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CHEST® Physician

THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Mitchel L. Zoler/MDedge News

Dr. Joshua B. Goldberg

Pulmonary embolism incidence nearly doubled over 2004-2015

MITCHEL L. ZOLER
MDedge News

NEW ORLEANS – The incidence of pulmonary embolism diagnosed in hospitalized U.S. patients nearly doubled during the period 2004-2015 based on data collected by the National Inpatient Sample.

During 2004-2015 the incidence of all diagnosed pulmonary embolism (PE), based on discharge diagnoses, rose from 5.4 cases/1,000 hospitalized patients in 2004 to 9.7 cases/1,000 hospitalized patients in 2015, an 80% increase, Joshua B. Goldberg, MD, said at the annual meeting of the American College of Cardiology. The incidence of major PE – defined as a patient who needed vasopressor treatment, mechanical ventilation, or had nonseptic shock – rose from 7.9% of all hospitalized PE diagnoses in 2004 to 9.7% in 2015, a 23% relative increase.

The data also documented a shifting pattern of treatment for all hospitalized patients with PE, and especially among patients with major PE. During the study period, treatment with systemic thrombolysis for all PE rose nearly threefold, and catheter-directed therapy began to show a steady rise in use from 0.2% of all patients in 2011 (and before) to 1% of all patients by 2015. Surgical intervention remained lightly used throughout, with about 0.2% of all PE patients undergoing surgery annually.

PULMONARY EMBOLISM // *continued on page 6*

PAP cut all-cause mortality in obese patients with severe OSA

BY ERIK GREB
MDedge News

The prescription of positive airway pressure is associated with reduced all-cause mortality, according to the results of a cohort study published in JAMA Otolaryngology–Head & Neck Surgery.

The association becomes evident several years after positive airway pressure (PAP) initiation, according to the researchers. Obstructive sleep apnea (OSA) is among the top 10 modifiable cardiovascular risk factors, and is associated with increased risks of coronary artery disease, stroke, and death. PAP is the most effective treatment for OSA, but this treatment's effect on all-cause and cardiovascular mortality is uncertain. Randomized trials have yielded inconclusive answers to this question, and evidence from observational studies has been weak.

To investigate the association between PAP prescription and mortality in patients with obesity and severe OSA, Quentin Lisan, MD, of the Paris Cardiovascular Research Center and his colleagues conducted a multicenter, pop-

PAP // *continued on page 7*

INSIDE HIGHLIGHT

NEWS FROM CHEST

SLEEP STRATEGIES
The role of sleep-related hypoxia

Page 56

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Medicare HF readmission penalty sparks concern

BY MITCHEL L. ZOLER
MDedge News

NEW ORLEANS – Mounting evidence shows that heart failure patient mortality increased as an unintended consequence of a Medicare program that penalizes hospitals with too many 30-day readmissions of heart failure patients. This has prompted discussions among cardiologists, Medicare officials, and other stakeholders in an attempt to modify the penalty program so it no longer considers just readmissions but instead bases penalties on broader and more nuanced measures of patient outcomes.

Staffers at the Centers for Medicare & Medicaid Services, the federal agency that manages Medicare, "said that they take this seriously and will look into it, and they are interested in next-generation measures that are

more patient centered" than simply the 30-day readmission rate, Gregg C. Fonarow, MD, said in an interview at the annual meeting of the American College of Cardiology. "This is a case where there is credible evidence of increased mortality that is consistent, reproducible, and strongly associated with the penalty and cannot be otherwise explained," said Dr. Fonarow, professor of medicine and cochief of cardiology at the University of California, Los Angeles.

He is among the most active researchers to document that, while CMS's Hospital Readmissions Reduction Program (HRRP) led to significantly reduced readmission rates in patients with heart failure, this came at a cost of a significant increase in mortality among the same patients. For example, an article he published in 2018 that analyzed more than 115,000 Medicare beneficiaries during 2006-2014 showed that during the penalty phase, which began in 2012, readmissions fell after adjustment by a relative 8%, but adjusted mortality rose by a relative 10%, compared with how patients had fared prior to launching the HRRP (JAMA Cardiol. 2018 Jan;3[1]:44-53). Recent reports from other research groups have had similar findings, such as a study of more than 3 million Medicare beneficiaries with heart failure during 2005-2015 that also showed significantly increased mortality after the penalty phase for readmissions began (JAMA. 2018 Dec 25;320[24]:2542-52). In a commentary that accompanied this report, Dr. Fonarow cited the multiple analyses that show consistent findings and the need for CMS to "initiate an expeditious reconsideration and revision" of their current approach to penalizing hospitals for heart failure readmissions (JAMA. 2018 Dec 25;320[24]:2539-41).

Dr. Fonarow

The groups recently in discussion with CMS about this issue include the American College of Cardiology, the American Heart Association, the Heart Failure Society of America, the American College of Physicians, the American Hospital Association, and several other medical professional groups, said Biykem Bozkurt, MD, who has worked with Dr. Fonarow and representatives from these organizations in talks with CMS.

"We are trying to find a harmonized approach with patient-centric outcomes that reflect true improvements in quality of care," she said in an interview. One possibility up for consideration is a combined measure of heart failure readmissions, mortality, and a patient-reported outcome. The measure would go to CMS directly from each patient's electronic medical record, making data collection less burdensome to clinicians, said Dr. Bozkurt, professor of medicine at Baylor College of Medicine and cardiology section chief at the VA Medical Center in Houston. She expressed hope that a change in the CMS metric might happen later this year.

"CMS can't simply stop the HRRP, so the discussion is on how to get a meaningful change. I'm increasingly optimistic, because the findings of harm [from current policies] are impossible to ignore," Dr. Fonarow said. "There will be increasing pressure on CMS to develop a pathway to make modifications. It's egregious to continue a policy that's been associated with harm" to heart failure patients.

Dr. Fonarow and Dr. Bozkurt had no relevant commercial disclosures.

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Pulmonary embolism // *continued from page 1*

Most of these intervention options focused on patients with major PE. Among patients in this subgroup with more severe disease, use of one of these three types of interventions rose from 6% in 2004 to 12% in 2015, mostly driven by a rise in systemic thrombolysis, which jumped from 3% of major PE in 2004 to 9% in 2015. However, the efficacy of systemic thrombolysis in patients with major PE remains suspect. In 2004, 39% of patients with major PE treated with systemic thrombolysis died in hospital; in 2015 the number was 47%. "The data don't support using systemic thrombolysis to treat major PE; the mortality is high," noted Dr. Goldberg, a cardiothoracic surgeon at Westchester Medical Center in Valhalla, N.Y.

Although catheter-directed therapy began to be much more widely used in U.S. practice starting in about 2015, during the period studied its use for major PE held fairly steady at roughly 2%-3%, but this approach also showed substantial shortcomings for the major PE population. These sicker patients treated with catheter-directed therapy had 37% mortality in 2004 and a 31% mortality in 2015, a difference that was not statistically significant. In general, PE patients enrolled in the catheter-directed therapy trials were not as sick as the major PE patients who get treated with surgery in routine practice, Dr. Goldberg said in an interview.

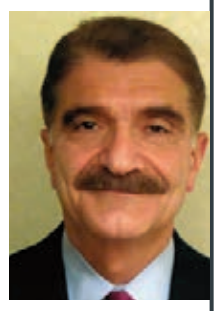
The data showed much better performance using surgery, although only 1,237 patients of the entire group of 713,083 PE patients studied in the database underwent surgical embolectomy. Overall, in-hospital mortality in these patients was 22%, but in a time trend analysis, mortality among all PE patients treated with surgery fell from 32% in 2004 to 14% in 2015; among patients with major PE treated with surgery, mortality fell from 52% in 2004 to 21% in 2015.

Dr. Goldberg attributed the success of surgery in severe PE patients to the definitive nature of embolectomy and the concurrent use of extracorporeal membrane oxygenation that helps stabilize acutely ill PE patients. He also cited refinements that surgery underwent during the 2004-2015 period based on the experience managing chronic thromboembolic pulmonary hypertension, including routine use of cardiopulmonary bypass during surgery. "Very high risk [PE] patients should go straight to surgery, unless the patient is at high risk for surgery because of conditions like prior sternotomy or very advanced age,

Continued on following page

VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments: With an aging population with higher comorbidities, there has been an increase in the incidence of pulmonary embolism (PE) in hospitalized patients and despite the advances in technology, major PE remains a highly lethal disease. Systemic anticoagulation and catheter-directed thrombolysis (CDT) have been advocated for and used by interventionalists (cardiologists, radiologists) for treatment of major PE with varying results from randomized, controlled trials and with survivors having a high chance of developing chronic thromboembolic pulmonary hypertension (CTEPH). Meta-analyses of randomized trials have also shown no major benefit of CDT in stable PE (Blood. 2015;125[14]:2191-9). The argument for the use of thrombolytic therapy as the preferred choice is based on the historical results of surgical intervention for thrombectomy in critically ill and unstable patients. The availability of mechanical circulatory support devices (MCSD) however, has changed the outlook for many patients who are in shock with a failing heart and with a low chance of survival. Already, there are encouraging results with the use of MCSD in the treatment of patients with another highly lethal condition, ie. postinfarction ventricular septal rupture. This should provide impetus for a change in the current practice pattern of considering surgery as the last resort to surgery as the preferred option for emergency surgical embolectomy and cardiac support for the failing heart in patients with major PE and right ventricular dysfunction to accomplish the dual goals of improving their chances of survival and preventing the development of CTEPH.



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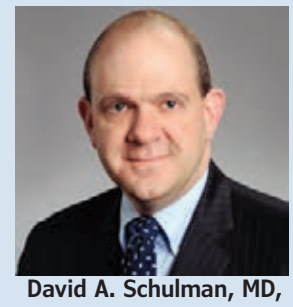

David A. Schulman, MD, FCCP, is Medical Editor in Chief of *CHEST Physician*.

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PAP studied for long-term impact

// *continued from page 1*

ulation-based cohort study. The researchers examined data for 392 participants in the Sleep Heart Health Study, in which adult men and women age 40 years or older were recruited from nine population-based studies between 1995 and 1998 and followed for a mean of 11.1 years. With each participant who had been prescribed PAP, the investigators matched as many as four participants who had not been prescribed PAP, on the basis of age, sex, and apnea-hypopnea index. Of this sample, 81 patients were prescribed PAP, and 311 were not.

All participants had a clinic visit and underwent overnight polysomnography at baseline. At 2-3 years, participants had a follow-up visit or phone call, during which they were asked whether their physicians had prescribed PAP. Participants were monitored for cardiovascular and all-cause mortality.

In all, 319 of the 392 participants were men; the population's mean age was 63 years. Patients who had received a PAP prescription had a higher body mass index and more education, compared with patients who had not received a prescription. Mean follow-up duration was 11.6 years in the PAP-prescribed group and 10.9 years in the nonprescribed group.

A total of 96 deaths occurred during follow-up: 12 in the PAP-prescribed group and 84 in the nonprescribed group. The crude incidence rate of mortality was 24.7 deaths per 1,000 person-years in the nonprescribed group and 12.8 deaths per 1,000 person-years in the PAP-prescribed group. The difference in survival between the prescribed and nonprescribed groups was evident in survival curves after 6-7 years of follow-up. After adjustments for prevalent cardiovascular disease, hypertension, diabetes, body mass index, education level, smoking status, and alcohol consumption, the hazard ratio of all-cause mortality for the prescribed group was 0.38, compared with the nonprescribed group.

Dr. Lisan and his colleagues identified 27 deaths of cardiovascular origin, one of which occurred in the prescribed group. After adjustment for prevalent cardiovascular disease, the hazard ratio of cardiovascular mortality for the prescribed group was 0.06, compared with the nonprescribed group.

One reason that the reduction in mortality associated with PAP was not found in previous randomized, controlled trials could be that their mean length of follow-up was not long enough, the researchers wrote. For example, the mean length of follow-up in the SAVE trial was 3.7 years, but the survival benefit was not apparent in the present analysis until 6-7 years after treatment initiation.

These results are exploratory and require confirmation in future research, Dr. Lisan and his colleagues wrote. No information on adherence to PAP was available, and the researchers could not account for initiation and interruption of PAP therapy. Nevertheless, "prescribing PAP in patients with OSA should be pursued and encouraged, given its potential major public health implication," they concluded.

The Sleep Heart Health Study was supported by grants from the National Institutes of Health.

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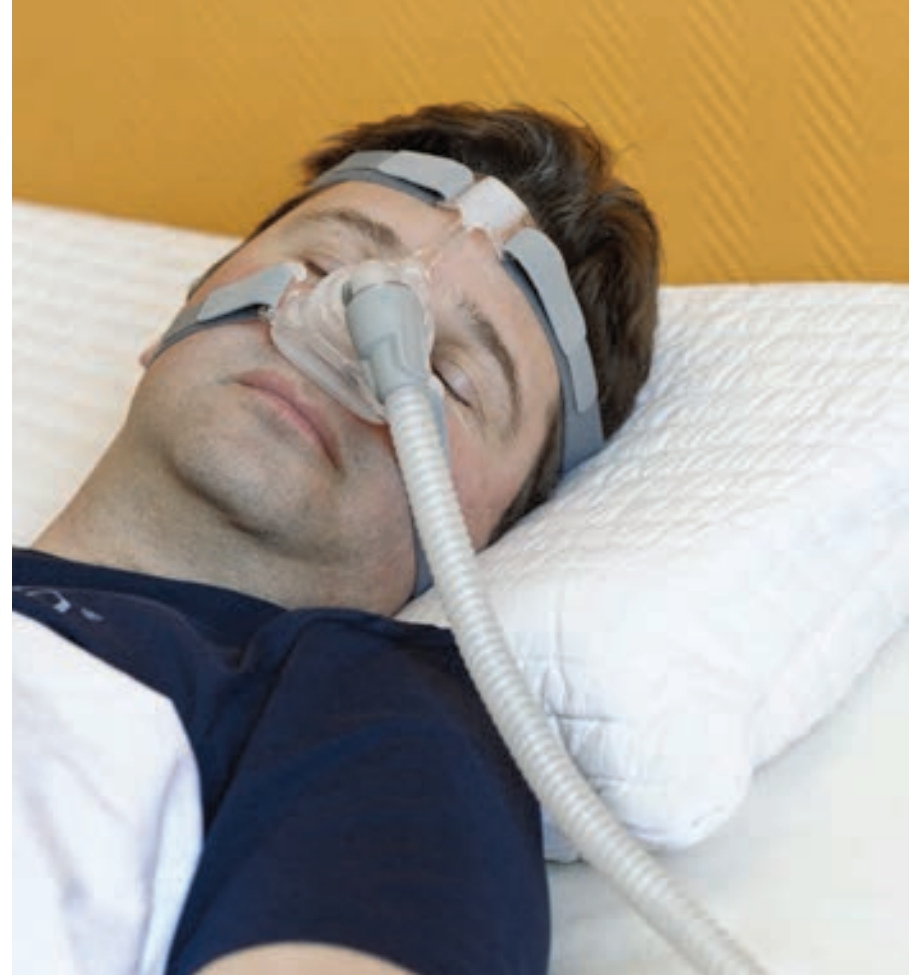
SOURCE: Lisan Q et al. *JAMA Otolaryngol Head Neck Surg*. 2019 Apr 11. doi: 10.1001/jamaoto.2019.0281.



GRAUSTUFE/THINKSTOCK

VIEW ON THE NEWS

Findings may help clinicians persuade patients to use PAP

Further confirmation of the benefits of positive airway pressure (PAP) on mortality in patients with obstructive sleep apnea (OSA) may follow the results published by Lisan et al., wrote Clete A. Kushida, MD, PhD, in an accompanying editorial. Dr. Kushida is a professor of psychiatry and behavioral sciences at Stanford (Calif.) University. "Of the study limitations described by Lisan et al., a major factor is the participants' use of PAP therapy: The participants self-reported if they were prescribed PAP therapy, but their PAP adherence data (i.e., duration and frequency of PAP use) were unknown. Discrepancies exist between self-reported versus objective PAP adherence, as well as between patterns of PAP adherence over time, and the lack of adherence data would be expected to limit our understanding of the effects of PAP therapy on mortality." A further limitation is that the study's findings are restricted to patients with obesity and severe OSA.

"Even taking into consideration the technological improvement in size, comfort, and convenience of these devices since PAP was first tried on patients with OSA, every knowledgeable sleep specialist has had difficulty in convincing some patients of the need to treat their OSA with these devices, and/or the need to improve their use of the devices once they have been prescribed," Dr. Kushida continued. "Although at this point experienced sleep specialists cannot say with certainty that use of PAP improves survival, the study by Lisan et al. will undoubtedly make these clinicians' jobs a little easier by enabling them to present to their patients evidence that PAP may be associated with reduced mortality, particularly in those with severe OSA and comorbid obesity."

Dr. Kushida receives salary support from a contract between Stanford University and Philips-Respironics for the conduct of a clinical trial. These comments are from an accompanying editorial (JAMA Otolaryngol Head Neck Surg. 2019 Apr 11. doi: 10.1001/jamaoto.2019.0345).

Continued from previous page

in which case catheter-directed therapy may be a safer option, he said. He cited a recent 5% death rate after surgery at his center among patients with major PE who did not require cardiopulmonary resuscitation.

The database Dr. Goldberg and his collaborator reviewed included 12,735 patients treated by systemic thrombolysis, and 2,595 treated by catheter-directed therapy. Patients averaged 63 years old. The most common indicator of major PE was mechanical ventilation, used on 8% of all PE patients in the study. Non-septic shock occurred in 2%, and just under 1% needed vasopressor treatment.

Published guidelines on PE management from several medical groups are "vague and have numerous caveats," Dr. Goldberg said. He is participating in an update to the 2011 PE management statement from the American College of Cardiology and American Heart Association (Circulation. 2011 Apr 26;123[16]:1788-830).

The study received no commercial funding. Dr. Goldberg had no disclosures.

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SOURCE: **Haider A** et al. J Amer Coll Cardiol. 2019 Mar;73:9(suppl 1). doi: 10.1016/S0735-1097(19)32507-0.

Candida auris: Dangerous and here to stay

BY KARI OAKES
MDedge News

Critical care units and long-term care facilities are on alert for cases of *Candida auris*, a novel fungal infection that is both dangerous to vulnerable patients and difficult to eradicate. The increased profile of *C. auris* is not a welcome development but is no surprise to critical care physicians.

This pathogen was first identified 10 years ago and has since been found in increasing numbers of patients all over the world. As expected, cases of *C. auris* are on the rise in the United States.

The Centers for Disease Control and Prevention stated, "*Candida auris* is an emerging fungus that presents a serious global health threat." This is an opportunistic pathogen that hits critically ill patients and those with compromised immunity.

On March 29, CDC reported that confirmed clinical cases of *C. auris* in the United States have more than doubled over the past year, from 257 cases in 2018 to 587 cases with an additional 1,056 colonized patients identified as of February 2019. "Most *C. auris* cases in the United States have been detected in the New York City area, New Jersey, and the Chicago area. Strains of *C. auris* in the United States have been linked to other parts of the world. U.S. *C. auris* cases are a result of inadvertent introduction into the United States from a patient who recently received health care in a country where *C. auris* has been reported or a result of local spread after such an introduction."

Case reports have found a mortality rate of up to 50% in patients with *C. auris* candidemia. The total number of cases is still small, but the trajectory is clear. The hunt is on in labs all over the world for optimal treatments and processes to handle outbreaks.

Expert looks at *C. auris* characteristics

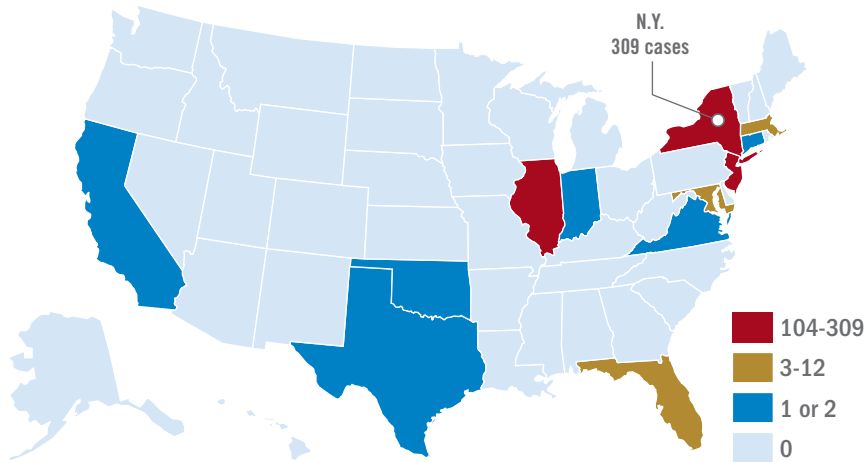
Jeniel Nett, MD, an infectious disease specialist, and a team of investigators at the University of Wisconsin, Madison, have focused their research on the characteristics of *C. auris* and its progression in patients and in medical facilities.

According to Dr. Nett, it's not clear why this emerging threat has cropped up in multiple locations globally. "*Candida auris* was first recognized in 2009, in Japan, and relatively quickly we saw emergence of this species in relatively distant locations," she said, adding that independent clades in these locations ruled out transmission as the source of the multiple outbreaks. Antifungal resistance is an epidemiologic area of concern and increased antifungal use may be a contributor, she said.

Once established, the organism is persistent: "It is found on mattresses, on bedsheets, IV poles, and a lot of reusable equipment," said Dr. Nett in an interview. "It appears to persist in the environment for weeks – maybe longer." In addition, "it seems to behave differently than a lot of the *Candida* species that we see; it readily colonizes the skin" to a much greater extent than does other *Candida* species, she said. "This allows it to be transmitted readily person to person, particularly in the hospitalized setting." However, it can also colonize both the urinary and respiratory tracts, she said.

"Many of these patients have undergone multiple procedures; they may have undergone mechanical ventilation as well as different surgical procedures," said Dr. Nett. Affected patients often have received many rounds of antibiotic and antifungal treatment as well, she said, and may have an underlying illness like diabetes or malignancy.

Confirmed clinical cases of *Candida auris* as of Feb. 28, 2019



MDedge News

Along with these 587 cases, *C. auris* colonization has been found in 1,056 other patients through targeted screening in seven states with clinical cases.

Outbreak progression studied

A prospective cohort study of a large outbreak of *C. auris* was conducted by Alba Ruiz-Gaitán, MD, and her colleagues at La Fe University and Polytechnic Hospital, Valencia, Spain (Expert Rev Anti Infect Ther. 2019 Apr;17[4]:295-305). The researchers followed 114 patients who were colonized with *C. auris* or had *C. auris* candidemia. The patients were compared with 114 case-matched controls within the hospital's adult surgical and medical intensive care units over an 11-month period during the hospital's protracted outbreak.

The investigators found a crude mortality rate of 58.5% at 30 days for patients with *C. auris* candidemia. All isolates in the study were completely resistant to fluconazole and had reduced susceptibility to voriconazole.

In critical care units at Hospital La Fe, investigators found *C. auris* on 25% of blood pressure cuffs, 10% of patient tables and keyboards, and 8% of infusion pumps.

Among the patients at Hospital La Fe, multivariable analysis revealed that those most likely to develop *C. auris* colonization or candidemia were individuals with polytrauma, cardiovascular disease, and cancer.

Patients receiving parenteral nutrition (odds ratio, 3.49) or mechanical ventilation (OR, 2.43), and especially those having indwelling central venous catheters (OR, 13.48) were more likely to be colonized or have candidemia as well, according to Dr. Ruiz-Gaitán and her coauthors.

Once identified, how should *C. auris* be treated? "The majority of strains – upward of 90% – are resistant to fluconazole," said Dr. Nett. "Moreover, 30%-50% of them are resistant to another antifungal, often amphotericin B. The isolates that we see in the United States are most often susceptible to an echinocandin, and echinocandins remain the choice for treatment of *Candida auris* pending susceptibility tests."

However, in Valencia, "The susceptibility to echinocandins presented interesting features. These antifungals were not fungicidal against *C. auris*," wrote Dr. Ruiz-Gaitán and her colleagues. They found that for caspofungin "most isolates presented a clear paradoxical growth after 24 hours of incubation." Additionally, fungal growth was inhibited at lower caspofungin concentrations, but rebounded at higher levels. Similar patterns were seen for anidulafungin and micafungin, they said.

Most large clinical laboratories, she said, can now detect *C. auris*. Matrix-assisted laser desorption/ionization–time of flight is the identification technique of choice, provided that the databases are updated.

Smaller laboratories that use phenotypic tests may misidentify *C. auris* as another *Candida* species, or even as *Saccharomyces cerevisiae* – common beer yeast. Facilities without matrix-assisted laser desorption/ionization can find guidance for interpretation of phenotypic testing on the CDC website as well, said Dr. Nett.

After experiencing what they believe to be the largest *C. auris* outbreak at a single European hospital, Dr. Ruiz-Gaitán and her colleagues offered best-practice tips for treatment of patients with *C. auris* candidemia. These include removing mechanical devices as early as is safely practical; performing ophthalmologic examinations for endophthalmitis, a known *C. auris* complication; obtaining blood cultures every other day to track antimicrobial therapy to the point of sterilization; and searching for metastatic foci if blood cultures remain positive.

Cases should be reported to CDC

All instances of *C. auris* laboratory identification should be reported to the CDC at candidaauris@cdc.gov, and to local and state health agencies. The CDC recommends strict isolation and cleaning protocols, similar to those used for the spore-forming *Clostridium difficile*.

Dr. Nett reported funding support from the National Institutes of Health, the Burroughs Wellcome Fund, and the Doris Duke Charitable Foundation. She reported no conflicts of interest. Dr. Ruiz-Gaitán and her collaborators reported funding from Instituto de Salud Carlos III, Spain, and the Spanish Ministry of Science and University. They reported no conflicts of interest.

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European NAVIGATE data support safety of electromagnetic navigation bronchoscopy

BY WILL PASS
MDedge News

Dr. Anne-Marie Dingemans

Dr. Kelvin Lau

PHOTOS WILL PASS/MDEDGE NEWS

GENEVA – For lung lesion biopsy, electromagnetic navigation bronchoscopy (ENB) offers high navigational success with a relatively low rate of pneumothorax, according to European data from the international NAVIGATE study.

In addition to lung lesion biopsy, ENB can facilitate concurrent lymph node sampling and fiducial placement during a single anesthetic event, reported lead author Kelvin Lau, MD, chief of thoracic surgery at Barts Thorax Centre in London, and his colleagues. According to Dr. Lau, who presented at the European Lung Cancer Conference, the findings from this European cohort add weight to previously published data from the NAVIGATE trial, which aims to demonstrate real-world use of ENB.

"The outcomes show that [ENB] is very safe in terms of pneumothorax rate, despite the fact that many of these patients were challenging and actually were turned down by the percutaneous radiologist before they came to us," Dr. Lau said at the meeting, presented by the European Society for Medical Oncology.

Out of 1,200 patients enrolled in the NAVIGATE trial in the United States and Europe, the present 1-month interim analysis showed experiences with 175 patients treated at eight European centers. Anyone undergoing navigational bronchoscopy was eligible. The primary outcome was pneumothorax rate and the secondary outcome was diagnostic yield.

Data analysis showed that lesions were most frequently in the upper lobe (62.6%) and in the peripheral third of the lung (72.7%), the latter of which is beyond the reach of a conventional bronchoscope. In two out of three patients (66.8%), a bronchus sign was present, which "means that the bronchoscope runs straight into the lesion, and theoretically means it's easier to access," Dr. Lau said. Almost all patients had ENB for lung biopsy (99.4%), while in a small minority (8.0%), ENB was used for fiducial marking. The median total procedure time was 43.5 minutes, of which 32.9 minutes were spent navigating and sampling with ENB.

The ENB-related pneumothorax rate was 7.4%, although a slightly lower percentage, 5.1%, required intervention or hospitalization. According to the ENB-related Common Terminology Criteria for Adverse Events, 2.3% of patients had grade 2 or higher bronchopulmonary hemorrhage and 0.6% of patients had grade 4 or higher respiratory failure. Although the secondary endpoint, diagnostic yield, was not met because of inadequate follow-up time, the navigational success rate, defined as access to the intended lung lesion, was 96.6%, which offers some sense of efficacy.

"The purpose of this study is to show that [ENB] is very safe," Dr. Lau said in an interview. "And the numbers are significantly better than historic CT-guided biopsy data."

Considering the choice between ENB and CT-guided biopsy, invited discussant Anne-Marie Dingemans, MD, of Maastricht (the Netherlands) University offered a different viewpoint.

"CT-guided biopsies are low cost ... and the sensitivity is very, very high," Dr. Dingemans said. "In good hands, with a good radiologist, you have a high chance that you will have a good diagnosis of the nodules." She also noted that a bronchus sign does not impact efficacy.

"I'm very into CT-guided biopsies," Dr. Dingemans continued, noting that the radiologist at her treatment center takes biopsies with a 10-gauge large-core needle. With this technique, Dr. Dingemans reported a 5.7% pneumothorax rate, which is comparable with the present NAVIGATE data.

However, Dr. Lau contested this figure.

"The pneumothorax rates [for CT-guided biopsy] in larger studies have always been about 20%-40%," Dr. Lau said. "You can't compare large overall practice in a pragmatic study capturing everyone versus one single center. The truth is, most centers will have a 20% pneumothorax rate."

Dr. Lau added that patient experiences are likely to be better with ENB than with CT-guided percutaneous biopsy.

"To me, patient comfort for biopsy is essential," Dr. Lau said. "Having a needle stuck into your chest – it's very uncomfortable. I've had patients who've come to me after they had a percutaneous biopsy and who for some reason needed a re-biopsy. ... Those patients almost always wish they had navigational bronchoscopy the first time because there would be no pain for them."

When asked about capital cost concerns surrounding ENB, Dr. Lau suggested that the benefits outweigh the costs.

"The most expensive procedure is the one you have to do again," Dr. Lau said. "So what we do is put a brush in, and a needle, and a biopsy, and hopefully, one of those three, if not all three, gets tissue, and we can do that with navigational bronchoscopy because there is one channel down. You can't repeatedly stick needles into patients. By definition, you can't throw three needle jabs, because you will get a 90% pneumothorax rate. And that's the beauty of navigational bronchoscopy as well, because in the NAVIGATE series, a number of patients, about 10%, had multiple lesions biopsied." Furthermore, Dr. Lau noted, percutaneous biopsy is "almost never" performed bilaterally, for fear of collapsing both lungs, but this is not the case with ENB. "We've done it on patients who have one lung," he said.

Dr. Lau predicted that costs of ENB will come down with time. "Because of the number of products increasing, the price will drop," he said.

Concluding the interview, Dr. Lau offered a summarizing message: "If you want to give the patient the safe option, you should do [ENB], and when it becomes more popular, the price will fall," he said.

Medtronic funded the study. The investigators reported financial relationships with Olympus, Ambu, PulmonX, Boston Scientific, and others.

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SOURCE: Lau et al. ELCC 2019, Abstract 680.

VIEW ON THE NEWS

Jacques Pierre Fontaine, MD, FCCP, comments: This study is an interim analysis of 175 patients out of the 1,200 patients enrolled in the NAVIGATE study. It reveals only that the complication rate of the procedure is very low. However, the results about the diagnostic yield of this procedure are not yet available. ENB is a safe procedure and certainly has an important role to play in the diagnostic workup of lung nodules but will not completely replace the need for CT-guided biopsies in certain patients.

Diagnostic test helps clinicians distinguish IPF from interstitial pneumonia

BY JEFF CRAVEN
MDedge News

Researchers used a machine learning algorithm to identify a molecular signature for usual interstitial pneumonia in patients with suspected idiopathic pulmonary fibrosis, according to recent research published in the Lancet Respiratory Medicine.

The results of the molecular test, called the Envisia Genomic Classifier (Veracyte; San Francisco), had a high positive predictive value of proven usual interstitial pneumonia, and could be used in place of surgical lung biopsy to confirm a diagnosis of idiopathic pulmonary fibrosis (IPF), wrote Ganesh Raghu, MD, director at the Center for Interstitial Lung Diseases and professor of medicine at the University of Washington, Seattle, and his colleagues. The Envisia Genomic Classifier recently received final Medicare local coverage determination for IPF diagnosis, according to a recent press release by Veracyte.


Dr. Raghu

"IPF is often challenging to distinguish from other [interstitial lung disease], but timely and accurate diagnosis is critical so that patients with IPF can access therapies that may slow progression of the disease, while avoiding potentially harmful treatments," Dr. Raghu stated in a press release. "Our results with molecular classification through machine learning [the Envisia classifier] are promising and, along with clinical information and radiological features in high-resolution CT imaging, physicians through multidisciplinary discussions, may be able to utilize the molecular classification as a diagnostic tool to make a more informed and confident diagnoses."

The researchers prospectively recruited 237 patients from 29 centers in the United States and Europe who were evaluated with the Bronchial Sample Collection for a Novel Genomic Test for suspected interstitial lung disease and who underwent surgical biopsy, transbronchial biopsy, or cryobiopsy for sample collection. They used histopathology and RNA sequence data from 90 patients to create a training data set of an unusual interstitial pneumonia pattern for the machine learning algorithm.

The classifier found usual interstitial pneumonia diagnoses in 49 patients; the test had a specificity of 88% (95% confidence interval, 70%-98%) and a sensitivity of 70% (95% CI, 47%-87%). Of 42 patients with inconsistent or possible usual interstitial pneumonia identified from high-resolution CT imaging, there was a positive predictive value of 81% (95% CI, 54%-96%). When multidisciplinary teams made diagnoses with the molecular classifier data, there was a clinical agreement of 86% (95% CI, 78%-92%) with diagnoses made using histopathology data. In 18 cases of IPF, there was an improvement in diagnostic confidence using the molecular classifier data, with 89% of diagnoses designated as high confidence, compared with 56% of cases based on histopathologic data (P = .0339). In 48 patients with nondiagnostic pathology or nonclassifiable fibrosis histopathology, 63% of diagnoses with the molecular classifier data were high confidence, compared with 42% using histopathologic data (P = .0412).

This study was funded by Veracyte, creator of the Envisia Genomic Classifier. Some authors reported relationships with Veracyte and other companies.

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SOURCE: Raghu G et al. Lancet Respir Med. 2019 Apr 1. doi: 10.1016/S2213-8587(19)300.

VIEW ON THE NEWS

Molecular classification could help identify less clear-cut IPF

Use of a molecular classifier could be most helpful in situations where patients have atypical radiology results or in cases where multidisciplinary teams disagree on the diagnosis, Simon Hart, PhD, wrote in a related editorial.

According to the 2018 international guidelines for idiopathic pulmonary fibrosis, usual interstitial pneumonia certainty is defined as honeycombing seen on high-resolution CT (HRCT), probable if there is presence of traction bronchiectasis but not honeycombing, and indeterminate if there is no presence of usual interstitial pneumonia or another diagnosis. As radiologists "often disagree on HRCT patterns," IPF sometimes becomes a working diagnosis based on progression of disease, Dr. Hart wrote. In these cases, molecular classifier samples could help identify IPF in patients who have undergone less invasive transbronchial lung biopsy.

Among patients for whom diagnoses using identical clinical features have different results, HRCT and pathology data, particularly in cases of nonspecific interstitial pneumonia and chronic hypersensitivity pneumonitis that follow a similar disease course to idiopathic pulmonary fibrosis, molecular classifier testing could help identify patients with these diseases so treatments such as to avoid treating these patients with anti-inflammatory or immunosuppressive therapy.

"It seems conceivable that in future interstitial lung diseases could be classified by a simple dichotomy: primarily scarring diseases characterized by molecular usual interstitial pneumonia to be treated with antifibrotics versus immune-driven conditions without usual interstitial pneumonia that need an anti-inflammatory approach," he wrote.

Dr. Hart is from the respiratory research group at Castle Hill Hospital in Cottingham, England. These comments summarize his editorial in response to Raghu et al. (Lancet Respir Med. 2019 Apr 1. doi 10.1016/S2213-2600[19]30058-X). He reported receiving grants and support to attend conferences, and consultancy fees from Boehringer Ingelheim.

NIH beginning first in-human trial of universal flu vaccine

BY LUCAS FRANKI
MDedge News

The National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, is launching the first in-human trial of a universal influenza vaccine candidate.

The experimental vaccine, H1ssF_3928, is derived from the stem of an H1N1 virus and has a surface made from hemagglutinin and ferritin. With only the stem of the virus included, which changes less than the head, the vaccine should require fewer updates. A similar vaccine made from the same materials was shown to be safe and well tolerated in humans.

The clinical trial (NCT03814720) will be conducted at the NIH Clinical Center in Bethesda, Md., and will gradually enroll at least 53 healthy adults aged 18-70 years. The first 5 participants will receive one 20-mcg intramuscular injection of the vaccine; the other 48 participants will receive two 60-mcg vaccinations 16 weeks apart. Patients will return for 9-11 follow-ups over a 12- to 15-month period, and will provide blood samples for analysis of anti-influenza antibodies.

"Seasonal influenza is a perpetual public health challenge, and we continually face the possibility of an influenza pandemic resulting from the emergence and spread of novel influenza viruses. This phase 1 clinical trial is a step forward in our efforts to develop a durable and broadly protective universal influenza vaccine," Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, said in the press release.

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Hookah smoking entails CV risk similar to cigarettes

BY HEIDI SPLETE
MDedge News

Smoking a water pipe, or hookah, can result in significant inhalation of toxins and an increased risk for short- and long-term cardiovascular health problems, according to a scientific statement issued by the American Heart Association on March 8.

In the statement, published in the journal Circulation, Aruni Bhatnagar, PhD, of the University of Louisville (Ky.) and his colleagues reviewed the potential dangers of water pipe use and offered strategies for prevention.

Data from the 2016 National Youth Tobacco Survey showed that current use (defined as use within the past 30 days) of water pipes by high school students increased in a nonlinear trend from 4.1% in 2011 to 4.8% in 2016, with a peak of 9.4% in 2014. Water pipe tobacco is sold in flavors such as cherry, chocolate, and coffee that appeal to younger consumers, and epidemiology data suggest that youth view water pipes as safer than conventional cigarettes because the water "filters out toxins" according to the statement.

Findings from the National Adult Tobacco Survey showed an increase as well, from 1.5% during 2009-2010 to 3.2% during 2013-2014. Adults cite cultural and social influences, as well as psychological benefits of reduced stress and anger and improved concentration, which may be attributable to nicotine, the researchers noted.

Water pipe smoking involves placing charcoal briquettes on top of a tobacco-filled bowl with a stem immersed in water such that the smoke is pulled through and bubbles up through the water into a mouthpiece. The harmful or potentially harmful constituents (HPHCs) involved in water pipe are similar to those in standard cigarettes and include tar, phenanthrene, carbon monoxide, heavy metals, and arsenic, as well as nicotine.

The patterns of exposure to toxins during water pipe smoking are unclear, the authors noted. But the risks for both short-term and long-term health effects are similar to those associated with cigarettes. "Overall, the short-term cardiovascular effects are consistent with the sympathomimetic effects of nicotine," according to the statement.

Data on the long-term effects of water pipe smoking on cardiovascular health are limited, but "lifetime exposures exceeding 40 water pipe–years (2 water pipes per day for a total of 20 years or 1 water pipe for 40 years) are associated with a threefold increase in the odds of angiographically diagnosed coronary artery stenosis. Dr. Bhatnagar received funding from the National Institutes of Health, but he had no other financial conflicts to disclose.

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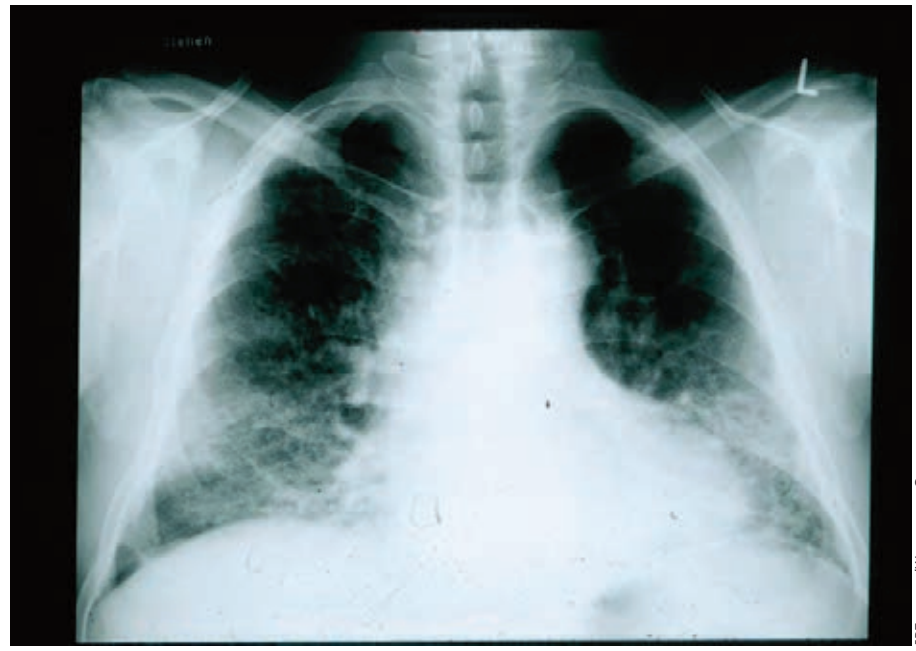
SOURCE: Bhatnagar A et al. Circulation. 2019 Mar 8. doi: 10.1161/CIR.0000000000000671.

Don't delay palliative care for IPF patients

BY THERESE BORDEN
MDedge News



IPFeditor/Wikimedia Commons

Rapid deterioration of life quality in patients with idiopathic pulmonary fibrosis (IPF) begins years before death and indicates that early, integrated palliative care should be a priority, according to the finding of a survey study.

"Patients with IPF suffer from exceptionally low [health-related quality of life] together with severe breathlessness and fatigue already 2 years before death. In addition, physical and emotional well-being further deteriorates near death concurrently with escalating overall symptom burden," wrote Kaisa Rajala, MD, and her colleagues at Helsinki University Hospital.

They conducted a substudy of patients in the larger FinnishIPF study to assess health-related quality of life (HRQOL) and symptom burden in the period before death. Among 300 patients invited to participate, 247 agreed. Patient disease and sociodemographic data were collected from the FinnishIPF records and the study group completed questionnaires five times at 6-month intervals. The study began in April 2015 and continued until August 2017, by which time 92 (37%) of the patients had died.

The investigators used self-reporting tools to look at HRQOL and symptom burden: RAND 36-item Health Survey (RAND-36), the Modified Medical Research and Council Dyspnea Scale (MMRC), the Modified Edmonton Symptom Assessment Scale (ESAS), and the Numeric Rating Scale (NRS).

About 35% of these patients were being treated with antifibrotic medication. Most of the patients had comorbidities, with cardiovascular disease being the most common.

The dimensions of HRQOL studied were physical function, general health, vitality, mental health, social function, and bodily pain. These patients experienced a gradual impairment in HRQOL similar to that of patients with chronic obstructive pulmonary disease (COPD), but with a pronounced, rapid deterioration beginning in the last 2 years of life.

The symptom burden also intensified in the last 2 years of life and ramped up significantly in the last 6 months before death. NRS scores are on a scale of 0-10, from no symptoms to worst symptoms. In most clinical situations, NRS scores equal to or greater than 4 trigger more comprehensive symptom assessment. The scores for symptoms for these patients during the last 6 months were dyspnea, 7.1 (standard deviation, 2.8); tiredness, 6.0 (SD, 2.5), cough, 5.0 (SD, 3.5), pain with movement, 3.9 (SD, 3.1), insomnia, 3.9 (SD, 2.9), anxiety, 3.9 (SD, 2.9), and depression, 3.6 (SD, 3.1).

Investigators noted the steep change in the proportion of patients with MMRC scores greater than or equal to 3 (needing to stop walking after approximately 100 m or a few minutes because of breathlessness) beginning in the last 2 years of life.

The study limitations are its relatively small size, the self-reported data, and the lack of lung function measurements in most patients in the last 6 months of life.

The findings point to the urgent need for early palliative care in IPF patients, the investigators concluded. They noted that the sharp decline in HRQOL is similar to that seen in lung cancer patients, in contrast to the more gradual trend seen in COPD patients.

But there are common benefits of an early palliative program for all of these patients, they stressed. "Early integrated palliative care for patients with lung cancer has shown substantial benefits, such as lower depression scores, higher HRQOL, better communication of end-of-life care preferences, less aggressive care at the end of life, and longer overall survival.

Similarly, a randomized trial demonstrated better control of dyspnea and a survival benefit with integrated palliative care in patients with COPD and interstitial lung disease. In addition to cancer patients, early integrated palliative care may reduce end-of-life acute care utilization, and allow patients with IPF to die in their preferred locations. Integrated palliative care in IPF patients seems to lower respiratory-related emergency room visits and hospitalizations and may allow more patients to die at home."

The study was funded by The Academy of Finland and various Finnish nonprofit organizations funded the study.

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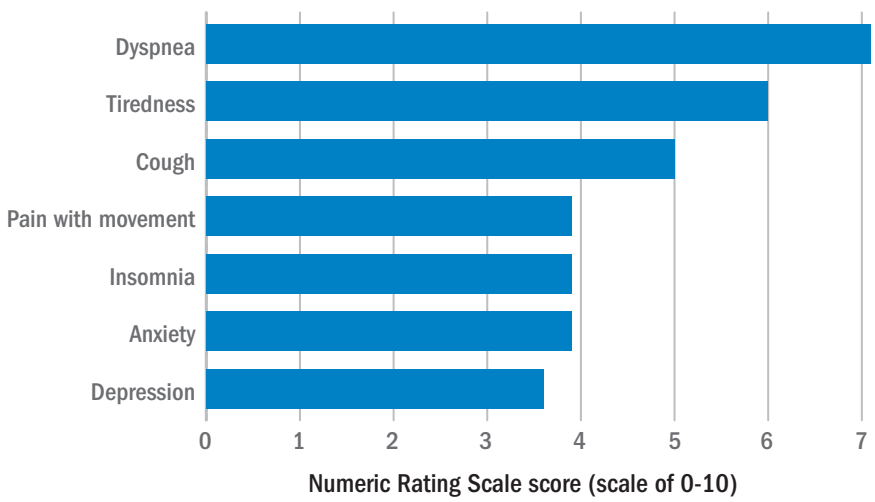
SOURCE: Rajala K et al. BMC Pulm Med. 2018;18:172. doi: 0.1186/s12890-018-0738-x.

Symptom burden in patients with idiopathic pulmonary fibrosis



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Note: Based on data for 247 patients from the larger FinnishIPF study.
Source: BMC Pulm Med. 2018;18:172. doi: 0.1186/s12890-018-0738-x

VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: As stated in the article, the impact of early involvement of palliative care services in patients with conditions with equal (or even better) longevity compared to IPF is well described, and we potentially could dramatically improve the overall care of our IPF patients with an early integrative approach with palliative care. Further, with early involvement, symptom management adapts as progression occurs, unnecessary and undesired care is avoided, and a more streamlined transition to hospice care is possible. There are several factors that may serve as barriers to palliative care referral – from recognition of the extent of our patients' symptoms, the focus on active treatment, and the availability of palliative care consultative services in the community. This study shines light on the fact that we as providers need to actively address this component of care, that patients should be asked about the real-life limitations resulting from their disease, and that health systems and payers need to ensure the availability of this vital and compassionate service to all types of patients who may benefit.

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CT scan honeycombing key to hypersensitivity pneumonitis prognosis

BY ANDREW D. BOWSER
MDedge News

FROM THE JOURNAL *CHEST*® ▪ In patients with hypersensitivity pneumonitis, presence of radiologic honeycombing suggests a poor prognosis in line with what might be expected with idiopathic pulmonary fibrosis, results of a recent study suggest.

When radiologic honeycombing was present, event-free survival was uniformly poor whether the patient had hypersensitivity pneumonitis (HP) or idiopathic pulmonary fibrosis (IPF). By contrast, HP patients with nonhoneycomb fibrosis had longer event-free survival than IPF patients with honeycomb features on CT, wrote researchers led by Margaret L. Salisbury, MD, of the division of pulmonary and critical care medicine at the University of Michigan, Ann Arbor.

"Given the uniformly poor outcome among subjects with radiologic honeycombing, pursuit of invasive diagnostic tests directed at differentiating IPF from HP may be of limited value," Dr. Salisbury and her coinvestigators wrote in Chest.

In the study, 117 patients with HP and 161 with IPF underwent high-resolution CT, results of which were evaluated by three thoracic radiologists. Patients with HP who had no fibrosis on CT had the best event-free median survival, or time to transplant or death, at greater than 14.73 years. For HP patients with nonhoneycomb fibrosis, that median survival was greater than 7.95 years, compared with just 5.20 years in IPF patients without honeycomb features.

Specifically for patients with honeycomb features, median event-free survival was poor for both HP and IPF patients, at 2.76 and 2.81 years, respectively.

The HP patients with no fibrosis had a significant improvement in percent predicted forced vital capacity over time, while fibrotic patients experienced significant declines, the investigators wrote. Thus, HP patients with nonhoneycomb fibrosis had forced vital capacity declines despite longer transplant-free survival.

"These results highlight the importance of making a correct diagnosis of HP versus IPF in patients with nonhoneycomb fibrosis, as well as the limited utility in differentiating HP from IPF among patients with radiologic honeycombing," Dr. Salisbury and her coinvestigators concluded.

Dr. Salisbury reported grants from the National Institutes of Health during the study. Her coauthors reported disclosures related to the NIH, Bayer, Centocor, Gilead, Promedior, Ikaria, Genentech, Nycomed/Takeda, Pfizer, and others.

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SOURCE: Salisbury ML et al. Chest. 2019 Apr;155(4):699-711.

VIEW ON THE NEWS

Daniel Ouellette, MD, FCCP, comments: My patient and I finally knew what was wrong. The robust man in his mid-50s had come to see me with new and progressive dyspnea. Although his chest CT scan had some honeycombing, the pattern of abnormalities was not specific enough to diagnose a particular interstitial lung disease. Now, after a lung biopsy, positive serology for avian antigens, and photos of pigeons in rooftop air ducts taken by my patient at his workplace, we knew that he had chronic hypersensitivity pneumonitis.

Like all physicians, I had hoped to stabilize or reverse the course of my patient's disease. Five years later, my patient is off oxygen, playing golf, and taking his kids on vacation: this happening after his lung transplantation. New information from Dr. Salisbury and colleagues will help us better predict these outcomes.

Dupilumab relieves severe sinusitis with polyposis

BY MITCHEL L. ZOLER
MDedge News

SAN FRANCISCO – Dupilumab, an anti-inflammatory drug already approved for use in the United States, met its efficacy endpoints for treating chronic rhinosinusitis with nasal polyps in a pivotal trial with 276 patients.

The results make it likely that dupilumab (Dupixent) will receive a new indication from the Food and Drug Administration, pending similar results in a second pivotal trial for nasal polyps that researchers will report soon. Dupilumab, which works by blocking a receptor for both interleukin 4 and interleukin 13 and thereby shutting down type 2 inflammation, is already approved in the United States for treating atopic dermatitis and asthma.

Type 2 inflammation drives polyp formation in patients with chronic rhinosinusitis that can produce severe nasal congestion, breathing difficulty, and substantially reduced quality of life.

In the new trial, the drug showed efficacy by significantly improving both the nasal congestion score reported by patients and the nasal polyp score measured by sinus endoscopy after 24 weeks on treatment, when compared with control patients on placebo, Joseph K. Han, MD, said at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

Patients enrolled in the study had chronic, severe sinusitis and nasal polyps that remained uncontrolled despite prior surgery, for 75% of enrolled patients, or treatment with systemic corticosteroids, used on about 90% of the patients within the prior 2 years. During the 24 weeks of treatment, 23% of patients in the control arm had to restart systemic corticosteroid treatment or have surgery, compared with 7% of patients on dupilumab treatment, a statistically significant difference.

The new drug is a "game changer," for these patients, Dr. Han said in a video interview.

In some patients, treatment produced complete polyp resolution. He and his colleagues in the otolaryngology field are now trying to decide exactly which patients with polyps secondary to sinusitis will be good candidates for dupilumab after it receives an expected indication for shrinking nasal polyps.

Roughly 4% of the adult population has chronic rhinosinusitis that generates polyps. How many of these patients are affected severely enough to warrant dupilumab treatment is not clear, but will likely include several hundreds of thousands of U.S. adults, said Dr. Han, professor of otolaryngology and chief of the division of allergy at Eastern Virginia Medical School in Norfolk.

The SINUS-24 (A Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps) trial enrolled patients at 76 sites in the United States and in several European countries. The study randomized 143 patients who received standard treatment plus a 300-mg dupilumab subcutaneous injection every 2 weeks, and 133 patients who received standard treatment plus placebo injections.

After 24 weeks of treatment, the endoscopically measured nasal polyp score, which averaged about 6 at baseline on a scale of 0-8, fell by an average of 2.06 points, compared with controls, which was a statistically significant and clinically meaningful change, said Dr. Han.

The second primary endpoint, patient self-assessment of nasal congestion on a scale of 0-3, showed an average 0.89 improvement, compared with controls, which was also a statistically significant and meaningful change from the average baseline score of about 2.4.

Other efficacy measures showed benefits from treatment, including a substantial improvement compared with controls in a quality-of-life measure. The safety profile was benign compared with placebo, and consistent with safety data for the drug.

SINUS-24 was funded by Regeneron and Sanofi, the companies that market dupilumab. Dr. Han has been an adviser to Regeneron and Sanofi.

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SOURCE: Han JK et al. AAAAI 2019, Abstract L4.

Vitamin C for sepsis? Experts take sides in debate

BY RANDY DOTINGA
MDedge News

SAN DIEGO – Powerful antibiotics come first to mind when hospitalized patients have sepsis, but a critical care pulmonology specialist urged colleagues to consider another treatment – heavy intravenous doses of vitamin C.

"There is evidence supporting benefit, and ample evidence supporting safety," Michael H. Hooper, MD, who practices in Norfolk, Va., said in a pro-and-con debate over the use of vitamin C in sepsis at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

Randy Dotinga/MDedge News

Dr. Andre Kalil

Dr. Hooper's debate opponent countered by noting the lack of quality research into vitamin C in sepsis and declared that its time has not yet come. "We need more data to know the safety of this drug," said Andre Kalil, MD, professor of internal medicine and director of Transplant Infectious Diseases at the University of Nebraska Medical Center, Omaha.

Dr. Hooper was part of a member of a team led by Paul E. Marik, MD, FCCP, of Eastern Virginia Medical School, Norfolk, that made waves in 2017 with a study in Chest suggesting IV vitamin C has tremendous potential as a treatment for sepsis (Chest. 2017 Jun;151[6]:1229-38).

The retrospective study compared two groups of 47 patients with sepsis – a control group and a group that received treatment with intravenous vitamin C, hydrocortisone, and thiamine. Remarkably, the team found that 9% (4 of 47) of those in the treatment group died in the hospital, compared with 40% (19 of 47) in the control group (*P* less than .001).

The findings make sense, Dr. Hooper said, in light of the fact that "our patients are remarkably deficient" in vitamin C. He pointed to a 2017 study that found nearly 40% of 24 patients with septic shock were deficient in vitamin C – despite getting recommended enteral nutrition, parenteral nutrition, or both – compared with 25% of patients who were not septic. The study authors believe the difference is probably due to "increased metabolism due to the enhanced inflammatory response observed in septic shock" (Crit Care. 2017 Dec 11;21[1]:300).

"We're dealing with a population of patients who need some sort of repletion of this vitamin," Dr. Hooper said.

Why not try oral administration of vitamin C? "Oral administration at regular doses doesn't work," he said. "If you have normal volunteers who are made deficient, then you administer the recommended allowance, it takes days or weeks to return levels to normal."

Dr. Hooper added that the goal of vitamin C therapy isn't simply to restore proper levels in plasma. In addition, he said, "we're trying to restore levels in crucial organs."

He said the cost of treatment with IV vitamin C is low, and no serious adverse events have been seen in studies of the vitamin's use in critical care.

In his comments at the debate, Dr. Kalil pointed to several weaknesses in the 2017 study of vitamin C in sepsis. According to him, it had many problems, including a sample size that lacked statistical power and imbalances in the two groups.

Dr. Kalil raised concerns about the study in a 2017 letter published in Chest titled "Vitamin C Is Not Ready for Prime Time in Sepsis but a Solution Is Close," noting that the control group was sicker and none of those patients had their vitamin C levels measured (Chest. 2017 Sep;152[3]:676).

He added that "acute renal failure is associated with high doses of vitamin C."

As of July 2018, several clinical trials into vitamin C, hydrocortisone, and thiamine for the treatment of septic shock were underway or planned, according to a report that described the current randomized, placebo-controlled, multicenter Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) trial in the United States.

The report notes that "robust evidence" for this approach is lacking, although "the potential effectiveness of this medication combination is rooted in biologic plausibility and supported by small clinical trials of the various individual components" (Crit Care. 2018;22:283).

Dr. Hooper is an executive committee member and principal investigator with the Vitamin C, Thiamine And Steroids in Sepsis (VICTAS) study. Dr. Kalil reports no relevant disclosures.

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VIEW ON THE NEWS

Eric Gartman, MD, FCCP, comments: Research conducted in the treatment of sepsis and septic shock has met many roadblocks over the past several decades and many once-promising approaches have proven to be less effective than initially advertised. As such, it is not surprising that many are in disbelief when approaching the very impressive mortality benefits represented in the limited data available on this therapy. This topic deserves the significant attention it is receiving – and given the vast number of patients who would be eligible to receive it, due diligence regarding its safety and effectiveness is warranted prior to its ubiquitous deployment in millions of ICU patients. At present, worldwide there are multiple well-designed studies aimed at providing the answers that we need to (hopefully) settle this debate.

Sepsis survivors face ongoing immune system challenges

BY JIM KLING
MDedge News

SAN DIEGO – Survivors of sepsis face ongoing challenges, including repeat hospitalizations for infections and repeat sepsis. Although it isn't clear if such episodes result from incomplete resolution of the index infection, or they are due to lingering changes in immune function, they do suggest that physicians should engage sepsis patients in an effort to improve long-term outcomes.

It's also an argument for biomarkers and precision immune modulation in these patients, Hallie Prescott, MD, a critical care physician at the VA Ann Arbor (Mich.) Healthcare System, said during a talk at the Critical Care Congress sponsored by the Society of Critical Care Medicine.

When sepsis was first defined in 1992, physicians tended to focus on the inflammatory component, but it's now understood that multiple pathways become dysregulated, and inflammation is no longer part of the most current definition of sepsis. "We now recognize that there is early activation of both pro- and anti-inflammatory pathways, but over the course of sepsis the balance tips from this proinflammatory state in the first few days toward, for most patients, an anti-inflammatory or immune-suppressed state in the later days," said Dr. Prescott.

As advances in care have increased initial survival rates, more patients go on to the later stages, leaving clinicians to address nosocomial and other secondary infections. Dr. Prescott cited an autopsy study that showed many patients who die of sepsis in the ICU have evidence of immune suppression. Another study of patients at the end of a pneumonia hospitalization found that many patients had elevated inflammatory markers even after hospital discharge, and that such elevation

Continued on following page

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was associated with increased mortality as far out as 1 year. The relationship was significant even after adjustment for age, comorbidity, and acute illness. "It suggests that this isn't just identification of patients who had a more severe septic episode," said Dr. Prescott.

The findings may mean that some patients take a long time to return to homeostasis, and other work suggests that about two-thirds of sepsis deaths occur after day 5.

A study by Dr. Prescott's group showed about a 40% 2-year mortality after sepsis hospitalization. When they compared sepsis survivors to matched controls, they found about half the deaths could not be explained by presepsis health status. "Rather, it [seems to be] due to the last sequelae of sepsis, or perhaps this increased risk of secondary infections," Dr. Prescott said.

Studies of the organisms causing secondary infections found increasing incidence of opportunistic infections, from 9% in the first 5 days of sepsis, to 18% in days 16 through 150. The frequency of Candida infection similarly increased, from 13% to 30%. "So in these later phases of sepsis, you're more likely to see [pathogens] that are relatively rare as the initial cause of sepsis," said Dr. Prescott.

Unfortunately, she said, research has not shown that prophylaxis improves outcomes. "My suspicion is that it's because these infections are one marker of a broader problem with immune dysfunction, and we probably need to boost or restore immune function more broadly as opposed to trying to prophylax against very specifically what the patient is at risk for," said Dr. Prescott.

SHAWN LOCKHART/CDC

The problems appear to continue after hospital discharge. A study from Dr. Prescott's group showed that about 40% of sepsis survivors were readmitted at least once within the next 90 days. The most common reason, at 6.4%, was another sepsis episode.

Compared with matched controls, sepsis patients had about a 2.5-fold higher risk for sepsis, and about a 1.5-fold increased risk an infection. "So there seems to be this heightened risk among people surviving sepsis that's not fully explained by the things that put them at risk for developing sepsis in the first place," said Dr. Prescott.

Dr. Prescott cited another study looking at the reason for recurring infections in sepsis survivors that found, in about one in five cases, the readmission was due to the same infectious organism in the same site, suggesting incomplete resolution. In about half of patients, the infection was due to a different organism, or the same organism at a different site, and in about a third of patients, the results were ambiguous due to culture-negative infections.

"I think this suggests a complex picture. Some people perhaps fail to fully eradicate the initial infection, and a larger group of people come back with something else. There's also a very high rate of infection in the same site – about 70% with a new bug have it in the same site as their initial sepsis. Some of this may be just be a reflection of the type of people who get sepsis the first time, but it still tells us that, among the patients we care for who survive sepsis, that they are over the long haul at increased risk of recurrent infections and recurrent episodes of sepsis," said Dr. Prescott.

She argued that real-time assessment of immune function may be needed and there may be a benefit of immune modulation in the later phases of sepsis. Such strategies are not likely to be implemented immediately, however. In the meantime, there are simple steps that clinicians can take, including screening of sepsis survivors and making sure they are up to date on vaccines, and then educating them about the risk of reinfection. "We know that the lay public awareness of sepsis is low. Even people who have sepsis are often unaware that they had it, and they are certainly unaware that they're at risk for having another episode," she said.

Dr. Prescott has no financial disclosures.

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More fiber looks safe, might benefit ICU patients

BY AMY KARON
MDedge News

MIAMI – High-fiber diets in the ICU were well tolerated and led to desirable shifts in the gut microbiome that correlated with decreased abdominal distension, according to the results of an observational cohort study.

"Higher fiber intake was associated with greater preservation of short-chain fatty acid–producing bacteria, even after we adjusted for antibiotics and acute severity of illness," said Yichun Fu, a fourth-year medical student at Columbia University, New York, at the annual Gut Microbiota for Health World Summit.

She explained that, after 72 hours on the high-fiber diet, only 11% of patients had abdominal distension noted in their EMRs, compared with 36% of patients who received no dietary fiber (*P* less than .01). Fiber was not associated with bowel obstruction, high gastric residuals, enteric infections, edema, or diarrhea. She and her associates presented the findings in a poster at the meeting sponsored by the American Gastroenterological Association and the European Society for Neurogastroenterology and Motility.

Dietary fiber is a prebiotic that increases the abundance of short-chain fatty acid (SCFA)–producing bacteria in the gut. Growing evidence links these bacteria and their metabolites – such as acetate, propionate, and butyrate – to immunomodulatory benefits and suggests that they help maintain gut barrier function, glucose homeostasis, adipose tissue lipolysis, and normal blood pressure. Thus, fiber for ICU patients might make sense, but relevant dietary guidelines rarely address the topic. In practice, fiber is often withheld in the ICU because of concerns that it might cause bloating or diarrhea, Ms. Fu said.

For the study, the researchers performed 16s ribosomal RNA sequencing on baseline and 72-hour rectal swabs collected from 129 consecutive adults newly admitted to the ICU. Patients were eligible for the study regardless of whether they received nothing by mouth, enteral feeding, or food by mouth. They were grouped in tertiles based on fiber intake over 72 hours, corrected by caloric intake. The resulting groups were dubbed "no fiber" (median and interquartile range, 0 grams), "low fiber" (median, 11.2 g; IQR, 3.8-18.2 g), and "high fiber" (median, 39.3 g; IQR, 4.7-50.2 g).

Patients in these three groups had a similar relative abundance of SCFA-producing bacteria at baseline. At 72 hours, the high-fiber group had a significantly greater relative abundance of SCFA producers

Amy Karon/MDedge News

Yichun Fu

than the no fiber group (*P* = .01). Compared with no fiber, high-fiber intake also correlated with significantly increased gut bacterial diversity (*P* = .04) and a lower relative abundance of *Enterococcus* bacteria (*P* less than .01). None of these measures differed significantly between the no-fiber and low-fiber groups.

The groups were demographically and clinically similar at baseline, except that the high-fiber group had lower Acute Physiology and Chronic Health Evaluation IV scores (*P* = .02) and was less likely to receive antibiotics, mechanical ventilation, hemodialysis, or vasopressors (*P* less than .01). After correction for these differences, each 10-g increase in fiber intake over 72 hours correlated with a 0.3% median increase in the relative abundance of SCFA-producing bacteria (estimated IQR, 0.10%-0.46%; *P* less than .01).

"Fiber may be a simple candidate therapy for ICU patients," the researchers concluded. The team is now designing a prospective, interventional study to further test whether fiber can modify the gut microbiome to benefit ICU patients, Ms. Fu explained.

Funders included the American Gastroenterological Association, the National Institutes of Health, and the Feldstein Medical Foundation. Ms. Fu reported no competing interests.

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New sleep apnea guidelines offer evidence-based recommendations

BY HEIDI SPLETE
MDedge News

New guidelines on treating obstructive sleep apnea with positive airway pressure include recommendations for using positive airway pressure (PAP) versus no therapy, using either continuous PAP (CPAP) or automatic PAP (APAP) for ongoing treatment, and providing educational interventions to patients starting PAP. The complete guidelines, issued by the American Academy of Sleep Medicine, were published in the Journal of Clinical Sleep Medicine.

The guidelines were driven by improvements in PAP adherence and device technology, wrote lead author Susheel P. Patil, MD, of Johns Hopkins University, Baltimore, and his colleagues.

The guidelines begin with a pair of Good Practice Statements to ensure effective and appropriate management of obstructive sleep apnea (OSA) in adults. First, "Treatment of OSA with PAP therapy should be based on a diagnosis of OSA established using objective sleep apnea testing." Second, "Adequate follow-up, including troubleshooting and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence, should occur following PAP therapy initiation and during treatment of OSA."

The nine recommendations, approved by the AASM board of directors, include four strong recommendations that clinicians should follow under most circumstances, and five conditional recommendations that are suggested but lack strong clinical support for their appropriateness for all patients in all circumstances.

The first of the strong recommendations, for using PAP versus no therapy to treat adults with OSA and excessive sleepiness, was based on a high level of evidence from a meta-analysis of 38 randomized, controlled trials and the conclusion that the benefits of PAP outweighed the harms.

The second strong recommendation for using either CPAP or APAP for ongoing treatment was based on data from 26 trials that showed no clinically significant difference between the two. The third strong recommendation that PAP therapy be initiated using either APAP at home or in-laboratory PAP titration in adults with OSA and no significant comorbidities was supported by a meta-analysis of 10 trials that showed no clinically significant difference between at-home and laboratory initiation, and that each option has its benefits. The authors noted that "the majority of well-informed adult patients with OSA and without significant comorbidities would prefer initiation of PAP using the most rapid, convenient, and cost-effective strategy." This comment supports the fourth strong recommendation for providing educational interventions to patients starting PAP.

The guidelines were developed by a task force commissioned by the AASM that included board-certified sleep specialists and experts in PAP use and will be reviewed and updated as new information surfaces.

The conditional recommendations include using PAP versus no therapy for adults with OSA and impaired quality of life related to poor sleep, such as insomnia, snoring, morning headaches, and daytime fatigue. Other conditional recommendations include using PAP versus no therapy for adults with OSA and comorbid hypertension, choosing CPAP or APAP over bilateral PAP for routine treatment of OSA in adults, providing behavioral interventions or troubleshooting during patients' initial use of PAP, and using telemonitoring-guided interventions to monitor patients during their initial use of PAP.

"The ultimate judgment regarding any specific care must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources," the authors noted.

"When implementing the recommendations, providers should consider additional strategies that will maximize the individual patient's comfort and adherence such as nasal/intranasal over oronasal mask interface and heated humidification," they added.

The guidelines were developed by a task force commissioned by the AASM that included board-certified sleep specialists and experts in PAP use, and will be reviewed and updated as new information surfaces, the authors wrote.

Dr. Patil reported no financial conflicts; several coauthors reported conflicts that were managed by their not voting on guidelines related to those conflicts.

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SOURCE: Patil SP et al. J Clin Sleep Med. 2018 Feb 15;15(2):335-43.

VIEW ON THE NEWS

Octavian C. Ioachimescu, MD, PhD, FCCP, comments: The last guidelines and practice parameters for the use of positive airway pressure (PAP) as therapy for adult patients with obstructive sleep apnea, were published in 2006 and 2008, respectively. Since then, new technological advances, an ever-growing body of literature, and shifting practice patterns led to an acute need for a thorough reassessment, a comprehensive update of the previous recommendations, and the potential of issuing new ones for emerging areas. As such, the American Academy of Sleep Medicine commissioned a task force of content experts to review the existing evidence, to issue new guidelines and to publish an associated systematic review and a meta-analysis of the literature on this topic.

These guidelines show that we still have so many areas insufficiently explored, with very conflicting or suboptimal level of evidence. A publication like this can help us see what our blind spots are in this area. For example, we do not know yet if patients without daytime sleepiness (most of the time defined bluntly by specific cutoffs of the Epworth Sleepiness Scale) benefit in the long term by instituting PAP therapy. Furthermore, impairments of other domains of quality of life have been insufficiently correlated with long-term, hard adverse outcomes. Another example: the utility of Multiple Sleep Latency testing as an objective methodology to assess residual sleepiness after PAP therapy initiation.

A welcome recommendation is the endorsement by the task force of the use of telemedicine capabilities in monitoring patients' adherence to PAP therapy. Another interesting aspect is that, while our literature is represented by a mix of both randomized and nonrandomized controlled trials, occasionally there seems to be an interesting dichotomy in the results. Randomized trials tend to point in one direction, while nonrandomized studies pooled in the meta-analysis seem to point to the contrary or to give the impression of more definitive effects. While this is not the place to make an extensive analysis of the strengths and the potential pitfalls of randomized vs nonrandomized studies, this clearly raises some issues. One is that our randomized studies are typically small, underpowered, and, hence, with nonconvincing risk or hazard reduction assessments. Second, the dichotomy in the results may be driven by publication bias, expense, and difficulty in performing adequately powered, long-term trials that essentially may be studying small effects.

Guidelines are not intended to be used in an Occam's razor approach but in a fashion that would allow individualization of therapy while critically appraising the existing evidence for various interventions in specific conditions and maintaining a very stringent and critical view on generalizability, expected results, and adequate management of reasonable expectations. In addition, the areas that are unclear, with conflicting evidence or in which the guidelines allow "too much" latitude to the treating clinician, may be seen as either an invitation to remain "creative," or one for abstaining from action in the name of equipoise. I would advise that both extremes are to be avoided.

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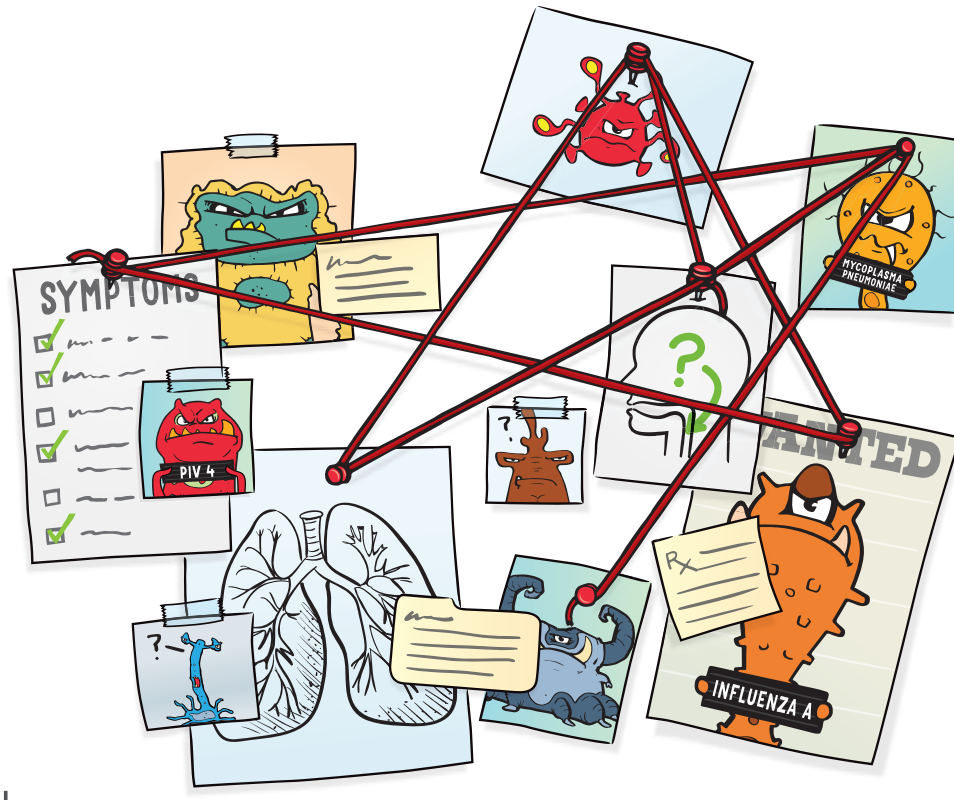

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Study disputes CPAP link to weight gain in OSA patients

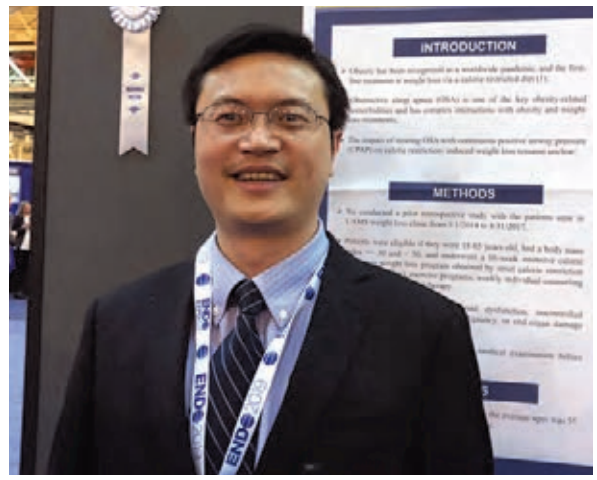
BY TED BOSWORTH
MDedge News

NEW ORLEANS – Contrary to previously published data suggesting continuous positive airway pressure (CPAP) produces weight gain in patients with obstructive sleep apnea (OSA), new study findings presented at the annual meeting of the Endocrine Society provided data supporting the exact opposite conclusion.

"We think the data are strong enough to conclude that combining CPAP with a weight-loss program should be considered for all OSA patients. The weight-loss advantage is substantial," reported Yuanjie Mao, MD, PhD, of the University of Arkansas for Medical Sciences, Little Rock.

Both weight loss and CPAP have been shown to be effective for the treatment of OSA, but concern that CPAP produces a counterproductive gain in weight was raised by findings in a meta-analysis in which CPAP was associated with increased body mass index (Thorax. 2015 Mar;70:258-64). As a result of that finding, some guidelines subsequently advised intensifying a weight-loss program at the time that CPAP is initiated to mitigate the weight-gain effect, according to Dr. Mao. However, he noted that prospective data were never collected, so a causal relationship was never proven. Now, his data support the opposite conclusion.

In the more recent study, 300 patients who had participated in an intensive weight-loss program at his institution were divided into three groups: OSA patients who had been treated with CPAP, symptomatic OSA patients who had not been treated with CPAP, and asymptomatic OSA patients not treated with CPAP. They were compared retrospectively for weight change over a 16-week period.



Ted Bosworth/MDedge News

Dr. Yuanjie Mao

"This was a very simple study," said Dr. Mao, who explained that several exclusions, such as thyroid dysfunction, active infection, and uncontrolled diabetes, were used to reduce variables that might also affect weight change. At the end of 16 weeks, the median absolute weight loss in the CPAP group was 26.7 lb (12.1 kg), compared with 21 lb (9.5 kg) for the symptomatic OSA group and 19.2 lb (8.7 kg) for the asymptomatic OSA group. The weight loss was significantly greater for the CPAP group (*P* less than .01), compared with either of the other two groups, but not significantly different between the groups that were not treated with CPAP.

"The differences remained significant after adjusting for baseline BMI [body mass index], age, and gender," Dr. Mao reported.

Asked why his data contradicted the previously reported data, Dr. Mao said that the previous studies were not evaluating CPAP in the context of a weight-loss program. He contends that when CPAP is combined with a rigorous weight-reduction regimen, there is an additive benefit from CPAP.

According to Dr. Mao, these data bring the value of CPAP for weight loss full circle. Before publication of the 2015 meta-analysis, it was widely assumed that CPAP helped with weight loss based on the expectation that better sleep quality would increase daytime activity. However, in the absence of strong data confirming that effect, Dr. Mao believes the unexpected results of the 2015 study easily pushed the pendulum in the opposite direction.

"The conclusion that CPAP increases weight was drawn from studies not designed to evaluate a weight-loss effect in those participating in a weight-loss program," Dr. Mao said. His study suggests that it is this combination that is important. He believes the observed effect from better sleep quality associated with CPAP is not necessarily related to better daytime function alone.

"Patients who sleep well also have more favorable diurnal changes in factors that might be important to weight change, such as leptin resistance and hormonal secretion," he said. Although more work is needed to determine whether these purported mechanisms are important, he thinks his study has an immediate clinical message.

"Patients with OSA who are prescribed weight loss should also be considered for CPAP for the goal of weight loss," Dr. Mao said. "We think this therapy should be started right away."

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SOURCE: Mao Y et al. ENDO 2019, Session SAT-095.

More sleep can help youth manage type 1 diabetes

BY STEVE CIMINO
MDedge News

More sleep can lead to better glycemic control in youth with type 1 diabetes mellitus, according to a study of sleep duration and quality in young diabetes patients.

"This study adds to the growing body of literature that supports the cascading effects of sleep on multiple aspects of diabetes-related outcomes," wrote lead author Sara S. Frye, PhD, of the University of Arizona, Tucson, and her coauthors, adding that the results "highlight the importance of assessing sleep in this population that appears to be at high risk for insufficient sleep duration." The study was published in Sleep Medicine.


JovanMandic/Getty Images

Dr. Frye and her colleagues recruited 111 children between the ages of 10 and 16 with type 1 diabetes mellitus to participate in their Glucose Regulation and Neurobehavioral Effects of Sleep (GRANES) study. The participants wore wrist actigraphs for an average of 5.5 nights to objectively measure sleep, including duration, quality, timing, and consistency. They completed self-reported sleep diaries each morning of the study. Glycemic control and diabetes management were assessed via hemoglobin A_{1c} (HbA_{1c}) levels and self-monitoring of blood glucose (SMBG) frequency, which were obtained via medical records. The participants and their parents also completed the Diabetes Management Scale.

Based on actigraphy data, the average total sleep time was 7.45 hours (standard deviation, 0.74), below the recommended duration of 9 hours for youths in this age group. All but one participant was recorded as sleeping less than the recommended amount. Average HbA_{1c} of 9.11% (SD, 1.95) indicated poor diabetic control, and the average SMBG frequency was 4.90 (SD, 2.71) with a range of 1-14 checks per day. Per mediation analysis, for every additional hour of sleep, HbA_{1c} was reduced by 0.33% and SMBG frequency went up by 0.88. In addition, SMBG frequency was related to HbA_{1c}, supporting previous findings that "self-management behaviors play a critical role in maintaining diabetes control."

The coauthors acknowledged the limitations of their study, including actigraphy data being logged over a 1-week period instead of the recommended 2 weeks. They also relied on medical records to determine HbA_{1c} and SMBG rather than collecting that information along with the actigraphy data. However, they did note that HbA_{1c} measures glucose levels over a 3-month period, which would have covered their participation in the study.

The study was supported by American Diabetes Association and cosponsored by the Order of the Amaranth Diabetes Foundation. The authors reported no conflicts of interest.

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SOURCE: Frye SS et al. Sleep Med. 2019 Feb 16. doi: 10.1016/j.sleep.2019.01.043.

Clinical depression found in a quarter of OSA patients

BY JEFF CRAVEN
MDedge News

About a quarter of patients with obstructive sleep apnea also had clinical depression and used antidepressants, recent research has shown.

Although patients in the study associated their sleep disorder with poorer quality of life as well as symptoms of anxiety and depression, it is unclear whether treating their obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) would alleviate these symptoms, said Melinda L. Jackson, PhD, from Monash University in Clayton, Victoria, Australia, and her colleagues.

"OSA is a modifiable factor that, if treated, may reduce the economic, health care, and personal burden of depression," Dr. Jackson and her colleagues wrote in their study, recently published in the journal Sleep Medicine. "Findings from the treatment phase of this study will help us determine whether clinical depression is alleviated with CPAP use, taking into account antidepressant use; whether there are subgroups of patients who respond better to treatment; and what are the characteristics of patients who respond compared to those who remain depressed."

The researchers used baseline data from 109 patients in the CPAP for OSA and Depression trial who were diagnosed with OSA. Participants (mean age, 52.6 years; 43.1% female) consecutively presented to a sleep laboratory where they answered interview questions to assess clinical depression and sleep habits. Data were collected using the structured clinical interview for depression (SCID-IV), Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), Epworth Sleepiness Scale, and Assessment of Quality of Life questionnaire. In addition, the researchers performed a meta-analysis of seven studies, including the current study, to determine the prevalence of clinical depression among patients with untreated OSA.

Overall, SCID-IV scores identified clinical depression in 25 participants (22.7%), and these participants said they had greater sleep disturbance and reported higher depressive, anxiety and stress as well as lower quality of life as a result of their clinical depression. Researchers found these participants also had significantly worse quality of sleep (*P* less than .05) and daytime dysfunction (*P* less than .05) as identified by PSQI scores, while FOSQ results showed participants with clinical depression had significantly lower activity levels, social outcomes, and general productivity, compared with patients without clinical depression (*P* less than .05). In a meta-analysis, Dr. Jackson and her colleagues found a pooled prevalence of 23% for clinical depression among participants with OSA.

Participants using antidepressants were examined separately from participants who had clinical depression. The researchers found 27 participants (24.8%) using antidepressants who also had reported higher symptoms of anxiety, depression, and stress; lower quality of life; and poorer sleep outcomes. Participants using antidepressants also were more likely to have bipolar disorder or a condition such as hypertension, chronic obstructive pulmonary disease, high cholesterol, or type 2 diabetes, and 75% of these participants reported having some type of comorbid condition.

The investigators noted they were uncertain whether depression or OSA occurred first, or whether depression exacerbated symptoms of OSA through other factors such as weight gain, sleep disruption, inactivity, or alcohol use. Depression and OSA may also present independently of one another, they added.

"Development of scales to better capture information about when symptoms commenced and the length of time an individual has experienced OSA will provide a clearer understanding of the consequences of OSA on psychological and medical conditions," the researchers said.

This study was funded by the Austin Medical Research Fund, and one authors reported support from an National Health and Medical Research Council Early Career Fellowship. The authors report no relevant conflicts.

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SOURCE: Jackson ML et al. Sleep Med. 2019 Mar 27. doi: 10.1016/j.sleep.2019.03.011.

Five pitfalls in optimizing heart failure management

BY BRUCE JANCIN
MDedge News

SNOWMASS, COLO. – Many of the abundant missed opportunities to optimize pharmacotherapy for heart failure with reduced ejection fraction revolve around not getting fully on board with the guideline-directed medical therapy shown to be highly effective at improving clinical outcomes, Akshay S. Desai, MD, asserted at the Annual Cardiovascular Conference at Snowmass sponsored by the American College of Cardiology.


Dr. Desai

"If you take nothing else away from this talk, the opportunity to improve clinical outcomes in your population through both optimization of selection of therapies and optimization of dose is really quite profound," declared Dr. Desai, director of the cardiomyopathy and heart failure program at Brigham and Women's Hospital, and a cardiologist at Harvard Medical School, Boston.

He highlighted five common traps or pitfalls for physicians with regard to medical therapy of patients with heart failure with reduced ejection fraction (HFrEF):

Underutilizing guideline-directed medical therapy

The current ACC/American Heart Association/Heart Failure Society of America guidelines on heart failure management (Circulation. 2017 Aug 8;136[6]:e137-61) reflect 20 years of impressive progress in improving heart failure outcomes through the use of increasingly effective guideline-directed medical therapy (GDMT). The magnitude of this improvement was nicely captured in a meta-analysis of 57 randomized controlled trials published during 1987-2015. The meta-analysis showed that, although ACE inhibitor therapy alone had no significant impact on all-cause mortality compared to placebo in patients with HFrEF, the sequential addition of guideline-directed drugs conferred stepwise improvements in survival. This approach culminated in a 56% reduction in all-cause mortality with the combination of an ACE inhibitor, beta-blocker, and mineralocorticoid receptor antagonist (MRA), compared with placebo, and a 63% reduction with an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blocker, and MRA (Circ Heart Fail. 2017 Jan;10[1]. pii: e003529).

Moreover, the benefits of contemporary GDMT extend beyond reductions in all-cause mortality, death due to heart failure, and heart failure–related hospitalizations into areas where one wouldn't necessarily have expected to see much benefit. For example, an analysis of data on more than 40,000 HFrEF patients in 12 clinical trials showed a sharp decline in the rate of sudden death over the years as new agents were incorporated into GDMT. The cumulative incidence of sudden death within 90 days after randomization plunged from 2.4% in the earliest trial to 1.0% in the most recent one (N Engl J Med. 2017 Jul 6;377[1]:41-51).

"We're at the point where we now question whether routine use of implantable cardioverter-defibrillators in primary prevention patients with nonischemic heart failure is really worthwhile on the backdrop of effective medical therapy," Dr. Desai observed.

But there's a problem: "We don't do a great job with GDMT, even with this incredible evidence base that we have," the cardiologist said.

He cited a report from the CHAMP-HF registry that scrutinized the use of GDMT in more than 3,500 ambulatory HFrEF patients in 150 U.S. primary care and cardiology practices. It found that 67% of patients deemed eligible for an MRA weren't on one. Neither were 33% with no contraindications to beta-blocker therapy and 27% who were eligible for an ACE inhibitor, angiotensin receptor blocker (ARB), or ARNI (J Am Coll Cardiol. 2018 Jul 24;72[4]:351-66).

Underdosing GDMT

The CHAMP-HF registry contained further disappointing news regarding the state of treatment of patients with HFrEF in ambulatory settings: Among those patients who were on GDMT, very few were receiving the recommended target doses of the medications as established in major clinical trials and specified in the guidelines. Only 14% of patients on an ARNI were on the target dose, as were 28% on a beta-blocker, and 17% of those on an ACE inhibitor or ARB. And among patients who were eligible for all classes of GDMT, just 1% were simultaneously on the target doses of an MRA, beta-blocker, and ARNI, ACE inhibitor, or ARB. This despite solid evidence that, although some benefit is derived from initiating these medications, incremental benefit comes from dose titration.

"Even for those of us who feel like we do this quite well, if we examine our practices systematically – and we've done this in our own practices at Brigham and Women's – you see that a lot of eligible patients aren't on optimal therapy. And you might argue that many of them have contraindications, but even when you do a deep dive into the literature or the electronic medical record and ask the question – Why is this patient with normal renal function and normal potassium with class II HFrEF not on an MRA? – sometimes it's hard to establish why that's the case," said Dr. Desai.

Interrupting GDMT during hospitalizations

This is common practice. But in fact, continuation of GDMT is generally well tolerated in the setting of acute decompensated heart failure in the absence of severe hypotension and cardiogenic shock. Moreover, in-hospital discontinuation or dose reduction is associated with increased risks of readmission and mortality.

And in treatment-naive HFrEF patients, what better place to introduce a medication and assess its tolerability than the hospital? Plus, medications prescribed at discharge are more likely to be continued in the outpatient setting, he noted.

Being seduced by the illusion of stability

The guidelines state that patients with NYHA class II or III HFrEF who tolerate an ACE inhibitor or ARB should be transitioned to an ARNI to further reduce their risk of morbidity and mortality. Yet many physicians wait to make the switch until clinical decompensation occurs. That's a mistake, as was demonstrated in the landmark PARADIGM-HF trial. Twenty percent of study participants without a prior hospitalization for heart failure experienced cardiovascular death or heart failure hospitalization during the follow-up period. Patients who were clinically stable as defined by no prior heart failure hospitalization or none within 3 months prior to enrollment were as likely to benefit from ARNI therapy with sacubitril/valsartan (Entresto) as were those with a recent decompensation (JACC Heart Fail. 2016 Oct;4[10]:816-22). "A key message is that stability is an illusion in patients with symptomatic heart failure," said Dr. Desai. "In PARADIGM-HF, the first event for about half of patients was not heralded by a worsening of symptoms or a heart failure hospitalization, it was an abrupt death at home. This may mean that a missed opportunity to optimize treatment may not come back to you down the road, so waiting until patients get worse in order to optimize their therapy may not be the best strategy."

Inadequately monitoring lab levels

The MRAs, spironolactone and eplerenone (Inspra), are the GDMT drugs for which laboratory surveillance takes on the greatest importance because of their potential to induce hyperkalemia. The guidelines are clear that a potassium level and measurement of renal function should be obtained within a week of initiating therapy with an MRA, again at 4 weeks, and periodically thereafter. "In general, this is done in clinical practice almost never," he said.

These agents should be avoided in patients with prior hyperkalemia or advanced chronic kidney disease, and used with care in groups known to be at increased risk for hyperkalemia, including the elderly and patients with diabetes.

He considers spironolactone equivalent to eplerenone so long as the dosing is adequate. He generally reserves eplerenone for patients with poorly tolerated antiandrogenic effects on spironolactone.

Dr. Desai reported serving as a paid consultant to more than half a dozen pharmaceutical or medical device companies.

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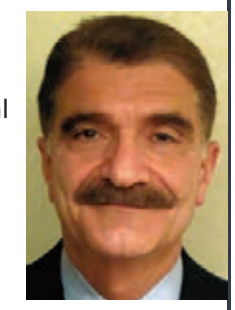
VIEW ON THE NEWS

G. Hossein Almassi, MD, FCCP, comments:



The stepwise institution of guideline-directed medical therapy for patients with HFrEF as suggested by the author should improve the clinical outcomes in this high-risk patient population.

PIONEER-HF extension: For heart failure patients, don't delay starting sacubitril/valsartan

BY BRUCE JANCIN
MDedge News

NEW ORLEANS – Waiting a few months after a patient has been hospitalized for acute decompensated heart failure before launching a switch from enalapril to sacubitril/valsartan imposes a steep price in terms of extra major cardiovascular events, compared with starting the angiotensin-neprilysin inhibitor during the initial hospitalization, according to the open-label extension of the PIONEER-HF trial.

"We think these data have important clinical implications: While sacubitril/valsartan decreases NT-proBNP compared with enalapril regardless of when it is initiated, the early improvement in postdischarge outcomes supports the in-hospital initiation of sacubitril/valsartan in stabilized patients with acute decompensated heart failure," Adam D. DeVore, MD, declared in presenting the PIONEER-HF Extension results at the annual meeting of the American College of Cardiology.

PIONEER-HF was a landmark, practice-changing, double-blind clinical trial in which 881 patients were randomized to initiation of sacubitril/valsartan (Entresto) or enalapril during hospitalization for acute decompensated heart failure. In the previously reported main outcome, 8 weeks after discharge the sacubitril/valsartan group had a 29% greater reduction in NT-proBNP (the N-terminal prohormone of brain natriuretic peptide) and a 42% lower rate of the composite clinical endpoint of cardiovascular death or heart failure rehospitalization than the enalapril group (N Engl J Med. 2019 Feb 7;380[6]:539-48).

The 4-week open-label extension of PIONEER-HF began at week 8, when participants initially randomized to enalapril during the double-blind phase were switched

Bruce Jancin/MDedge News

Dr. Adam D. DeVore

to sacubitril/valsartan, while those assigned to in-hospital initiation of the angiotensin receptor-neprilysin inhibitor (ARNI) stayed the course.

At week 12, after 4 weeks of open-label treatment, patients on sacubitril/valsartan from the start experienced an additional 18.5% drop in NT-proBNP from their week 8 baseline of 1,218 pg/mL. Meanwhile, the NT-proBNP level in the switch group plunged by 35.8% from a week 8 baseline of 1,630 pg/mL. As a result, both groups ended up at the same much-improved biomarker level at week 12, observed Dr. DeVore, a cardiologist at Duke University in Durham, N.C.

Clinical event rates, however, were another story altogether. The clinical event gap between the two study arms documented at week 8 in the double-blind phase of the trial didn't close significantly in the 4 weeks after the enalapril group crossed over to open-label sacubitril/valsartan. Indeed, the relative risk of the composite endpoint of cardiovascular death, heart failure rehospitalization, or left ventricular assist device implantation during the 4-week extension phase was 33% lower in the continuous sacubitril/valsartan group than in the switchers. The absolute risk reduction was 5.6%, with a favorable number needed to treat of 18.

This difference was driven mainly by less rehospitalization for heart failure.

"But this is an important thing as we think about what we're trying to accomplish in heart failure: trying to find tools that improve rehospitalization rates after people leave the hospital is extremely important," Dr. DeVore said. "We do know that the really vulnerable period for rehospitalization is early on, so my suspicion – though I can't prove it – is that's the important part. That's when we need to have patients on the best therapy."

He was asked how practical it is to initiate sacubitril/valsartan during hospitalization for acute decompensated heart failure in real-world clinical practice, given that it can be done only after patients achieve hemodynamic stability.

"I think the definition of hemodynamic stability we used in the trial was a fairly straightforward one, very clinical, and one we can translate to the bedside," Dr. DeVore replied. "Patients had to have a systolic blood pressure of 100 mm Hg or greater for 6 hours, which is easily documented in the hospital, no changes in IV diuretics or IV vasodilators for 6 hours, and no IV inotropes for the last 24 hours. That's how we defined hemodynamic stability. I think we should be able to find these patients."

Average length of stay in the index hospitalization in PIONEER-HF was just over 5 days, but the study protocol actually resulted in longer-than-needed hospitalization because it required that patients had to receive three double-blind doses of their study medication before discharge. In routine practice, it's unlikely that in-hospital initiation of sacubitril/valsartan will result in a length of stay greater than the national average of about 4.5 days, according the cardiologist.

Current ACC/American Heart Association/Heart Failure Society of American guidelines on management of heart failure include a Class Ia recommendation to switch patients from an ACE inhibitor or angiotensin inhibitor to sacubitril/valsartan (Circulation. 2017 Aug 8;136[6]:e137-61). But heart failure specialists are concerned by national data showing that sacubitril/valsartan remains widely underprescribed.

Dr. DeVore reported serving as a consultant to Novartis and receiving research grants from a half dozen pharmaceutical companies as well as the American Heart Association, National Heart, Lung, and Blood Institute, and the Patient-Centered Outcomes Research Institute.

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FDA: Programmable heart failure device approved

BY CHRISTOPHER PALMER
MDedge News

The Food and Drug Administration has approved the Optimizer Smart system for patients with chronic, moderate to severe heart failure. Specifically, these patients are unsuited for other treatments, have marked physical limitations related to their heart failure, and have remained symptomatic despite optimal medical therapy. They also have a regular heart rhythm, are not candidates for resynchronization, and possess a left ventricular ejection fraction of 25%-45%.

The cardiac contractility modulation system is indicated to improve 6-minute hall walk distance, quality of life, and functional status in these patients.

The system is made up of several components, including the implantable pulse generator, a programmer, and software. The pulse generator is connected to three leads that have been implanted in the heart, after which the device is tested and programmed to deliver pulses during normal heartbeats, which improves the heart's squeezing capability. In randomized, multicenter clinical trials, the system plus optimal medical therapy demonstrated improvements in distance during 6-minute walking tests and standard assessments of heart failure symptoms when compared with optimal medical therapy alone.

The Breakthrough Device designation means this system treats a life-threatening disease and addresses unmet medical needs among some patients. "The FDA recognized the unmet need for these patients and worked with the manufacturer through our Breakthrough Device Program to efficiently bring this product to market, while ensuring it meets our regulatory requirements for safety and effectiveness," Bram Zuckerman, MD, the director of the division of cardiovascular devices in the FDA's Center for Devices and Radiological Health said in a news release from the agency.

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BP control slowed white-matter lesion progression

BY MITCHEL L. ZOLER
MDedge News

NEW ORLEANS – Hypertensive elderly patients treated to maintain an ambulatory systolic blood pressure of 130 mm Hg had significantly slower progression of white-matter lesions in their brains than did control hypertensive patients maintained at an ambulatory systolic pressure of about 145 mm Hg during 3 years of follow-up in a randomized, single-center study with 199 patients.

The results also showed similar rates of death, syncope episodes, and falls in the intensively and less rigorously treated subgroups, and the patients treated to a systolic of 130 mm Hg also had significantly fewer nonfatal cardiovascular disease events, further documenting the safety and efficacy in elderly patients of a more aggressive blood pressure goal like the one promoted in current guidelines from the American College of Cardiology and American Heart Association, William B. White, MD, said at the annual meeting of the American College of Cardiology.

COURTESY DR. WILLIAM B. WHITE

Dr. William B. White

The study's findings also showed that, in one measure of cognitive function, the serial reaction time task, the patients treated to a systolic pressure of 130 mm Hg had an average 23-millisecond improvement in their reaction time from baseline to their 3-year follow-up, while patients in the control group treated to a systolic pressure of 145 mm Hg had a 33-millisecond increase in their average reaction time during follow-up. This 56-millisecond between-group difference from baseline in average change in reaction time over 3 years was both statistically significant and represents a clinically meaningful difference for a measure of both processing speed and executive function, said Dr. White, professor of medicine at the University of Connecticut in Farmington. However, the participants also underwent assessment by five other clinical measures of cognitive function and in none of the other five tests did more intensive blood pressure control link with an improvement, compared with the results in control patients.

The study had two primary endpoints. One was progression

of white-matter hyperintensity on brain MR images, which is a measure of neuron necrosis in the brain, and this analysis showed that the growth of white matter occurred at a 40% reduced rate among 99 patients treated to an average ambulatory systolic blood pressure of 130 mm Hg, compared with the average progression among 100 controls treated to an average ambulatory systolic of 145 mm Hg. The second measure was improvement during 3 years, compared with controls, in any of six different measures of mobility, including gait speed. The results showed no significant differences between the treatment arms in any of these measures. The average progression of white-matter disease among control patients after 3 years was of a magnitude that would trigger concern in a neurologist who saw these scans, said Dr. White. The researchers could already begin to see a between-group difference in the accumulation of white-matter hyperintensity on the MR scans of patients at 18 months in the study, he added.

During his presentation, Dr. White suggested that the absence of discerned improvements in mobility from more aggressive blood pressure control despite the observed slowed progression of white-matter disease may have resulted from the study's relatively brief follow-up.

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The INFINITY (Intensive versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline in the Elderly) study enrolled hypertensive patients at least 75 years old who already showed visible evidence of white-matter hypertrophy on their brain MR scan at baseline but also had normal mobility and mental function (their baseline score on the mini mental state examination had to be within the normal range, with an average score of 28 among enrolled patients), and they had no history of any chronic neurological condition (Am Heart J. 2013 Mar;165[3]:258-65). The median age of enrolled patients was 80 years. They had an average of 15 years of education, indicating a study cohort with a high level of education and function, Dr. White noted. The inclusion and exclusion criteria led to a study population

The growth of white matter occurred at a 40% reduced rate among 99 patients treated to an average ambulatory systolic blood pressure of 130 mm Hg, compared with the average progression among 100 controls treated to an average ambulatory systolic of 145 mm Hg.

that was substantially older but without as much comorbidity as patients enrolled in the SPRINT MIND study (JAMA. 2019 Jan 28;321[6]:553-61), he said. The study exclusively used 24-hour ambulatory monitoring for baseline and follow-up blood pressure measurements.

The participating clinicians successfully maintained patients in each of the treatment groups at close to their goal systolic blood pressures. At 18 months, the actual average systolic pressures among patients in the two study groups were 132 mm Hg and 146 mm Hg, and at 36 months their pressures averaged 131 mm Hg and 146 mm Hg for 163 patients who remained in the study out to 36 months. Maintenance of the lower pressure generally required treatment with one additional antihypertensive medication, compared with the control patients' treatment, Dr. White said.

The rates of total falls and falls causing injury were virtually identical in the two treatment groups. The incidence of nonfatal cardiovascular disease events over 3 years, including MI, strokes, and cardiovascular disease hospitalizations, was 4 cases in the intensively treated patients and 17 among those treated to a higher systolic pressure, a statistically significant and unexpected difference, Dr. White reported.

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Pembrolizumab approved for 1st-line stage III NSCLC

BY LAURA NIKOLAIDES
MDedge News

The Food and Drug Administration has approved pembrolizumab (Keytruda) for the first-line treatment of patients with stage III non–small cell lung cancer (NSCLC) who are not candidates for surgical resection or definitive chemoradiation, and for stage IV NSCLC.

Patients' tumors must express programmed death-ligand 1 (PD-L1) as determined by an FDA-approved test (tumor proportion score ≥ 1%) and have no epidermal growth factor receptor or anaplastic lymphoma kinase mutations.

The checkpoint inhibitor was previously approved as a single agent for the first-line treatment of patients with metastatic disease with PD-L1 expression at a higher level (TPS ≥ 50%), the FDA stated.

Approval was based on statistically significant overall survival improvement with pembrolizumab, compared with investigator's choice of a carboplatin-containing regimen with either pemetrexed or paclitaxel in KEYNOTE-042. The trial enrolled 1,274 patients with stage III or IV NSCLC who had not received prior systemic treatment for metastatic NSCLC and whose tumors expressed PD-L1 (TPS ≥ 1%).

Overall survival was improved in all three subgroups for pembrolizumab, compared with chemotherapy: in the TPS ≥ 50% subgroup, the TPS ≥ 20% subgroup, and the overall population (TPS ≥ 1%). The median overall survival in the TPS ≥ 1% population was 16.7 for pembrolizumab and 12.1 months for the chemotherapy arms (hazard ratio, 0.81; 95% confidence interval, 0.71-0.93; $P = .0036$). For the TPS ≥ 50% subgroup, the estimated median overall survival was 20 months for pembrolizumab and 12.2 months for the chemotherapy arm (HR, 0.69; 95% CI, 0.56-0.85; $P = .0006$).

The most common adverse reactions reported for patients who received pembrolizumab included fatigue, decreased appetite, dyspnea, cough, rash, constipation, diarrhea, nausea, hypothyroidism, pneumonia, pyrexia, and weight loss.

The most common adverse reactions reported for patients who received pembrolizumab included fatigue, decreased appetite, dyspnea, cough, rash, constipation, diarrhea, nausea, hypothyroidism, pneumonia, pyrexia, and weight loss, the FDA said.

The recommended dose for NSCLC is 200 mg as an IV infusion over 30 minutes every 3 weeks.

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Prior antibiotics exposure may hamper checkpoint inhibitor efficacy

BY NEIL OSTERWEIL
MDedge News

SAN FRANCISCO – Antibiotic exposure in the month before cancer immunotherapy starts may hamper the efficacy of immune checkpoint inhibitors, investigators caution.

A prospective study of 196 patients treated with immune checkpoint inhibitors for various cancers showed that the 29 patients who received antibiotics within 30 days of starting immunotherapy had significantly worse overall survival than patients without antibiotic exposure; this effect was seen across cancer types, reported David James Pinato, MD, PhD, from Imperial College London.

In contrast, concurrent antibiotic and checkpoint inhibitor use was not significantly associated with overall survival differences, he said at the American Society of Clinical Oncology (ASCO) – Society for Immunotherapy of Cancer (SITC): Clinical Immuno-Oncology Symposium.

"I think these data are quite interesting in showing an independent detrimental effect, both on response and survival, in unselected patients treated with immune checkpoint inhibitors in routine clinical practice," Dr. Pinato said.

The data also suggest "the timing of antibiotic exposure is crucial," he added. Antibiotic treatment concurrent with immunotherapy did not appear to affect prognosis. Alternatively, prior antibiotic therapy appeared to have "a sort of a priming effect towards the immune system."


Neil Osterweil/MDedge News

Dr. David James Pinato

Broad-spectrum antibiotics can affect the diversity of the gut microbiome, which influences mucosal immunity, dendritic cell function, and antigen presentation. Alternatively, enrichment of the microbiome with several bacterial species can enhance the potency of checkpoint inhibitors by facilitating the process of tumor rejection, Dr. Pinato explained.

To see whether antibiotic disruption, or "dysbiosis" of the gut microbiome, could hinder responsiveness to checkpoint inhibitors regardless of the tumor site and whether there were time-dependent effects of antibiotic exposure on response to checkpoint inhibitors, the investigators conducted a prospective, observational study in 196 patients treated with checkpoint inhibitors for non–small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, head and neck cancer, transitional cell carcinoma of the bladder, and other cancers.

The researchers defined prior antibiotic exposure as more than 30 days before the start of checkpoint inhibitor therapy and concurrent exposure as antibiotics begun on the first day of the first cycle of checkpoint inhibitor dosing.

Of the 196 patients, 29 had previously received antibiotics, and 68 received them concurrently. The most frequently prescribed antibiotics were beta-lactam agents given in a single, short course. Other classes of drugs, used in eight or fewer patients each, included quinolones, macrolides, sulfonamides, tetracyclines, aminoglycosides, and nitroimidazole.

Median overall survival for the entire cohort, one of two primary outcomes, was 2 months for patients who had received prior antibiotics and 26 months for patients with no prior exposure. This difference was similar for patients with NSCLC (2.5 vs. 26 months), melanoma (3.9 vs. 14 months), and other cancers combined (1.1 vs. 11.0 months; log-rank *P* less than .01 for all comparisons).

In multivariate analysis, only response to checkpoints inhibitors (complete vs. partial response, stable disease, or progression) and prior antibiotic exposure were significantly associated with survival. The hazard ratio for survival for patients who had not previously received antibiotics was 3.5 (*P* less than .001).

In contrast, concurrent antibiotic and checkpoint inhibitor use did not have a significant effect on survival.

An analysis of radiologic responses also showed that patients with prior antibiotic exposure had a significantly higher probability of primary disease progression than those without (81% vs. 44%; *P* less than .001). There were no associations, however, between specific classes of antibiotics or corticosteroid use.

The findings indicate that "certainly, mechanistic studies are required here, not just to investigate the prognostic role of antibiotic-mediated dysbiosis, but perhaps transform this into an actual driver of antitumor immunity," Dr. Pinato concluded.

The study was internally supported. Dr. Pinato reported receiving grant funding from Merck and Bristol-Myers Squibb unrelated to the study, as well as honoraria from ViiV Healthcare.

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SOURCE: Pinato DJ et al. ASCO-SITC, Abstract 147.

Data from routine lung cancer visits yield research insights

BY HEIDI SPLETE
MDedge News

A continuously updating database of clinical and genomic details on patients with non–small cell lung cancer accurately represented correlations between genomics and outcomes, based on an analysis of more than 4,000 patients.

"Most efforts to identify clinicogenomic associations currently rely on clinical trials, single-institution series, or national registries," wrote Gaurav Singal, MD, of Foundation Medicine in Cambridge, Mass., and colleagues in JAMA.

To explore the feasibility of a clinicogenomic database, the researchers combined clinical data from electronic health records with comprehensive genetic profiling data from 28,889 patients; 4,064 adults with non–small cell lung cancer were included in the analysis of associations among tumor genomics, patient characteristics, and clinical outcomes. The data were collected between Jan. 1, 2011, and Jan. 1, 2018, from 275 U.S. oncology practices.

The researchers examined implications of clinical and genomic features for 3,522 patients with advanced disease. Among these, the median overall survival was 10.3 months and the 5-year survival rate was 3.8%. Factors influencing a longer overall survival included never smoking and having nonsquamous pathology; the presence of mutations in genes TP53 and RB1 were associated with shorter survival.

For each patient, researchers calculated the tumor mutational burden (TMB), defined as "a measure of the number of somatic mutations identified per megabase of DNA sequenced." TMB was significantly higher among smokers, compared with nonsmokers, and "alterations in EGFR, ALK, ROS1, and RET were associated with significantly lower TMB than wild-type cases," the researchers wrote. Overall, the results "replicated previously described associations between clinical and genomic characteristics, driver mutations and response to targeted therapy, and TMB and response to immunotherapy," the researchers wrote.

The findings were limited by several factors, notably the quality and completeness of mortality data, as well as potential biases from the inclusion of comprehensive genetic profiling results and analysis of therapeutic exposures in an unrandomized trial, as well as a study population limited to patients with advanced stage disease, the researchers noted.

However, the results support data from similar studies and further show that clinicogenomic databases can be used in research to augment drug development and improve the design of clinical trials, they wrote.

The study was supported by Flatiron Health and Foundation Medicine, which are both owned by the Roche Group. Dr. Singal and several coauthors are employees of Foundation Medicine.

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SOURCE: Singal G et al. JAMA. 2019;321:1391-9.

CHEST™ Physician
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FROM THE PRESIDENT

Expanding our educational reach

BY CLAYTON T. COWL, MD, FCCP

CHEST Congress Thailand concluded in Bangkok last month with more than 1,000 attendees from 56 countries. Attendees heard experts speak on several clinical tracks, including lung cancer, severe airway disease, pulmonary infections, interventional pulmonary management, and sleep-related disordered breathing. Panel discussions were held covering controversial topics across pulmonary, critical care, and sleep medicine, and close to 400 submitted abstracts were presented. Registration continues to build for the next CHEST international meeting to be held in conjunction with the Hellenic Thoracic Society in Athens, Greece, June 25-27. This meeting will feature clinicians and academicians providing relevant clinical updates to providers throughout that region in more of a "board review-like" format.


Dr. Cowl

Why is it so important that CHEST spread its brand of education to an international audience?

Clinicians are yearning for up-to-date information regardless of geography

Having the opportunity to visit with clinicians from Southeast Asia and Australia, it became clear to me that there is a need for high quality educational opportunities to be shared across the globe. Many attendees in Bangkok had never had the opportunity to attend a CHEST annual meeting within North America; their exposure to state-of-the-art reviews using interactive audience participation was a format that was clearly appreciated. Hands-on educational opportunities through simulation, as well as novel interactive tools such as serious gaming, were modalities not previously available to many attendees, and the reviews received were overwhelmingly positive.

Access to cutting-edge training in certain areas in the world has become more limited

Resources for international travel have become more limited. Industry sponsorship in certain regions has dwindled and, for certain countries, the ability to access medical meetings within the United States or other areas in Europe or North America has become burdensome, if not logistically impossible. Bringing the CHEST brand of education to members and other practicing providers outside North America within the represented specialties has allowed access to experts and the most effective formats for education without extended travel and excess cost.

Having the opportunity to visit with clinicians from Southeast Asia and Australia, it became clear to me that there is a need for high quality educational opportunities to be shared across the globe.

Smaller international meetings allow for more tailored curricula designed to meet local needs

The ability to build the curriculum around specific requests of a national society has allowed for a more focused educational platform designed to meet the needs of what regional leaders feel is the most critical for the highest prevalence of patients seen in that specific area. The international strategy of CHEST calls for an annual congress outside of North America and at least one smaller "board review-type" meeting in a different region elsewhere across the world each academic year. Co-hosting more meetings will not only help address unmet educational needs outside of the United States and Canada but also extend our reach to participants who may not have otherwise had the ability to participate in the CHEST brand of education. During multiple sessions, there were literally dozens of questions for which there was time to address each in real time. The panel discussions were lively, well-moderated, and also stimulated multiple questions and comments from the audience.

Education by podium lecture is fast becoming outdated

Although a compelling lecture using a didactic format from a podium at the front of a room is not going to be replaced completely any time soon, educational delivery trends are moving toward virtual classrooms, use of simulation, problem solving online, serious gaming, and hands-on experiential education. As an innovator and leader in medical education, CHEST will continue to provide a variety of options for delivering education utilizing a variety of platforms. By opening a multimedia production studio at CHEST Global Headquarters in Glenview, Illinois, this past February, the organization is positioning itself to continue to refine its ability to produce and distribute a variety of courses available to all CHEST members in an archivable, easily accessible format. The Board of Regents has doubled down on its digital strategy toward improving communication across the entire user experience, and offering courses to our international members closer to home is one way to execute this strategy.

Networking and new friendships underscore what's important

Meeting new colleagues from across the globe has made me realize that we are all focused on providing the very best care possible to our patients every day. Ultimately, education is communication. The ability to share how CHEST educates its membership will improve patient care worldwide and foster lifelong friendships with those we meet in other lands. Those opportunities to share ideas on health-care delivery will keep us on the cutting edge technologically and keep us focused on how to use resources responsibly and in a way that best serves the communities where we practice.

NEWS FROM THE BOARDS AND CHEST LEADERSHIP

Highlights from the spring leadership meeting

BY VICTOR J. TEST, MD, FCCP

CHEST leadership meets quarterly in person, but the fall and spring meetings include all of the combined committees of CHEST. As the fall meeting takes place during the CHEST Annual Scientific Meeting, the spring meeting takes on a particular importance in providing the impetus of the upcoming year. The meeting spanned from March 27 to March 30. Traditionally, the first day consists of committee meetings, such as the Council of Networks, Training and Transition, Education, Membership, Guideline Oversight, and Professional Standards. On the morning of the second day, the following committees met: Finance, Diversity, and the Governance Committee. The afternoon of the second day was a combined boards meeting with all members of the Board of Trustees and the Board of Regents, where we received updates from each of the committees. In addition, all of the board members underwent professional media training as professional development.

On the 29th, the Foundation Board of Trustees had their meeting, which was attended by several of the members of the Board of Regents (highlights listed below). In the afternoon, we had the biannual meeting of the CHEST Industry Advisory Council, where CHEST leadership meets with our industry partners, working together to anticipate the needs of our members and our patients. The Board of Regents convened on March 30 for our formal board meeting.

Highlights of the spring combined meeting: CHEST leadership committees

Education Committee: Under the leadership of the Chair, Dr. Alex Niven, the Education Committee

Continued on following page

Continued from previous page

has grown in scope and focus with the increasing strength of their subcommittees, including Live Learning, Simulation, Peer Review, Outcomes, Innovations, and Educator Development.

The Education Committee is now working to develop a revolving education curriculum to ensure that our members have a solid base at the annual meeting, as well as in online learning. The committee is working to increase coordination with the APCCMPD, as well.

Membership Committee: The Membership Committee reported on several accomplishments during the year, including an increase in nonphysician membership and rolling out several new programs, including automatic membership renewal option and adjusted membership fees for international members and retired members.

Finance Committee: The financial report for the last quarter of the CHEST fiscal year was robust with solid outlook for the year.

Training and Transitions

The T & T Committee has had marked success with a dramatic increase in fellow education programs and learners at the CHEST annual meeting. This year will bring new fellow courses in pulmonary nodules and lung transplantation. In addition, the committee is also reviewing abstract submissions for trainees at a record pace, with case report submissions exceeding last year's record number of 1,015 submissions.

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Guideline Oversight

There are currently 12 guidelines in development, in addition to the 6 guidelines that were completed last fiscal year. This committee updated us regarding the ongoing development of "living guidelines."

Scientific Program Committee

Dr. Bill Kelly, chairman of CHEST 2019 in New Orleans, reported on the meeting, including the record number of submissions in all curriculum areas. He updated us regarding the ongoing maintenance of certification (MOC) credits for the meeting, as well as important new initiatives, such as child care and innovative electronic options for the meeting, designed to make the experience "easy" on attendees in New Orleans - The Big Easy.

CHEST Foundation Board of Trustees

Doreen Addrizzo-Harris, MD, FCCP, President of the Foundation, updated us on the quarterly activities of the foundation and guided the board through some of the novel fundraising opportunities, including the 6th Annual Irv Feldman Poker Night, the Inaugural CHEST Foundation Derby Dinner and Auction in New York, and the Popovich Endowment Dinner and future gala. The Foundation is sponsoring a number of activities at CHEST in New Orleans, including a Lung Health Experience, Breakfast of Champions, Women & Pulmonary Luncheon, the Young Professionals Reception, and the Foundation Reception.

CHEST Board of Regents (BoR)

The Board of Regents, led by Clayton Cowl, MD, FCCP, President of CHEST, had a packed session. The session started off with a unique team building exercise. The Board approved the Master Fellow Award selection that will honor Dr. Darcy Marciniuk. The Digital Strategy Task Force, led by Dr. Chris Carroll, Nicki Augustyn, and Ron Moen, reported on their findings, which led to a lively discussion on how to move forward with an innovative and successful digital plan. A report was also given on the membership recruitment and retention initiative. Finally, the BoR approved a new agreement with PA Consulting to assist in the ongoing CHEST Analytics program.

CHEST 2019 and southern culture

CHEST Annual Meeting 2019

Get a glimpse of the rich southern culture of New Orleans this October by checking out a few of these locations and events.

Visit a museum – Backstreet Cultural Museum

The Backstreet Cultural Museum is located in a small, former funeral home in the historic Treme neighborhood. The museum displays the permanent collection of Mardi Gras Indians costumes, second-line parade outfits, jazz funeral photos, and music memorabilia from curator Sylvester Francis. Interested in upcoming parades and festivals happening nearly every weekend in New Orleans? Learn about these at the museum, as well as more NOLA arts and traditions.

View the local art in Jackson Square

Jackson Square is an area where you'll see tarot readers, street performers, and artists. It has an open-air artist community where their works are hung on the iron railings around the square. Spend time getting your portrait done, buy a new art piece from a local, or have fun watching a street performance.

Diego Delso, delso.photo/CC-BY-SA

Jackson Square

Enjoy the architecture of the French Quarter

Explore New Orleans' oldest neighborhood, The French QuaSrter, with its mix of French Creole and Spanish influenced architecture. You'll find hints of this on old tiled street names and the French Fleur de Lys emblem noticeable all around the city. There are also Caribbean, African, and other European influences throughout the area. Take in the gorgeous mansions, the colorful Creole houses with their porches and swing chairs, the townhouses with beautiful ironwork balconies, and more!

Head to Oktoberfest

New Orleans also has a rich German history. You can celebrate this October with the city's own version of Oktoberfest, which takes place the first three weekends in the month. Experience some of the best of German culture by drinking a rare beer, trying authentic cuisine, and listening to live music during this celebration.

New Orleans Film Festival

From October 16-24, the New Orleans Film Society will be hosting the 2019 New Orleans Film Festival (NOFF). You can check out showings in different venues throughout the city. Local filmmakers are showcased during the festival, and their films and any shown during NOFF can qualify for the Oscars in all three Academy-accredited categories: Narrative Short, Documentary Short, and Animated Short.

Check out more things you can do in NOLA (https://tinyurl.com/yxnqswv5).

CMS proposal threatens home mechanical ventilators access

BY PHIL PORTE

Executive director, NAMDRC

CMS announced in a press release in mid-March that as it revamped the competitive bidding program for durable medical equipment, it would move to include no invasive ventilation (NIV) in the revamped program, slated to take effect January 1, 2021.

While the implementation date is still more than 18 months in the future, the regulatory timetable for a formal announcement, as well as time for CMS to introduce its revamped bidding process, actually creates a relatively short window for aggressive action to thwart the CMS proposal.

In late November 2018, when CMS was seeking public comment on the idea of such a move, CHEST, NAMDRC and numerous other societies submitted strongly worded comments opposed to the recommendation, citing a wide array of clinical risks associated with such a proposal. The comments also highlighted CMS' total failure to revamp its own coverage policies, frequently cited by the pulmonary medicine community and the Office of the Inspector General as the primary root cause for significant problems.

Background: Under current law, Medicare is required to pay for certain ventilators under a "frequent and substantial servicing" payment methodology, with payment continuing as long as medical necessity is documented. Nearly 2 decades ago, CMS (then HCFA) sought to circumvent those statutory requirements by declaring that some ventilators are really not ventilators (as FDA classifications indicate) but are actually "respiratory assist devices."

The long-term impact of that unilateral policy decision has been ongoing chaos, as well as flawed coverage policies. For example, it is much more challenging for a physician to order a cheaper bi-level device than to order a ventilator for treatment of "respiratory failure." As there are no limitations or qualifying criteria tied to "respiratory failure," the community has responded with the path of least resistance while pleading with CMS to restructure their coverage policies to reflect the standards of care for home mechanical ventilation.

Since 2014, the community has repeatedly tried to convince CMS of the importance, and cost savings, associated with such a revamp, to no avail. Given 5 years of well documented efforts, it is likely that the only genuine solution will be a legislative one that forces CMS to behave in certain ways.

The challenges: There are complicating variables that the clinical community will need to address:

1. If the term "ventilator" is included in any legislative effort, CMS could expand its infamous concept "just because FDA calls a device a ventilator doesn't make it one." Using particular CPT or HCPCS codes would open the door for CMS to simply change coding to circumvent legislative intent.

2. If a legislative effort receives serious support, it ought to include specific guidance to CMS to force it to change its coverage policies for home mechanical ventilation to reflect standards of care and state-of-the-art devices.

For example, because devices are designed today to serve a wide range of respiratory issues, one device may be used to provide critical life support for an ALS patient, while *that same device* could also be used to provide nocturnal or intermittent support for other neuromuscular or COPD patients. Because the durable medical equipment benefit is focused on devices, CMS' move to change to focus from a device to a patient is questionable.

3. Forcing CMS to move in a particular direction regarding coverage and device usage must be flexible enough to allow for technological and medical innovations; after all, no one wants to recommend legislative policies that would have to be revisited to address potential/likely advances in this field.

Broad strategies: While the durable medical equipment community is also challenging this proposal, they agreed that the medical and patient communities should take the lead. And, in principle, we agree. But implementation of that effort is a bit of a challenge as it requires a significant grassroots effort from concerned physicians, as well as patient groups to contact their legislators in Congress. After all, the worst case scenario is for a Senator to say, "How come I haven't heard from any constituents about this problem if it is as bad as you say it is?" That is a fair and common refrain, and we must be prepared to engage the broad physician and patient communities to ensure success in this effort.

Once there is formal introduction of a proposal to move this matter forward, there will be outreach to physicians and respiratory therapists across the country to urge support of the legislation. *Keep watching for such requests for action!*

SLEEP STRATEGIES

The burgeoning role of sleep-related chronic hypoxia in long-term outcomes

BY KRISHNA M. SUNDAR, MD, FCCP

Clinicians are well aware of the acute effects of hypoxemia when encountered in conditions such as pulmonary embolism, pulmonary edema, COPD exacerbation, and others, whereas effects of chronic hypoxemia, such as pulmonary hypertension and polycythemia, are more difficult to recognize. Chronic hypoxemia is frequent in chronic lung diseases, such as COPD, but how it leads to increased mortality in severe COPD is unknown (NHLBI Working Group for LTOT in COPD. *Am J Respir Crit Care Med*. 2006;174:373). Chronic hypoxemia following high altitude exposure tends to have more unpredictable effects. Chronic hypoxemia, greater than that expected for the altitude of residence, is encountered frequently in high altitude dwellers. Here it has been implicated in the pathophysiology of chronic mountain sickness (Villafeurte and Corante. *High Alt Med Biol*. 2016;17[2]:61) and low birth weights (Maatta J, et al. *Sci Rep*. 2018;8[1]:13583), even though high altitude residence has been linked to better cardiovascular outcomes and reduced cancer-related deaths (Burstcher M. *Aging Dis*. 2013;5[4]:274). Chronic hypoxia effects at high altitude may, therefore, be variegated depending on a number of factors that include organ-system-specific effects, severity of chronic hypoxia, and a propensity to disease determined by genetic background and generations of residence.


Dr. Sundar

Such diverse effects of chronic sleep-related hypoxemia are also being reported with obstructive sleep apnea (OSA). While sleep can result in sustained drops in ventilation and consequent hypoxemia similar to what is seen in COPD, OSA is typified by a form of sleep-related hypoxemia in a pattern termed as chronic intermittent hypoxia (CIH). CIH is characterized by rapid fluctuations in oxygen saturations (Figure 1) that are virtually pathognomonic of sleep apnea either from recurrent upper airway obstructions (as in OSA) or pauses in respiratory generator firing (as in central sleep apnea). OSA-driven CIH has received most attention, given its purported role in in the causation of the wide range of pathologic conditions associated with OSA. Outcomes from cross-sectional and longitudinal studies have correlated time spent below 90% or recurrent oxygen desaturations to a number of OSA-related outcomes such as cardiovascular disease, diabetes, and cognitive dysfunction (Dewan et al. *Chest*. 2015;147[1]:266). While these effects of OSA-related intermittent hypoxemia occur over long periods of time, as with other forms of chronic hypoxia, some effects, such as hypertension, are demonstrable in animal models after much shorter durations of sleep-related intermittent hypoxia exposure. As seen with other forms of chronic hypoxemia, an opposing beneficial effect has also been demonstrated on the size of myocardial infarct during acute coronary events and from mild OSA-related mortality in elderly subjects (Javaheri et al. *J Am Coll Cardiol*. 2017;69[7]:841).

Given how common sleep-related hypoxemia and OSA are, it is important to understand the implications of different patterns of sleep-related hypoxemia that a vast segment of the population experiences on a nightly basis. A number of factors may determine chronic outcomes with sleep-related hypoxemia that include the pattern of sleep-related hypoxemia (chronic sustained hypoxemia associated with sleep-related hypoventilation vs chronic intermittent hypoxemia of OSA), degree of hypoxemia, presence of underlying disease, and hitherto undescribed individual factors. While a correlation between hypoxemic burden secondary to sleep-disordered breathing and cardiovascular outcomes has been shown (Azabarzin A, et al. *Eur Heart J*. 2018 Oct 30), CPAP interventional studies that address OSA-related CIH have shown mixed results for prevention of cardiovascular disease (McEvoy RD, et al. *N Engl J Med*. 2016;375[10]:919). It has also been difficult to draw upon results of oxygen supplementation in other forms of hypoxemia, such as COPD, when specifically targeted to addressing the hypoxemia seen only at night or with exercise (LOTT Research Group. *N Engl J Med*. 2016;375:1617). To complicate this further, high altitude residence (that may result in similar levels of sleep-related hypoxemia) is not associated with any differences in life-expectancy but may provide a reduction in cardiovascular outcomes (Ezzati, et al. J *Epidemiol Community Health*. 2012;66[7]:e17).

Chronic hypoxemia is frequent in chronic lung diseases, such as COPD, but how it leads to increased mortality in severe COPD is unknown.

How do we reconcile such disparate effects of chronic hypoxemia? Part of the difference may be in the pattern of chronic intermittent hypoxemia noted with OSA characterized not only by rapid drops in oxygen but also rapid reoxygenation events secondary to arousals terminating an apnea – these reoxygenation events have been attributed to the increased oxidant stress demonstrable in multiple tissues. While chronic hypoxia itself may cause increased oxidant stress, such effects seen with sustained forms of hypoxia, such as sleep-related hypoventilation or high altitude residence, may be more gradual resulting in lesser degrees of tissue effects and regulation of antioxidant defenses with sustained exposure. Herein lies the importance of understanding physiologic and biological effects stemming from chronic hypoxia to explain its variegated effects on different organ systems. In this regard, the role of the carotid body, a structure with unique vascular supply and with the ability to respond to minor changes in oxygen saturation as is seen in patients with OSA is key to the causation of hypertension associated with OSA (Shell et al. *Curr Hyperten Rep*. 2016;18[3]:19). Carotid body activation by intermittent hypoxia and long-term sensory facilitation drive the elevated sympathetic activity and consequent increases in blood pressure that can be improved by supplemental oxygen (Turnbull CD, et al. *Am J Respir Crit Care Med*. 2019;199[2]:211).

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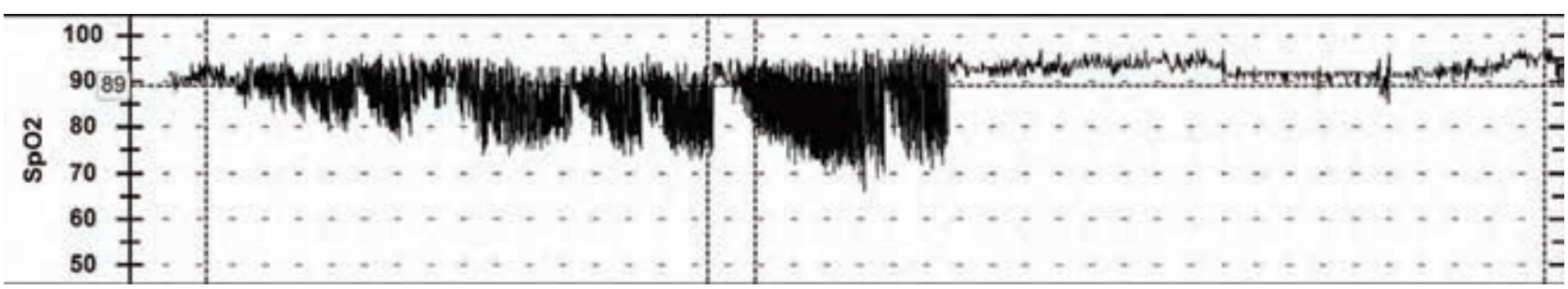

Figure 1: Demonstration of the pattern of intermittent hypoxemia in OSA characterized by oximetric desaturations and re-saturations that resolve with CPAP application.

Continued from previous page

While carotid body responses are key to the pathophysiology of OSA, every organ in the body (in fact, every cell within the body) has the ability to sense and respond to hypoxia. This ability to sense oxygen tensions is ingrained in every cell by virtue of oxygen's critical role in the genesis of life and evolution. These cellular responses to hypoxia are mediated by hypoxia-inducible factors (HIFs), isoforms of which include the more ubiquitous HIF-1 found in all parenchymal cells and HIF-2 found in specialized erythropoietin-producing cells of the kidney and the pulmonary circulation (the polycythemia and pulmonary vasoconstrictive responses from hypoxia are mediated through HIF-2). HIFs mediate the transcription of hundreds of genes, and they have been implicated in the pathobiology of a wide range of phenomena, from cancer to atherosclerotic vascular disease, metabolic syndrome, neurodegenerative disorders, pulmonary hypertension, and nonalcoholic fatty liver disease (Prabhakar and Semenza. *Physiol Rev*. 2012;92[3]:967). While HIF activation is an attractive target for examining the effects of chronic hypoxia of high altitude and sleep-disordered breathing, HIF activation varies from tissue to tissue and interacts with a number of other cellular systems in leading to differential effects. The short half-life of HIF proteins make them difficult to detect in tissues, so a number of secondary HIF-effects has been measured with mixed results depending on animal model utilized, pattern and degree of hypoxia studied, and the target effect measured. Comparative effects of intermittent vs sustained hypoxemia need to be systematically studied in different organ systems in different species, given the differing oxygen thresholds of individual cells due to unique blood flows and variations in the system of co-factors and prolyl hydroxylases that regulate the activation of HIFs. While the thrust of the work has been centered on HIF-related effects and the role of NF-kB-driven inflammation seen in OSA, there is substantial evidence to the role of oxidant stress that may be directly related to reoxygenation events occurring with CIH (Lavie L. *Sleep Med Rev*. 2015;20:27).

Chronic intermittent hypoxia is characterized by rapid fluctuations in oxygen saturations that are virtually pathognomonic of sleep apnea.

For life that has been intricately involved with oxygen from its genesis, it is not unreasonable to expect adaptations of cells, organs, and the whole individual to a wide range of oxygen tensions. Attempts to understand the import of sleep-disordered breathing has led to a need to unravel the implications of OSA-related chronic intermittent hypoxia and sleep-hypoventilation. This has led to a resurgence of interest in hypoxia-related research. Whether such chronic sleep-related sustained and intermittent hypoxemia is a harbinger of chronic disease is still not fully clear. A number of challenges exist with the understanding of these chronic hypoxia effects that include the long time needed for disease occurrence, its differential effects on organ systems, the role of hypoxia vs reoxygenation injury, importance of local blood flow, etc. Understanding these pathways will be crucial in prognosticating the role of sleep-related hypoxemia, the recognition of which has become part and parcel of routine management in sleep medicine.

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This month in the journal *CHEST*®

Editor's Picks

BY RICHARD S. IRWIN, MD, MASTER FCCP

Giants in Chest Medicine
John Heffner, MD, FCCP

ORIGINAL RESEARCH
The Landscape of US Lung Cancer Screening Services-Figure 1
By M. S. Kale, et al.

Systemic Markers of Inflammation in Smokers With Symptoms Despite Preserved Spirometry in SPIROMICS
By S. Garudadri, et al.

Prevalence of Atrial Fibrillation in Hospital Encounters With End-Stage COPD on Home Oxygen: National Trends in the United States
By X. Xiao, et al.

INDEX OF ADVERTISERS

NetWorks

LC screening. microRNAs. Impulse oscillometry. PH definition change. LC & women.

Interventional Chest/ Diagnostic Procedures

Complications and economic burden of diagnostic procedures for lung abnormalities in the community setting

The influential National Lung Screening Trial (NLST) reported a 20% reduction in lung cancer-related deaths using low-dose CT scan when compared with plain chest radiography (Aberle et al. *N Engl J Med*. 2011;365[5]:395). Many medical societies responded by recommending screening individuals at high-risk for lung cancer, and community-based lung cancer screening programs were developed across the United States. A concerning feature of the study was the rate (23.3%) of false-positive findings after three rounds of screening and the potential for complications secondary to diagnostic invasive procedures.

Using a 2008-2013 cohort of community inpatient and outpatient practice settings, Hou and colleagues searched administrative databases for procedure and diagnostic codes used in the NLST (Hou et al. *JAMA Intern Med*. 2019;179 [3]:324). The study team created an age-matched control cohort that did not have an invasive procedure and used the difference in complications rates as an indicator of a procedure-related complication. Additionally, they estimated 1-year medical costs associated with complications. More than 340,000 patients were included in the study, and the overall complication rate was far higher than what was reported in the NLST. This difference was more pronounced in the older group in the study cohort (23.8% vs 8.5%). The associated economic burden of complications was substantial, and cost more than the initial procedure itself.

Dr. Cardenas-Garcia

Although this was not a lung cancer screening cohort and used an administrative database, some valuable lessons can be offered from this study. First, complication rates of procedures like those performed in the NLST are likely to be higher in low-volume centers. Second, in order to minimize procedures, associated complications, and costs, we should be cognizant of the diagnostic limitations of each type of intervention when evaluating patients with lung nodules, wisely choosing the correct procedure for the correct patient after multidisciplinary discussion. We should seek to minimize biopsies of lesions that are likely benign.

Third, it is evident that more research is needed regarding this topic. The ideal study would need to include both academic and community-based lung cancer screening programs, and, prospectively, analyze the diagnostic yield and complication rates, as well as downstream costs. Finally, the results of this study call all of us to properly follow the lung cancer screening guidelines and reconcile them with our common sense when evaluating a patient with a screen-detected nodule. Injudicious testing invites unnecessary complications, increases the cost of care, and diverts resources from those more likely to benefit from appropriate interventions.

Jose Cardenas-Garcia, MD, FCCP
Steering Committee Member
Douglas Arenberg, MD, FCCP
NetWork Member

Pediatric Chest Medicine

microRNAs: A New Biomarker

Biomarkers are essential tools in a clinician's armamentarium. Biomarkers have multiple uses being indicators of a pathologic or physiologic process. One promising biomarker, now studied across multiple disorders, is microRNA (miRNA).

miRNAs are short (18–22 nucleotide) regulatory RNAs that bind mRNAs and decrease protein translation. miRNAs are generally co-transcribed with neighboring genes or co-transcribed within a cluster of miRNAs (a polycistronic cluster). Over 2,000 miRNAs are listed on miRBase (http://www.mirbase.org/), considered the central repository.

Function and biomarker utility of miRNAs are specific to the cells in which they are expressed. miRNAs isolated from circulating plasma exosomes have been shown to be stable over time, which is key in establishing their utility (Sanz-Rubio, et al. *Sci Rep*. 2018;8[1]:10306). miRNAs have been credited with the function of micromanaging the circadian clock and sleep homeostasis in virtually all living organisms (Goodwin, et al. *Cell Rep*. 2018;23[13]:3776; Mehta, et al. *J Mol Biol*. 2013;425[19]:3609).

Dr. Rao

Preliminary work has identified dysregulated miRNAs in patients with obstructive sleep apnea (Li, et al. *Medicine (Baltimore)*. 2017;96[34]:e7917). Exosomal miRNA has been shown to predict and protect against severe bronchopulmonary dysplasia (Lal, et al. *JCI Insight*. 2018;3[5]. pii: 93994).

Circadian miRNAs in salivary samples were found to have "altered" expression in autistic children with disordered sleep relative to peers with typical sleep (Hicks, et al. *PLoS One*. 2018;13[7]:e0198288). Collection from salivary samples facilitates multiple timed collection feasible at home and has multiple benefits.

Work on miRNAs, though preliminary, appears promising in providing a much-needed new perspective on pathophysiology and treatment in many disease processes.

Harish Rao, MD
Steering Committee Member

Pulmonary Physiology, Function, and Rehabilitation

Using impulse oscillometry in clinical practice

Impulse oscillometry (iOS) is an effort-independent test that requires minimal cooperation from the patient. It provides measures of respiratory mechanics during normal tidal breathing, including resistance (R), reactance (X), and impedance (Z) (Oostveen E, et al. *Eur Respir J*. 2003;22[6]:1026).

Airway R is largely, but not entirely, determined by cross-sectional area

(Poiseuille's Law). X is a surrogate for lung elastance, which is the inverse of compliance. Z is the combination of R and X and isn't used clinically.

There are several benefits to using iOS, as opposed to or in conjunction with standard spirometry. First, iOS yields respiratory function measurements for patients, like the elderly and young children, who cannot provide acceptable and reproducible spirometry (Pezzoli L, et al. *Age Ageing*. 2003;32[1]:43). Second, it provides a real-world assessment of lung function because R and X values are obtained during tidal breathing. Humans don't use the forced maneuvers needed for spirometry during normal daily activities, which weakens the correlation of FEV_1 with respiratory symptoms. Forced maneuvers also create artifacts from gas compression and cause small airway closure, which limits inferences made from standard spirometry (Brusasco V, et al. *Eur Respir J.* 2005;26[5]:948). Lastly, R and X provide information not available from spirometry, and iOS is particularly sensitive for detecting small airway dysfunction (Berger K, et al. *Chest*. 2015;148[5]:1131).


Dr. Holley

Clinical and disease-specific indications for iOS are still being established. As discussed above, iOS is appropriate for any patient unable to perform spirometry. As new inhalers designed to deliver medication to the distal airways become available, subtle abnormalities detected via iOS will provide a target for specific therapies (Lipworth B. *Ann Allergy Asthma Immunol.* 2013;110[4]:233). iOS shows significant promise as a noninvasive assessment for supraglottic diseases, like vocal cord dysfunction, and can quantify changes over time following invasive intervention to relieve upper airway obstruction (Bikov A, et al. *Chest*. 2015;148[3]:731; Horan T, et al. *Chest*. 2001:120[1]:69). As their comfort level with interpretation improves, pulmonologists will find iOS is an important tool for disease diagnosis and treatment.

Aaron Holley, MD, FCCP
Steering Committee Member

Pulmonary Vascular Disease
Hemodynamic definition of pulmonary hypertension changed

Many patients worldwide went to bed February 26, 2018, with normal pulmonary pressures and woke up the next morning with pulmonary hypertension (PH). That day, experts met at the World Symposium on PH in Nice, France, and changed the definition of resting PH from a mean pulmonary artery pressure (mPAP) of greater than or equal to 25 mm Hg to a mPAP greater than 20 mm Hg (Simmoneau, et al. *Eur Respir J*. 2019;53:1801913). The First World Health Organization symposium on PH in 1973 established the 25 mm Hg cutoff to distinguish primary PH from what was then considered less severe forms of PH. This definition, acknowledged as arbitrary and conservative at the time, has persisted due to a paucity of data establishing a definitively abnormal mPAP threshold.


Dr. Kingrey

Two contemporary findings provide justification for the definition change: (1)Normal mPAP is 14 ± 3.3 mm Hg in healthy subjects (Kovacs, et al. *Eur Respir J.* 2009;34[4]:888). (2) Patients with mPAP greater than 20 mm Hg suffer worse outcomes compared with control subjects (Maron, et al. *Circulation*. 2016;133[13]:1240).

Preserving the other hemodynamic criteria for group 1 PH, pulmonary artery wedge pressure less than or equal to 15 mm Hg and pulmonary vascular resistance greater than or equal to 3 Wood units, experts also recommend applying the new definition to all pre-capillary PH, including groups 3, 4, and applicable group 5 diagnoses.

Importantly, new guidelines do not recommend treating PH patients with mPAP 21-24 mm Hg: "A change in the hemodynamic definition of PH due to [pulmonary vascular diseases] does not imply treating these additional patients, but highlights the importance of close monitoring in this population."

John Kingrey, MD
Steering Committee Member

Thoracic Oncology
Lung Cancer and Women

While the overall incidence of lung cancer (LC) has decreased among both men and women, the decline among men has been steeper compared with women. Further, in women born in the 1950s to 1960s, the incidence has actually increased and cannot be fully explained by sex differences in smoking behavior (Jemal, et al. *N Engl J Med.* 2018;378[21]:1999). Data suggest that women may be more susceptible to the harmful effects of tobacco and that the biology of LC may be different in women. In addition, LC in nonsmokers is more likely to occur in women.


Dr. Gonzalez

LC is the leading cause of cancer death in both women and men worldwide, but the dramatic rise in the mortality rate from LC in women was qualified as a "full blown epidemic" in the Surgeon General's 2001 Women and Smoking report (*MMWR*. 2002;51[RR12]:1-30).

The benefits of lung cancer screening (LCS) in the National Lung Screening Trial (NLST) were higher in women than in men and significantly greater in the subset of women (16%) who entered the Nelson trial – reduction in 10-year LC mortality of 61% vs 26% in men (De Koning, et al. IASLC. 19th World Congress on Lung Cancer. 2018. Abstract PL02.05). A retrospective review of patients diagnosed with LC between 2005 and 2011 showed that only 37% of women vs 50% of men met LCS criteria (Wang, et al. *JAMA*. 2015;313[8]:853).

Lung cancer needs to be recognized as an important women's health issue, and there is need for continued attention to sex differences in LC risk, LCS criteria, and outcomes.

Anne Gonzalez, MD, FCCP
Steering Committee Member

CHEST Regional Congress 2019 Athens

Athens, Greece, one of the oldest cities in the world, will set a perfect backdrop for our upcoming CHEST Regional Congress, hosted by the Hellenic Thoracic Society and CHEST. Athens attracts millions of people from all over the world every year and has both historical and modern features including the Acropolis of Athens, which contains the remains of ancient buildings of great architectural significance such as the Parthenon; the Theatre of Dionysus, the oldest theater in Greece; and the National Archaeological Museum, which houses a large collection of artwork dating back to the Neolithic Age. The historic scenery and infectious energy will invigorate you as you partake in the top pulmonary medicine review courses.

This pulmonary review will give attendees access to world-class faculty from regional and international centers of excellence. A group of exceptional CHEST and Hellenic Thoracic Society faculty, including Drs. Kevin Brown Stephanie Levine, Nicholas Pastis, and Doreen Addrizzo-Harris, Vasilis Skouras, and Vlasis Poylchronopoulos, will come together to host outstanding sessions covering a multitude of topics, including interstitial lung disease, COPD, asthma, lung cancer, pleural disease, sarcoid, and pulmonary hypertension, among others. Also experience innovative and diverse education opportunities incorporating the best of the CHEST Pulmonary Medicine Board Review courses, CHEST Games, and a simulation demonstration opportunity on the final day of the meeting.

Information at athens.chestnet.org.

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We look forward to seeing you 27-29 June at CHEST Regional Congress Athens!

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