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CHEST Physician®

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Palliative care practitioners can provide comprehensive management of symptoms beyond those limited to the lungs.

SDI Productions/E+/Getty Images

Palliative care specialists seek greater role in lung disease

BY RANDY DOTINGA
MDedge News

Mrs. S.'s long-term chronic obstructive pulmonary disease (COPD) prognosis was grim, and she faced a harder time getting through each day. But neither she nor her primary care physician was willing to embrace strategies other than drugs.

"She felt guilty for continuing to smoke, but also expressed a need to smoke to help her deal with her husband's cancer and eventual death," recalled Georgia Narsavage, PhD, RN, ANP-BC, professor emerita of nursing at West Virginia University. "Her primary care physician was reluctant to introduce any treatment other than medications because her family was resistant to facing 'mother dying.' "

But things changed when Mrs. S. was referred to a palliative care clinical nurse specialist following a hospitalization. "The goal of palliative care is to support quality of life by relieving symptoms and decreasing suffering. She was assisted to improve functioning overall, and home support services were provided," Dr. Narsavage said. "They allowed her to live at home relatively pain free with decreased dyspnea for 3 more years until her transition to hospice care a few months before death.

It wasn't quite a happy ending. But it was a happier ending, and one that palliative care (PC)

PALLIATIVE CARE // *continued on page 6*

Coronavirus can spread to heart, brain days after infection

BY CAROLYN CRIST

The coronavirus that causes COVID-19 can spread to the heart and brain within days of infection and can survive for months in organs, according to a new study by the National Institutes of Health.

The virus can spread to almost every organ system in the body, which could contribute to the ongoing symptoms seen in "long COVID" patients, the study authors wrote. The study is considered one of the most comprehensive reviews of how the virus replicates in human cells and persists in the human body. It is under review for publication in the journal Nature (2021 Dec 20. doi: 10.21203/rs.3.rs-1139035/v1).

"This is remarkably important work," Ziyad Al-Aly, MD, director of the Clinical Epidemiology Center at the Veterans Affairs St. Louis Health Care System, told Bloomberg News. Dr. Al-Aly wasn't involved with the NIH study but has researched the long-term effects of COVID-19.

"For a long time now, we have been scratching our heads and asking why long COVID seems

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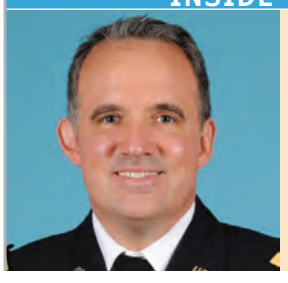
INSIDE HIGHLIGHT



NEWS FROM CHEST

Pulmonary Perspectives®
Dr. Aaron Holley tackles ICS for COVID-19

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Palliative care // *continued from page 1*

advocates hope will become more common in pulmonary care. They're working to convince colleagues that PC is neither another word for hospice nor a sign that anyone is giving up on a patient.

Underutilized but beneficial

"Palliative care is underutilized in patients with chronic pulmonary disease, and it's a missed opportunity to potentially alleviate symptoms and improve quality of life," said Hilary DuBrock, MD, an internist and critical care pulmonologist with the Mayo Clinic in Rochester, Minn. "Chest physicians should know that it's important to recognize your limitations in addressing all aspects of a chronic disease, and it's OK to ask for help from a specialty multidisciplinary team of palliative care providers."

Statistics back up Dr. DuBrock's perspective about how PC isn't common in pulmonary care. A 2017 study examined 181,689 U.S. adult patients who had COPD, received oxygen at home, and were hospitalized for exacerbations from 2006 to 2012 (CHEST. 2017 Jan 1;151[1]:41-6). Just 1.7% received PC, although the number grew over the study period.

Another study published in 2017 examined 3,166 patients over the same period with end-stage idiopathic pulmonary fibrosis (IPF) who were on ventilators (Am J Hosp Palliat Care. 2017 Jun 12. doi: 10.1177/10499091177139900). The use of PC is group rose from 2.3% in 2006 to 21.6% in 2012.

A more recent meta-analysis (Palliat Med. 2020 Jun 2. doi: 10.1177%2F0269216320929556) examined 19 studies and found that patients with lung cancer were much more likely to receive PC than were those with COPD (odds ratio, 9.59; $P < .001$, for hospital-based PC and OR, 8.79; $P < .001$, for home-based PC).

Patients with lung cancer vs. COPD were also less likely to receive invasive ventilation (OR, .26; $P < .001$), noninvasive ventilation (OR, .63; $P = .009$) or CPR (OR, .29; $P < .001$) or die at a nursing home/long-term care facility (OR, .32; $P < .001$).

Other studies support PC in COPD: Research in Europe has linked PC in COPD to fewer in-hospital deaths and lower end-of-life expenses. A Canadian study also linked PC to fewer in-hospital deaths in COPD (Ann Am Thorac Soc. 2021. doi: 10.1513/AnnalsATS.202007-859OC).

Dr. DuBrock said she believes there are a couple reasons why PC isn't more widely accepted in pulmonology. "There has been little evidence in chronic pulmonary disease regarding the role of PC, and there is a lack of standardized guidelines to help clinicians determine appropriate timing and patient selection for referral," she said. "There is also a reluctance to refer patients to palliative care since some may think that referral implies that they are giving up on their patients."

In fact, she said, "if appropriatly explained and discussed with patients, PC does not necessarily need to imply to patients that you are giving up on them, but rather that you care enough about them to try to find novel ways to improve their quality of life and relieve their symptoms. Additionally, palliative care can be provided alongside ongoing medical care and treatment of their chronic lung disease."

More than standard care

Another obstacle comes from pulmonologists who claim PC isn't necessary because they're handling patient care themselves, said University of Alabama at Birmingham critical care pulmonologist Anand S. Iyer, MD. "They'll say: 'I do palliative care; I palliate their breathing. I treat breathlessness and cough; that's what I do.'"

But these symptoms brush only the surface of patient needs, he said. "I don't think that the average pulmonologist goes beyond that to comprehensive symptom assessment and management of a whole host of symptoms beyond those limited to the lungs – depression, anxiety, fatigue, malnutrition."

On that latter front, he said, pulmonologists "are really good at having end-of-life conversations at the end of life. We do that every day in the ICU." Advocates for PC, he said, "want to push that to the clinic a year or 2 earlier."

Timing and use of PC

When should pulmonologists call in a PC team? Specialists recommend early consultations, even right after a pulmonary disease is diagnosed. "When a pulmonologist diagnoses a condition as a serious illness – especially chronic pulmonary disease – a consultation with a palliative care physician or advanced practice registered nurse" can help assess the need for care and the best time to introduce palliative care to the patient and family "to provide relief

PALLIATIVE CARE *continued on following page*

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to affect so many organ systems," he said. "This paper sheds some light and may help explain why long COVID can occur even in people who had mild or asymptomatic acute disease."

The NIH researchers sampled and analyzed tissues from autopsies on 44 patients who died after contracting the coronavirus during the first year of the pandemic. They found persistent virus particles in multiple parts of the body, including the heart and brain, for as long as 230 days after symptoms began. This could represent infection with defective virus particles, they said, which has also been seen in persistent infections among measles patients.

"We don't yet know what burden of chronic illness will result in years to come," Raina MacIntyre, PhD, a professor of global biosecurity at the University of New South Wales, Sydney, told Bloomberg News.

"While the highest burden of SARS-CoV-2 is in the airways and lung, the virus can disseminate early during infection and infect cells throughout the entire body, including widely throughout the brain."

"Will we see young-onset cardiac failure in survivors or early-onset dementia?" she asked. "These are unanswered questions which call for a precautionary public health approach to mitigation of the spread of this virus."

Unlike other COVID-19 autopsy research, the NIH team had a more comprehensive postmortem tissue collection process, which typically occurred within a day of the patient's death, Bloomberg News reported. The researchers also used a variety of ways to preserve tissue to figure out viral levels. They were able to grow the virus collected from several tissues, including the heart, lungs, small intestine, and adrenal glands.

"Our results collectively show that, while the highest burden of SARS-CoV-2 is in the airways and lung, the virus can disseminate early during infection and infect cells throughout the entire body, including widely throughout the brain," the study authors wrote. ■

PALLIATIVE CARE *continued from previous page*

and enhance quality of life," West Virginia University's Dr. Narsavage said. "Initial diagnosis is not too early to think about the trajectory.

Dr. Iyer agreed that early PC consultation is key. "We're talking about comprehensive support for the physical, emotional, and spiritual needs of patients and their families. It can grow as needs of patients become more severe."

For her part, Dr. DuBrock urged colleagues to focus on patient experiences. "The exact timing of when to refer patients with pulmonary disease is not well established," she said. "Thus, it's important to take cues from our patients. If they are experiencing significant symptom burden or impaired quality of life or having difficulty coping with their lung disease, then it may be helpful to call in palliative care to address these issues alongside education and discussion with the patient about the role of palliative care to address their unmet needs."

As an example, Dr. DuBrock spoke of one of her own patients who has pulmonary hypertension (PH), connective tissue disease, and interstitial lung disease. "Her hypertension was relatively well controlled, but she was still quite symptomatic as well as depressed and having difficulty sleeping. I struggled with wanting to help her feel better but I also recognized that more PH therapy wasn't necessarily the answer," Dr. Dubrock said. "After some discussions, I referred her to palliative care, and they were extremely helpful with addressing her symptoms with a combination of pharmacologic and nonpharmacologic therapy and also addressing some of her underlying concerns and fears regarding her prognosis and issues related to advance-care planning. Social work was also helpful with addressing some of her financial concerns. I continue to see her on regular basis and treat her PH, but her overall quality of life, sleep, and mood have improved substantially."

First steps

According to specialists, the first step in the PC process with patients is to make sure they understand their conditions, their prognoses, and the role of palliative care itself.

Kathleen Oare Lindell, PhD, RN, associate professor of nursing at Medical University of South Carolina, Charleston, who specializes in PC in pulmonary disease, remembers taking the histories of patients with grim prognoses and "their look on their face was like, 'I just have a common cold.' " In other cases, she said, patients may fear they'll die immediately when they have 3-5 years to live.

"When a pulmonologist diagnoses a condition as a serious illness – especially chronic pulmonary disease – a consultation with a palliative care physician or advanced practice registered nurse" can help assess the need for care.

Dr. Lindell, who has worked at a center for patients with interstitial lung disease, emphasized the importance of speaking in layperson terms that patients understand, such as referring to idiopathic pulmonary fibrosis as "unknown lung scarring." She also said it's crucial to be up front about their prognoses.

As for patient understanding of PC, she said, "people think it's hospice that they're giving. Palliative care is neither. Instead, it helps to address symptom management: I always tell patients, 'You'll be scared; you'll have a cough. There are medicines and nonpharmacological therapies [that can help], and that's what palliative care does.' "

Keith Swetz, MD, an internist and palliative care specialist at the University of Alabama at Birmingham, agreed that a concise discussion of prognosis is vital. "What do they know about their illness, and what do they understand about what will happen when things get worse?" he said.

"With pulmonary disease, they may be looking at months to years punctuated with a lot of ICU admissions, trips to the hospital, symptom burden, and decline in function. Some will want aggressive treatment and say they're fine being in the hospital, while others will say being comfortable at home is more important."

Dr. Swetz's patients commonly have COPD, interstitial lung disease, pulmonary fibrosis, or PH, and some may have concurrent heart failure. While their prognoses may be poor, he said, discussion about their wishes probably aren't happening outside of the PC setting.

Or if they are happening, he said, they're lower quality, boiling down complicated care questions to "Do you want us to do everything, yes or no?"

"A lot of it has to do with time," he said. "Clinicians are busy, they might have a full ICU or pulmonary clinic with 15 minutes to see patients. Sitting down and talking about these things isn't something that's prioritized or fits into the work stream very well, and often it hasn't been reimbursed."

There typically aren't insurance hassles regarding referrals for PC, Dr. Iyer said, although finding available specialists may be challenging. A 2019 study (Health Aff. 2019 Jun. doi: 10.1377/hlthaff.2019.00018) projected a wave of retirements of older PC physicians over the next few years, and the ratio of patients to PC specialists may not return to 2019 levels for decades. Rural areas are especially shorthanded. But telehealth may improve access, Dr. Iyer said.

What's next? Specialists are trying to pin down guidelines for when PC consultation is appropriate in pulmonary disease.

Triggers to PC

Dr. Iyer, Dr. Lindell, and others authored a 2021 report in the journal CHEST that offers guidance about triggers for PC consultation (doi: 10.1016/j.chest.2021.10.032). The authors cited four "levers" or triggers that are important: worsening lung function, severe symptoms or high burden of care needs, poor prognosis, and frequent severe exacerbations. "The overall point here is that integrating palliative care into COPD practice isn't an on-off switch; rather, it should be based upon multiple factors and can evolve over time," they wrote.

They noted that, "patients with COPD accept palliative care as early as moderate COPD (FEV_1 < 80%), so patients may be ready sooner than clinicians think." They added that, "if prognosis is such a concern that a clinician is considering referral for lung transplant evaluation, then concurrent referral to specialist palliative care should be routine practice.

Finally, frequent severe exacerbations, i.e., those that require hospitalization or an emergency room visit, carry a high risk for posthospitalization mortality and are ideal inflection points in the illness trajectory of COPD."

In the big picture, the authors contend, "palliative care should be integrated early and concurrently with COPD-directed therapies, and its intensity should increase over time as symptoms, needs, and exacerbations worsen approaching EOL [end of life]."

None of the interviewees or other authors reported having any relevant conflicts for this story. ■

Frail COPD patients at high risk of disability and death

BY PAM HARRISON

Thinkstock

Patients with chronic obstructive pulmonary disease (COPD) who are both frail and who have poor lung function or dyspnea are at especially high risk of disability within 3-5 years as well as all-cause mortality years later, a prospective cohort study of community-dwelling adults has shown.

"Frailty, a widely recognized geriatric syndrome characterized by multidimensional functional decline in bio-psycho-social factors, is associated with functional disability and mortality," senior author Tze Pin Ng, MD, National University of Singapore, and colleagues explain.

"Our results ... suggest that beyond traditional prognostic markers such as FEV_1% (forced expiratory volume in 1 second) and dyspnea, the physical frailty phenotype provides additional useful prognostic information on future risks of disability and mortality," the authors suggest.

The study was published online in CHEST (2021. doi: 10.1016/j.chest.2021.12.633).

SLAS-1 and SLAS-2

Data from the Singapore Longitudinal Ageing Study (SLAS-1) and SLAS-2 were collected and analyzed. SLAS-1 recruited 2,804 participants 55 years of age and older from September 2003 through December 2004, while SLAS-2 recruited 3,270 participants of the same age between March 2009 and June 2013. "Follow-up visits and assessments were conducted approximately 3-5 years apart," the investigators noted.

Mortality was determined at a mean of 9.5 years of follow-up for SLAS-1 participants and a mean of 6.5 years' follow-up for SLAS-2 participants. A total of 4,627 participants were eventually included in the analysis, of whom 1,162 patients had COPD and 3,465 patients did not. COPD was classified as mild if FEV_1% was greater than or equal to 80%; moderate if FEV_1% was greater than or equal to 50% to less than 80%, and severe if FEV_1% was less than 50%.

Frailty in turn was based on five clinical criteria, including weakness, slowness, low physical activity, exhaustion, and shrinking. Participants were classified as frail if they met three or more of these criteria and prefrail if they met one or two criteria.

Adverse health outcomes were judged on the basis of instrumental or basic activities of daily living (IADL/ADL), while disability was judged by self-reported difficulties in or requiring assistance with at least one IADL or ADL.

Frail or prefrail

Almost half of the participants were frail or prefrail, as the authors reported, while 25% had COPD. Among the participants with COPD, 30% had moderate to severe COPD, 6.4% had dyspnea, and almost half had prefrailty, while approximately 7% were classified as frail.

This percentage was 86% higher than it was for participants without COPD, among whom just 3.2% were assessed as frail, at an odds ratio of 1.86 (95% CI, 1.35-2.56). Further adjustments for possible confounders reduced the gap between frail COPD and frail non-COPD participants, but frailty remained significantly associated with COPD, at an OR of 1.61 (95% CI, 1.15-2.26), the investigators note.

Furthermore, compared to those without COPD, a diagnosis of COPD without and with dyspnea was associated with a 1.5- and 4.2-fold increase in prevalent frailty (95% CI, 1.04-2.08; 1.84-9.19), respectively, although not with prefrailty. Again, with adjustment for multiple confounders, FEV_1%, dyspnea, and both prefrailty and frailty were associated with an approximately twofold higher prevalence of IADL/ADL disability, while the prevalence of IADL/ADL disability for participants with COPD was approximately fourfold higher in those with co-occurring FEV_1% less than 80% with either prefrailty, frailty, or dyspnea.

Furthermore, the presence of prefrailty or frailty in combination with a lower FEV_1% or dyspnea was associated with a 3.7- to 3.8-fold increased risk of having an IADL or ADL disability.

Frailty and mortality

Some 1,116 participants with COPD were followed for a mean of 2,981 days for mortality outcomes. Both FEV_1% less than 50% and the presence of prefrailty and frailty almost doubled the risk of mortality, at an adjusted hazard ratio of 1.8 (95% CI, 1.24-2.68) compared to patients with an FEV_1% greater than or equal to 80%. In combination with either FEV_1% less than 80% or prefrailty/frailty, dyspnea almost more than doubled the risk of mortality, at an HR of 2.4 for both combinations.

"However, the mortality risk of participants with COPD was highest among those with FEV_1% less than 80% and prefrailty/frailty," the authors note, more than tripling mortality risk at an adjusted HR of 3.25 (95% CI, 1.97-5.36). Interestingly, FEV_1 less than 80% and prefrailty/frailty – both alone and in combination – were also associated with a twofold to fourfold increased risk of IADL or ADL disability in participants without COPD but were less strongly associated with mortality.

Researchers then went on to create a summary risk score containing all relevant variables with values ranging from 0 to 5. The highest risk category of 3-5 was associated with a 7- to 8.5-fold increased risk for IADL and ADL disability and mortality among participants with COPD, and that risk remained high after adjusting for multiple confounders.

Of note, frailty did not significantly predict mortality in women, while dyspnea did not significantly predict mortality in men. "Recognition and assessment of physical frailty in addition to FEV_1% and dyspnea would allow for more accurate identification and targeted treatment of COPD at risk of future adverse outcomes," the authors suggest.

Frailty scoring system

Asked to comment on the study, Sachin Gupta, MD, FCCP, a pulmonologist and critical care specialist at Alameda Health System in Oakland, Calif., noted that the current study adds to the body of literature that outcomes in patients with COPD depend as much on objectively measured variables as on qualitative measures.

"By applying a frailty scoring system, these researchers were able to categorize frailty and study its impact on patient characteristics and outcomes," he told this news organization in an email.

The summary risk assessment tool developed and assessed is familiar: It carries parallels to the widely utilized BODE Index, replacing body mass index and 6-minute walk distance with the frailty scale, he added. "Findings from this study support the idea that what meets the eye in face-to-face visits – frailty – can be codified and be part of a tool that is predictive of outcomes," Dr. Gupta underscored.

The authors had no conflicts of interest to declare. Dr. Gupta disclosed that he is also an employee and shareholder at Genentech. ■

Is early-detection stage shift driving mortality decline?

BY JIM KLING

In non–small cell lung cancer (NSCLC), earlier detection may be an underappreciated factor in recent trends of declining mortality, according to a new analysis of data from the Surveillance, Epidemiology, and End Results (SEER) registries published in JAMA Network Open (2021 Dec 17. doi: 10.1001/jamanetworkopen.2021.37508). Between 2006 and 2016, a stage shift occurred with an increase in stage 1 and 2 diagnoses and a decrease in stage 3 and 4 diagnoses.

While targeted therapy and immunotherapy have rightfully been credited with improved NSCLC survival, the new results underline the importance of screening, according to study author Emanuela Taioli, MD, PhD, director of the Institute for Translational Epidemiology and the associate director for population science at the Tisch Cancer Institute at Mount Sinai, New York.

She noted that the average survival for stage 1 or stage 2 patients was 57 months, but just 7 months when the stage diagnosis was 3 or 4. "So being diagnosed with stage 1 and 2 is a major driver of better survival," said Dr. Taioli in an interview.

The study included 312,382 individuals diagnosed with NSCLC (53.4% male; median age, 68). Incidence-based, 5-year mortality declined by 3.7% (95% confidence interval, 3.4%-4.1%). Stage 1 or 2 diagnoses increased from 26.5% to 31.2% of diagnoses between 2006 and 2016 (average annual percentage change, 1.5%; 95% CI, 0.5%-2.5%).

"Immunotherapy is a very exciting field. And it is an important contributor for people who have a disease that can be treated with immunotherapy, so that's why people focus on that. But if you can diagnose the cancer earlier, that's the best bet."

Unfortunately, many patients and physicians haven't received that message. Even though computed tomography lung cancer screening is covered by Medicare for current or former smokers, only about 7% of eligible patients undergo annual screening. Dr. Taioli said that a belief persists that lung cancer is so deadly that early detection isn't effective.

But advances in therapy and surgery have changed that outlook. "It's not true anymore. People don't know, and physicians are not educated to the idea that lung cancer can be diagnosed earlier and save lives," she said.

People who have quit smoking may be relatively easy to convince. "They made a big step, because quitting smoking is incredibly hard. I think they will be amenable to screening because they are in a phase [of life] in which they want to take care of themselves. The physician should really explain the benefits, and I don't think they do it very clearly now," Dr. Taioli said.

The study is limited by its retrospective nature. Dr. Taioli has no relevant financial disclosures. ■

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Adaptive D-dimer thresholds may rule out PE

BY HEIDI SPLETE

Adapted D-dimer thresholds based on pretest probability were effective for ruling out pulmonary embolism (PE) in subgroups of high-risk individuals without the use of imaging in a review of data.

In a patient suspected to have a PE, "diagnosis is made radiographically, usually with CT pulmonary angiogram, or V/Q scan," Suman Pal, MD, of the University of New Mexico, Albuquerque, said in an interview.

"Validated clinical decision tools such as Wells's score or Geneva score may be used to identify patients at low pretest probability of PE who may initially get a D-dimer level check, followed by imaging only if D-dimer level is elevated," explained Dr. Pal, who was not involved with the new research, which was published in Annals of Internal Medicine (2021 Dec 14. doi: 10.7326/M21-2625).

According to the authors of the new paper, while current diagnostic strategies in patients with suspected PE include use of a validated clinical decision rule (CDR) and D-dimer testing to rule out PE without imaging tests, the effectiveness of D-dimer tests in older patients, inpatients, cancer patients, and other high-risk groups has not been well-studied.

Lead author of the paper, Milou A.M. Stals, MD, and colleagues said their goal was to evaluate the safety and efficiency of the Wells rule and revised Geneva score in combination with D-dimer tests, and also the YEARS algorithm for D-dimer thresholds, in their paper.

Dr. Stals of Leiden (the Netherlands) University Medical Center, and coinvestigators conducted an international systemic review and individual patient data meta-analysis that included 16 studies and 20,553 patients, with all studies having been published between Jan. 1, 1995, and Jan. 1, 2021. Their primary outcomes were the safety and efficiency of each of these three strategies.

In the review, the researchers defined safety as the 3-month incidence of venous thromboembolism after PE was ruled out without imaging at baseline. They defined efficiency as the proportion of patients for whom PE was ruled out based on D-dimer thresholds without imaging.

Overall, efficiency was highest in the subset of patients aged younger than 40 years, ranging from 47% to 68% in this group. Efficiency was lowest in patients aged 80 years and older (6.0%-23%), and in patients with cancer (9.6%-26%).

The efficiency was higher when D-dimer thresholds based on pretest probability were used, compared with when fixed or age-adjusted D-dimer thresholds were used.

The key finding was the significant variability in performance of the diagnostic strategies, the researchers said.

"The predicted failure rate was generally highest for strategies incorporating adapted D-dimer thresholds. However, at the same time, predicted overall efficiency was substantially higher with these strategies versus strategies with a fixed D-dimer threshold as well," they said. Given that the benefits of each of the three diagnostic strategies depends on their correct application, the researchers recommended that an individual hospitalist choose one strategy for their institution.

"Whether clinicians should rely on the Wells rule, the YEARS algorithm, or the revised Geneva score becomes a matter of local preference and experience," Dr. Stals and colleagues wrote.

The study findings were limited by several factors including between-study differences in scoring predictors and D-dimer assays. Another limitation was that differential verification biases for classifying fatal events and PE may have contributed to overestimation of failure rates of the adapted D-dimer thresholds.

Strengths of the study included its large sample size and original data on pretest probability, and that data support the use of any of the three strategies for ruling out PE in the identified subgroups without the need for imaging tests, the authors wrote.

Overall, efficiency was highest in the subset of patients aged younger than 40 years, ranging from 47% to 68% in this group. Efficiency was lowest in patients aged 80 years and older, and in patients with cancer.

"Pending the results of ongoing diagnostic randomized trials, physicians and guideline committees should balance the interlink between safety and efficiency of available diagnostic strategies," they concluded.

Adapted D-dimer benefits some patients

"Clearly, increasing the D-dimer cutoff will lower the number of patients who require radiographic imaging (improved specificity), but this comes with a risk for missing PE (lower sensitivity). Is this risk worth taking?" Daniel J. Brotman, MD, of Johns Hopkins University, Baltimore, asked in an editorial accompanying the new study (Ann Intern Med. 2021 Dec 14. doi: 10.7326/M21-4295).

Dr. Brotman was not surprised by the study findings.

"Conditions that predispose to thrombosis through activated hemostasis – such as advanced age, cancer, inflammation, prolonged hospitalization, and trauma – drive D-dimer levels higher independent of the presence or absence of radiographically apparent thrombosis," he said. However, these patients are unlikely to have normal D-dimer levels regardless of the cutoff used.

Adapted D-dimer cutoffs may benefit some patients, including those with contraindications or limited access to imaging, said Dr. Brotman. D-dimer may be used for risk stratification regardless of PE, since patients with marginally elevated D-dimers have better prognoses than those with higher D-dimer elevations, even if a small PE is missed.

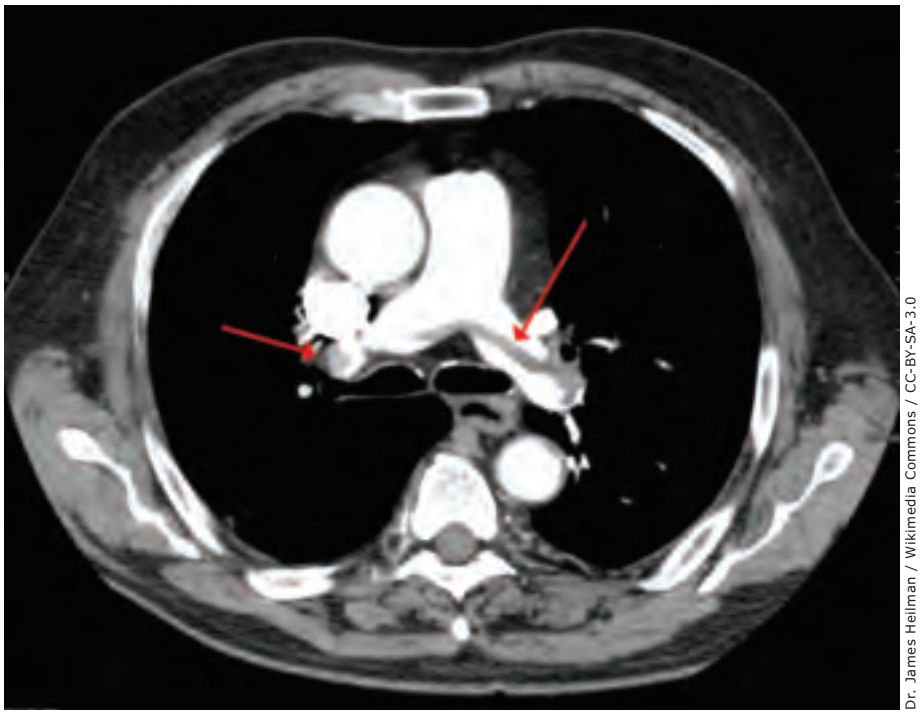
Dr. Brotman wrote that increasing D-dimer cutoffs for high-risk patients in the subgroups analyzed may spare some patients radiographic testing, but doing so carries an increased risk for diagnostic failure. Overall, "the important work by Stals and colleagues offers reassurance that modifying D-dimer thresholds according to age or pretest probability is safe enough for widespread practice, even in high-risk groups."

Focus on single strategy 'based on local needs'

"Several validated clinical decision tools, along with age or pretest probability–adjusted D-dimer threshold are currently in use as diagnostic strategies for ruling out pulmonary embolism," Dr. Pal said in an interview.

The current study is important because of limited data on the performance of these strategies in specific subgroups of patients whose risk of PE may differ from the overall patient population, he noted.

"Different diagnostic strategies for PE have a variable performance in patients with differences of age, active cancer, and history of VTE," said Dr. Pal. "However, in this study, no clear preference for one strategy over others could be established



Dr. James Heilman / Wikimedia Commons / CC-BY-SA-3.0

CT scan shows radiographic evidence of pulmonary embolism (arrows).

THRESHOLDS *continued on following page*

THRESHOLDS *continued from previous page*

for these subgroups, and clinicians should continue to follow institution-specific guidance.

"A single strategy should be adopted at each institution based on local needs and used as the standard of care until further data are available," he said.

"The use of D-dimer to rule out PE, either with fixed threshold or age-adjusted thresholds, can be confounded in clinical settings by other comorbid conditions such as sepsis, recent surgery, and more recently, COVID-19," he said.

"Since the findings of this study do not show a clear benefit of one diagnostic strategy over others in the analyzed subgroups of patients, further prospective head-to-head comparison among the subgroups of interest would be helpful to guide clinical decision-making," Dr. Pal added.

YEARS-specific study supports D-dimer safety and value

A recent paper published in JAMA supported the results of the meta-analysis (2021 Dec 7. doi: 10.1001/jama.2021.20750). In that study, Yonathan Freund, MD, of Sorbonne Université, Paris, and colleagues focused on the YEARS strategy combined with age-adjusted D-dimer thresholds as a way to rule out PE in PERC-positive ED patients.

The authors of this paper randomized 18 EDs to either a protocol of intervention followed by control, or control followed by intervention. The study population included 726 patients in the intervention group and 688 in the control group.

The intervention strategy to rule out PE consisted of assessing the YEARS criteria and D-dimer testing. PE was ruled out in patients with no YEARS criteria and a D-dimer level below 1,000 ng/mL and in patients with one or more YEARS criteria and D-dimers below an age-adjusted threshold (defined as age times 10 ng/mL in patients aged 50 years and older).

The control strategy consisted of D-dimer testing for all patients with the threshold at age-adjusted levels; D-dimers above these levels prompted chest imaging.

Overall, the risk of a missed VTE at 3 months was noninferior between the groups (0.15% in the intervention group and 0.80% in the controls).

"The intervention was associated with a statistically significant reduction in chest imaging use," the researchers wrote.

This study's findings were limited by randomization at the center level, rather than the patient level, and the use of imaging on some patients despite negative D-dimer tests, the researchers wrote. However, their findings support those of previous studies and especially support the safety of the intervention, in an emergency medicine setting, as no PEs occurred in patients with a YEARS score of zero who underwent the intervention.

Downsides to applying algorithms to every patient explained

In an editorial accompanying the JAMA study (JAMA. 2021 Dec 7. doi: 10.1001/jama.2021.19282), Marcel Levi, MD, and Nick van Es, MD, of Amsterdam University Medical Center, emphasized the challenges of diagnosing PE given that many patients present with nonspecific clinical manifestations and without typical signs and symptoms. High-resolution CT pulmonary angiography allows for a fast and easy diagnosis in an emergency setting. However, efforts are ongoing to develop alternative strategies that avoid unnecessary scanning for potential PE patients, many of whom have alternative diagnoses such as pulmonary infections, cardiac conditions, pleural disease, or musculoskeletal problems.

On review of the JAMA study using the YEARS rule with adjusted D-dimer thresholds, the editorialists noted that the data were robust and indicated a 10% reduction in chest imaging. They also emphasized the potential to overwhelm busy clinicians with more algorithms.

"Blindly applying algorithms to every patient may be less appropriate or even undesirable in specific situations in which deviation from the rules on clinical grounds is indicated," but a complex imaging approach may be time consuming and challenging in the acute setting, and a simple algorithm may be safe and efficient in many cases, they wrote. "From a patient perspective, a negative diagnostic algorithm for pulmonary embolism does not diminish the physician's obligation to consider other diagnoses that explain the symptoms, for which chest CT scans may still be needed and helpful."

The Annals of Internal Medicine study was supported by the Dutch Research Council. The JAMA study was supported by the French Health Ministry. Dr. Stals, Dr. Freund, Dr. Pal, Dr. Levi, and Dr. van Es had no financial conflicts to disclose. ■

PULMONARY MEDICINE

Idiopathic pulmonary fibrosis – a mortality predictor found?

BY JIM KLING
MDedge News

A low lymphocyte-to-monocyte ratio (LMR) is associated with worse survival in newly-diagnosed patients with idiopathic pulmonary fibrosis (IPF), according to a new retrospective, single-center analysis. Patients with both IPF and lung cancer also had a lower LMR than patients with IPF alone.

The study, published online in Respiratory Medicine (2021 Nov 23. doi: 10.1016/j.rmed.2021.106686), was conducted among 77 newly diagnosed patients, 40 end-stage IPF patients, and 17 patients with IPF and lung cancer. All received at least 1 year of antifibrotic therapy (pirfenidone or nintedanib). The researchers collected demographic and clinical data between December 2014 and December 2020.

The disease course of IPF is difficult to predict, with some patients progressing slowly, and others suffer a rapid decline to respiratory failure. Previous studies found that higher levels of monocytes are associated with higher mortality in IPF and other fibrotic lung disease, and both neutrophil-to-lymphocyte ratio (NLR) and LMR have been shown to predict mortality in lung cancer.


Dr. Herzog

A previous study found that IPF patients had a higher NLR and a lower LMR than controls, but that research did not consider the impact of antifibrotic treatment, which may improve outcomes

PREDICTOR *continued on following page*

Experimental plasma exchange shows promise for IPF flares in preliminary study

BY RICHARD MARK KIRKNER

Acute flares of idiopathic pulmonary fibrosis can have a mortality rate as high as 90% or more. But an experimental regimen that includes autoantibody reduction was found to improve survival significantly, as well as oxygen levels and walk distances, according to a preliminary study published in PLOS ONE (2021 Nov 23. doi: 10.1371/journal.pone.0260345).

"It's a preliminary study, but it's very exciting," Amit Gaggar, MD, PhD, an endowed professor of medicine at the University of Alabama at Birmingham, said in an interview. "We don't really have a treatment for acute exacerbations of pulmonary fibrosis, and the mortality is extremely high, so it's really critical that we start thinking outside the box a little bit for therapeutics." Dr. Gaggar isn't affiliated with the study.

Study leader Steven R. Duncan, MD, also of UAB, acknowledged that the experimental therapy has its detractors. "There's been a tremendous bias against the role of immunologic therapy in idiopathic fibrosis, although it seems to be lessening."

The preliminary study treated 24 patients who had acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) with a 19-day regimen called triple-modality autoantibody reduction. The three contributing modalities are therapeutic plasma exchange (TPE), rituximab, and intravenous immunoglobulin treatments. The standard treatment for AE-IPF consists of antibiotics and corticosteroids.

Dr. Duncan led the only other study of autoantibody reduction for AE-IPF, published in PLOS ONE in 2015. The latest preliminary study is a precursor to a National Heart, Lung, and Blood Institute–funded phase 2 randomized clinical trial, called STRIVE-IPF, currently enrolling AE-IPF patients at six sites.

In the preliminary study, 10 patients survived at least a year, an overall survival rate of 42%. Overall survival rates at 1, 3, and 6 months were 67%, 63%, and 46%. The study couldn't identify characteristics of survivors versus nonsurvivors, although the latter had a trend toward greater initial oxygen requirements. Among the 10 patients who needed less than 25 L/min supplemental O_2, the survival rate was 57%. In patients who needed more than 25 L/min, the survival rate was 20% ($P = .07$). Only one of five patients who needed greater than 40 L/min survived a year ($P = .36$).

"We don't really have a treatment for acute exacerbations of pulmonary fibrosis, and the mortality is extremely high, so it's really critical that we start thinking outside the box a little bit for therapeutics."

After the 19-day regimen, 15 patients, or 63%, had significant drops in supplemental O_2 requirements, from an average of 15 L/min to 3 L/min ($P = .0007$). Thirteen (87%) of the patients who were taking an antifibrotic medication (either pirfenidone or nintedanib) at baseline needed less O_2 and/or had increased walking distances, compared with five who weren't prescribed either of the agents ($P = .15$), although 1-year survival didn't vary significantly with antifibrotic use.

"Plasma exchange rapidly gets rid of the antibodies," he added in an interview. "It's the basis for a number of autoantibody-mediated diseases, such as myasthenia gravis."

While the TPE removes the B cells, they have a proclivity to re-emerge, hence the rituximab treatment, he said. IV Ig further inhibits B-cell activity. "The IV Ig probably works in large part by feedback inhibition of the B cells that have survived the rituximab," Dr. Duncan said.

He added that with the TPE and rituximab patients had "sometimes amazing response" but then would relapse. "Since we added IV Ig, we see far fewer relapses," he said. "And interestingly, if they do relapse, we can salvage them by giving them this treatment again."

The preliminary study doesn't make clear what patients would benefit most from the triple-modality therapy, but it did provide some clues. "We found that patients who have higher levels of antibodies against epithelial cells tend to do the best, and patients who had less severe disease – that is, less disturbance of gas exchange requiring less O_2 – tend to do better," Dr. Duncan said. The STRIVE trial should serve to identify specific biomarkers, he said.

Dr. Gaggar, a UAB professor who's not affiliated with the study, concurred that it's "too early to tell" which patients would benefit. "Certainly, these patients that undergo exacerbations would be of high interest," he said, "but the potential is there that the other chronic lung diseases that have exacerbations may also benefit from this kind of therapy."

He noted that, "In many of these studies where we limit ourselves to a single autoantibody population, we might be at the tip of iceberg," Dr. Gaggar said.

"There might be autoantibodies generated from other cells in the lung or the body that might be also pathogenic. This is really powerful because this is a subgroup of autoantibodies, but they still had that kind of impact in this small study."

Dr. Duncan disclosed relationships with Novartis and Tyr Pharma outside the study subject. Dr. Gaggar has no relevant disclosures. ■

PREDICTOR *continued from previous page*

(Lung. 2020 Oct;198[5]:821-7).

There has been accumulating cellular and molecular evidence that leukocyte population abnormalities are associated with IPF outcomes, but that work was more discovery based and relied on tests that aren't readily available clinically, said Erica L. Herzog, MD, PhD, who was asked to comment on the study.

"It's provided a lot of insight into potential new mechanisms and potential biomarkers, but their clinical utility for patients is limited. So the use of lymphocyte-to-monocyte ratios that can be obtained from a complete blood cell count, which is a test that can be done in any hospital, would really be a game-changer in terms of predictive algorithms for patients with IPF," said Dr. Herzog, who is a professor of medicine and pathology at Yale University, New Haven, Conn., and director of the Yale ILD Center of Excellence.

In humans, abnormalities in circulating monocytes and lymphocytes have individually been linked worse IPF outcomes. Animal studies have implicated monocyte-derived cells in lung fibrosis, but because animal studies have shown that lymphocyte populations are not required for fibrosis, more work is needed.

"I think what we're finding is that lymphocytes probably have a regulatory role, and there's probably a protective population and potentially a pathogenic population. Something about the balance between adaptive immunity, which is reflected by your lymphocytes, and innate immunity, which is reflected by your monocytes. Something about that balance is important for tissue homeostasis, and then when it's disrupted or perturbed, fibrosis ensues," said Dr. Herzog.

Newly diagnosed patients were older (mean age, 70 years) than end-stage IPF patients (mean age, 60 years) and patients with IPF and lung cancer (64 years; $P < .0001$).

Among newly diagnosed IPF patients, a receiving operating characteristic analysis before antifibrotic treatment determined a cutoff LMR value of less than 4.18, with an area under the curve of 0.67 ($P = .025$). Values below 4.18 were associated with shorter survival (hazard ratio, 6.88; $P = .027$). Patients with LMR less than 4.18 were more likely to be men (89% vs. 67%; $P = .036$), had a lower percent predicted forced vital capacity (76% vs. 87%; $P = .023$), and were more likely to die or undergo lung transplant (34% vs. 5%; $P = .009$).

A Kaplan-Meier curve illustrated a stark difference between patients with LMR of 4.18 or higher, nearly all of whom remained alive out to almost 100 months of follow-up. Around 30% of those with LMR less than 4.18 remained alive while close to 100% of the patients with LMR below this value showed worsened outcomes. "You don't normally see curves like that," said Dr. Herzog.

There was no significant difference in blood cell counts and ratios at the time of IPF diagnosis and after 1 year of antifibrotic treatment, which suggests that the risk profile is independent of treatment.

Patient with IPF and lung cancer had the lowest mean LMR (2.2), followed by newly diagnosed patients (3.5), and those with end-stage disease (3.6; $P < .0001$).

The study authors reported financial relationships with various pharmaceutical companies. Dr. Herzog had no relevant financial disclosures. ■

CHEST™ Physician
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Heavy snoring in early pregnancy linked to increased insulin resistance

BY KRISTIN JENKINS
MDedge News

Severe maternal sleep-disordered breathing (SDB) is a known risk factor for gestational diabetes, which is commonly diagnosed in the second or third trimester of pregnancy.

Now, a new study suggests that increases in insulin resistance, a precursor for gestational diabetes, may take place as early as the first trimester of pregnancy in women with risk factors for obstructive sleep apnea (OSA), such as overweight and habitual snoring.

This finding could potentially provide physicians with a window of opportunity to improve outcomes by screening at-risk women early in pregnancy or even prior to conception, Laura Sanapo, MD, assistant professor of medicine (research) at Brown University, Providence, R.I., and colleagues wrote in Sleep (2022 Jan 6. doi: 10.1093/sleep/zsab281).

Brandon B. Seay, MD, comments: This paper highlights the possible utility of OSA/sleep-disordered breathing screening in patients who may not have elevated BMI, which is typically present in individuals at risk for OSA, if they show other symptoms (snoring, excessive daytime sleepiness). Early intervention with positive airway pressure therapy could possibly help decrease the risk of progressing to gestational diabetes and the detrimental effects of that on a pregnancy.

"Further studies are needed to investigate the association and its impact on the development of gestational diabetes, and to establish whether early-gestation or pregestational treatment of SDB would improve glucose metabolic outcomes in pregnancy," they wrote.

Waiting until mid-pregnancy to screen for OSA "is too late to make significant changes in the care of these women. By the time you diagnose gestational diabetes, the cat is out of the bag."

"What this paper demonstrates is that the changes that predate gestational diabetes are seen much earlier in pregnancy," senior study author Ghada Bourjeily, MD, professor of medicine at Brown University, said in an interview. Women should be screened for SDB rather than insulin resistance in early pregnancy since continuous positive airway pressure therapy (CPAP) is a highly effective intervention.

Waiting until mid-pregnancy to screen for OSA "is too late to make significant changes in the care of these women," said Dr. Bourjeily, who is also director of research and training at the Women's Medicine Collaborative at The Miriam Hospital in Providence. "By the time you diagnose gestational diabetes, the cat is out of the bag."

For the study, women with early singleton pregnancies and risk factors for OSA such as habitual snoring and a median body mass index of at least 27 kg/m^2 were recruited from two prospective clinical trial studies enriched for OSA positivity. Women with a history of pregestational diabetes and those using CPAP or receiving chronic steroid therapy were excluded from the current study.

A total of 192 study participants underwent home sleep apnea test (HSAT) and homeostatic model assessment (HOMA) between 11 and 15 gestational weeks, respectively. The association between continuous measures of SDB as a respiratory-event index as well as oxygen-desaturation index and glucose metabolism parameters such as insulin resistance (HOMA-IR) were analyzed after adjusting for gestational age, maternal age, BMI, ethnicity, race, and parity.

In all, 61 women (32%) were diagnosed with OSA based on respiratory event index values greater than or equal to five events per hour. These participants were more likely to be older, to have a high BMI, and to be multipara, compared with women who didn't have a diagnosis of OSA. Women with a diagnosis of OSA exhibited higher glucose and C-peptide values and a higher degree of insulin resistance, compared with women without OSA, the researchers found. An increase of 0.3 in HOMA-IR related to maternal SDB in early pregnancy may significantly affect glucose metabolism.

Although the findings of the current study cannot be extrapolated to women who don't have overweight or obesity, some women with normal-range BMI (18.5-24.9) are also at increased

PREGNANCY *continued on following page*

FDA OKs new adult insomnia medicine

BY ERIK GREB

The Food and Drug Administration has approved the dual orexin receptor antagonist daridorexant (Quviviq) for the treatment of insomnia in adults, the drug's manufacturer, Idorsia, has announced.

The FDA's decision was based partly on a phase 3 trial of adults with moderate to severe insomnia who were randomly assigned to receive 25 or 50 mg of daridorexant or matching placebo. Daridorexant was associated with dose-dependent improvements in wake after sleep onset, total sleep time, and latency to persistent sleep.

Whereas the overall results are very positive, the improvements in daytime functioning are especially "exciting," Thomas Roth, PhD, director of the Sleep Disorders and Research Center at Henry Ford Hospital in Detroit, said in an interview.

"That's sort of a big deal. For me, that's the biggest deal there is," said Dr. Roth, who was a consultant on the design of the phase 3 trial and on the interpretation of the data.

The drug will be available in doses of 25 mg and 50 mg, and the FDA has recommended that it be classified as a controlled substance. After it is scheduled by the Drug Enforcement Administration, daridorexant is expected to be made available in May.

Favorable safety profile

Insomnia is a common disorder characterized by difficulty falling asleep or staying asleep and by early-morning awakenings. Patients with insomnia often report fatigue, irritability, and difficulty with concentration. The condition can also result in significant problems with work and social activities, thus contributing to anxiety or depression.

As with other dual orexin receptor antagonists, daridorexant competitively binds with both orexin receptors in the lateral hypothalamus to block the activity of orexin in a reversible way. This approach decreases the downstream action of the wake-promoting neurotransmitters that are overactive in patients with insomnia.

The phase 3 trial measured daytime functioning using the new Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), a patient-reported outcome instrument. Daridorexant was associated with significant improvements in daytime function, particularly in sleepiness and mood.

Previous trials of other dual orexin receptor antagonists did not use the IDSIQ as an outcome, so it is not possible to compare daridorexant with those drugs in this respect, Dr. Roth noted. Researchers also have not conducted head-to-head trials of the drug with other dual orexin receptor antagonists.

Daridorexant also had a favorable safety profile and was not associated with rebound insomnia or withdrawal effects. The most common adverse events were headache and somnolence or fatigue.

"They had no effect on sleep stage distribution [and] they had no significant effects on sleep and breathing in people with mild to moderate sleep apnea," said Dr. Roth, who presented the phase 3 findings at SLEEP 2020.

In addition to serving as a consultant for Idorsia on the trial design and interpretation of results, Dr. Roth has also served as a consultant for other companies that develop sleep agents. ■

OSA linked to white-matter hyperintensities

BY JIM KLING

Individuals diagnosed with obstructive sleep apnea (OSA) have higher volumes of white-matter hyperintensities (WMHs), according to a new analysis of data from the SHIP-Trend-0 cohort in Western Pomerania, Germany, which is part of the Study of Health In Pomerania. The association was true for individual measures of OSA, including apnea-hypopnea index (AHI) and oxygen desaturation index (ODI).

WMHs are often seen on MRI in older people and in patients with stroke or dementia, and they may be an indicator of cerebral small-vessel disease. They are linked to greater risk of abnormal gait, worsening balance, depression, cognitive decline, dementia, stroke, and death. Suggested mechanisms for harms from WMHs include ischemia, hypoxia, hypoperfusion, inflammation, and demyelination.

WMHs have been linked to vascular risk factors like smoking, diabetes, and hypertension. Brain pathology studies have found loss of myelin, axonal loss, and scarring close to WMHs.

Although a few studies have looked for associations between WMHs and OSA, they have yielded inconsistent results. The new work employed highly standardized data collection and more comprehensive covariate adjustment. The results, published in JAMA Network Open (2021 Oct 5. doi: 10.1001/jamanetworkopen.2021.28225), suggest a novel, and potentially treatable, pathological WMH mechanism, according to the authors.

"This is an important study. It has strong methodology. The automated analysis of WMH in a large population-based cohort helps to eliminate several biases that can occur in this type of assessment. The data analysis was massive, with adequate control of all potential confounders and testing for interactions. This generated robust results," said Diego Z. Carvalho, MD, who was asked to comment on the findings. Dr. Carvalho is an assistant professor of neurology at the Center for Sleep Medicine at the Mayo Clinic, Rochester, Minn.

"The association varies according to the degree of apnea severity, so mild OSA is probably not associated with increased WMH, while severe OSA is most likely driving most of the associations."

Worse apnea, worse hyperintensity

"The association varies according to the degree of apnea severity, so mild OSA is probably not associated with increased WMH, while severe OSA is most likely driving most of the associations," said Dr. Carvalho.

If a causal mechanism were to be proven, it would "bring a stronger call for treatment of severe OSA patients, particularly those with increased risk for small-vessel disease, [such as] patients with metabolic syndrome. Likewise, patients with severe OSA would be the best candidates for therapeutic trials with [continuous positive airway pressure] with or without possible adjunctive neuroprotective treatment for halting or slowing down WMH progression," said Dr. Carvalho.

Stuart McCarter, MD, who is an instructor of neurology at the Center for Sleep Medicine at the Mayo Clinic, Rochester, Minn., also found the results interesting but pointed out that much more work needs to be done. "While they found a relationship between OSA as well as OSA severity and WMH despite adjusting for other known confounders, it is unlikely that it is as simple as OSA is the main causal factor for WMH, given the complex relationship between OSA, hypertension, and metabolic syndrome. However, this data does highlight the importance of considering OSA in addition to other more traditional risk factors when considering modifiable risk factors for brain aging," said Dr. McCarter. The study cohort was mostly of White European ancestry, so more work also needs to be done in other racial groups.

The study underlines the importance of screening among individuals with cognitive impairment. "If OSA represents a modifiable risk factor for WMH and associated cognitive decline, then it would represent one of the few potentially treatable etiologies, or at least contributors of cognitive impairment," said Dr. McCarter.

The SHIP-Trend-0 cohort is drawn from adults in Western Pomerania. The researchers analyzed data from 529 patients who had WMH and for whom intracranial volume data were available. Each member of the cohort also underwent polysomnography.

Brandon M. Seay, MD, comments: I agree with the comments by Dr. Carvalho. If OSA is a possible modifiable risk factor for developing cognitive decline in older age, then this would make it an important condition to screen, diagnose, and treat at younger ages. Further research into a possible mechanism would be very interesting, as there is no clear direct mechanism outside of OSA's relation to metabolic syndrome, hypertension, and episodes of hypoxia.

Based on AHI criteria, 24% of the overall sample had mild OSA, 10% had moderate OSA, and 6% had severe OSA.

After adjustment for sex, age, intracranial volume, and body weight, WMH volume was associated with AHI (beta = 0.024; $P < .001$) and ODI (beta = 0.033; $P < .001$). WMH counts were also associated with AHI (beta = 0.008; $P = .01$) and ODI (beta = 0.011; $P = .02$).

The effect size increased with greater OSA severity, as measured by AHI for both WMH volume (beta = 0.312, 0.480, and 1.255 for mild, moderate, and severe OSA, respectively) and WMH count (beta = 0.129, 0.107, and 0.419). The ODI regression models showed similar associations for WMH volume (beta = 0.426, 1.030, and 1.130) and WMH count (beta = 0.141, 0.315, and 0.538).

Dr. Carvalho and Dr. McCarter disclosed no relevant financial relationships. ■

PREGNANCY *continued from previous page*

risk of glucose metabolism changes, Dr. Bourjeily pointed out. This includes those of Southeast Asian descent. "We found that the association of SDB parameters with insulin resistance was actually happening independently of BMI and other factors."

Ideally, screening for SDB would begin prior to pregnancy, Dr. Bourjeily said. A BMI greater than 25 should be taken into account and patients asked if they snore and if so, whether it's loud enough to wake their partner. They should also be asked about experiencing daytime sleepiness.

"Based on these answers, especially in women screened prior to pregnancy, there will be time to make the diagnosis of sleep apnea and get the patient on CPAP," Dr. Bourjeily said.

"This is an interesting study and one of the rare ones looking at early pregnancy and some of the mechanisms that could possibly be contributing to gestational diabetes," commented Grenye O'Malley, MD, assistant professor in the division of endocrinology, diabetes, and bone disease at the Icahn School of Medicine at Mount Sinai, New York. Dr. O'Malley was not involved in the study.

"It confirms our suspicions that there's probably a lot of things happening earlier in pregnancy before a diagnosis of gestational diabetes. It also confirms that some of the mechanisms are probably very similar to those involved in the association between disordered sleep and the development of type 2 diabetes."

However, it's too early to determine whether screening for SDB and the use of CPAP will prevent glycemic changes, Dr. O'Malley said in an interview. "Whenever we screen, we ask whether we have an intervention that changes outcomes and we don't know that yet."

Some of the symptoms of SDB are also common in early pregnancy, such as a BMI greater than 25 and daytime sleepiness, Dr. O'Malley pointed out. It was unclear whether the study participants had a propensity to develop type 2 diabetes or whether they were at risk of gestational diabetes.

This study was funded by the National Heart, Lung, and Blood Institute; the National Institute for Child Health; and the National Institute of General Medical Sciences. Dr. Bourjeily and colleagues, as well as Dr. O'Malley, reported having no potential financial conflicts of interest. ■

CARDIOLOGY

Reassuring data on rare myocarditis after COVID-19 vaccination

BY MEGAN BROOKS

Adolescents and adults younger than age 21 who develop myocarditis after mRNA COVID-19 vaccination frequently have abnormal findings on cardiac MRI (cMRI) but most have a mild clinical course with rapid resolution of symptoms, a new study concludes.

"This study supports what we've been seeing. People identified and treated early and appropriately for the rare complication of COVID-19 vaccine–related myocarditis typically experienced only mild cases and short recovery times," American Heart Association President Donald M. Lloyd-Jones, MD, said in a podcast.

"Overwhelmingly, the data continue to indicate [that] the benefits of COVID-19 vaccine far outweigh any very rare risks of adverse events from the vaccine, including myocarditis," Dr. Lloyd-Jones added.

The study was published online Dec. 6 in Circulation (2021. doi: 10.1161/CIRCULATIONAHA.121.056583).

Using data from 26 pediatric medical centers across the United States and Canada, the researchers reviewed the medical records of 139 patients younger than 21 with suspected myocarditis within 1 month of receiving a COVID-19 vaccination.

"People identified and treated early and appropriately for the rare complication of COVID-19 vaccine–related myocarditis typically experienced only mild cases and short recovery times."

They made the following key observations:

- Most patients were male (90.6%) and White (66.2%); the median age was 15.8 years.
- Suspected myocarditis occurred in 136 patients (97.8%) following mRNA vaccine, with 131 (94.2%) following the Pfizer-BioNTech vaccine; 128 cases (91.4%) occurred after the second dose.
- Symptoms started a median of 2 days (range 0-22 days) following vaccination administration.
- Chest pain was the most common symptom (99.3%), with fever present in 30.9% of patients and shortness of breath in 27.3%.
- Patients were treated with nonsteroidal anti-inflammatory drugs (81.3%), intravenous immunoglobulin (21.6%), glucocorticoids (21.6%), colchicine (7.9%), or no anti-inflammatory therapies (8.6%).
- Twenty-six patients (18.7%) were admitted to the intensive care unit; two received inotropic/vasoactive support; and none required extracorporeal membrane oxygenation or died.
- Median time spent in the hospital was 2 days.
- A total of 111 patients had elevated troponin I (8.12 ng/mL) and 28 had elevated troponin T (0.61 ng/mL).
- More than two-thirds (69.8%) had abnormal electrocardiograms and/or arrhythmias (seven with nonsustained ventricular tachycardia).
- Twenty-six patients (18.7%) had left ventricular ejection fraction

MYOCARDITIS *continued on following page*

Jonathan Ludmir, MD, FCCP, comments: This is an important study. I think it is also important to highlight some of the comparative studies demonstrating high risk of myocarditis associated with COVID-19 compared with the COVID vaccine.

Dr. Ludmir

***Editor's Note**: According to the CDC (www.cdc.gov/mmwr/volumes/70/wr/mm7035e5.htm): "After adjusting for patient and hospital characteristics, patients with COVID-19 during March 2020–January 2021 had, on average, 15.7 times the risk for myocarditis compared with those without COVID-19."*

MYOCARDITIS *continued from previous page*

less than 55% on echocardiogram; LVEF had returned to normal in the 25 who returned for follow-up.

- Seventy-five of 97 patients (77.3%) who underwent cMRI at a median of 5 days from symptom onset had abnormal findings; 74 (76.3%) had late gadolinium enhancement, 54 (55.7%) had myocardial edema, and 49 (50.5%) met Lake Louise criteria for myocarditis.

"These data suggest that most cases of suspected COVID-19 vaccine–related myocarditis in people younger than 21 are mild and resolve quickly," corresponding author Dongngan Truong, MD, Division of Pediatric Cardiology, University of Utah and Primary Children's Hospital, Salt Lake City, said in a statement.

"We were very happy to see that type of recovery. However, we are awaiting further studies to better understand the long-term outcomes of patients who have had COVID-19 vaccination–related myocarditis. We also need to study the risk factors and mechanisms for this rare complication," Dr. Truong added.

Dr. Lloyd-Jones said these findings support the AHA's position that COVID-19 vaccines are "safe, highly effective, and fundamental to saving lives, protecting our families and communities against COVID-19, and ending the pandemic."

The study received no funding. Dr. Truong consults for Pfizer on vaccine-associated myocarditis. A complete list of author disclosures is available with the original article. ■

NEWS FROM CHEST

In Memoriam

Edward C. Rosenow III, MD, Master FCCP

Past President (1989-1990) of the American College of Chest Physicians, leader, educator, mentor, and friend, Dr. Ed Rosenow died on December 21, 2021, in Rochester, Minnesota. He was a compassionate and humble man who believed that physicians are given a gift by being invited into a patient's life to make a difference – a lesson that he applied and taught throughout his career.

Dr. Rosenow joined the Mayo Clinic in 1966 as a consultant in Internal Medicine (Thoracic Diseases). His distinguished career in pulmonary and critical care medicine spanned 31 years at Mayo, marked by his deep commitments to medical education and patient care. Ed's leadership positions included President of the Mayo Clinic Staff and Chair of the Division of Pulmonary and Critical Care Medicine. He will be remembered as the ultimate educator and mentor, who influenced the lives and professions of innumerable physicians. Among his many accolades and awards at Mayo, his most cherished was the Mayo Clinic Karis (caring) Award, which is given to staff who live the Mayo Clinic Values in an extraordinary way.

Ed joined CHEST in 1968, and he went on to take his place as a remarkable and memorable leader for the organization. His multitude of honors and distinguished roles, far too numerous to list here, included CHEST President, Master Fellow, Co-founder and President of The CHEST Foundation, and an Endowed Master Teacher Honor Lecture award created in his name. So many other selfless and dedicated commitments of his time and expertise are witness to his passion for fostering the development of physicians-in-training and improving patient care.

Dr. Rosenow

CHEST extends heartfelt condolences to Dr. Rosenow's wife of 64 years, Connie Grahame Rosenow, the Rosenow family, and many friends and colleagues.

A personal reflection from two close colleagues and long-time friends of Dr. Rosenow will be shared in the March issue of *CHEST Physician*. ■

NETWORKS

Get to know your new Networks' leadership

Last month, we introduced the new Networks structure. This month, we invite you to get to know your new Networks leadership. Under the new structure, previously defined steering committees are now known as Sections.

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

We're pleased to introduce your new Network Chairs, who are dedicated to advancing and promoting the specialty areas of interest that matter to you.

Dr. Blaivas

Airway Disorders Network Chair

Allen Blaivas, DO, FCCP, is a clinical assistant professor at Rutgers University Medical School and the Medical Director, Sleep Services at VA New Jersey Health Care System. Dr. Blaivas chaired the previous Airway Disorders Network Steering Committee from 2020-2021. Under his leadership, the group published several articles and infographics for the COVID-19 Task Force and *CHEST Physician*. His clinical research interests include obstructive sleep apnea and COPD.

Dr. Carroll

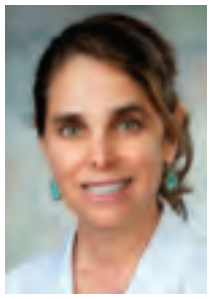
Critical Care Network Chair

Christopher Carroll, MD, FCCP, is the Medical Director, Surgical Critical Care and Research Director, Pediatric Critical Care at the Connecticut Children's Medical Center. Dr. Carroll chaired the previous Critical Care Network Steering Committee from 2019-2021 and has been a long-time champion of the Networks and a leader in a myriad of other CHEST committees. He is passionate about using social media as a tool for education.

Dr. Restrepo

Chest Infections & Disaster Response Network Chair

Marcos Restrepo, MD, PhD, FCCP, is a professor of medicine and the Associate Program Director of the Pulmonary/Critical Care Medicine Fellowship Program at the University of Texas Health Science Center at San Antonio. He is also an investigator and Medical Director of the Medical Intensive Care Unit at the South Texas Veterans Health Care System. Dr. Restrepo chaired the previous Chest Infections Network Steering Committee from 2019-2021. He is also a member of the *CHEST* Journal Editorial Board for Chest Infections.



Dr. Levine

Diffuse Lung Disease & Lung Transplant Network Chair

Deborah Jo Levine, MD, MS, FCCP, is a professor of medicine and the Medical Director, Lung Transplant and Director of the Pulmonary Hypertension Center at University of Texas Health Science Center at San Antonio. Dr. Levine has been involved with the Networks for 10 years. She chaired the Lung Transplant Network Steering Committee from 2012-2014 and was a member of the Pulmonary Vascular Disease Network Steering Committee from 2019-2021. Her interests include evaluation and therapy for antibody-mediated rejection in lung transplantation, and PH.

Dr. Bowton

Pulmonary Vascular & Cardiovascular Network Chair

David Bowton, MD, FCCP, is the Professor Emeritus, Critical Care Section, Department of Anesthesiology at Wake Forest Baptist Medical Center. He has a long history of serving the Networks. He was a member of the Critical Care Network Steering Committee and chair of both the Respiratory Care Network from 2017-2019 and the Cardiovascular Medicine & Surgery Network Steering Committee from 2019-2021. He further served as member of the Executive Committee of the Council of Networks from 2017-2021. Pneumonia, clinical reasoning, and improving processes in critical care are a few of his clinical and research interests.

Dr. D'Ambrosio

Sleep Medicine Network Chair

Carolyn D'Ambrosio, MD, FCCP, is an associate professor of medicine and Vice Chief for Fellowship Training in the section of Pulmonary Critical Care at Yale School of Medicine. She served as the Women's Lung Health Network Chair from 2017-2019 and as a member of the Sleep Medicine Network Steering Committee from 2012-2016. Dr. D'Ambrosio's current tenure as a CHEST FoundationTrustee and Chair of the Women & Pulmonary Work Group will also help guide and inform the Network going forward.

Dr. Tanner

Thoracic Oncology & Chest Procedures Network Chair

Nichole Tanner, MD, FCCP, is a professor of medicine at Medical University of South Carolina and a pulmonologist at the Ralph H. Johnson VA Medical Center. She most recently chaired the Thoracic Oncology Network Steering Committee from 2020-2021 and served on the Executive Committee of the Council of Networks. Dr. Tanner has been active with the Thoracic Oncology group since 2015. Her academic focus is on lung cancer and translational research.

If you are interested in serving on a Network Section, keep an eye out for our annual Call for Committee Applications opening this spring.

Here are ways to stay (or get) involved with the Networks:

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

Visit the new Network webpages at *chestnet.org/networks*. ■

INDEX OF ADVERTISERS

Past President's perspective

BY STEVEN Q. SIMPSON, MD, FCCP

It's January 1, 2022, as I write, and my CHEST presidency came to an end last night as the fireworks lit up the sky. With COVID-19 waxing and waning across the United States and around the world, I have been a wartime president. CHEST has not been able to do a number of the things that we would normally have done in person, including that there has not been an in-person CHEST annual meeting during my entire presidency. We have, nonetheless, achieved some important things that I will share with you.

If you're a typical CHEST member, you probably don't spend a lot of time wondering about CHEST's finances, nor should you. Nevertheless, CHEST - your organization - does have to be fiscally responsible if we desire to continue our educational and research missions, and that is the job of your Board of Regents, your presidents, and your professional staff at the CHEST headquarters. I'm happy to tell you that your organization is in healthy financial condition, in spite of a challenging economic environment and, being forced into remote, online annual meetings and board reviews for 2 years. What that means to us and to you is that we get to maintain and improve our full array of educational activities, including our annual meeting, our journal, our board reviews, our hands-on courses at the CHEST headquarters, and our web content. And, we get to accelerate our advocacy activities for our patients and for the clinical folks who care for them (us!). CHEST is primed for emerging from this pandemic stronger, because we have had to make the most of every dollar we have, and more innovative, because that's how we have done it. We are ready for new ways of interacting and for innovative new ways of delivering education, sponsoring research, fostering networking, and leading in the clinical arena of chest medicine.

During my time as CHEST President, many of us have become progressively more aware of the blatant inequities that continue in society – and, yes, even in medicine. Perhaps more than anything, it both saddens and angers me when anyone values or devalues someone else's life because of the color of their skin, who they feel attracted to or love, the sex they were born with or their knowledge that nature gave them the wrong physical characteristics for their gender, what physical impairments they have, where they were born, where they were educated - or not, what language is their first language, or what opportunities they were presented with in their lives.

Everyone deserves the opportunity to be who and what they are and to be respected for who they are.

Dr. Simpson

Everyone deserves the opportunity to be who and what they are and to be respected for who they are, and everyone deserves the opportunity to excel. The strongest collaborations have diverse constituents with unified goals, and I want for CHEST to be among the strongest of professional collaborations. It has been deeply important to me during my presidency to champion these values, and we have worked hard to make CHEST an inclusive and diverse organization. Much remains to be done, but we did make some good progress this year.

We established a spirometry working group to look at the science around race-based adjustments for normal values, to call out if there are mistakes or omissions in that approach, and to propose the work that needs to be done to correct them. We invited the American Thoracic Society and the Canadian Thoracic Society to join us in this effort. Race is a social construct, not a physiologic principle, and some data suggest that apparent differences in physiology could actually reflect differences in socioeconomic status of study participants. In similar work, our nephrology colleagues demonstrated that apparent differences in normal glomerular filtration rate (GFR) are related to socio-economic and health care access issues; they called for labs to no longer report race-based norms for creatinine and GFR values. Our colleagues believe that race-based GFR norms have harmed patients by promoting delay in treatments aimed at preventing dialysis or by causing delays in the initiation of dialysis. In our world, asbestos companies have argued that African American and other populations of color should receive lower asbestosis settlements on the basis that they began with lower predicted lung function and, therefore, had been less damaged by exposure to asbestos. I am very interested to see our working group's output. I think it could result in landmark changes in our evaluation and treatment of patients with lung diseases.

A very important undertaking for us this year was a top to bottom analysis of our own practices around diversity, equity, and inclusion. We started by taking lessons from the CHEST Foundation-sponsored listening tour across the nation. Many of our patients of color lack adequate access to the care they need, which informs our efforts in advocacy and health policy. We also learned that, as a profession, we have not earned the trust of our patients of color, and we must take steps to remedy that. CHEST began this effort by developing the First 5 Minutes program, which teaches all of us how to take the first moments of our interactions with patients to enhance our empathy and to establish trusting relationships with them. You will hear more about this program in the months to come.

CHEST is dedicated to ensuring that all of our members have equitable opportunities to take part in our learning activities, both as participants and as developers. Likewise, we want any member who desires to advance in our organization to have wide open opportunity to develop and use their skills. We hired a consulting firm who specializes in aiding nonprofits with their diversity, equity, and inclusion goals to help us find our weaknesses in that area. They spent several months interviewing members at all stages of their careers and in a variety of job types, with the goal of determining what it is like to be a CHEST member of color, a woman, a member of the LGBTQIA community, or a member of any group that has been made to feel "other." We are currently working to turn their findings into concrete steps to make CHEST the most diverse and inclusive medical society possible. Finally, our consultants are helping us to ensure that the people we hire to work for our organization full time have equitable opportunities in their workplace, and that CHEST headquarters feels inclusive and is diverse for them.

COVID-19 rages on. In fact, daily case numbers at this writing are skyrocketing, higher than at any time during the pandemic, and hospitalization rates, while lower than with some of the previous waves, are following. Many of us are stressed, and in many of our ICUs, we have fewer nurses than we did at the outset of the pandemic. The CHEST COVID-19 task force continues on the job, though, with fresh content to match the current circumstances. These dedicated individuals, who I recognized with a Presidential Citation for 2021, have worked since the early days of the pandemic to scour the literature and the landscape to find the right data and the right experts to inform the topical infographics, reviews, webinars, and podcasts that are freely available to all and are posted on the CHEST website (https://tinyurl.com/3e9cps3s). I hope that you have availed yourself of the material

PERSPECTIVE *continued on following page*

CHEST President takes you behind the scenes with "Piece by Piece"

Dr. Schulman

CHEST President David Schulman, MD, MPH, FCCP (https://tinyurl.com/2dsbyvdn), begins his term by sharing new ways to make CHEST more accessible to all. Through a monthly email, Dr. Schulman will highlight key CHEST priorities and introduce you to a wide variety of members in his video and podcast series, Piece by Piece. Listen as the participants discuss their journey in medicine, their passions, and how they got involved with CHEST. Watch the first video (https://tinyurl.com/kuxeys66). ■

PERSPECTIVE *continued from previous page*

there, and, if not, you have missed some valuable learning opportunities. Missed them in real time, that is; they are all on the site for you to use at will. We are optimistic that someday soon, there will be less of a need for the COVID-19 task force, but the members are all ready to continue their work until that time comes..

I've highlighted just a few of the higher profile things that CHEST achieved in 2021. It would be impossible for me to cover all that CHEST has accomplished this past year. My sources tell me that during my presidency, we generated, signed on, or declined to join nearly 100 advocacy statements on topics ranging from recall of home CPAP machines to access to appropriate supplemental oxygen for patients with interstitial lung disease, to the acquisition of a nebulizer company by a tobacco company. We held successful board review sessions and repeated our all online, yet interactive, version of the CHEST annual meeting, with more than 4,000 total attendees – not as large as an in-person meeting, but not terribly far off, either. I will add that our program chairs and their committee pivoted from a meeting in Vancouver to a meeting in Orlando to, with only 6 weeks' notice, a meeting in the ether. We are fortunate to have worked with such talented and dedicated individuals, and all of us owe them a lot for their efforts.

If, as I say, I have been a wartime president, then the worldwide viral pandemic that directly affects those of us in chest medicine has been the war. In spite of the current tsunami of cases, I am optimistic that the war ends relatively soon. CHEST will not simply return to normalcy, though. Dr. David Schulman, a brilliant and innovative educator, has taken the leadership reins of the organization, and I foresee exhilarating times ahead.

We are making it through a challenging environment, and CHEST is stronger for it. I will look forward to seeing all of you in Nashville, when we, at long last, can look one another in the eye, shake one another's hand, and enjoy the experience of the CHEST annual meeting together. And if you don't mind me asking, when you see me in Nashville, will you please do exactly that? ■

PULMONARY PERSPECTIVES®

Inhaled corticosteroids for COVID-19

BY AARON HOLLEY, MD, FCCP

Dr. Holley is Program Director, Pulmonary and Critical Care Medicine Fellowship; and Associate Professor of Medicine USU, Walter Reed National Military Medical Center, Bethesda, Maryland. He also serves as Section Editor for Pulmonary Perspectives®.

Since the onset of the pandemic, the role for corticosteroids (CS) as a therapy for COVID-19 has evolved. Initially, there was reluctance to use oral corticosteroids (OCS) outside of COVID-19-related sepsis or acute respiratory distress syndrome (ARDS). This was in keeping with community-acquired pneumonia (CAP) guidelines (Metlay JP, et al. *Am J Respir Crit Care Med.* 2019; 200:e45-e67) and reflected concerns that OCS might worsen outcomes in viral pneumonias. At my hospital, the reluctance to use OCS was extended to inhaled corticosteroids (ICS), with early protocols advising cessation in patients with COVID-19.

In fairness, the hesitation to use ICS was short-lived and reflected attempts to provide reasonable guidance during the early pandemic data vacuum. Over time, OCS therapy has gained acceptance as a treatment for moderate-to-severe COVID-19. On top of this, the relationship between COVID-19 and asthma has proved to be complicated. It seemed intuitive that asthmatics would fair worse in the face of a highly transmissible respiratory pathogen. Data on COVID-19 and asthma provide a mixed picture, though. It also appears that the interaction varies by phenotype (Zhu Z, et al. *J Allergy Clin Immunol.* 2020;146:327-329).

Improvements with OCS and the complicated interaction between COVID-19 and asthma led some to speculate that ICS, the primary treatment for asthma, may actually be protective. There is biologic plausibility to support this concept. Generally, we've seen a variety of immunomodulators show efficacy against moderate or severe disease. Specific to ICS, data have shown a down-regulation in COVID-19 gene expression and reduction in proteins required by the virus for cell entry. This includes a reduction in the evil, much maligned ACE-2 receptor (Peters M, et al. *Am J Respir Crit Care Med.* 2020;202:83-90).

Like much with COVID-19, the initial asthma phenotype and ICS data were observational and hypothesis-generating, at best. More recently, a series of randomized trials has tested the effects of ICS in patients with milder forms of COVID-19. The data are promising and are worth a thorough review by all physicians caring for COVID-19 outside of the hospital.

The STOIC trial (Ramakrishnan S, et al. Lancet Respir Med. 2021;9:763–772) randomized 146 patients to budesonide via dry powder inhaler (DPI), 800 ug twice per day (BID), versus usual care. The primary outcome was clinical deterioration, defined as presentation to acute or emergency care or need for hospitalization. There was a number of secondary outcomes designed to assess time-to-recovery, predominantly by self-report via questionnaires. The results were nothing short of spectacular. There was a significant difference in the primary outcome with a number-needed to treat (NNT) of only 8 to prevent one instance of COVID-19 deterioration. A number of the secondary outcomes reached significance, as well.

The PRINCIPLE trial, only available in preprint form (https://tinyurl.com/mr4cah7j), also randomized patients to budesonide via ICS vs usual care. PRINCIPLE is one of those cool, adaptive platform trials designed to evaluate multiple therapies simultaneously that have gained popularity in the pandemic era. These trials include predefined criteria for success and futility that allow treatments to be added and others to be dropped. The dosage of budesonide was identical to that in STOIC, and, again, it was delivered via DPI. By design, patients were older with co-morbidities, and there were two primary outcomes. The first was a composite of hospitalization and death, and the second was time to recovery.

The PRINCIPLE preprint is only an interim analysis. There were 751

COVID-19 *continued on following page*

Optimal NIV Medicare access promotion – a hopeful way forward for users of NIV

BY NANCY COLLOP, MD, MASTER FCCP

Use of positive airway pressure (PAP) devices for treatment of sleep apnea was first described in 1981. Subsequent use of PAP devices expanded to treat patients with respiratory failure. While the treatment in this population has rapidly gained widespread use and undoubtedly has reduced morbidity and mortality in these populations, policies governing these prescriptions have not really kept up with the burgeoning need.

In 2020, Drs. Peter Gay and Robert Owens brought together a technical expert panel (TEP) to systematically review the CMS policies with an eye to remove "regulatory barriers" to improve access for these patients with the mantra: "the right device gets to the right patient at the right time."

The panel focused on "Optimal NIV Medicare Access Promotion (ONMAP)," and members with specific expertise were recruited for five patient groups: Thoracic Restrictive Disorders (TRD), COPD, Central Sleep Apnea (CSA), Hypoventilation Syndromes (HVS), and Obstructive Sleep Apnea (OSA). Each group reviewed the current coverage, outlined the deficiencies, and suggested revisions. Herein, I will briefly highlight each group's most important points.

TRD: The goal for this group was to bring the US standards of care closer to the rest of the world. This group advocates that the start of noninvasive ventilation (NIV) should be substantially earlier, to provide the largest improvement in disease outcome and stability. Other prominent features submitted included arterial blood gases (ABG) to not be the only form of CO_2 measurement allowed; paying for a second device if patients are using NIV continuously; qualification for a BiPAP to include if vital capacity is ≤ 80%; and, to obtain a home mechanical ventilator, a patient must either fail BiPAP or have extreme loss of function, high pressure requirements, or need mouthpiece ventilation.

CSA: The big challenges with this diagnosis related to qualifying coverage language in the current policies, which are confusing for many providers. Additionally, these policies often deny certain PAP devices and/or oxygen therapy. The group proposed: a single definition of CSA; eliminate discussion of hypoventilation; mirror qualifying symptoms, and, continuing coverage, to the same as that for OSA treatment; and remove need for a prior failure of BiPAP without a backup rate (BUR). The group also had specific recommendations for when oxygen therapy should be covered in patients with CSA.

Dr. Collop

COPD: This group also focused on the oxygen therapy and promoting use of devices with a BUR. Two problematic areas included the requirement that nocturnal oxygen saturation must drop to ≤ 88% for at least 5 cumulative minutes, and, that patients must begin with an S mode device (no BUR) for at least 2 months and can only then be prescribed a device with a BUR if CO_2 fails to drop. The group advocates for the removal of both, the need for a nocturnal oximetry test, and, to "try" an S mode device. The panel advocated giving the prescribing physician discretion in making this determination. The panel also provided recommendations on when a home mechanical ventilator (HMV) should be considered instead of BiPAP therapy.

HVS: Hypoventilation syndromes are a heterogeneous group of disorders with hypercapnia, defined as a $PaCO_2$ ≥45 mm Hg. This panel noted that the current coverage criteria are outdated and fail to recognize the spectrum of disease severity and advances in technology, which often leads to circumvention by prescribing more costly home mechanical ventilators (HMV). Consistent with the TRD group, this panel recommended acceptance of surrogate noninvasive end tidal and transcutaneous PcO_2 and venous blood gases in lieu of arterial blood gases. Additionally, they suggested no longer requiring CO_2 measures while using prescribed oxygen; eliminating the need for a sleep study to avoid delays in care for patients being discharged from the hospital; removing spirometry as a requirement; and no longer a failure of BiPAP without a BUR.

OSA: The initial purpose of examining OSA in this process was to examine when BiPAP should be utilized for treatment; however, it necessitated examination of the entire policy for PAP. The areas that were identified as needing revision included: expansion of the symptom list for patients with OSA; revising the "4 hour rule," suggesting that 2 hours has been proven to provide benefit; eliminating the need for another sleep study to re-qualify for PAP or supplemental oxygen; and embracing telehealth as a way to improve accessibility for follow-up visits.

For details, please review the papers published in the November 2021 issue of the journal *CHEST*® (2021; 160[5]:1579-1990, e377-e543).

We now await what CMS will do with our recommendations and work for "the right device to the right patient at the right time." ■

Acknowledgment: Drs. Gerald Criner, Nicholas Hill, Babak Mohklesi, Timothy Morgenthaler, and Lisa Wolfe assisted with the content.

COVID-19 *continued from previous page*

and 1,028 patients who received budesonide and usual care, respectively. Time to recovery was significantly shorter in the budesonide group, but budesonide failed to meet their prespecified criteria for reducing hospitalization/death. The authors noted that the composite outcome of hospitalization or death did not occur at the rates originally anticipated, presumably due to high vaccination rates. This may have led to type II error.

In a third trial published online in November (Clemency BM, et al. JAMA Intern Med. 2021;10.1001/jamainternmed.2021.6759), patients were randomized to 640 micrograms per day of the ICS ciclesonide. Delivery was via metered-dose inhaler (MDI) for a total duration of 30 days. Unlike the STOIC and PRINCIPLE trials, this one wasn't open label. It was blinded and placebo-controlled. The investigators found no difference in their primary outcome, time to resolution of symptoms. Ciclesonide did reduce the composite secondary outcome of ED visits or hospital admissions. The number needed to treat was 23.

Please indulge me while I overreact. It seems we've got a positive signal in all three. In the era of the Omnicron variant and limited health resources, a widely available therapy that curtails symptoms and prevents acute care visits and hospitalizations could have a tremendous impact. It doesn't require administration in a clinic and, in theory, efficacy shouldn't be affected by future mutations of the virus.

A more sober look mutes my enthusiasm. First, as the authors of the ciclesonide article note, open-label trials tracking subjective outcomes via self-assessment can be prone to bias. The ciclesonide trial was double-blinded and didn't find a difference in time to symptom resolution, only the two open-label trials did. Second, the largest study (PRINCIPLE) didn't show a difference in escalation of care.

Given, they defined "escalation" as hospitalization or death, and vaccines and patient selection (enrolled only outpatients with mild disease) made proving a statistical reduction difficult. However, in the text they state there wasn't an improvement in "health care services use" either. In essence, the largest trial showed no change in escalation of care, and the trial with the best design did not show reduction in symptoms.

Although three randomized trials are enough for the inevitable meta-analysis that'll be published soon; don't expect it to shed much light. Combining data won't be particularly helpful because the PRINCIPLE trial is larger than the other two combined, so its results will dominate any statistical analysis of combined data. Not to worry though – there are several more ICS COVID-19 trials underway (NCT04355637, NCT04331054, NCT04193878, NCT04330586, NCT04331054, NCT04331470, NCT04355637, NCT04356495, and NCT04381364). Providers will have to decide for themselves whether what we have so far is sufficient to change practice. ■

CRITICAL CARE COMMENTARY

The Rapid Shallow Breathing Index and liberation from mechanical ventilation

BY VATSAL TRIVEDI, MD, AND KAREN E.A. BURNS, MD, MSC

Patients recovering from respiratory failure requiring invasive mechanical ventilation typically undergo spontaneous breathing trials (SBTs) to assess their ability to breathe on minimal (eg, pressure support [PS] with positive end-expiratory pressure [PEEP], continuous positive airway pressure [CPAP]) or no support (eg, T-piece). Once a patient has passed an SBT, they are considered liberated from the ventilator. However, a separate assessment (ability to clear and mobilize secretions, protect airway, etc) is needed to assess whether a patient is ready to be liberated from the endotracheal tube.

The Rapid Shallow Breathing Index (RSBI) is one of the parameters that can be used by clinicians to assess an individual patient's readiness to undergo an SBT. Discussion of the role of the RSBI as a tool to predict SBT success or extubation success would be remiss without mentioning the seminal prospective observational study conducted by Yang and Tobin (Yang KL, Tobin MJ, *N Engl J Med*. 1991;324(21):1445-1450). The investigators calculated the RSBI as the ratio between frequency of breaths (f) and tidal volume in liters (Vt) using a Wright's spirometer in 100 patients. Whereas weaning success in this study was defined as the ability to maintain spontaneous ventilation for at least 24 hours after extubation, weaning failure was defined as the need (using objective and subjective criteria) to be reconnected to the ventilator at the end of a weaning trial or the need for reintubation within 24 hours of extubation. They found that an RSBI < 105 was 97% sensitive and 64% specific for predicting weaning failure, with the latter metric suggesting that there are some false positive test results. In the subgroup analysis of patients who had a duration of mechanical ventilation of less than 8 days, the investigators found that an RSBI < 105 was 100% sensitive and 63% specific for weaning failure. While these initial results showed promise for the use of RSBI as a predictive metric, it is important to note how the primary outcome was defined and reported in this study.

Following the initial description of the performance characteristics of the RSBI, several studies were conducted to validate these findings. A meta-analysis published by Meade and colleagues found that an RSBI < 105 was associated with a small pooled positive Likelihood Ratio of 1.49 (Meade M, et al. *CHEST*. 2001;120(6 Suppl):400S-424S) for predicting extubation success. An international survey of mechanical ventilation discontinuation practices of 1,144 intensivists in six regions found that only 32.2% of respondents used an RSBI threshold of 105 or less to proceed to an SBT and 50.7% did not consider or use the RSBI to evaluate SBT readiness (Burns KEA, et al. *Ann Am Thorac Soc*. 2018;15(4):494-502).

To assess whether the evidence base has changed over the past 20 years to support use of RSBI as a measure of extubation success, we conducted an updated meta-analysis of 48 studies (n=10,946 observations) (Trivedi V, et al. *CHEST*. 2022;161(1):97-111). In our study, we identified moderate pooled sensitivity (0.83; moderate certainty), poor specificity (0.58; moderate certainty), and a diagnostic odds ratio (DOR) (5.9) of an RSBI < 105 for predicting extubation with significant heterogeneity (P = 95%). Although we noted practice variation in the timing of RSBI measurement (before, during, or at the end of SBT completion) and how RSBI measurements were made (PS vs CPAP vs T-piece), the sensitivity of pooled RSBI measurements was comparable across selected subgroups, including

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RSBI thresholds of <80 (sensitivity, 0.84) and RSBI measurements made on T-piece (sensitivity, 0.83) and PS (sensitivity, 0.83). Similarity, the specificity of pooled measurements was comparable among selected subgroups, including studies enrolling only patients with chronic obstructive pulmonary disease, using RSBI thresholds < 80, and including RSBI measurements made on T-piece and at the end of an SBT.

To this end, we did not identify credible subgroup effects based on patient characteristics, measurement techniques, timing of RSBI measurement, or different RSBI thresholds. Sensitivity analyses based on individual study risk of bias also did not explain the heterogeneity noted in our pooled estimates. As a standalone test, these data suggest that the RSBI has only moderate predictive ability to rule out extubation success and does not adequately predict successful extubation.

At present, considerable controversy remains regarding the best SBT technique for clinicians to utilize to conduct SBTs. A recent meta-analysis comparing all alternative SBT techniques found that trials have most often compared CPAP with T-piece SBTs and PS with T-piece SBTs. In pooled analyses, patients who underwent PS vs T-piece SBTs were equally likely to pass an SBT, but patients who underwent PS (vs T-piece) SBTs were 6% more likely to be successfully extubated, with a number needed to treat (NNT) of 22 (Burns KEA, et al. *Crit Care*. 2017;21(1):127). The authors postulated that additional PS during an SBT may not only overcome the resistance of the endotracheal tube but may also compensate for clinicians "reluctance to extubate."

A large, randomized control trial conducted in 18 ICUs in Spain (n=1153) compared shorter SBTs (30 minutes) performed with PS with longer SBTs (120 minutes) performed with T-piece. The authors found an absolute increase in successful extubation of 8.2% favoring the shorter and less-demanding strategy (30-min PS SBTs) with similar reintubation rates (Subira C, et al. *JAMA*. 2019;321(22):2175-2185). These findings may, at least in part, be explained by a physiologic review that identified that SBTs conducted on PS reduced work of breathing to a larger extent than SBTs conducted on CPAP or T-piece (Sklar MC, et al. *Am J Resp Crit Care Med*. 2017;195(11):1477-1485).

The poor performance characteristics of the RSBI in predicting successful extubation suggests that additional factors may be important in predicting extubation outcome (success/failure). For example, the predictive ability of the RSBI may be influenced by the patient cohorts in which it was evaluated and their duration of exposure to invasive mechanical ventilation – factors that could best be explored in an individual patient meta-analysis. In addition, there was considerable variation in the criteria (subjective, objective) used to assess and report outcomes such as weaning success/failure and extubation success/failure. It is also important to acknowledge the difference between successful completion of an SBT (signaling liberation from the ventilator) and extubation success, with the later outcome heralding successful liberation from the endotracheal tube but being hopelessly confounded by successful liberation from the ventilator. As a brief and dynamic measure of respiratory mechanics, the RSBI may be particularly well-suited to determining suitability of patients to undergo an SBT but may not be a sufficient standalone test to predict successful extubation. One potential role for the RSBI may be to aid in identifying which patients, who meet conventional permissive criteria to undergo an SBT, should be subjected to a formal SBT. This rapid assessment may be particularly helpful before conduct of a T-piece SBT, which requires assembling a T-piece circuit and disconnecting the patient from the ventilator and its alarms.

Future research should evaluate the role of the RSBI as a permissive criterion to undergo a SBT and its impact on SBT outcome (passing/failing an SBT), as opposed to extubation outcome, especially for patients who are at intermediate pretest probability of passing an SBT. ■

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Editor's comment: Physicians in the intensive care unit are faced with the daily challenge of liberating patients from mechanical ventilation. We know that the longer patients receive mechanical ventilation, the higher the mortality rate. The counterpoint to this is that a failed extubation attempt describes a cohort of patients who have a very high mortality rate.

The spontaneous breathing trial (SBT) represents a commonly used assessment tool in this decision-making process. Trivedi and his colleagues provide valuable information demonstrating that the rapid shallow breathing index (RSBI) obtained during the SBT has limitations when used as a sole decision-making metric. Physicians must use careful global judgement when interpreting the results of an SBT while awaiting the outcomes of further research.

Daniel Ouellette, MD, FCCP, Section Editor

Blog, tweet, and share to expand your clinical reach

Social media is a powerful tool clinicians should be using to combat misinformation, engage with patients, and share data. In the Social Media, Digital Scholarship, Teaching Portfolios: Everything You Wanted to Know session at CHEST 2021, speakers discussed how a strong social media presence can be used on a CV to leverage academic promotions and tenure. Read more in the CHEST Daily News (https://tinyurl.com/yc6bbu8e) about this session. CHEST 2021 registrants can access the session recording (https://tinyurl.com/mrvnnwsw) until October 1, 2022. ■

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Editor in Chief

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By Dr. P. Maisonneuve, et al.

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