hospitalization risk.

In the current study, the authors note, patients were hospitalized, which allowed investigators to observe administration of ivermectin with a high adherence rate. Additionally, the researchers used clearly defined criteria for determining progression to severe disease.

Limitations of the current study include that the open-label design might lead to under-reporting of adverse events in the control group while overestimating the drug effects of ivermectin. The study was also not designed to assess the effects of ivermectin on mortality from COVID-19. ■

## NEWS FROM CHEST

### NETWORKS

## Vaccine hesitancy and update: addressing disparities

### Chest Infections and Disaster Response

#### Addressing disparities of socioeconomic status, race, and education in vaccine hesitancy and uptake

Vaccine hesitancy is described by the World Health Organization (WHO) as a “delay in acceptance or refusal of vaccination, despite availability of vaccine services.”<sup>1</sup> Disparities in COVID-19 vaccine uptake, in addition to preexisting views of vaccine hesitancy, are consistently in the mainstream news.

The United States has a high rate of vaccine hesitancy, with a third of the country surveyed in 2021 stating they were unlikely to become vaccinated against COVID-19.<sup>2</sup> This is in contrast to over 90% of people in Australia, China, and Norway saying they were highly likely to become vaccinated. Prepandemic, however, vaccination rates for preventable respiratory illness were already suboptimal. In fact, in 2019, the WHO declared vaccine hesitancy a top 10 priority due to the threat



Dr. Felzer



Dr. Kennedy

low vaccination causes on globally.<sup>1</sup>

U.S. health care systems’ cost to patients may serve as a disincentive for health care utilization, decreasing health care contacts. Further, changes in insurance can lead to provider discontinuity, which may erode the trusted patient-physician relationship. These realities may contribute to vaccine hesitancy that has been inversely correlated to both number of health care visits and trust in health care providers. Vaccine hesitancy exacerbates health disparities.<sup>1</sup> Health literacy (understanding of health), education level, and general vaccine knowledge contribute to

vaccine hesitancy also. Additionally, high social vulnerability (a score calculated from factors related to socioeconomic status, race, household makeup, housing type, and transportation) is strongly inversely correlated with vaccination rates. In places with both high social vulnerability and vaccine hesitancy, the vaccine-hesitant individuals have far fewer vaccinations.<sup>3</sup>

Providers can impact vaccine uptake. Broadly, efforts to understand and address issues of trust in health care are needed. Educational materials should be disseminated to high-risk and medically underserved communities. At medical appointments, assessment of vaccination status, followed by providing individualized information regarding vaccine benefits and specific concerns may help increase uptake. In a survey of high-risk adults, only 14.8 and 18.5% of patients stated that the pneumococcal vaccine was offered in the last year and 5 years, respectively.<sup>1</sup> Providers can have a strong impact on people obtaining vaccines; over half of patients

receive vaccines when their provider recommends it.<sup>1,4</sup>

As a medical community focused on respiratory health, we need to prioritize offering vaccinations during inpatient and outpatient encounters.

Jamie R. Felzer, MD, MPH  
Network Member

Cassie C. Kennedy, MD, FCCP  
Vice-Chair, Council of Networks

Dr. Felzer is a Fellow and Dr. Kennedy is Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN.

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(See more **NETWORKS** on page 21)

# Meet our new CHEST President-Designate

**W**e are happy to introduce John (Jack) D. Buckley, MD, MPH, FCCP, who will serve his term as CHEST President in 2024. A pulmonologist and critical care physician with an extensive background in education, he currently serves as the division leader of Pulmonary and Critical Care Medicine for the Henry Ford Medical Group and Health System.

Dr. Buckley received his undergraduate degree from Kalamazoo College and medical degree from Wayne State University. His residency in internal medicine and fellowships in pulmonary and critical care and health services research were completed at Indiana University. He additionally earned a Master of Public Health degree, also from Indiana University.



Dr. Buckley

His impressive academic record includes authoring or co-authoring more than 40 publications and book chapters, as well as presenting over 100 lectures at international conferences. As a former fellowship program training director at two institutions, Dr. Buckley has long been committed to championing and furthering pulmonary and critical care medical education. In a collaboration between the Chinese Thoracic Society and CHEST, he served 6 years on a steering committee to help establish pulmonary and critical care medicine as a subspecialty in China. He and the group assisted with the development of fellowship training programs and presented at several Chinese Thoracic Society annual meetings and board review events.

For Dr. Buckley's dedication to advancing PCCM education and faculty development, he received the CHEST Master Clinician Educator Award in 2016 and has been an annual Distinguished CHEST Educator (DCE) recipient since the award's inception in 2017.

Dr. Buckley has been an active and engaged member of CHEST since 1997. He has served in leadership roles across many domains of the organization, including CHEST 2022 Congress Italy, Chair of the CHEST 2013 Scientific Program Committee, Board of Regents, Compensation Committee, Governance Committee, Training and Transitions Committee (Chair, 2011-2012) and Bylaws Committee (Chair, 2010-2012), Honor Lecture and Awards Committee, and the Affiliate NetWork. He currently serves on the CHEST SEEK™ Pulmonary Medicine Editorial Board and is the Chair of the Pulmonary Medicine Board Review.

We look forward to welcoming Dr. Buckley as CHEST President in 2024. ■

## Nonphysician practitioner (NPP) billing for evaluation and management (E/M) and critical care services: A sea change now in effect!

**BY AMY AHASIC, MD, MPH, FCCP; SCOTT MANAKER, MD, PHD, FCCP; AND MICHAEL E. NELSON, MD, FCCP; FOR THE CHEST HEALTH POLICY AND ADVOCACY WORKGROUP\***

**I**n the 2022 Medicare Physician Fee Schedule, the Centers for Medicare and Medicaid Services (CMS) further refined E/M billing by addressing split/shared visits between nonphysician practitioners (such as nurse practitioners and physician assistants) (see <https://www.govinfo.gov/content/pkg/FR-2021-11-19/pdf/2021-23972.pdf>, pp. 65150-9).

A split/shared visit is “an E/M visit in the facility setting that is performed in part by both a physician and an NPP who are in the same group, in accordance with applicable laws and regulations.” CMS recognized team-based care increased utilization of NPPs in the inpatient setting, typically under physician supervision rather than completely independent NPP practice. NPP-physician team-based care is widely prevalent on critical care, hospitalist, and specialty consultation services.

These new changes from CMS went into effect January 1, 2022. CMS now mandates the practitioner providing the “substantive portion” of

the service must bill for the service. For the past 20 years, the substantive portion was largely defined by medical decision making (MDM): the physician often spent less face-to-face and/or non-face-to-face time than the NPP, but the physician could bill for the service based on MDM, including a nuanced synthesis of data, and final approvals or revisions to decisions on additional evaluation and treatment. Beginning January 1, 2023, CMS will

no longer define MDM as the substantive portion of the visit “because MDM is not necessarily quantifiable and can depend on patient characteristics (for example, risk).” Thus, CMS will define the “substantive portion” of the visit as the practitioner who spent >50% of the total of both face-to-face and non-face-to-face time, on the calendar day. The year 2022 is a transitional year allowing “the practitioner who spends more than half of the total time, or performs the history, exam, or MDM to be considered to have performed the substantive portion and can bill for the split (or shared) E/M visit.” During

2022, the visit level can be chosen based on MDM or time. In 2023, the visit level can still be chosen based upon MDM, but the billing provider is determined by who performed the “substantive portion” of the visit, which will be exclusively based upon which provider spent the most amount of time.

During 2022, when billing based on time, the practitioner spending the most time (the NPP or the physician) dictates who will be the billing provider. Alternatively, billing based on the substantive portion of the visit allows billing by the provider (NPP or physician) who completely performs the key component (history, physical examination, or medical decision making) that determines the level of the visit. With the new documentation guidelines, MDM is the only key component that can determine the visit level in the office setting. In 2023, only time-based billing will be in effect for choosing the billing provider in the inpatient hospital setting. Most importantly, time-based billing is already the only method for

determining the billing provider for billing critical care services, based on the provider (NPP or physician) with the greater individual time total.

This change represents a major shift in reimbursement for physician-NPP teams. Many physician compensation plans are based on a work relative value unit (wRVU) system. This time-based billing may shift attribution to the NPP and, thereby, disadvantage the physicians working with NPPs as they will no longer receive wRVU credit for team-based care delivery. This shift demands we all reexamine our compensation models and how organizations attribute work value across their providers (both NPPs and physicians), with special consideration for how to credit physicians for their essential supervision of team-based care delivered and now billed by NPPs. Ideally, options for revising compensation models without changing the care delivery model would preserve the essential partnership between physicians and NPPs. ■

*\*Including Nikki Augustyn; Geoffrey D. Bass, MD; Jamie Cummings; Ian Nathanson, MD, FCCP; Emily Petraglia; Gulshan Sharma, MD, FCCP; Kelly Shriner; and John E. Studdard, MD, FCCP.*



# President's report

New year, new CHEST President. Same as it has always been, except it has never been this way before. In past years, the transition of the CHEST Presidency occurred at our annual meeting, with a formal handover of leadership and a large reception. While there's no Presidential football to hand over or secret codes to change for the incoming administration, there are usually several pending issues related to ongoing endeavors that need to be discussed between the outgoing and incoming leadership, in addition to some pearls of wisdom and the figurative "keys to the car."

Now that CHEST has changed its President's year to transition alongside the calendar year, there are few associated formalities. I awakened on New Year's Day with my new title and the associated responsibility. Past President Steve Simpson, the mensch that he is, sent along with my colluding spouse a lovely and inspirational message for me to peruse, full of thoughtful advice and reflections on his year as President. I don't know if this has ever been done before, but it is a tradition that I fully intend on continuing at the end of my term.

What has CHEST been up to during the first few months of my tenure? January saw us hold our first Board of Regents meeting for 2022, as well as the meeting of the CHEST Critical Care SEEK editorial board, where they worked to put together Volume 32, which will be out later this year. Watching some of the best and brightest medical minds from around the country discuss hot topics in critical care was a great experience (even if I didn't have much to offer this august group), but the educational content was secondary to the interactions. Not only are these really smart folks teaching and learning from each other, but many of them are also clearly long-term

colleagues, and watching this medical meeting was a lot like watching a reunion of friends who hadn't seen each other in years. And, it struck me that what I've really been missing the most in the context of the social isolation that has accompanied the medical challenges of the pandemic is the pleasure of meeting in person with other folks to share stories, tell jokes, commiserate a bit, and catch up on the time that COVID-19 has stolen from us.

As we move further into 2022, I'm hoping that CHEST and our sister societies can help make up for this lost time by giving us the chance to meet in person once again. And to help build these experiences, we held an experiential design team along with our annual CHEST Program Committee meeting in February. Not only will the 2022 annual meeting in Nashville have the opportunity to hear from and network the best and brightest in pulmonary, critical care, and sleep medicine, but to celebrate our getting back together

for the first time in years, we are also putting together some special surprises that CHEST has never done before. Keep an eye out for sneak peeks of these plans later in the spring and summer.

Another of our foci in 2022 is our ongoing push to help historically disenfranchised groups feel more engaged with CHEST. Many of you contributed to last year's initiative to gather data on the kinds of things that we can do better, and I've just put together a presidential task force to develop final recommendations to further our goals of improving diversity, equity, and inclusion and to present to the Board of Regents for our April meeting.

Hopefully, many of you have seen some of the "Pardon the Introduction" series that CHEST has been featuring on its social media channels. We've put these



David Schulman, MD, MPH, FCCP

*One of my main initiatives for the year is to make sure we are meeting the needs of as many of our members as possible, and this is something we can only do well if the lines of communication are wide open.*



ACCP

together to showcase some of our leadership, their experiences, and opportunities for our members to get more involved with the College. Selfishly, I admit that they have also served as an excuse for me to catch up with some old friends and share our CHEST stories. We will be continuing to produce this series throughout the year; please let us know if there are specific folks you'd like us to feature!

Lastly, I wanted to thank the

many of you who have reached out to me with questions, comments, and feedback. One of my main initiatives for the year is to make sure we are meeting the needs of as many of our members as possible, and this is something we can only do well if the lines of communication are wide open.

Please continue to reach out to me, either by emailing me at [president@chestnet.org](mailto:president@chestnet.org) or messaging me on Twitter @ChestPrez. ■



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# A mentor in medicine ... a mentor in life

**Edward Carl Rosenow III, MD, Master FCCP**  
**November 2, 1934 - December 21, 2021**  
*We remember our close friend and colleague*

On Monday, January 3, 1972, in Rochester, Minnesota, the weather was as expected - a high of 20 F and a low of -5 F. At 7:30 that morning, a group of three young physicians, residents in internal medicine on a month-long rotation in the inpatient pulmonary ward in one of the Mayo Clinic hospitals, was awaiting the arrival of the staff consultant to begin the rounds. It was the very first day of his first-year residency at Mayo for one of the residents. He had applied for residency training to begin in July but, instead, accepted Mayo's offer to join the residency program 6 months earlier, in January - in Minnesota. That new resident was me. The pulmonary consultant had a friendly and disarming demeanor and gentle visage. He introduced himself to me with a smile, saying, "Welcome to Mayo. I am Ed Rosenow. Let me know if I can be of help in your training."

Thus began my almost half-century relationship with Ed. During my residency in internal medicine and fellowship in pulmonary and critical care medicine, he was a constant and

dependable fount of wisdom and knowledge. His daily lectures with chest x-rays after the morning rounds were legendary. By one estimate, he had collected over 4,500 chest x-rays to teach. These were hard copies and heavy to carry around. Ed lugged them under his arms daily for the lectures (there were no digital radiology or CT or MRI scanners then).

Ed was voted the "teacher of the year" every year for countless years. He was my first teacher in bronchoscopy and esophagoscopy. At that time, the division of pulmonary diseases was known as the division of thoracic diseases, and consultants in thoracic diseases performed bronchoscopy and rigid esophagoscopy.

Ed exemplified the best in compassion, amicability, collegiality, thoughtfulness, and a caring personality. In

addition to possessing superb clinical acumen, he volunteered in local medical clinics for the less fortunate. In my mind, it is not too farfetched to describe Ed as "A man for all seasons."\*

Among Ed's many professional accomplishments, his dedication and loyalty to the American College of Chest Physicians (CHEST) and the CHEST Foundation remain unsurpassed. In the years before and after he became the President of CHEST, Ed spent countless hours rewriting the 'constitution' of the organization, its bylaws. Many of the current

committee structures, rules, and regulations are based on Ed's work. During a meeting of the regents, one regent said, "ACCP is Rosenow and Rosenow is ACCP!"

Ed was a founding member of the CHEST Foundation, the philanthropic arm of the College. Ed's constant encouragement of young pulmonologists to participate in CHEST surely resulted in a significant increase in membership. He was the ceaseless force behind my work and deep involvement with CHEST and the CHEST Foundation.

Describing my long association with Ed transcends this note. Suffice it to say that my being named the first Edward W. and Betty Knight Scripps Professor of Medicine in Honor of Edward C. Rosenow III, MD, at Mayo Medical School is the greatest honor that I fondly cherish. I like to think that Ed strived for nearly a half-century to help me be a good person and a good doctor. I often question myself if I have met his goal. This question will linger in my mind for the rest of my life.

Udaya B. S. Prakash, MD, Master FCCP,  
 Rochester, MN

Past President, American College of  
 Chest Physicians (2002-2003)

\*A man for all seasons: A man who is ready to cope with any contingency and whose behavior is always appropriate to every occasion. The English grammarian Robert Whittington (1480-1553) applied this description to the English statesman and scholar Sir Thomas More (1478-1535), and Robert Bolt used it as the title of his 1960 play about More.

My association with Dr. Rosenow dates back to 2002. I was attending the CHEST annual meeting, and I saw Dr. Rosenow walking toward me. He came up and said, "Hi. My name is Ed Rosenow. What is yours?" "Suhail Raoof," I answered. Taking me aside, we spent almost a half-hour discussing

happening in my life—the good, the bad, the important, and the mundane. My problems would become his problems; solutions to my problems would become joint solutions. He guided me on my path to leadership with CHEST, culminating in my presidency.

Ed taught thousands of his colleagues the true meaning and power of mentorship. Early in his career, he realized that true happiness comes from helping and guiding others. Dr. Rosenow experienced a sense of genuine happiness and pride in witnessing the accomplishments of his friends and trainees. His gentle ways, unparalleled kindness, and modesty made him the quintessential role model, who one and all tried to emulate.

Aptly stated by Dr. John Studdard, FCCP, one of his students at Mayo Clinic, "Ed Rosenow was the finest doctor I have ever known, but an even better person. He balanced a great intellect and curiosity with great humility, was an incredible teacher, educator, and mentor, and all

of this with a special sense of humor."

Among his many positive traits, Ed possessed two qualities that played very important roles in his life— inquisitiveness and perseverance. In the early 1960s, there was a paucity of information on drug-induced lung disease. He embraced this gap in knowledge, resolved to fill it, and, for the next almost 50 years, Dr. Rosenow extensively researched, published, and lectured on drug-related lung injury.

Ed felt strongly that a good pulmonologist had to be a skilled chest radiologist. He was instrumental in introducing "Chest Imaging for the Pulmonologist" sessions at the annual CHEST meetings. With his enduring cataloging of consultation cases and collection of teaching file chest x-rays, it is no wonder that he amassed one of the best teaching resources, including some of the most rare lung conditions.

Ed was a visionary. He envisioned CHEST to be a closely knit "family of professionals," united in the desire to provide compassionate care of the highest order to patients and help each colleague accomplish their

goals and aspirations. During his CHEST presidency, he and Dr. Bart Chernow realized the importance of having a philanthropic arm of the College that would support worthy projects through fundraising. Soon after the establishment of the CHEST Foundation, Ed became its President and then Chair.

Dr. Rosenow's hard work, dedication, and unwavering commitment to professional and social organizations he served earned him the highest of accolades and honors. He had the rare distinction of being recognized as a Master by two professional organizations—CHEST and the American College of Physicians. Awards of the highest order were showered upon him by the Mayo Clinic, including establishing the Mayo Fellows Hall of Fame of Outstanding Teachers. Several endowed professorships and honors are named after him. The award he cherished most was the Karis Award (karis meaning "to care" in Greek). When I asked him how he felt to be the recipient of

ROSENOW continued on following page



*"Ed exemplified the best in compassion, amicability, collegiality, thoughtfulness, and a caring personality."*

Dr. Prakash



*"Ed was a visionary. He envisioned CHEST to be a closely knit 'family of professionals,' united in the desire to provide compassionate care."*

Dr. Raoof

my family, where I work, my career goals, and how the College could help me achieve some of those goals. His unassuming nature, humility, and sincere desire to help rang out loud and clear.

That day proved to be a turning point in my life. For the next almost 17 years, Ed and I set up monthly calls to connect. Each time, he was eager to listen and know what was



## NETWORKS

# FeNO guidelines. Marijuana use in pregnancy.

## Airway disorders

### FeNO guidelines and the art of clinical medicine

The American Thoracic Society (ATS) recently published new guidelines on the use of fractional exhaled nitric oxide (FeNO) in the management of asthma (Khatri S. *Am J Respir Crit Care Med*. 2021;204[10]:e97-e109). The previous iteration dealt with questions about the interpretation of FeNO levels. However, the updated guidelines address a single question: Should patients with asthma in whom treatment is being considered undergo FeNO testing?



Dr. Majumdar

Several roles of nitric oxide (NO) have been discovered, including as a marker of eosinophilic airway inflammation or T2-inflammation. The fraction of NO during steady-state exhalation, easily measured by a handheld device, is a standardized quantitative noninvasive method to assess severity of airway eosinophilic inflammation. However, factors like concomitant sinusitis, bronchoconstriction, obesity, and smoking can also affect FeNO levels, and interpretation is context-dependent. Moreover, some biologic agents have variable effects on FeNO while still being effective in controlling T2 inflammation. Therefore, FeNO is neither the broadest nor the most sensitive signal of T2 inflammation, and there is much unknown about using FeNO to guide asthma treatment. Heterogeneity is one of the many challenges, as different endotypes and clinical subsets vary in the inflammatory pathways leading to airway hyperresponsiveness and remodeling.

The panel assessed the value of FeNO testing in improving asthma control questionnaire scores (ACT, ACQ-7), oral corticosteroid use, asthma exacerbations, lung function, health care

utilization, and cost-effectiveness. FeNO-guided therapy compared with therapy without FeNO reduced exacerbations and oral corticosteroid use, though effect size was modest. While the trend favored FeNO, it did not reach statistical significance. Adverse effects of FeNO testing were trivial, and the cost is moderate though dependent on the institution size and testing frequency. Thus, for clinicians who manage adults and children 4 years of age and older, in whom treatment for asthma is being considered, it is suggested that FeNO testing be done in addition to usual care. The guidelines do not recommend specific steps to modify treatment based on FeNO results but suggest a decision framework, reminding us that clinical context is key and FeNO is merely one signal. In recognizing its own fallibility, this document suggests that in the continually evolving world of asthma, the art of clinical medicine still reigns supreme.

Uddalak Majumdar, MD

Dr. Majumdar is a Fellow, Pulmonary & Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH.

## Sleep medicine

### Marijuana use in pregnancy

Marijuana is the most commonly used illegal drug in the United States. According to the CDC, about 1 in 20 women report using marijuana while pregnant (<https://www.cdc.gov/marijuana/health-effects/pregnancy.html>). As states legalize marijuana for medicinal or recreational purposes, its use by pregnant women could increase even further. While some use it to ease morning sickness and anxiety, they may not be aware that it can pose risks.

Research has been raising concerns about the effects of marijuana use during pregnancy for years. A study from 1978 linked maternal cannabis use with children's behavioral problems

and deficits in language comprehension, visual perception, attention, and memory (*Life Sci*. 1995;56[23-24]:2159-68). More recent research has linked use to low birth weight, reduced IQ, autism, delusional thoughts, and attention problems, although some other studies have not identified such associations.



Dr. Rajagopal

A new study shows that children of women who use marijuana during or soon after pregnancy were twice as likely to become anxious, aggressive, or hyperactive. This corresponded with widespread reductions in immune-related gene expression in the placenta, which correlated with anxiety and hyperactivity (*Proc National Acad Sci*. 2021;118[47]:e2106115118).

Chemicals from marijuana can be passed to the baby through breast milk. THC is stored in body fat and slowly released over time. Exposure could still occur even after stopping use (Marijuana use during pregnancy and lactation. ACOG Committee Opinion, Number 722, October 2017, <https://tinyurl.com/yes3trcu>).

Studies have shown that THC can pass through the mother's bloodstream to the placenta and the fetus. This occurs independent of how cannabis is consumed (smoking, vaping, eating, or oils/creams). Patients should be educated that no amount has been proven safe to use during pregnancy or breastfeeding.

Anita Rajagopal, MD, FCCP

With the Respiratory-Related Sleep Disorders Section, Member-at-Large Dr. Rajagopal is Network Medical Director, Community Physician Network, Sleep Medicine/Medical Director, Community Health Network Sleep-Wake Disorders Center, Community Health Network, Indianapolis, IN.

ROSENOW continued from previous page

so many awards, he blushed and said, "Gee, there were plenty others who deserved them more than me. I was just doing my job."

To everyone he met, Ed emphasized the importance of the "culture of caring and giving." He taught his students that medicine is not a profession; it is a way of life. It is as much an art as it is a science. He reiterated his platinum rule to "Take care of every patient like you would want a member of your family cared for."

Today, thousands of his students, including me, are deeply indebted to Dr. Rosenow for the impactful and profound role he played in our lives and for teaching us the core values that really matter. He left an

indelible mark on our profession and our outlook. He redefined our responsibilities to our patients and colleagues. In his own quiet and effective way, Ed nurtured and inspired us to dream, think, persevere, and accomplish. His legacy will live on as we try to emulate his teachings, exceptional qualities, and humanistic approach. He will be missed greatly.

"His life was gentle, and the elements mixed so well in him that Nature might stand up and say to all the world, 'This was a man.'"

Shakespeare

Suhail Raoof, MD, Master FCCP,  
New York, NY  
Past President, American College of  
Chest Physicians (2011-2012)

## Edward C. Rosenow III, MD, Master FCCP/Master Endowment - Master Teacher Endowment Lecture

The legacy and impact of Ed Rosenow, MD, Master FCCP, will never be forgotten. CHEST nominates and recognizes those physicians who embody that passion and commitment of Dr. Rosenow with an awarded lecture fully funded by the Ed Rosenow III, MD, Master FCCP Endowment through the CHEST Foundation.

Be a part of Dr. Rosenow's legacy and make a donation in his memory to the Rosenow Endowment today at [chestfoundation.org](http://chestfoundation.org). ■



Dr. Rosenow

# Partnership news from the CHEST Foundation: New grant concentrated on diversity, equity, and inclusion

*American College of Chest Physicians, American Thoracic Society, and American Lung Association partner to support historically marginalized physician-scientists targeting lung disease*

The American College of Chest Physicians (CHEST), the American Thoracic Society (ATS), and the American Lung Association (ALA) are pleased to announce that they are partnering to sponsor a scholar in pulmonary and critical care medicine in the prestigious Harold Amos Medical Faculty Development Program (AMFDP), a Robert Wood Johnson Foundation initiative.

Developed to increase the pool of applicants from historically marginalized backgrounds pursuing careers in medicine, dentistry, or nursing, the AMFDP invites applicants to apply each year to help shape medicine into a more equitable, more accessible practice.

Together, CHEST, ATS, and ALA will provide funding for awards of \$420,000 over 4 years to support pulmonary/critical care medicine scholars.

"I am immensely proud to be leading an initiative that has continued to help shape the careers of so many physician-scientists in such a meaningful way," said David Wilkes, MD, National Director of the Harold Amos Medical Faculty Development Program for the Robert Wood

Johnson Foundation, and a member of ATS and CHEST. "That these three highly respected respiratory societies are joining efforts to help fulfill the AMFDP's mission speaks volumes about their commitment as allies and influencers in the quest



to eliminate lung health disparities. This is a model for other specialty societies to collaborate on addressing disparities."

"In the context of an increasingly diverse population, it is more important than ever that our patients have confidence and trust in those who care for them, something that will be easier to develop as we diversify our workforce," said CHEST President David Schulman, MD, MPH, FCCP. "CHEST is incredibly excited to be working with the American Lung Association, the American Thoracic Society, and the Harold

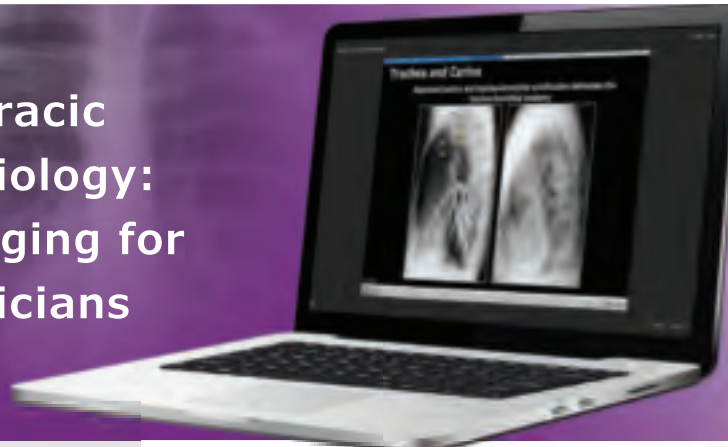
Amos Medical Faculty Development Program to fund training for individuals who have been traditionally underrepresented in medicine as they pursue careers in pulmonary and critical care medicine."

"Health equity is woven into the fabric of the ATS," said ATS President Lynn Schnapp, MD, ATSE. "And, partnering with our peers in the pulmonary and critical care space is a wonderful opportunity to advance our shared goal of cultivating the next generation of leaders in health access and equity."

"The American Lung Association has historically funded researchers at the beginning of their careers, helping to build the foundation for the next great group of leaders," said Albert Rizzo, MD, Chief Medical Officer for the ALA. "It is critical to the advancement of lung health and the care of patients to have physicians and scientists from diverse backgrounds, so we are honored to provide support for these individuals and increase diversity in pulmonary medicine."

The call for application is now open. To learn more and to apply go to [rwjf.org](http://rwjf.org). ■

## Thoracic Radiology: Imaging for Clinicians



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- Airways
- Infections
- Diffuse lung diseases
- Solitary and multiple nodules
- Pleura/mediastinum
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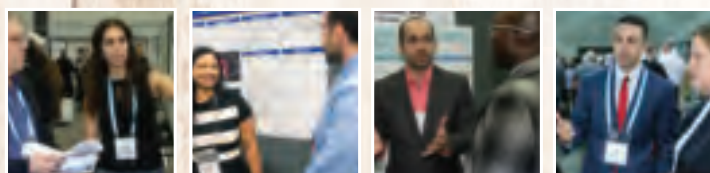
## Call for Abstracts and Case Reports

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# Off to the races with the CHEST Foundation

The CHEST Foundation cordially invites CHEST members and colleagues, health care professionals, and others to champion lung health and attend the annual Belmont Stakes Dinner and Auction, Saturday, June 11, in New York at the beautiful Water Club overlooking the East River.

Hosted by CHEST President-Elect Doreen Addrizzo-Harris, MD, FCCP, this year's celebration will include a lively cocktail reception, a silent and live auction, dinner, and a rooftop after-party for young professionals to network with colleagues and CHEST leadership and take the challenge for a chance to win great prizes, including a Peloton, ultrasound machine, and access to CHEST courses and events. Immerse yourself in the event, and wear your race-day best!

This year, we are honoring two outstanding patients and advocates, Betsy Glaeser and Fred Schick, for

their remarkable achievements in patient empowerment and access. Glaeser, who was diagnosed with nontuberculous mycobacteria (disease NTM) more than 20 years ago, pioneered opportunities for NTM-specific research funding and runs a hundreds-strong support group for people with NTM and bronchiectasis. Schick, who has pulmonary fibrosis, is an active ambassador in the patient community in Chicago and also leads local support groups for others with the disease.

All proceeds from the evening's events will benefit the CHEST Foundation's continued work toward bringing impactful, informative resources to patients.

As the patient-focused philanthropic arm of the American College of Chest Physicians, the CHEST Foundation is on a mission to champion lung health and strives



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to give health care professionals, patients, and caregivers opportunities to come together, give back, and advocate for change.

Since its inception, the Foundation has provided more than \$8 million in research grants and \$3 million in community grants, created free patient education resources for more than 80 disease states, and provided thousands of units of personal protective equipment and \$1 million

for pandemic relief efforts through COVID-19 Reaction Microgrants.

Support the continued work of the Foundation – and watch some of the most exciting few minutes in sports among colleagues and friends – at this year's Belmont Stakes Dinner and Auction. To buy a ticket, or to learn more about sponsorship benefits or underwriting opportunities, contact Angela Perillo at [aperillo@chestnet.org](mailto:aperillo@chestnet.org) or +1 (224) 521-9520. ■



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All proceeds from the Belmont Stakes Dinner and Auction will benefit the CHEST Foundation's continued work bringing impactful, informative resources to patients.

## Victor Test, MD, FCCP, receives Medal of Valor from AMA

The American Medical Association (AMA) honored CHEST Board Member Victor J. Test, MD, FCCP, with the AMA Medal of Valor for his work on behalf of patients and his community during the COVID-19 pandemic.

The award, which recognizes physicians who demonstrate courage under extraordinary circumstances, was presented to Dr. Test because of his quick decisive



Dr. Test

actions during the onset of the pandemic, including personally securing personal protective equipment to supply the critical care faculty and fellows at the Texas Tech University hospital in Lubbock and building plexiglass and PVC chambers for the physicians and nursing staff caring for patients with COVID-19.

Read more here: <https://tinyurl.com/4p48exev>. ■

## This month in the journal *CHEST*®

### Editor's picks

BY PETER J. MAZZONE, MD, MPH, FCCP

**Bronchial thermoplasty in severe asthmatics at 5 years: The PAS2 study.**

By Dr. G. Chupp, et al.

**Significant spirometric transitions and preserved ratio-impaired spirometry (PRISm) among ever-smokers.**

By Dr. E. Wan, et al.

**Addressing advance care planning in patients with COPD.**

By Dr. E. Rose, et al.

**The cost of ARDS: A systematic review.**

By Dr. P. Boucher, et al.

**Acute management of high- and intermediate-risk pulmonary embolism in**



**children: A review.**

By Dr. C. Ross, et al.

**Surgical outcomes for early-stage non-small cell lung cancer at facilities with stereotactic body radiation therapy programs.**

By Dr. Y. Syed, et al.

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